NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 420

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRIAMTERENE

(CAS NO. 396-01-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

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

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

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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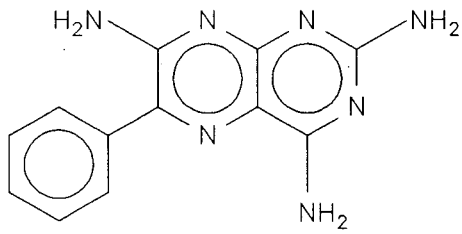
ABSTRACT



TRIAMTERENE

CAS No. 396-01-0

Chemical Formula: $C_{12}H_{11}N_7$ Molecular Weight: 253.26

Synonyms: 6-Phenyl-2,4,7-pteridinetriamine; 6-phenyl-2,4,7-triaminopteridine; 2,4,7-triamino-6-phenypteridine; ademin; pterofen; pterophane; NSC-77625; SKF 8542

Trade names: Dyrenium, Dyazide, Dyren, Dytac, Jatropur, Maxzide, Noridyl, Triteren, Teriam, Urocaudal

Triamterene is a potassium-sparing diuretic used in the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and other diseases in which edema may occur. Toxicity and carcinogenicity studies were conducted by administering triamterene (greater than 99% pure) in feed to groups of male and female F344/N rats and B6C3F$_1$ mice for 15 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary cells.

15-Day Studies: Groups of five male and five female rats were fed diets containing 0, 1,000, 3,000, 10,000, 30,000, or 60,000 ppm triamterene. The diets containing 10,000 ppm or more were unpalatable, and feed consumption by the 3,000 ppm groups was reduced. Rats exposed to 1,000 or 3,000 ppm triamterene received approximate doses of 80 or 60 mg/kg body weight per day (males) or 70 or 50 mg/kg per day (females). One male rat and two female rats receiving 3,000 ppm died during the second week of the study. The final mean body weights of 3,000 ppm male and female rats were significantly lower than those of controls. Rats in the 3,000 ppm groups had renal tubule regeneration and cytoplasmic vacuolization of the zona glomerulosa of the adrenal gland.

Groups of five male and five female mice were fed diets containing 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm triamterene, but the diets containing 10,000 or 30,000 ppm were unpalatable. All mice receiving 3,000 ppm died by day 6. Mice exposed to 300 or 1,000 ppm triamterene received approximate doses of 40 or 155 mg/kg body weight per day (males) or 45 or 170 mg/kg body weight per day (females). The final mean body weights of mice in the 300 and 1,000 ppm groups were similar to those of the controls. Renal tubule degeneration and necrosis were observed in the kidney of 3,000 ppm mice.

13-Week Studies: Groups of 10 male and 10 female rats were fed diets containing 0, 150, 300, 600, 1,200, or 2,400 ppm triamterene. All rats receiving 2,400 ppm died before the end of the study; all other rats survived to the end of the study. Rats exposed to 150, 300, 600, or 1,200 ppm triamterene received approximate doses of 10, 20, 40, or 70 mg/kg body weight per day (males) or 10, 20, 40, or 80 mg/kg per day (females). Body weight gains and final mean

body weights of rats in the 1,200 ppm groups were significantly lower than those of controls. There were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters among exposed and control rats. Calculi were observed in the renal pelvis of four male rats in the 1,200 ppm group. Chemical-related lesions were observed in the kidney and adrenal gland of rats in the 1,200 and 2,400 ppm groups. These consisted of degeneration and regeneration of the renal tubule epithelium and cytoplasmic vacuolization of cells of the zona glomerulosa of the adrenal cortex. Depletion of hematopoietic cells from the bone marrow and of lymphocytes from the spleen and thymus of rats in the 2,400 ppm groups may have been related to debilitation and reduced feed consumption rather than chemical exposure.

Groups of 10 male and 10 female mice were fed diets containing 0, 100, 200, 400, 800, or 1,600 ppm triamterene. All mice receiving 1,600 ppm, one 800 ppm female, one 200 ppm male, and four 100 ppm males died before the end of the study. Mice exposed to 100, 200, 400, or 800 ppm triamterene received approximate doses of 15, 25, 50, or 90 mg/kg body weight per day (males) or 15, 25, 50, or 115 mg/kg per day (females). The body weight gain and final mean body weight of male mice receiving 800 ppm were significantly lower than those of the controls. The total leukocyte and lymphocyte counts of males receiving 800 ppm and of females receiving 100, 400, or 800 ppm were significantly lower than those of controls. No other differences in hematologic, clinical chemistry, or urinalysis parameters were considered to be biologically significant. Necrosis of lymphocytes was observed in the lymph node, spleen, and thymus of mice in the 800 and 1,600 ppm groups.

2-Year Studies: The doses selected for the 2-year studies were based on lower body weights, mortality, and chemical-related lesions observed in exposed animals during the 13-week studies. Groups of 70 male and 70 female rats were fed diets containing 0, 150, 300, or 600 ppm triamterene and groups of 70 male and 70 female mice were fed diets containing 0, 100, 200, or 400 ppm. Ten animals from each group were included for interim evaluations at 3 and 15 months. Because of a dosing error involving the high-dose mice at week 40, a second study was conducted with groups of 60 male and 60 female mice fed diets containing 0 or 400 ppm triamterene.

In the 2-year studies, rats exposed to 150, 300, or 600 ppm triamterene received approximately 5, 10, or 25 mg/kg body weight per day (males) and 5, 15, or 30 mg/kg (females) and mice exposed to 100, 200, or 400 ppm received approximately 10, 25, or 45 mg/kg (males) and 15, 30, or 60 mg/kg (females) per day.

3-Month and 15-Month Interim Evaluations in the 2-Year Studies: There were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters between exposed and control rats or mice at the 3- or 15-month interim evaluations. At necropsy, the mean body weights of exposed rats and mice were similar to those of the controls. There were no chemical-related lesions in exposed rats at 3 months or in exposed mice at 3 or 15 months. At the 15-month evaluation, basophilic, clear cell, and mixed cell foci of the liver occurred in exposed male rats. No chemical-related lesions were observed in female rats at 15 months.

Survival, Body Weights, Clinical Findings, and Feed Consumption in the 2-Year Studies: Survival of exposed rats was similar to that of controls (males: 0 ppm, 25/47; 150 ppm, 25/50; 300 ppm, 19/50; 600 ppm, 27/50; females: 29/50, 34/50, 34/50, 29/50). The mean body weights of 600 ppm rats were consistently lower than, but within 5% of, those of controls after week 49. Feed consumption by male and female rats was similar among exposed and control groups throughout the studies. There were no clinical findings of toxicity.

Survival of 400 ppm male mice in the first study was lower than that of controls because of the dosing accident at week 40. Survival of 100 and 200 ppm male mice and of all exposed groups of female mice in the first study and of exposed males and females in the second study was similar to controls (males: first study, 0 ppm, 47/50; 100 ppm, 45/50; 200 ppm, 46/50; 400 ppm, 46/60; second study, 0 ppm, 43/50; 400 ppm, 39/50; females: first study, 38/50; 43/50; 43/50; 43/60; second study, 40/50; 38/51). Mean body weights of exposed mice were similar to those of controls throughout the first study with one exception; in the week following the dosing error, the mean body weight of 400 ppm males was 16% lower than that of controls. In the second study, mean body weights of 400 ppm mice were slightly lower than those of controls during the final 8 weeks. Feed consumption by exposed mice was similar to that by controls

throughout the studies. There were no clinical findings of toxicity in exposed mice.

Neoplasms and Nonneoplastic Lesions in the 2-Year Studies: The incidences of mixed cell foci and focal hyperplasia of the liver were significantly increased in 300 and 600 ppm male rats, and the incidences of clear cell and mixed cell foci were significantly increased in 300 and 600 ppm female rats. Hepatocellular adenomas occurred in all groups of exposed male rats, but none occurred in controls; the incidence of hepatocellular adenoma in the 150 ppm males was significantly higher than that of controls (0 ppm, 0/50; 150 ppm, 6/50; 300 ppm, 4/50; 600 ppm, 3/49). Hepatocellular adenomas were observed in two 600 ppm female rats, but not in the lower exposure groups or in controls. No hepatocellular carcinomas were seen in exposed or control rats.

The incidences of nephropathy in exposed rats were similar to those of controls, but the average severity of the lesion was marginally increased in male rats receiving 300 ppm and in female rats receiving 600 ppm (males: 47/50, 2.4; 49/50, 2.7; 50/50, 3.0; 49/50, 2.8; females: 38/50, 1.1; 45/50, 1.2; 45/50, 1.3; 45/50, 1.4).

Although in the first study the incidences of hepatocellular adenoma in exposed male mice were similar to that of controls, the incidences of multiple adenomas were greater in the exposed groups, and the incidence of hepatocellular carcinoma in the 400 ppm group was marginally greater (hepatocellular adenoma: 0 ppm, 17/50; 100 ppm, 22/50; 200 ppm, 19/50; 400 ppm, 20/60; hepatocellular carcinoma: 5/50; 7/50; 3/50; 13/60). In the second study, the incidence of hepatocellular adenoma in the 400 ppm males was significantly higher than that of controls (hepatocellular adenoma: 0 ppm, 21/50; 400 ppm, 36/50; hepatocellular carcinoma: 9/50; 11/50).

The incidences of hepatocellular adenoma in exposed female mice in the first and second studies were significantly greater than those of controls (hepatocellular adenoma, first study: 10/50; 22/50; 23/50; 36/60; second study: 7/50; 28/51). The incidences of multiple adenoma were also increased in the exposed groups. Although the incidences of hepatocellular carcinoma were similar among exposed and control female mice in the first study, the incidence of hepatocellular carcinoma in the 400 ppm females in the second study was marginally greater than that of controls (hepatocellular carcinoma, first study: 4/50; 4/50; 3/50; 8/60; second study: 5/50; 11/50). In both studies, hepatocellular foci (basophilic, eosinophilic, clear cell, or mixed cell) also occurred more frequently in exposed female mice than in controls.

The incidences of thyroid gland follicular cell hyperplasia in the 200 and 400 ppm males and in all exposed groups of females were significantly greater than those of controls in the first study. These findings were confirmed in the second study (follicular cell hyperplasia: males, first study, 3/50, 8/50, 16/50, 20/60; second study, 0/50, 16/50; females, first study, 4/49, 17/49, 18/50, 28/60; second study, 9/50, 32/51). The incidences of follicular cell neoplasms were similar among exposed and control mice in both studies.

The incidences (28/50, 36/50, 43/50, 49/60) and average severity (0.56, 0.80, 1.00, 1.07) of nephropathy were marginally higher in exposed female mice than in controls in the first study. In the second study, the differences in incidence (15/50, 21/50) and severity (0.38, 0.55) were not as great. It is uncertain if these increases were related to the ingestion of triamterene. The incidences and severity of nephropathy were similar among exposed and control male mice in both studies.

Genetic Toxicology: Triamterene was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without exogenous metabolic activation (S9). It did not induce chromosomal aberrations in Chinese hamster ovary cells, with or without S9. Positive results were obtained for induction of sister chromatid exchanges in Chinese hamster ovary cells with and without S9.

Conclusions: Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of triamterene in male F344/N rats based on a marginal increase in the incidence of hepatocellular adenoma. There was *no evidence of carcinogenic activity* of triamterene in female F344/N rats administered 150, 300, or 600 ppm. There was *some evidence of carcinogenic activity* of triamterene in male B6C3F$_1$ mice based on a marginal increase in the incidence of hepatocellular carcinoma in the first study and a significantly increased incidence of hepatocellular adenoma in the second study. There was *some evidence of carcinogenic activity* of

triamterene in female B6C3F$_1$ mice based on significantly increased incidences of hepatocellular adenoma and of adenoma and carcinoma (combined).

Exposure to triamterene was associated with an increased incidence of hepatocellular foci, primarily mixed cell type, and an increase in the severity of nephropathy in female rats. In mice, exposure to triamterene was associated with an increased incidence of hepatocellular foci in females and an increased incidence of thyroid gland follicular cell hyperplasia in males and females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Triamterene

Variable	Male F344/N Rats	Female F344/N Rats
Doses	0, 150, 300, or 600 ppm in feed (approximately 5, 10, or 25 mg/kg body weight)	0, 150, 300, or 600 ppm in feed (approximately 5, 15, or 30 mg/kg body weight)
Body weights	Exposed groups similar to controls	600 ppm group lower than controls
2-Year survival rates	25/47, 25/50, 19/50, 27/50	29/50, 34/50, 34/50, 29/50
Nonneoplastic effects	Liver: hyperplasia (0/50, 3/50, 5/50, 10/49); eosinophilic foci (2/50, 3/50, 2/50, 8/49); mixed cell foci (0/50, 6/50, 8/50, 12/49)	Liver: clear cell foci (3/50, 3/50, 4/50, 9/50); mixed cell foci (2/50, 2/50, 8/50, 13/50); Kidney: nephropathy (38/50, 45/50, 45/50, 45/50); severity grades (1.1, 1.2, 1.3, 1.4)
Neoplastic effects	None	None
Uncertain findings	Liver: adenoma (0/50, 6/50, 4/50, 3/49); Kidney: nephropathy severity (2.4, 2.7, 3.0, 2.8)	None
Level of evidence of carcinogenic activity	Equivocal evidence	No evidence

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Triamterene (continued)

Variable	Male B6C3F$_1$ Mice		Female B6C3F$_1$ Mice	
	First Study	Second Study	First Study	Second Study
Doses	0, 100, 200, or 400 ppm in feed (approximately 10, 25, or 50 mg/kg body weight)	0 or 400 ppm (approximately 40 mg/kg body weight)	0, 100, 200, or 400 ppm in feed (approximately 15, 30, or 60 mg/kg body weight)	0 or 400 ppm (approximately 60 mg/kg body weight)
Body weights	High-dose group lower than controls	Exposed group similar to controls	Exposed groups similar to controls	Exposed group similar to controls
2-Year survival rates	47/50, 45/50, 46/50, 46/60	43/50, 39/50	38/50, 43/50, 43/50, 43/60	40/50, 38/51
Nonneoplastic effects	Thyroid gland: follicular cell hyperplasia (3/50, 8/50, 16/50, 20/60)	Thyroid gland: follicular cell hyperplasia (0/50, 16/50)	Liver: basophilic cell foci (1/50, 6/50, 6/50, 11/60); clear cell foci (0/50, 1/50, 4/50, 3/60); all foci (8/50, 16/50, 24/50, 19/60)	Liver: basophilic cell foci (0/50, 5/51); clear cell foci (0/50, 4/51); all foci (10/50, 20/51)
			Thyroid gland: follicular cell hyperplasia (4/49, 17/49, 18/50, 28/60)	Thyroid gland: follicular cell hyperplasia (9/50, 32/51)
Neoplastic effects	Liver: hepatocellular carcinoma (5/50, 7/50, 3/50, 13/60); hepatocellular adenoma or carcinoma (20/50, 26/50, 19/50, 29/60)	Liver: hepatocellular adenoma (21/50, 36/50); hepatocellular adenoma or carcinoma (25/50, 38/50)	Liver: hepatocellular adenoma (10/50, 22/50, 23/50, 36/60); hepatocellular adenoma or carcinoma (13/50, 26/50, 25/50, 37/60)	Liver: hepatocellular adenoma (7/50, 28/51); hepatocellular adenoma or carcinoma (10/50, 31/51)
Uncertain findings	None	None	None	None
Level of evidence of carcinogenic activity	Some evidence		Some evidence	
Genetic toxicology				
Salmonella typhimurium gene mutation:	Negative with and without S9 metabolic activation			
Sister chromatid exchanges				
Chinese hamster ovary cells *in vitro*:	Positive with and without S9 metabolic activation			
Chromosomal aberrations				
Chinese hamster ovary cells *in vitro*:	Negative with and without S9 metabolic activation			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on triamterene on November 21, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 21, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of triamterene received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of triamterene by discussing the chemical's use and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in rats and mice.

The proposed conclusions were *equivocal evidence of carcinogenic activity* of triamterene in male F344/N rats; *no evidence of carcinogenic activity* in female F344/N rats; *some evidence of carcinogenic activity* in male B6C3F$_1$ mice; and *some evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Dr. Carlson, a principal reviewer, agreed with the proposed conclusions. He suggested more relevant toxicology data on triamterene should be added to the introduction, mainly to help focus on possible target organs such as the liver and kidneys. Dr. Dunnick noted that many of the toxicity studies performed in industry had not been reported in the literature.

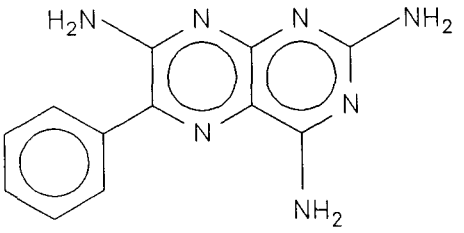
Dr. Davidson, the second principal reviewer, agreed with the proposed conclusions. Her agreement for the conclusions in male mice was based primarily on the results from the second study. She suggested that combined incidences of hepatocellular adenoma and carcinoma be added to the statement for both studies in male mice. She stated that the dosing error in the high-dose mice in the 2-year study was a concern. Dr. Dunnick said the staff considered that both studies supported the conclusion of *some evidence* in male mice.

Dr. Hayden, the third principal reviewer, agreed with the proposed conclusions. He said there should be some discussion of thyroid lesions in exposed male mice since they are statistically significant and dose-related. Dr. Dunnick said severity grades would be added to the table and more discussion of thyroid follicular cell hyperplasia in treated mice would be included.

Dr. Goodman commented that since triamterene had been on the market for 30 years, more information could be included about human toxicity, placing it in context with the rodent toxicity data (p. 64). Dr. Hayden and Dr. McKnight suggested that rats in the 2-year studies might have tolerated higher doses because mean body weights of exposed rats were within 5% of controls and terminal survival rates for control and 2-year survival rates of exposed groups were similar (see p. 62 for dosing rationale).

Dr. Carlson moved that the Technical Report on triamterene be accepted with the revisions discussed and with the conclusions as written for male F344/N rats, *equivocal evidence of carcinogenic activity,* for female F344/N rats, *no evidence of carcinogenic activity,* and for male and female B6C3F$_1$ mice, *some evidence of carcinogenic activity.* Dr. Bailey seconded the motion. Dr. Goodman offered an amendment that the conclusion in male mice be changed to *equivocal evidence of carcinogenic activity.* The amendment was tabled for lack of a second. Dr. Davidson offered an amendment that adenoma and carcinoma (combined) be added to the conclusion statement for male mice. The amendment was tabled for lack of a second. Dr. Carlson's motion was then accepted by eight yes votes to one no vote (Dr. Goodman) with one abstention (Dr. van Zwieten).

INTRODUCTION



TRIAMTERENE

CAS No. 396-01-0

Chemical Formula: $C_{12}H_{11}N_7$ Molecular Weight: 253.26

Synonyms: 6-Phenyl-2,4,7-pteridinetriamine; 6-phenyl-2,4,7-triaminopteridine; 2,4,7-triamino-6-phenypteridine; ademin; pterofen; pterophane; NSC-77625; SKF 8542

Trade names: Dyrenium, Dyazide, Dyren, Dytac, Jatropur, Maxzide, Noridyl, Triteren, Teriam, Urocaudal

Physical and Chemical Properties

Triamterene is a yellow, odorless, crystalline powder with a melting point of 316° C. It is practically insoluble in water and slightly soluble in alcohol (*Merck Index*, 1983). Triamterene was first synthesized by Spickett and Timmis (1954) by a reaction of 4-amino-5-nitrosopyrimidine with phenylacetonitrile.

Use and Production

Triamterene has been used since 1961 as a potassium-sparing diuretic in the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and the nephrotic syndrome, as well as in the treatment of other diseases in which edema may occur. Diuresis usually occurs within 2 to 4 hours after drug administration and diminishes in approximately 7 to 9 hours. The usual initial adult oral dose of triamterene is 100 mg twice daily, and maintenance therapy is 100 mg once daily. Although triamterene is not usually administered to children, the recommended dose is 4 mg/kg daily or 115 mg/m^2 (body surface area) daily. The maximum therapeutic dose of triamterene is 5 mg/kg daily. Because of its low water solubility, triamterene is administered orally and is not available for parenteral administration (Laragh *et al.*, 1961; Weinstock and Wiebelhaus, 1963; Weiner, 1990; *Physicians' Desk Reference*, 1991). In a 1990 survey, Dyazide, which contains triamterene, was the sixth most frequently prescribed drug in the United States (*American Druggist*, 1991). Information on the number of prescriptions written per year for triamterene was not available in the literature.

Although triamterene (Dyrenium) is effective alone, it is used frequently in combination therapy with other diuretics (e.g., hydrochlorothiazide) that act at different sites in the nephron. Products containing both triamterene and hydrochlorothiazide are Dyazide (50 mg triamterene and 25 mg hydrochlorothiazide) and Maxzide (75 mg triamterene and 50 mg hydrochlorothiazide) (Hollenberg and Bannon, 1986; Sica and Gehr, 1989).

Pharmacology and Toxicity

Diuretics are designed to increase urine flow, and triamterene acts as a diuretic agent at the distal tubule in the nephron by increasing sodium excretion by 2% to 3%. While triamterene increases the excretion of sodium, it decreases excretion of potassium. Triamterene is usually used in combination

with the thiazides, which increase potassium excretion, to block kaliuresis (Greenberg, 1986).

Laragh *et al.* (1961) originally suggested that the basis of diuretic action of triamterene was aldosterone antagonism. However, Baba *et al.* (1962a,b) reported that triamterene directly affects the renal tubule cells. Others have suggested that triamterene regulates the activity of renal plasma membrane Na-K-ATPase, an enzyme considered to be a biochemical vehicle for the active transport of sodium across the cell membrane (Ožegović *et al.*, 1979). Triamterene primarily affects the distal tubule, where it inhibits sodium reabsorption and potassium excretion. Although it acts as an aldosterone antagonist, triamterene functions in adrenalectomized animals and in patients in which aldosterone has been chemically blocked (Nielsen and Lassen, 1963; Cohen, 1966). Analysis of urine samples collected from rats at two sites along the distal tubule (at the beginning and end of the distal tubule) demonstrated an inhibition of potassium secretion and an increase in sodium excretion in the distal tubule after triamterene treatment (Lacy *et al.*, 1980; Lant, 1985).

In humans, the most frequent side effect from triamterene therapy is electrolyte imbalance, mainly hyperkalemia. Hyperkalemia, because it can lead to cardiac arrhythmia, is the most serious toxic effect of overexposure (Weiner, 1990). Triamterene is a pteridine that is structurally similar to folic acid and other inhibitors of dihydrofolate reductase (e.g., methotrexate) and is a weak inhibitor of dihydrofolate reductase. Increased blood urea nitrogen concentrations have occurred during therapy and serum creatinine levels may be increased. Other side effects reported include nausea, vomiting, diarrhea, and gastrointestinal disturbances. Hemolytic anemia has been reported in patients treated with triamterene (Takahashi and Tsukada, 1979). Schiffl and Schollmeyer (1985) reported that with appropriate management, patients could be treated with triamterene and hydrochlorothiazide for 71 months with minimal side effects.

Triamterene administration has been associated with lithiasis, and it is estimated that the incidence of triamterene-induced kidney stones in Dyazide users is about 1 in 1,500. The kidney stones of Dyazide users consisted of triamterene, calcium oxalate monohydrate and dihydrate, uric acid, and protein (Sörgel *et al.*, 1985a,b; 1986).

When triamterene was administered by gavage to CD-1 male mice for 5 consecutive days, at doses of 5 to 300 mg/kg, renal cortical tubule dilation and basophilia occurred at doses of 50 mg/kg and greater (Manson *et al.*, 1986). These alterations were accompanied by an increase in blood urea nitrogen and creatinine levels. Also in this study, male mice treated for 5 days with triamterene at doses of 5 to 100 mg/kg were mated to untreated female mice. There were no adverse effects on mating or fertility and no evidence of induced dominant lethal mutations. Fischer rats given daily doses of 30 to 45 mg/kg triamterene for 3 weeks had renal damage characterized by degenerative changes of the renal cortical and medullary tubules (Ožegović *et al.*, 1981). Histological alterations were most severe in the proximal convoluted tubules and consisted of vacuolar degeneration with a loss of periodic acid-Schiff-staining of the brush border. In the medullary tubules, a few hyaline casts occurred. These renal lesions were not seen at doses of 3.6 to 15 mg/kg, which more closely approximate the dose levels used in humans.

The oral LD_{50} is 285 mg/kg for mice and 400 mg/kg for rats (RTECS, 1991). No 2-year rodent toxicity or carcinogenicity studies of triamterene were found in the literature.

METABOLISM

In humans triamterene is rapidly absorbed from the gastrointestinal tract. The plasma half-life of triamterene after oral administration is 1.5 to 2 hours. Peak plasma concentrations of 50 to 280 ng/mL are achieved within 2 to 4 hours following oral administration of a single 100 or 200 mg dose. The major metabolite of triamterene in humans is the hydroxytriamterene sulfuric acid ester, which is excreted in the bile as well as in the urine. The oral bioavailability of triamterene is estimated to be 50% to 80% (Pruitt *et al.*, 1977; Hasegawa *et al.*, 1982; Gilfrich *et al.*, 1983; Mutschler *et al.*, 1983; Loew *et al.*, 1984; Sörgel *et al.*, 1986).

In patients with liver disease, the pharmacokinetics of triamterene may be markedly altered, and in older patients, the elimination of triamterene may be impaired (Mutschler *et al.*, 1983; Williams *et al.*, 1986). After an oral dose of 50 mg, the mean peak concentration of triamterene in older patients was 84 ng/mL compared with 41 ng/mL in younger

patients. Villeneuve *et al.* (1984) reported that when patients with cirrhosis were administered triamterene orally, the apparent clearance of the drug was reduced 92%. Dao and Villeneuve (1988) reported that after an oral dose of 200 mg, the mean plasma concentration in normal patients was 45 ng/mL for triamterene and 967 ng/mL for hydroxytriamterene sulfate, while in patients with cirrhosis, the mean concentration increased to 586 ng/mL for triamterene but was reduced to 747 ng/mL for hydroxytriamterene sulfate.

After intravenous administration of 1 to 4 mg/kg of ^{14}C-triamterene to Sprague-Dawley rats, the drug was recovered in the kidney, liver, heart, lungs, and skeletal muscle, but there was little accumulation of the radioactivity in the brain, testes, or fat. The plasma half-life of triamterene was estimated to be 2.7 hours (Kau and Rama Sastry, 1977). In Sprague-Dawley rats receiving a subcutaneous dose of ^{14}C-triamterene (2 mg/kg), 45% and 50% of the total radioactivity was excreted in the urine and feces, respectively, during the 72 hours following treatment. Triamterene accounted for 72% to 79% of the radioactivity recovered in the urine and feces. The major metabolites found in the urine were free *p*-hydroxytriamterene (10% to 15%) and its sulfuric acid ester conjugate (1% to 5%). When the bile duct was ligated, metabolites were not found in either the urine or feces, suggesting that the liver is a major metabolic site (Kau *et al.*, 1975). Leilich *et al.* (1980) demonstrated that the hydroxytriamterene sulfuric acid ester has a diuretic effect in rats.

Genetic Toxicity

Triamterene is not a bacterial mutagen. It did not inhibit growth in *Bacillus subtilis* due to DNA damage (Kawachi *et al.*, 1980) and did not induce gene mutations in *Salmonella typhimurium* with or without S9 activation (Kawachi *et al.*, 1980; Ishidate *et al.*, 1981; Mortelmans *et al.*, 1986). Triamterene was also negative in the silkworm gene mutation assay (Kawachi *et al.*, 1980). However, results of *in vitro* tests in mammalian cells indicated a capability to induce chromosomal damage in some cell types. In the absence of S9, triamterene induced chromosomal aberrations (Kawachi *et al.*, 1980; Ishidate *et al.*, 1981), sister chromatid exchanges (Kawachi *et al.*, 1980; Sasaki *et al.*, 1980), and micronuclei (Sasaki *et al.*, 1980) in Chinese hamster lung cells. However, in human embryo cell cultures, triamterene induced sister chromatid exchanges without S9 (Kawachi *et al.*, 1980; Sasaki *et al.*, 1980), but did not induce chromosomal aberrations (Sasaki *et al.*, 1980) or micronuclei (Kawachi *et al.*, 1980). Few data are available for evaluation of the genetic toxicity of triamterene *in vivo*, and the data that do exist contrast with the positive results observed for induction of chromosomal effects in mammalian cells *in vitro*. *In vivo*, triamterene was negative in tests for induction of chromosomal aberrations in bone marrow cells and dominant lethal mutations in germ cells of CD-1 male mice (Manson *et al.*, 1986). In the chromosomal aberrations test, a maximum dose of 250 mg/kg was administered by intraperitoneal injection and cells were sampled from 6 to 24 hours after treatment; in the dominant lethal test, triamterene was administered daily by gavage for 5 consecutive days at a maximum dose of 100 mg/kg. In male rats, triamterene did not induce chromosomal aberrations in bone marrow cells (Kawachi *et al.*, 1980) or unscheduled DNA synthesis in hepatocytes (Mirsalis *et al.*, 1983).

Study Rationale

Triamterene was selected for toxicity and carcinogenicity testing in F344/N rats and B6C3F$_1$ mice because of its widespread use as a diuretic agent and the lack of data on the potential effects of long-term exposure. The oral route of administration was chosen because this is the route of exposure in humans.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TRIAMTERENE

Triamterene, manufactured by Secifarma (Milan, Italy), was obtained from Gyma Laboratories of America (Garden City, NJ). One lot (84/1) was used during the 15-day, 13-week, and 2-year studies. The identity and purity analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Details of the analyses are presented in Appendix H.

The study chemical, a yellow microcrystalline solid, was identified as triamterene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Figures H1 and H2). Purity was found to be greater than 99% by elemental analysis, Karl Fischer water analysis, potentiometric titration of the amine functional group, thin-layer chromatography, and high-performance liquid chromatography (HPLC). No impurities were detected by HPLC with a peak area greater than or equal to 0.1% of the major peak area. Lot 84/1 met the United States Pharmacopeia requirements for purity.

Stability studies were performed by the analytical chemistry laboratory using HPLC. The chemical was found to be stable in bulk form when stored protected from light for 2 weeks at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically at the study laboratory using titration of the amine group and HPLC and no degradation of the study chemical was detected. To ensure stability, the bulk chemical was stored at 5° C or lower in the dark during the 15-day, 13-week, and 2-year studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing triamterene with a small amount of feed to form a premix. The premix and additional feed were layered into a blender and mixed. Dose formulations were prepared weekly for the 15-day studies and every 2 weeks for the 13-week and 2-year studies. Homogeneity and stability studies were conducted by the analytical chemistry laboratory on the dosed feed preparations. Dose formulations in feed were homogeneous and stable for up to 2 weeks when stored at 5° C and protected from light. Details of the preparation and analyses of the dose formulations are presented in Appendix H.

The dose formulations were analyzed once at the beginning of the 15-day studies by the study laboratory and were within 10% of the target concentrations (Table H2). During the 13-week studies, the dose formulations were analyzed at the beginning and midpoint of the studies; all rat and 15 of 17 mouse formulations were within 10% of the target concentrations (Table H3). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks (Table H4). All dose formulations were within 10% of the target concentrations, except dose formulations prepared in week 40 for rats receiving 600 ppm and for mice receiving 400 ppm. Rats in the 600 ppm group received 0 ppm for approximately 1% of the dosing duration, which was considered to have no effect on the results. Mice in the 400 ppm group received approximately 1,600 ppm, which caused 16 deaths. Survivors of the dosing accident were returned to the appropriate dose formulation (first study), and a second set of 2-year studies was started with exposure levels of 0 and 400 ppm. Throughout the second study, the 400 ppm formulation was within 10% of the target concentration. Periodic analyses of the dose formulations of triamterene were performed by the study laboratory and the analytical chemistry laboratory with either an HPLC or ultraviolet spectroscopy method. Results of the analyses performed by the analytical chemistry laboratory indicated good agreement with the results of the study laboratory (Table H5).

15-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories

(Portage, MI). Rats were observed for 14 days and mice were observed for 15 days before being assigned to groups. The rats were 42 to 49 days old and the mice were 50 to 65 days old when the studies began.

Groups of five male and five female rats were fed diets containing 0, 1,000, 3,000, 10,000, 30,000, or 60,000 ppm triamterene for up to 14 days, and groups of five male and five female mice were fed diets containing 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm triamterene for up to 14 days. After 14 days on a dosed diet, surviving animals were fed an untreated diet for 1 day. Animals were housed five per cage. Water and feed were available *ad libitum*. Details of study design, animal maintenance, and method of sacrifice are described in Table 1.

Animals were weighed at the beginning of the studies and on days 8 and 15. Animals were observed twice daily, except on weekends. Feed consumption was measured weekly. Complete necropsy was performed on all animals 16 days after exposure began.

Organs weighed at the end of the studies included the brain, heart, right kidney, liver, lungs, right testis, and thymus. Complete histopathologic examinations were performed on rats fed 3,000 ppm and on mice fed 1,000 and 3,000 ppm. Selected tissues from rats fed 0 and 1,000 ppm were examined. Tissues examined microscopically are listed in Table 1.

13-Week Studies

These studies were conducted to evaluate the cumulative toxic effects of repeated exposure to triamterene. Male and female F344/N rats and B6C3F$_1$ mice were obtained from the Charles River Breeding Laboratories (Portage, MI). Rats were observed for 13 days and mice were observed for 16 days before being assigned to groups. The rats were 41 to 48 days old and the mice were 57 to 68 days old when the studies began.

Groups of 10 male and 10 female rats were fed a diet containing 0, 150, 300, 600, 1,200, or 2,400 ppm triamterene for 13 weeks. Groups of 10 male and 10 female mice were fed diets of 0, 100, 200, 400, 800, or 1,600 ppm for 13 weeks. Rats and mice were housed five per cage. Feed and water were available *ad libitum*. Details of study design, animal maintenance, and method of sacrifice are described in Table 1.

Animals were observed twice daily. Individual animal weights were recorded initially, once weekly, and at the end of the studies. Feed consumption was measured weekly. Organs weighed at the end of the studies included the brain, heart, right kidney, liver, lungs, right testis, and thymus. Blood for hematology and clinical chemistry was collected from the orbital sinus plexus of rats and mice, which were fasted for approximately 20 hours prior to blood sample collection. Urine for urinalysis was collected during this 20-hour fasting period from animals housed in metabolism cages. Clinical pathology parameters were evaluated at 13 weeks from blood and urine collected from rats fed 0, 150, 600, and 1,200 ppm and from mice fed 0, 100, 400, and 800 ppm. Complete histopathologic examinations were performed on all animals killed moribund or that died before the end of the studies, on all rats fed 0 or 2,400 ppm, and all mice fed 0 or 1,600 ppm. Selected tissues from animals in the other exposure groups were examined. The tissues routinely examined microscopically are listed in Table 1. The health of the rats was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

2-Year Studies

Study Design

Groups of 70 male and 70 female rats were fed diets containing 0, 150, 300, or 600 ppm triamterene for 104 weeks. Ten rats per group were designated for interim evaluation at 3 and 15 months. Groups of 70 male and 70 female mice were fed diets containing 0, 100, 200, or 400 ppm triamterene for 104 weeks. As a result of a dose formulation error at week 40, high-dose mice received diets containing 1,600 ppm for 7 days, which resulted in the death of 16 animals. Ten mice per group were designated for interim evaluation at 3 and 15 months, but because of the dosing error the 15-month interim evaluation was not conducted for mice at 400 ppm. Because of the uncertain effect of the overdose on mice, a second study was begun with 60 male and 60 female mice fed 0 and 400 ppm triamterene for 103 weeks, and 10 mice per group were designated for interim evaluation at 15 months. The organs weighed at the 3- and 15-month interim evaluation were the brain, kidney, and liver. Blood for hematology and clinical chemistry was collected from the retroorbital sinus of rats and mice at the 3- and 15-month evaluations. Urine for urinalysis was collected overnight from animals

housed in metabolism cages before the 3- and 15-month evaluations. The tissues routinely examined microscopically are listed in Table 1.

Source and Specification of Animals

The male and female F344/N rats and B6C3F$_1$ mice used in the 2-year studies were obtained from Frederick Cancer Research Facility (Frederick, MD). Rats were 28 days old when received by the study laboratory and were quarantined for 13 days. Mice were 28 days old when received by the study laboratory; the quarantine period was 12 days for the first study and 13 days for the second study. During quarantine, the animals were observed daily. To assess the health status of the animals before the start of the studies, five male and five female rats and five male and five female mice in the first study, and five male and four female mice in the second study were killed and examined for evidence of disease and parasite infection. The rats were 41 days old and the mice were 40 or 41 days old when the studies began. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured once every 4 weeks. Cages were rotated clockwise on the racks every 2 weeks and cage racks were rotated clockwise to a new location in the animal room every 2 weeks. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights and clinical findings were recorded weekly for the first 13 weeks and then once every 4 weeks until the end of the studies. All animals were necropsied. At necropsy, all organs and tissues were examined for gross lesions.

Complete histopathologic examinations were performed on all animals that died or were killed moribund before the end of the studies, all animals that reached study termination, all rats from the 0 and 600 ppm groups at the 3- and 15-month interim evaluations, all mice from the 0 and 400 ppm groups in the first study at the 3-month interim evaluation, and all mice from the 0 and 200 ppm groups in the first study and from the 0 and 400 ppm groups in the second study at the 15-month interim evaluation. Selected tissues were examined from rats and mice in other groups at the 3- and 15-month interim evaluations. Tissues examined microscopically are listed in Table 1. At necropsy all organs and tissues were fixed and preserved in phosphate-buffered neutral formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Nonneoplastic lesions were rated using a four-step grading system of minimal, mild, moderate, and marked.

Pathology evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet-tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. A quality assessment pathologist reviewed the liver of male and female rats, the pituitary gland of female rats, the liver, pituitary gland, and thyroid gland of male and female mice, the ovary and uterus of female mice in both study groups, and the harderian gland of male and female mice in the second study for accuracy and consistency of lesion diagnosis.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed selected tissues for which there was disagreement in diagnosis between the laboratory and the quality assessment pathologist. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnosis between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. The PWG included the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of exposure level or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the PWG consensus. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For later analyses of pathology data, the

diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found 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 Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidence of neoplasms or nonneoplastic lesions is given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. 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 gland neoplasms) before histologic sampling or when lesions (e.g., mononuclear cell leukemia) had multiple potential sites of occurrence, the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

The majority of neoplasms in these studies 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 neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm 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 control and exposed 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 neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm 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), which is appropriate for rapidly lethal neoplasms, the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals. Tests of significance include pairwise comparisons of each exposed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described above were also used to evaluate selected nonneoplastic lesions. For further discussion of these methods, refer to 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 neoplasm incidence. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Hematology, clinical chemistry, and urinalysis data, which typically have skewed distributions, were analyzed using the multiple comparison methods of Shirley (1977) or Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams' test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's test). Average nephropathy severity

values for the 2-year studies were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Quality Assurance Methods

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

Genetic Toxicology

Triamterene was tested for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with preincubation in the presence and in the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. The induction of sister chromatid exchanges and chromosomal aberrations was tested using Chinese hamster ovary cells with and without S9 activation.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Triamterene

15-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
International Research and Development Corp. (Mattawan, MI)	International Research and Development Corp. (Mattawan, MI)	Battelle Columbus Division (Columbus, OH)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Frederick Cancer Research Facility (Frederick, MD)
Time Held Before Study		
Rats: 14 days Mice: 15 days	Rats: 13 days Mice: 16 days	Rats: 13 days Mice: First study, 12 days; Second study, 13 days
Age When Placed on Study		
Rats: 42-49 days Mice: 50-65 days	Rats: 41-48 days Mice: 57-68 days	Rats: 41 days Mice: First study, 40 days; Second study, 41 days
Date of First Dose		
Rats: 4 May 1982 Mice: 5 May 1982	Rats: 13 September 1982 Mice: 16 September 1982	Rats: 10 September 1984 Mice: First study, 17 September 1984; Second study, 26 August 1985
Date of Last Dose		
Rats: 17 May 1982 Mice: 19 May 1982	Rats: 14 December 1982 Mice: 15 December 1982	Rats: 1 September 1986 Mice: First study, 9 September 1986; Second study, 17 August 1987
Duration of Dosing		
14 days	13 weeks	104 weeks
Average Age at Necropsy		
Rats: 8-9 weeks Mice: 7-8 weeks	Rats: 19-20 weeks Mice: 22-23 weeks	Rats: 3-month interim evaluation, 19 weeks; 15-month interim evaluation, 71 weeks; terminal, 111 weeks Mice: First study, 3-month interim evaluation, 19 weeks; 15-month interim evaluation, 71 weeks (except for 400 ppm group); terminal, 110 weeks Second study, 15-month interim evaluation, 72 weeks; terminal, 110 weeks

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Triamterene (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Necropsy Dates		
Rats: 19 May 1982 Mice: 20 May 1982	Rats: 13-14 December 1982 Mice: 16-17 December 1982	Rats: 3-month interim evaluation, 11-14 December 1984; 15-month interim evaluation, 9 December 1985; terminal, 8-10 September 1986 Mice: First study, 3-month interim evaluation, 18-21 December 1984; 15-month interim evaluation, 16-17 December 1985; terminal, 15-16 and 18-19 September 1986; Second study, 15-month interim evaluation, 1 December 1986; terminal, 24-25 August 1987
Size of Study Groups		
5 males and 5 females	10 males and 10 females	Rats: 70 males and 70 females Mice: First study, 70 males and 70 females; Second study, 60 males and 60 females
Animals per Cage		
Rats: 5 Mice: 5	Rats: 5 Mice: 5	Rats: 5 Mice: 1
Method of Animal Distribution		
Animals were weighed and randomized into dose groups using a pseudo-random number generator.	Same as 15-day studies	Animals were weighed and randomized into exposure groups by partitioning algorithm using the Xybion® Pathology/Toxicology Data System
Method of Animal Identification		
Rats: Ear tag Mice: Toe clip	Rats: Ear tag Mice: Toe clip	Rats: Toe mark Mice: Toe mark
Diet		
NIH-07 Rat and Mouse Open Formula, mash diet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*, feeders exchanged weekly	Same as 15-day studies	NIH-07 Rat and Mouse Open Formula, meal diet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*, feeders exchanged weekly
Water		
Well water from Village of Mattawan, MI, and IRDC wells. Available *ad libitum* using an Edstrom Industries automatic watering system (Waterford, WI)	Same as 15-day studies	City of Columbus, OH, municipal water supply, available *ad libitum* using an Edstrom Industries automatic watering system (Waterford, WI)
Cages		
Polycarbonate, solid bottoms (Hazleton System, Inc., Aberdeen, MD, and Lab Products, Inc., Maywood, NJ); changed twice weekly	Same as 15-day studies; changed biweekly. Cages rotated within exposure groups on racks	Same as 15-day studies. Cages were changed weekly (mice) or twice weekly (rats). Cages were rotated clockwise on the racks every 2 weeks.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Triamterene (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Racks		
Stainless steel, (Unifab Corporation, Kalamazoo, MI, and Wahmann Manufacturing Co., Timonium, MD); changed once every 2 weeks	Same as 15-day studies, changed once every 2 weeks and racks rotated in the animal room once every 2 weeks	Same as 15-day studies. Cage racks were changed and rotated clockwise to a new location in the animal room once every 2 weeks
Bedding		
BetaChips®, heat-treated hardwood chips (Northeastern Products Corp., Warrensburg, NY), changed twice weekly	Same as 15-day studies	BetaChips®, heat-treated hardwood chips (Northeastern Products Corp., Warrensburg, NY), changed weekly (mice) or twice weekly (rats)
Cage Filters		
Reemay spun-bonded polyester fiber filters (Snow Filtration, Cincinnati, OH), changed once every 2 weeks	Same as 15-day studies	Dupont 2024, spun-bonded polyester fiber filters (Snow Filtration, Cincinnati, OH), changed once every 2 weeks
Animal Room Environment		
Average temperature: 24° C Relative humidity: 47% Fluorescent light: 12 hours/day Room air flow: minimum of 10 changes/hour	Average temperature: 22° C Relative humidity: 50% Fluorescent light: 12 hours/day Room air flow: minimum of 10 changes/hour	Rats: Temperature: 20°-26° C Relative humidity: 31%-73% Fluorescent light: 12 hours/day Room air flow: minimum of 15 changes/hour Mice (first study): Temperature: 20°-26° C Relative humidity: 20%-66% Fluorescent light: 12 hours/day Room air flow: minimum of 10 changes/hour Mice (second study): Temperature: 20°-24° C Relative humidity: 28%-66% Fluorescent light: 12 hours/day Room air flow: minimum of 10 changes/hour
Doses		
Rats: 0, 1,000, or 3,000, 10,000, 30,000, or 60,000 ppm in feed Mice: 0, 300, 1,000, 3,000, 10,000, or 30,000 ppm in feed	Rats: 0, 150, 300, 600, 1,200, or 2,400 ppm in feed Mice: 0, 100, 200, 400, 800, or 1,600 ppm in feed	Rats: 0, 150, 300, or 600 ppm in feed Mice: First study, 0, 100, 200, or 400 ppm in feed; Second study, 0 or 400 ppm in feed
Type and Frequency of Observation		
Observed twice/day; body weight initially, on day 8, and on day 15; feed consumption measured daily and recorded weekly; clinical findings were noted daily	Observed twice/day; body weight once/week until the end of the studies; feed consumption measured daily and recorded weekly; clinical observation once weekly.	Observed twice/day; body weights once/week for the first 13 weeks, then once/month until the end of the study; feed consumption measured approximately every 4 weeks; clinical findings noted at body weight determinations.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Triamterene (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Method of Sacrifice Carbon dioxide asphyxiation	Same as 15-day studies	Same as 15-day studies
Necropsy Necropsy performed on all animals. Organs weighed on animals surviving to the end of the studies were brain, heart, right kidney, liver, lungs, right testis, and thymus.	Same as 15-day studies	Necropsy performed on all animals. Organs weighed at 3-month and 15-month interim evaluations were brain, kidney, and liver.
Histopathology Complete histopathologic examinations were performed on rats in the 3,000 ppm groups and on mice in the 1,000 and 3,000 ppm groups. Tissues examined microscopically included adrenal gland, bone (including marrow), brain, epididymis, esophagus, gallbladder (mice only), gross lesions, heart, kidney, large intestine, liver, lung, mammary gland, mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, small intestine, spinal cord, spleen, stomach, testis, thymus, thyroid gland, tissue masses, trachea, urinary bladder, and uterus. Selected tissues examined from rats fed 0 or 1,000 ppm were: bone and bone marrow, kidney, mammary gland, adrenal gland, and gross lesions.	Complete histopathologic examinations were performed on all rats in the 0, 1,200, and 2,400 ppm groups, on all mice in the 0, 800, and 1,600 ppm groups and all animals that died prior to study termination. Tissues routinely examined microscopically were the same as those included in the 15-day studies. Adrenal gland, kidney, and gross lesions were examined from rats in the 150, 300, and 600 ppm groups. Thymus and gross lesions were examined from mice in the 100, 200, and 400 ppm groups.	Complete histopathologic examinations were performed on all rats and all mice (from both first and second studies) that died or were killed moribund prior to the end of the studies or survived to study termination. At the 3- and 15-month interim evaluations, complete histopathologic examinations were performed on all rats from the 0 and 600 ppm groups; in the 150 and 300 ppm groups only gross lesions were examined at the 3-month evaluation while gross lesions, hearts in males, and kidneys in females were examined at the 15-month evaluation. At the 3-month interim evaluation of mice (conducted in first study only) complete histopathologic examinations were performed on all mice in the 0 and 400 ppm groups and only gross lesions were examined in the other groups. At the 15-month interim evaluation, complete histopathologic examinations were performed on all mice from the 0 and 200 ppm groups in the first study and on the 0 and 400 ppm groups in the second study; kidneys and gross lesions were examined from 100 ppm groups in the first study. Tissues routinely examined microscopically included adrenal gland, bone (including marrow), brain, clitoral gland (rats only), epididymis, esophagus, gallbladder (mice only), gross lesions, heart, kidney, large intestine, liver, lung, mammary gland, mandibular lymph node, mesenteric lymph node, nose, ovary, pancreas, parathyroid gland (continued)

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Triamterene (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
		(continued) pituitary gland, preputial gland (rats only), prostate gland, salivary gland, skin, small intestine, spleen, stomach, testis, thymus, thyroid gland, tissue masses, trachea, urinary bladder, and uterus.
Clinical Pathology		
None	Blood and urine were collected from rats in the 0, 150, 600, and 1,200 ppm groups and from mice in the 0, 100, 400, and 800 ppm groups. ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential leukocyte counts ***Clinical chemistry:*** creatinine, calcium, chloride, potassium, phosphorus, and sodium ***Urinalysis:*** specific gravity and volume	Clinical pathology studies were made at 3- and 15- month interim evaluations. Blood collected from the retroorbital sinus following methoxyflurane anesthesia and urine collected overnight in metabolism cages. ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential leukocyte counts, platelets, reticulocytes ***Clinical chemistry:*** bilirubin, urea nitrogen, pH, bicarbonate, creatinine, calcium, chloride, potassium, phosphorus, and sodium. ***Urinalysis:*** specific gravity and volume

RESULTS

RATS

15-DAY STUDY

The diets containing triamterene at levels of 10,000 ppm or more were unpalatable. Reduced palatability of the diet containing 3,000 ppm was also evident and the feed consumption by rats in these groups was less than that by controls (Table 2). Rats exposed to 1,000 or 3,000 ppm received approximate triamterene doses of 80 or 60 mg/kg per day (males) or 70 or 50 mg/kg per day (females). One male and two females receiving 3,000 ppm died on day 14 or 15. The deaths of these rats were likely due primarily to malnutrition associated with the reduced feed consumption, although physiological and pathological renal effects associated with triamterene may have contributed to their deaths. There were no clinical findings attributed to triamterene.

The final mean body weights of males and females in the 3,000 ppm group were 52% and 42% lower than controls (Table 2). The absolute organ weights of rats receiving 3,000 ppm were lower than those of the controls primarily as a result of the reduced feed consumption and lower body weights observed in these groups (Table F1).

Microscopic examination of the kidneys of all males and three females receiving 3,000 ppm revealed one or a few scattered individual tubules with basophilic epithelial cells containing vesicular nuclei. The nuclear and cytoplasmic features of the epithelium in the affected renal tubules were characteristic of epithelial regeneration following tubule damage. Cellular debris was observed in the lumens of a few scattered tubules in males but not in females. Cytoplasmic vacuolization of cells of the zona glomerulosa

TABLE 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 15-Day Feed Study of Triamterene

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	187 ± 5	243 ± 4	56 ± 2		18.1	15.3
1,000	5/5	186 ± 7	237 ± 7	51 ± 2	97	16.7	16.6
3,000	4/5[d]	187 ± 7	117 ± 5**	−74 ± 6**	48	4.2	1.8
10,000	0/5[d]	184 ± 5	–	–	–	–	–
30,000	0/5[d]	183 ± 7	–	–	–	–	–
60,000	0/5[d]	186 ± 7	–	–	–	–	–
Female							
0	5/5	136 ± 3	159 ± 4	24 ± 2		12.0	11.6
1,000	5/5	135 ± 4	157 ± 3	23 ± 1	99	9.1	11.3
3,000	3/5[d]	136 ± 5	92 ± 10**	−44 ± 5**	58	2.4	1.6
10,000	0/5[d]	134 ± 4	–	–	–	–	–
30,000	0/5[d]	135 ± 3	–	–	–	–	–
60,000	0/5[d]	135 ± 5	–	–	–	–	–

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/number initially in group. Animals were given dosed feed for 14 days followed by 1 day of undosed feed.
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. No data were calculated for groups with 100% mortality.
[c] Grams of feed consumed per animal per day
[d] All deaths occurred between days 11 and 15

was observed in the adrenal gland of all males and one female receiving 3,000 ppm. The bone marrow of rats receiving 3,000 ppm contained fewer hematopoietic cells than that of controls, presumably due to the reduced feed consumption and lower body weights.

Because of the poor palatability of diets containing triamterene at levels of 3,000 ppm or more and the chemical-related kidney and adrenal gland lesions observed in the 3,000 ppm groups in the 15-day feed study, the high dose selected for the 13-week study in rats was 2,400 ppm.

13-WEEK STUDY

All rats in the 2,400 ppm group died during the first 4 weeks, apparently as a result of reduced feed consumption (Table 3) as well as the nephrotoxic effects of triamterene. All rats receiving 1,200 ppm or less survived to the end of the study. Clinical findings of toxicity observed only in rats in the 2,400 ppm groups were piloerection and inactivity and, finally, body tremors, ataxia, bradypnea, and prostration. These findings commonly accompany debilitation as a result of reduced feed consumption and toxicity and may not be the result of specific, chemical-related morphological or functional alterations. During the first 4 weeks of the study, feed consumption by rats in the 2,400 ppm group was markedly lower than that by controls. It is uncertain if the reduced feed consumption was related to decreased palatability of the diet or to anorexia resulting from toxicity. Feed consumption by rats receiving 1,200 ppm or less was similar to that by controls. Rats exposed to 150, 300, 600, or 1,200 ppm triamterene received approximate doses of 10, 20, 40, or 70 mg/kg per day (males) or 10, 20, 40, or 80 mg/kg per day (females).

TABLE 3
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of Triamterene

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	164 ± 3	390 ± 8	226 ± 8		18.8	16.1
150	10/10	163 ± 4	383 ± 11	220 ± 7	98	19.3	16.4
300	10/10	163 ± 6	382 ± 9	219 ± 6	98	19.6	15.0
600	10/10	163 ± 4	375 ± 7	213 ± 7	96	18.6	15.3
1,200	10/10	164 ± 4	338 ± 6**	174 ± 4**	87	15.6	14.9
2,400	0/10[d]	158 ± 4	–	–	–	–	–
Female							
0	10/10	121 ± 3	218 ± 3	97 ± 5		12.8	8.3
150	10/10	121 ± 2	214 ± 2	92 ± 2	98	11.9	10.0
300	10/10	120 ± 3	209 ± 4	89 ± 2	96	11.5	9.9
600	10/10	120 ± 3	210 ± 3	90 ± 1	96	11.9	9.8
1,200	10/10	117 ± 3	192 ± 2**	75 ± 3**	88	10.4	9.4
2,400	0/10[e]	119 ± 3	–	–	–	–	–

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. No data were calculated for groups with 100% mortality.
[c] Grams of feed consumed per animal per day
[d] Week of death: 3, 3, 3, 3, 4, 4, 4, 4, 4, 4
[e] Week of death: 2, 2, 3, 3, 3, 3, 4, 4, 4, 4

There were slight differences in the mean values of several hematologic, clinical chemistry, or urinalysis parameters in rats receiving 1,200 ppm (Table G1). These were not considered biologically significant and were not clearly related to the administration of triamterene.

The final mean body weights and body weight gains of rats in the 1,200 ppm groups were 13% and 23% lower than those of controls for males and 12% and 23% lower for females. At 1,200 ppm, the absolute weights of brain and kidney in males and of brain, heart, kidney, lungs, and thymus in females were significantly lower than those of controls (Table F2). Since the relative organ-weight-to-body-weight ratios were not significantly affected, the absolute organ weight changes were attributed to reduced body weight and not to organ toxicity.

At necropsy, minute, sand-like calculi were observed in the renal pelvis of four male rats receiving 1,200 ppm triamterene; none were observed in the kidney of females in the 1,200 ppm group or in males or females of any other group. Chemical-related microscopic lesions were observed in the kidney and adrenal gland (Table 4). Mild regeneration of the renal tubule epithelium was observed in all males and most females in the 2,400 ppm groups. The lesions were often most extensive in the outer stripe of the outer medulla and extended into the inner regions of the cortex. Although the straight portions of the renal tubules were most often affected, there were also segmental areas involving the full thickness of the cortex. The epithelium of the affected renal tubules was more basophilic than normal with slightly enlarged, vesicular nuclei. A few necrotic cells and mitotic figures were also observed and, infrequently, tubule lumens contained cellular debris or hyaline (protein) casts. The kidney lesions in the 1,200 ppm groups were less severe and involved fewer tubules. Minimal renal tubule regeneration involving a few scattered individual tubules was observed in most male rats in the lower dose groups and controls and was typical of spontaneous nephropathy.

Cytoplasmic vacuolization of cells of the zona glomerulosa was observed in the adrenal glands of nearly all male rats, but the severity of this lesion was greater in rats receiving 2,400 ppm (Table 4). In females, both the incidence and severity of cytoplasmic vacuolization were greater in the 2,400 ppm group than in the controls. Bone marrow hypocellularity and lymphoid depletion in the spleen and thymus of rats receiving 2,400 ppm may have been the result of emaciation and debilitation rather than direct chemical toxicity.

Dose selection rationale: Dietary concentrations of triamterene selected for the 2-year feed study in rats were 0, 150, 300, and 600 ppm. Exposure levels of 1,200 ppm were considered too great for the 2-year study, primarily because of the kidney lesions observed in 1,200 ppm rats in the 13-week study. Spontaneous renal disease occurrs in aging rats, particularly males, and is a major contributing cause of death. This age-related disease, in combination with renal toxicity related to triamterene ingestion may have reduced life-span, and thus negatively affected the sensitivity to detect carcinogenic effects.

TABLE 4
Incidences of Treatment-Related Lesions in Rats in the 13-Week Feed Study of Triamterene

	0 ppm		150 ppm		300 ppm		600 ppm		1,200 ppm		2,400 ppm	
Male												
n	10		10		10		10		10		10	
Kidney												
Tubule degeneration	0		0		0		0		8**	(1.3)[b]	10**	(3.1)
Tubule dilatation	0		0		0		0		8**	(1.3)	0	
Cast	0		0		0		0		4*	(2.0)	5*	(1.0)
Tubule regeneration	8	(1.1)	6	(1.0)	5	(1.0)	6	(1.0)	10	(1.8)	9	(1.7)
Calculi[a]	0		0		0		0		4		0	
Adrenal gland, cortex												
Vacuolar change	9	(1.0)	9	(1.0)	10	(1.0)	7	(1.0)	2	(1.0)	10	(2.6)
Bone marrow												
Hypocellularity	0		–[c]		–		–		0		10**	(3.2)
Spleen												
Lymphoid depletion	0		–		–		–		0		8**	(1.6)
Thymus												
Lymphoid depletion	0		–		–		–		0		8**	(3.4)
Female												
n	10		10		10		10		10		9	
Kidney												
Tubule degeneration	0		0		0		0		3	(1.7)	8**	(3.0)[d]
Tubule dilatation	0		0		0		1	(1.0)	3	(1.3)	2	(1.0)
Cast	0		0		0		0		2	(1.0)	0	
Tubule regeneration	0		0		0		1	(1.0)	5*	(1.2)	5*	(2.2)
Adrenal gland, cortex												
Vacuolar change	0		0		1	(1.0)	0		2	(1.0)	8**	(1.9)
Bone marrow												
Hypocellularity	0		–		–		–		0		9**	(3.2)
Spleen												
Lymphoid depletion	0		–		–		–		0		6**	(2.3)
Thymus												
Lymphoid depletion	0		–		–		–		0		7**	(3.3)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Calculi were observed by macroscopic examination at necropsy; all other lesions were observed by microscopic examination.
[b] Average severity grade for affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[c] Not examined microscopically at this exposure level

2-Year Study

3-Month Interim Evaluation

There were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters between exposed and control rats (Table G2). At necropsy the mean body weights of 150 and 300 ppm male rats and of 300 and 600 ppm female rats were slightly lower than those of controls (Table F3). The body weight decrement of the 150 and 300 ppm males was not considered to be chemical related because the mean body weight of the 600 ppm group was similar to controls. The absolute kidney weights of 300 and 600 ppm females and the absolute and relative kidney weights of 150 ppm males were slightly lower than those of controls, apparently because of the lower body weights of these groups (Table G2). No chemical-related gross or microscopic lesions were observed in rats after exposure to triamterene for 3 months.

15-Month Interim Evaluation

There were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters between exposed and control rats (Table G3). At necropsy, the mean body weights of exposed rats were within 5% of the controls. Differences in absolute or relative organ weights between some exposed groups and controls were associated with slight differences in mean body weight and were not considered chemical related (Table F4). Basophilic, clear cell, and mixed cell foci occurred in the liver of exposed male rats, but not in controls (Table A5). No liver neoplasms were observed in rats at 15 months.

Body Weights, Feed Consumption, and Clinical Findings

The mean body weights of 600 ppm rats were consistently lower than, but within 5% of, those of controls after week 49 of the studies (Tables 5 and 6, Figure 1). After week 90 the decrement in mean body weight between 600 ppm males and controls diminished. Feed consumption by exposed male and female rats was similar to that by controls throughout the study. Dietary levels of 150, 300, or 600 ppm resulted in average daily consumption levels of 5, 10, or 25 mg/kg (males) and 5, 15, or 30 mg/kg (females) (Tables I1 and I2). No chemical-related clinical findings of toxicity were observed.

Survival

Estimates of 2-year survival probabilities for male and female rats are presented in Table 7 and in the Kaplan-Meier survival curves in Figure 2. Survival of exposed male and female rats was similar to the controls.

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Triamterene

Week on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	150 ppm Av. Wt. (g)	150 ppm Wt. (% of controls)	150 ppm No. of Survivors	300 ppm Av. Wt. (g)	300 ppm Wt. (% of controls)	300 ppm No. of Survivors	600 ppm Av. Wt. (g)	600 ppm Wt. (% of controls)	600 ppm No. of Survivors
1	136	70	133	98	70	132	97	70	132	97	70
2	182	70	178	97	70	174	96	70	176	97	70
3	219	70	215	98	70	211	96	70	211	96	70
4	241	70	237	99	70	234	97	70	231	96	70
5	263	70	263	100	70	254	97	70	255	97	70
6	279	70	279	100	70	270	97	70	275	99	70
7	290	70	292	101	70	283	98	70	287	99	70
8	303	70	302	100	70	292	96	70	291	96	70
9	316	70	317	100	70	308	98	70	305	97	70
10	328	70	330	100	70	325	99	70	324	99	70
11	333	70	333	100	70	330	99	70	330	99	70
12	350	70	349	100	70	347	99	70	347	99	70
13	356	67	358	100	70	355	100	70	355	100	70
17[a]	379	57	384	101	60	378	100	60	374	99	60
21	396	57	399	101	60	391	99	60	390	99	60
25	414	57	415	100	60	409	99	60	408	99	60
29	425	57	426	100	60	417	98	60	418	98	60
33	444	57	445	100	60	441	99	60	434	98	60
37	451	57	457	101	60	448	99	60	439	97	60
42	455	57	458	101	60	453	100	60	447	98	60
45	465	57	467	101	60	460	99	60	449	97	60
49	479	56	483	101	59	470	98	60	458	96	60
53	482	56	481	100	58	472	98	60	459	95	59
57	481	56	488	102	58	478	99	60	466	97	59
61	485	56	488	101	58	476	98	60	467	96	59
65	484	56	491	101	58	477	99	60	466	96	59
69[a]	489	45	493	101	48	483	99	50	470	96	49
73	490	43	489	100	48	480	98	50	463	95	49
77	488	41	486	100	48	473	97	49	466	96	46
81	487	40	489	100	46	477	98	46	466	96	44
85	482	39	482	100	46	473	98	45	459	95	43
89	471	38	467	99	41	462	98	43	455	97	41
93	454	37	449	99	39	447	98	40	446	98	39
97	435	33	439	101	34	421	97	34	426	98	36
101	420	31	415	99	31	405	96	24	401	95	30
104	382	27	418	109	25	391	102	20	393	103	27
Mean for weeks											
1-13	277		276	100		270	97		271	98	
14-52	434		437	101		430	99		424	98	
53-104	466		470	101		458	98		450	97	

[a] Interim evaluations occurred during weeks 13 and 65.

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Triamterene

Week on Study	0 ppm		150 ppm			300 ppm			600 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	108	70	107	100	70	107	100	70	106	98	70
2	131	70	129	99	70	129	98	70	127	97	70
3	146	70	145	99	70	144	99	70	141	97	70
4	155	70	154	99	70	151	98	70	150	97	70
5	164	70	162	99	70	160	98	70	159	97	70
6	170	70	168	99	70	169	99	70	167	98	70
7	178	70	176	99	70	177	99	70	175	98	70
8	181	70	180	100	70	179	99	70	178	99	70
9	188	70	186	99	70	183	98	70	184	98	70
10	190	70	189	100	70	190	100	70	187	99	70
11	191	70	190	99	70	192	101	70	189	99	70
12	197	70	196	100	70	196	100	70	193	98	70
13	200	70	199	99	70	199	100	70	192	96	70
17[a]	206	60	204	99	60	207	100	60	203	99	60
21	211	60	210	100	60	211	100	60	208	99	60
25	214	60	212	99	60	214	100	60	212	99	60
29	221	60	219	99	60	221	100	60	217	98	60
33	229	60	227	99	60	230	100	60	224	98	60
37	241	60	237	99	60	240	100	60	235	97	60
41	246	60	244	99	60	241	98	60	241	98	60
45	252	60	248	98	60	250	99	60	245	97	60
49	262	60	258	99	60	262	100	60	252	96	60
53	276	60	273	99	60	272	99	60	264	96	60
57	284	60	283	100	60	286	101	57	274	97	60
61	290	60	287	99	60	290	100	57	279	96	60
65	298	60	295	99	60	297	100	57	284	96	60
69[a]	304	49	301	99	49	303	99	47	290	95	49
73	314	49	310	99	49	313	100	47	297	95	49
77	319	48	316	99	48	315	99	47	301	94	47
81	327	47	324	99	48	321	98	47	307	94	45
85	335	45	327	98	48	326	97	47	309	92	44
89	344	44	333	97	45	323	94	47	305	89	44
93	343	44	331	97	44	331	97	44	312	91	40
97	339	41	332	98	42	324	96	42	309	91	37
101	337	37	336	100	39	332	99	37	318	94	33
104	333	30	337	101	34	332	100	34	317	95	29
Mean for weeks											
1-13	169		168	99		167	99		165	98	
14-52	231		229	99		231	100		226	98	
53-101	317		313	99		312	98		298	94	

[a] Interim evaluations occurred during weeks 13 and 65.

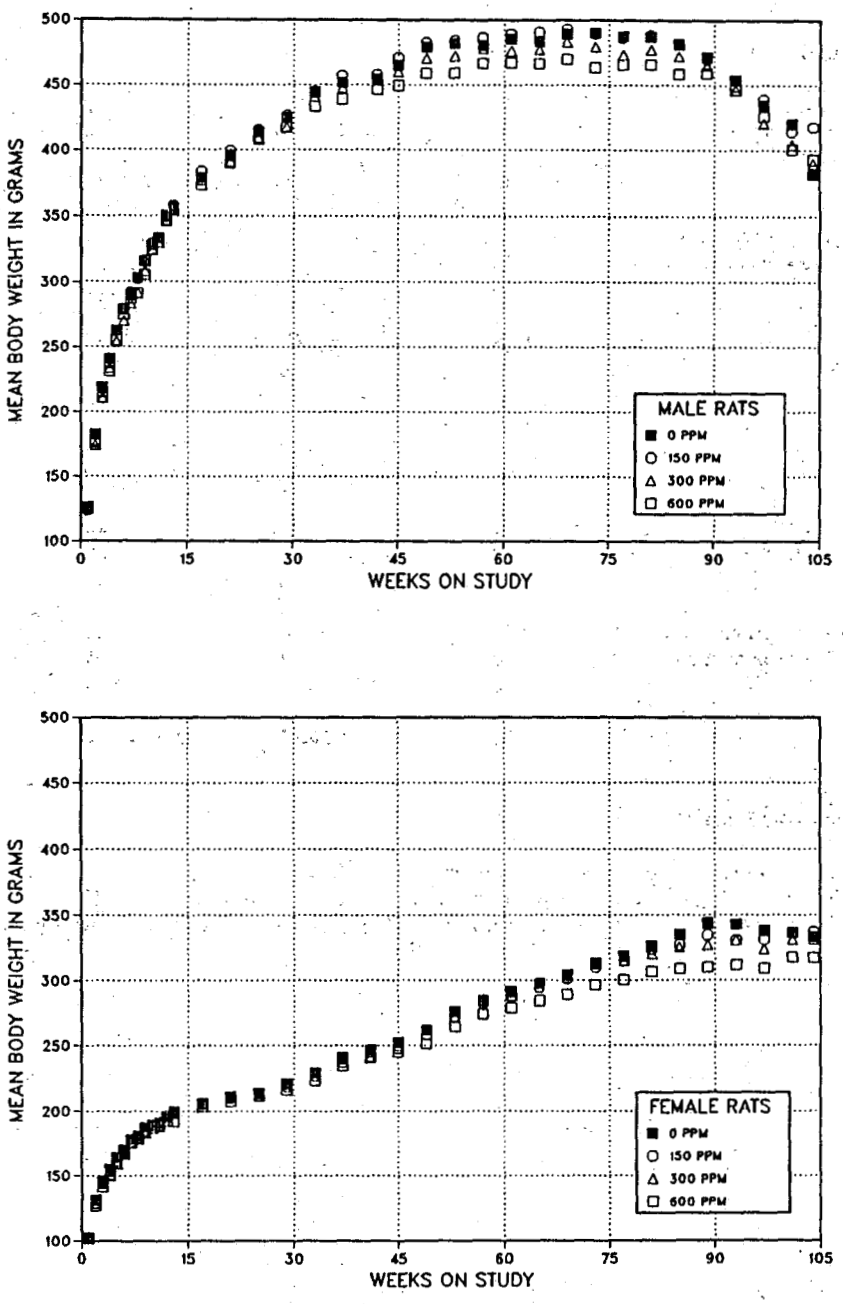


FIGURE 1
Growth Curves for Male and Female Rats Administered Triamterene in Feed for 2 Years

TABLE 7
Survival of Rats in the 2-Year Feed Study of Triamterene

	0 ppm	150 ppm	300 ppm	600 ppm
Male				
Animals initially in study	70	70	70	70
3-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]	3	0	0	0
Moribund	18	20	18	17
Natural deaths	4	5	13	6
Animals surviving to study termination	25	25	19	27
Percent probability of survival at end of study[b]	53	50	38	54
Mean survival days[c]	535	563	567	565
Survival analysis[d]	P=1.000N	P=0.901	P=0.287	P=1.000N
Female				
Animals initially in study	70	70	70	70
3-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	10	10	10
Moribund	17	11	12	18
Natural deaths	4	5	4	3
Animals surviving to study termination	29	34	34	29
Percent probability of survival at end of study	58	68	69	58
Mean survival days	576	581	575	570
Survival analysis	P=0.722	P=0.383N	P=0.455N	P=0.985

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or lower mortality in an exposure group is indicated by N.

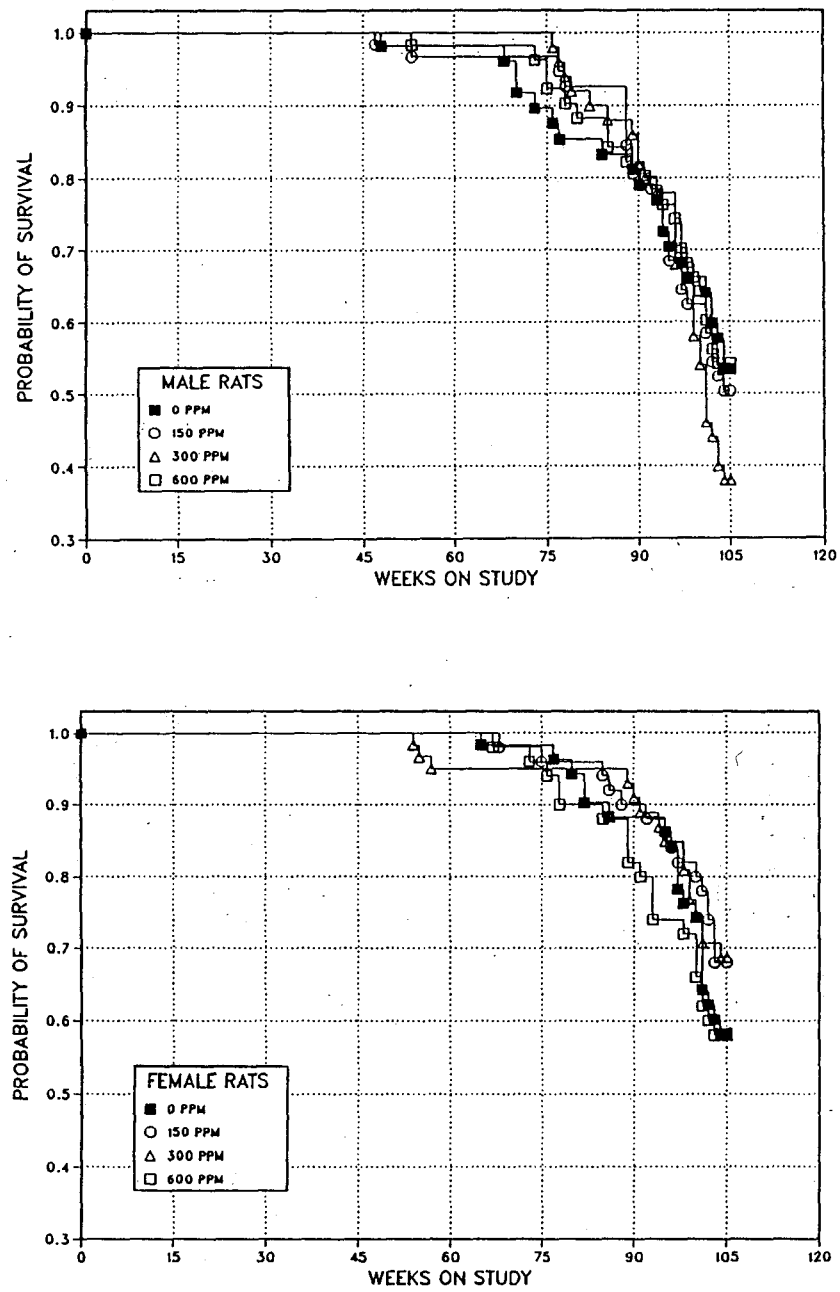


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Triamterene in Feed for 2 Years

Pathology and Statistical Analyses of Results

Statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions in the liver, kidney, and uterus are described below. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendixes A for male rats and B for female rats.

Liver: The incidence of mixed cell foci occurred with a significant positive trend in male and female rats, and the incidences in the 300 and 600 ppm groups were significantly greater than those of the controls by pairwise comparisons (Table 8). Moreover, the incidences of eosinophilic foci in males and clear cell foci in females were marginally greater in the 600 ppm groups. In contrast, the incidence of basophilic foci in 300 ppm males was significantly less than that of controls.

Lesions classified as hyperplasia were also increased in exposed male rats. All males in the 150 and 300 ppm groups with hyperplasia and half the males in the 600 ppm group with hyperplasia also had mononuclear cell leukemia. The Pathology Working Group believed that hyperplasia in some of these rats may have represented a regenerative response to the hepatocellular degeneration associated with the mononuclear cell leukemia. However, there was no obvious hepatocellular degeneration in the remaining (leukemia-free) 600 ppm rats with hyperplasia.

Hepatocellular adenomas occurred at low incidence in all groups of exposed male rats but not in control males (Table 8). The incidence of hepatocellular adenoma in the 150 ppm group, but not those of the 300 or 600 ppm groups, was significantly greater than that of concurrent controls and exceeded the range for historical controls from recent NTP feed studies (Table A4). Hepatocellular adenomas were seen in only two females in the 600 ppm group, none were seen in the controls or in the 150 or 300 ppm groups, and the incidences were within the historical control range (Table B4). No hepatocellular carcinomas were observed in exposed or control rats.

Foci (basophilic, eosinophilic, clear cell, or mixed cell) were generally the size of one or two hepatic lobules and consisted of cells with either basophilic, eosinophilic, or clear-staining cytoplasm, or a mixture of cells with these staining properties. These staining properties are determined by the relative amounts of the various cytoplasmic constituents, particularly ribosomes or polyribosomes, which are responsible for the basophilia; proteins, which are responsible for the eosinophilia; and glycogen or lipids, which are responsible for the clear or vacuolated appearance. The lobular architecture of the foci was normal or minimally altered and there was no compression of adjacent parenchyma. Lesions classified as hyperplasia were similar to the various foci but were generally larger, often several lobules or more in size. The hepatocellular adenomas observed in exposed male rats were generally similar to foci but were larger and more circumscribed with distinct borders and some compression of the adjacent normal parenchyma. There was some alteration in growth pattern with subsequent distortion or loss of lobular architecture. The hepatocytes were generally arranged in plates one or two cell layers thick and had basophilic, eosinophilic, or clear cytoplasm similar to the foci. The hepatocytes were well differentiated with no cytologic atypia.

TABLE 8
Incidences of Liver Lesions in Rats in the 2-Year Feed Study of Triamterene[a]

	0 ppm	150 ppm	300 ppm	600 ppm
Male				
Hyperplasia	0/50 (0%)	3/50 (6%)	5/50 (10%)*	10/49 (20%)**
Basophilic focus	16/50 (32%)	10/50 (20%)	3/50 (6%)**	19/49 (39%)
Clear cell focus	4/50 (8%)	5/50 (10%)	4/50 (8%)	7/49 (14%)
Eosinophilic focus	2/50 (4%)	3/50 (6%)	2/50 (4%)	8/49 (16%)
Mixed cell focus	0/50 (0%)	6/50 (12%)*	8/50 (16%)**	12/49 (24%)**
Hepatocellular Adenoma[b]				
Overall rates	0/50 (0%)	6/50 (12%)	4/50 (8%)	3/49 (6%)
Adjusted rates[c]	0.0%	20.9%	15.6%	9.3%
Terminal rates[d]	0/25 (0%)	4/25 (16%)	2/19 (11%)	2/27 (7%)
First incidence (days)	–[f]	610	668	508
Logistic regression tests[e]	P=0.355	P=0.021	P=0.069	P=0.108
Female				
Hyperplasia	1/50 (2%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Basophilic focus	37/50 (74%)	36/50 (72%)	34/50 (68%)	34/50 (68%)
Clear cell focus	3/50 (6%)	3/50 (6%)	4/50 (8%)	9/50 (18%)*
Eosinophilic focus	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Mixed cell focus	2/50 (4%)	2/50 (4%)	8/50 (16%)*	13/50 (26%)**
Hepatocellular Adenoma[g]				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rates	0.0%	0.0%	0.0%	6.9%
Terminal rates	0/29 (0%)	0/34 (0%)	0/34 (0%)	2/29 (7%)
First incidence (days)	–	–	–	729 (T)
Logistic regression tests	P=0.052	–	–	P=0.246

* Significantly different (P≤0.05) from the control group by logistic regression test
** P≤0.01
[a] Number of animals with lesion/number of animals examined microscopically
[b] 2-Year historical incidence for untreated control groups in NTP feed studies (mean ± standard deviation): 19/799 (2.4% ± 2.9%); range 0%-8%
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between that controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[f] Not applicable; no neoplasms in animal group
[g] 2-Year historical incidence: 3/800 (0.4% ± 1.5%); range 0%-6%

Kidney: Nephropathy occurred in nearly all male rats and most female rats, but the average severity of this disease was marginally greater in exposed male and female rats (Table 9). Because of the marginal and subtle nature of these findings, the histologic sections of kidney were reevaluated in a "blind" procedure. The findings were generally confirmed by the "blind" reevaluation. In the first evaluation of male rats, the group average severity grade of nephropathy of the 300 ppm group was significantly greater than that of the controls. Since the average severity of nephropathy in the 600 ppm group in the first evaluation and that of all groups in the blind evaluation were not significantly greater than controls, it is uncertain if the marginal increase was chemical related. In contrast, the average severity of nephropathy in 600 ppm female rats in both the first and blind evaluations was significantly greater than controls. Therefore, the slight increase in severity in 600 ppm female rats was considered to be related to the ingestion of triamterene.

Nephropathy was characterized by glomerulosclerosis, degeneration and regeneration of the renal tubule epithelium, thickening of the renal tubule basement membrane, dilatation of renal tubule lumens with the formation of hyaline and granular casts, interstitial fibrosis, and chronic inflammation. The severity of nephropathy was graded as minimal, mild, moderate, or marked depending on the extent of the disease and approximate amount of renal parenchyma affected (minimal, 5%-25% of the renal tubules; mild, 25%-50%; moderate, 50%-75%; marked, >75%).

Uterus: Two 600 ppm females had uterine leiomyomas (Table B1). Smooth muscle neoplasms are relatively uncommon in female F344/N rats (NTP historical controls: 6/800, 0.1%; range 0%-2%).

TABLE 9
Incidences and Severity of Nephropathy in Rats in the 2-Year Feed Study of Triamterene[a]

Dose	0 ppm		150 ppm		300 ppm		600 ppm	
Male								
Nephropathy								
First evaluation	47/50	(2.4)[b]	49/50	(2.7)	50/50	(3.0)**	49/50	(2.8)
Blind evaluation	48/49	(3.0)	–[c]		50/50	(3.2)	49/50	(3.3)
Female								
Nephropathy								
First evaluation	38/50	(1.1)	45/50	(1.2)	45/50	(1.3)	45/50	(1.4)*
Blind evaluation	36/50	(0.9)	–		42/50	(1.2)	49/50	(1.6)**

* Significantly different (P≤0.05) from the control group by the Mann-Whitney U test
** P≤0.01
[a] Number of animals with lesion/number of animals examined microscopically
[b] Group average severity grade for all animals: 0=none; 1=minimal; 2=mild; 3=moderate; 4=marked
[c] The 150 ppm groups were not evaluated in the blind microscopic examination.

MICE

15-DAY STUDY

The diets containing triamterene at levels of 10,000 or 30,000 ppm were unpalatable, and feed consumption by mice in the 3,000 ppm groups was substantially less than that by controls. Mice exposed to 300 or 1,000 ppm triamterene received approximate doses of 40 or 155 mg/kg per day (males) or 45 or 170 mg/kg per day (females). All mice receiving 3,000 ppm triamterene died on day 5 or 6; all other mice survived until the end of the study (Table 10). The final mean body weights of mice in the 300 or 1,000 ppm groups were within 5% of controls. The absolute heart weight of females, the relative heart and kidney weights of males and females, and the relative liver weight of females receiving 1,000 ppm were lower than those of controls, whereas the relative liver weight of males in this group was greater than that of controls (Table F5). The significance of these organ weight differences is uncertain. There were no clinical findings attributed to the ingestion of triamterene.

Microscopic examination of the kidney of all 3,000 ppm mice revealed mild to moderate degeneration and necrosis of the epithelium of the convoluted tubules (nephrosis). This lesion did not occur in any animal in the 1,000 ppm groups. Lymphoid depletion in the thymus and spleen was also observed in most mice receiving 3,000 ppm and may have been related to debilitation and stress rather than to a specific cytotoxic effect of the chemical.

Because of the poor palatability of diets containing 3,000 ppm or more triamterene and the nephrosis in the 3,000 ppm groups in the 15-day feed study, the high dose selected for the 13-week feed study was 1,600 ppm.

TABLE 10
Survival, Mean Body Weights, and Feed Consumption of Mice in the 15-Day Feed Study of Triamterene

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	22.6 ± 0.6	24.8 ± 0.7	2.2 ± 0.4		3.1	3.4
300	5/5	22.2 ± 0.5	23.8 ± 0.6	1.7 ± 0.5	96	2.8	3.1
1,000	5/5	22.8 ± 0.9	23.8 ± 1.0	1.1 ± 0.5	96	3.2	3.9
3,000	0/5[d]	22.8 ± 1.0	–	–	–	–	–
10,000	0/5[d]	22.2 ± 0.9	–	–	–	–	–
30,000	0/5[d]	22.1 ± 0.9	–	–	–	–	–
Female							
0	5/5	18.8 ± 0.5	20.5 ± 0.6	1.8 ± 0.2		2.7	3.1
300	5/5	18.6 ± 0.6	19.5 ± 0.6	0.9 ± 0.1	95	2.5	3.0
1,000	5/5	18.9 ± 0.4	19.9 ± 0.4	1.0 ± 0.6	97	2.2	4.3
3,000	0/5[d]	18.6 ± 0.3	–	–	–	–	–
10,000	0/5[d]	18.8 ± 0.5	–	–	–	–	–
30,000	0/5[d]	19.4 ± 0.4	–	–	–	–	–

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. No data were calculated for groups with 100% mortality. Differences from the control group were not significant by Williams' or Dunnett's test.
[c] Grams of feed consumed per animal per day
[d] All deaths occurred between days 4 and 6

13-Week Study

All mice receiving 1,600 ppm triamterene died by week 2 (Table 11). The deaths of one male mouse in the 200 ppm group during week 7, one female mouse in the 800 ppm group during week 9, and four males in the 100 ppm group during the first week were not clearly related to triamterene exposure. Clinical signs of toxicity observed in the 1,600 ppm groups included emaciation, decreased activity, and piloerection. Feed consumption by mice receiving 1,600 ppm was substantially lower than that by controls during the first week of the study. Feed consumption by the other groups was similar to controls (Table 11). Mice exposed to 100, 200, 400, or 800 ppm triamterene received approximate doses of 15, 25, 50, or 90 mg/kg per day (males) or 15, 25, 50, or 115 mg/kg per day (females).

The total leukocyte and lymphocyte counts of males receiving 800 ppm and of females receiving 100, 400, or 800 ppm were significantly lower than those of the controls and were considered to be related to the lymphoid depletion observed in the thymus and spleen (Table G4). No other differences in hematologic, clinical chemistry, or urinalysis parameters were considered to be biologically significant.

TABLE 11
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of Triamterene

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	24.4 ± 0.6	31.6 ± 0.9	7.2 ± 1.4		3.2	3.8
100	6/10[d]	24.5 ± 0.5	30.2 ± 1.1	5.7 ± 0.9	96	3.5	3.8
200	9/10[e]	23.7 ± 0.8	30.3 ± 1.0	7.0 ± 0.5	96	3.3	3.6
400	10/10	23.8 ± 0.6	30.0 ± 0.8	6.2 ± 0.5	95	3.4	3.6
800	10/10	24.3 ± 0.5	27.4 ± 1.2*	3.1 ± 1.1*	87	2.9	3.0
1,600	0/10[d]	24.1 ± 0.9	–	–	–	–	–
Female							
0	10/10	19.0 ± 0.4	23.8 ± 0.5	4.8 ± 0.4		2.6	3.1
100	10/10	18.8 ± 0.5	23.7 ± 0.6	4.9 ± 0.2	100	2.7	3.1
200	10/10	18.6 ± 0.3	24.3 ± 0.4	5.6 ± 0.4*	102	3.1	3.3
400	10/10	18.9 ± 0.3	23.7 ± 0.3	4.9 ± 0.3	100	2.6	3.2
800	9/10[f]	18.8 ± 0.4	24.3 ± 0.4	5.5 ± 0.3*	102	3.1	3.2
1,600	0/10[g]	19.0 ± 0.2	–	–	–	–	–

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No data were calculated for groups with 100% mortality.
[c] Grams of feed consumed per animal per day
[d] Week of death: all deaths occurred during week 1
[e] Week of death: 7
[f] Week of death: 9
[g] Week of death: nine deaths during week 1, one death during week 2

The final mean body weight and body weight gain of male mice receiving 800 ppm were significantly lower than those of the controls (Table 11). The final mean body weight of male mice in the 800 ppm group was 13% lower than that of the controls. In the 800 ppm groups, the absolute and relative thymus weights of male mice and the relative kidney weight of female mice were significantly less than those of the controls (Table F6).

On microscopic examination, lesions were observed in the lymphoid organs of male and female mice (Table 12). Necrosis of lymphocytes in the lymph node, spleen, and thymus was observed primarily in mice in the 800 and 1,600 ppm groups; necrosis in the thymus occurred infrequently in other groups (Table 12). Necrosis was characterized by scattered individual or small foci of lymphocytes with pyknotic or fragmented nuclei and macrophages filled with cellular debris. Lymphoid depletion characterized by the reduction in thickness of the thymic cortex or periarteriolar lymphocytic sheaths in the spleen was also apparent in a few mice in the 1,600 ppm groups. Whether these lesions were related to debilitation and stress or to the direct cytotoxic effects of triamterene is unknown.

Dose selection rationale: Dietary concentrations of triamterene selected for the 2-year studies in mice were 0, 100, 200, and 400 ppm. Doses of 800 ppm or more were considered too great because of the mortality observed in mice receiving 1,600 ppm and the lesions observed in the 800 and 1,600 ppm groups in the 13-week study.

TABLE 12
Incidences of Treatment-Related Lesions in Mice in the 13-Week Feed Study of Triamterene

	0 ppm	100 ppm	200 ppm	400 ppm	800 ppm	1,600 ppm
n	10	10	10	10	10	10
Male						
Spleen						
Necrosis	0	–[a]	–	–	3 (2.3)[b]	4* (1.5)
Lymphoid depletion	0	–	–	–	0	2 (2.5)
Thymus						
Necrosis	0	3 (2.7)	1 (1.0)	1 (2.0)	8** (1.6)	8** (3.0)
Lymphoid depletion	0	0	0	0	0	2 (3.0)
Lymph node						
Necrosis	0	–	–	–	1 (2.0)	4* (1.5)
Female						
Spleen						
Necrosis	0	–	–	–	5* (1.4)	7** (2.0)
Lymphoid depletion	0	–	–	–	0	3 (2.3)
Thymus						
Necrosis	0	2 (2.0)	0	3 (2.0)	1 (1.0)	10** (3.0)
Lymph node						
Necrosis	0	–	–	–	0	2 (2.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Not examined microscopically at this exposure level
[b] Average severity grade for affected animals: 1=minimal; 2=mild; 3=moderate

2-YEAR STUDIES

3-Month Interim Evaluation

The values of several hematologic and clinical chemistry parameters of 200 or 400 ppm mice varied slightly from those of controls (Table G5). These differences were not considered biologically significant and their relationship to the ingestion of triamterene is uncertain. At necropsy the mean body weights of all groups of exposed mice were similar to those of the controls (Table F7). The absolute kidney and liver weights of male mice in the 400 ppm group were significantly lower than those of the controls, but the relative weights were similar (Table F7). There were no other significant differences in organ weights. No chemical-related lesions were observed during necropsy or microscopic examination.

15-Month Interim Evaluations

Because of an error in preparation of feed for the 400 ppm group in week 40, 12 male and four female mice died. The 15-month interim evaluation, therefore, was conducted only on mice from the 0, 100, and 200 ppm groups. For this reason, a second 2-year feed study was conducted in male and female mice using only control and 400 ppm groups; mice in this study were also evaluated at 15 months.

The values of several hematologic or clinical chemistry parameters in the 200 (first study) and 400 ppm groups (second study) varied slightly from those of controls (Tables G6 and G7). None of these differences were considered biologically significant or chemical related. In 400 ppm females in the second study, the urine volume was significantly greater than controls, and the urine specific gravity was significantly lower. These differences may have been chemical related, although a similar finding was not observed in males.

Mean body weights of exposed mice in both studies were similar to those of controls (Tables F8 and F9). The absolute brain weights of 400 ppm males in the second study were significantly greater than those of controls. Since the relative brain weight was similar to controls, the marginal difference in mean brain weights was not considered chemical related. The incidences of nonneoplastic lesions and neoplasms in exposed mice were similar to those of controls at the 15-month interim evaluations. The occurrence of liver neoplasms in mice evaluated at 15 months is notable because of the chemical-related increase in hepatocellular adenomas in the core 2-year study. In males in the first study, hepatocellular adenomas were observed in one control, three 100 ppm, and two 200 ppm mice; none were seen in the 400 ppm males (Table C1a). In the second study, an adenoma was observed in a 400 ppm male and none were observed in the controls (Table C1b). No hepatocellular carcinomas were observed in male mice. In female mice in the first study, adenomas were observed in two control, two 100 ppm, and two 200 ppm mice; in the second study a carcinoma was observed in one control female (Tables D1a, D1b).

Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of exposed mice were similar to those of the controls throughout most of the first 2-year study with one notable exception (Tables 13a,b and 14a,b, Figure 3). The mean body weight of 400 ppm males was 16% lower than controls at week 41 following the dosing error during week 40. The decrement in body weight gradually decreased over the next several weeks. The mean body weights of 400 ppm males in the second study (Figure 4) and of females receiving 400 ppm in the first and second studies were slightly lower than controls during the final 8 weeks of the studies. Feed consumption by exposed mice was similar to that by the controls throughout the studies, and approximately 10, 25, or 45 mg/kg (males) and 15, 30, or 60 mg/kg of triamterene per day was ingested by mice fed diets containing 100, 200, or 400 ppm (Tables I3, I4, I5, and I6). There were no clinical findings of toxicity in exposed mice.

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 15 and in the Kaplan-Meier curves in Figures 5 and 6. Survival of 400 ppm males in the first study was significantly lower than that of the controls, primarily because of the dosing error in week 40. Sixteen 400 ppm mice died shortly after the dosing error, and the deaths of 11 males and 3 females were attributed, in part, to renal toxicity. The cause of death for the remaining two mice was undetermined. Survival of exposed mice in the second study was similar to that of the controls.

TABLE 13a
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Triamterene: First Study

Week on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors	200 ppm Av. Wt. (g)	200 ppm Wt. (% of controls)	200 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	20.0	70	20.2	101	70	20.1	101	70	20.2	101	70
2	22.2	70	22.6	102	70	22.5	101	70	22.5	101	70
3	23.5	70	23.6	100	70	23.5	100	70	23.5	100	70
4	24.2	70	24.4	101	70	24.5	101	70	24.4	101	70
5	25.4	70	25.2	99	70	25.1	99	70	25.3	100	70
6	26.0	70	26.1	100	70	26.1	100	70	26.2	101	70
7	26.6	70	26.9	101	70	26.8	101	70	26.7	100	70
8	27.8	70	27.7	100	70	27.6	99	70	27.4	99	70
9	28.7	70	28.8	100	70	28.2	98	70	28.3	99	70
10	29.5	70	29.4	100	70	29.4	100	70	29.1	99	70
11	30.4	70	30.0	99	70	30.1	99	70	29.7	98	70
12	30.8	70	30.5	99	70	30.5	99	70	30.0	97	70
13	31.5	70	31.3	99	70	31.4	100	70	30.7	98	70
18[a]	34.0	60	33.9	100	60	33.7	99	60	33.6	99	60
21	34.4	60	34.8	101	60	34.3	100	60	34.0	99	60
25	34.5	60	35.2	102	60	34.6	100	60	34.7	101	60
29	36.0	60	36.7	102	60	35.9	100	60	35.6	99	60
33	37.9	60	38.4	101	60	37.6	99	60	37.3	98	60
37	38.3	60	39.0	102	60	38.6	101	60	38.5	101	60
41	39.4	60	40.5	103	60	39.4	100	60	32.9	84	49
45	40.7	60	41.0	101	60	40.5	100	60	38.0	93	48
49	41.6	60	41.9	101	60	41.1	99	60	39.3	95	48
53	42.3	60	43.3	102	60	42.3	100	60	40.9	97	48
57	43.1	60	43.8	102	60	42.8	99	60	41.9	97	48
61	43.8	60	44.1	101	60	42.9	98	60	42.5	97	48
65	44.8	60	44.9	100	60	43.6	97	60	43.1	96	48
69[a]	44.8	50	45.8	102	50	44.4	99	50	44.2	99	48
73	45.2	50	46.2	102	50	45.2	100	50	44.8	99	48
77	45.5	50	46.6	102	49	45.7	100	50	45.5	100	48
81	45.5	50	46.1	101	48	45.2	99	50	44.5	98	48
85	45.7	49	46.2	101	48	45.2	99	50	44.7	98	48
89	44.9	48	46.0	102	46	44.6	99	49	44.3	99	47
93	47.1	48	46.9	100	46	45.5	97	48	44.9	95	47
97	46.6	48	48.3	104	46	45.8	98	48	45.3	97	47
101	46.0	47	46.6	101	45	45.2	98	46	45.0	98	47
104	44.4	47	45.1	102	45	43.8	99	46	43.0	97	46
Mean for weeks											
1-13	26.7		26.7	100		26.6	100		26.5	99	
14-52	37.4		37.9	101		37.3	100		35.8	96	
53-104	45.0		45.7	102		44.4	99		43.9	98	

[a] Interim evaluations occurred during week 13 for all exposure groups and during week 65 for 0, 100, and 200 ppm groups.

TABLE 13b
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Triamterene: Second Study

Week on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	19.9	60	20.0	101	60
3	22.7	60	22.7	100	60
4	23.8	60	24.0	101	60
5	24.8	60	24.6	99	60
6	26.2	60	26.1	100	60
7	27.0	60	27.2	101	60
8	27.6	60	27.9	101	60
9	28.4	60	28.6	101	60
10	29.6	60	29.8	101	60
11	30.0	60	30.2	101	60
12	31.5	60	31.4	100	60
13	31.6	60	31.6	100	60
17	34.4	60	34.3	100	60
21	36.9	60	36.9	100	60
25	38.9	60	39.3	101	60
29	40.8	60	40.9	100	60
33	42.1	60	42.8	102	60
37	43.2	60	43.6	101	60
41	44.0	60	44.3	101	60
45	44.6	60	45.0	101	60
49	45.8	60	46.1	101	60
53	45.8	60	46.0	100	60
57	45.2	60	45.8	101	60
61	46.4	60	46.9	101	60
65	46.2	59	46.1	100	60
69[a]	46.7	49	47.0	101	50
73	47.2	49	48.1	102	49
77	46.7	49	47.7	102	48
81	46.5	48	46.9	101	47
85	47.4	48	47.5	100	47
89	45.9	48	46.0	100	46
93	45.6	47	44.4	97	45
97	45.4	47	42.9	95	43
101	43.4	46	41.4	95	41
Mean for weeks					
1-13	26.9		27.0	100	
14-52	41.2		41.5	101	
53-101	46.0		45.9	100	

[a] Interim evaluation occurred during week 65.

TABLE 14a
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Triamterene: First Study

Week on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors	200 ppm Av. Wt. (g)	200 ppm Wt. (% of controls)	200 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	16.4	70	16.4	100	70	16.5	101	70	16.4	100	70
2	18.6	70	18.6	100	70	18.6	100	70	18.3	98	70
3	19.8	70	19.7	100	70	19.6	99	70	19.6	99	70
4	20.7	69	20.7	100	70	20.6	100	70	20.5	99	70
5	21.7	69	21.5	99	70	21.5	99	70	21.3	98	70
6	22.5	69	22.4	100	70	22.3	99	70	22.3	99	70
7	22.9	69	22.9	100	70	22.9	100	70	22.7	99	70
8	24.1	69	24.0	100	70	23.9	99	70	23.9	99	70
9	25.0	69	24.8	99	70	24.6	98	70	24.8	99	70
10	25.0	69	24.7	99	70	24.6	98	70	24.6	98	70
11	25.7	69	25.6	100	70	25.2	98	70	25.0	97	70
12	26.3	69	25.9	99	70	26.0	99	70	25.6	97	70
13	26.8	69	26.7	100	70	26.8	100	70	26.3	98	70
18[a]	30.3	58	30.1	99	60	30.0	99	60	29.7	98	60
21	31.6	58	31.0	98	60	31.1	98	60	30.4	96	60
25	33.5	58	33.2	99	60	33.4	100	60	32.9	98	60
29	36.2	58	35.6	98	60	35.4	98	60	35.2	97	60
33	37.5	58	36.9	98	60	37.1	99	60	36.4	97	60
37	39.7	58	39.1	99	59	38.5	97	60	37.6	95	60
41	40.6	58	40.3	99	59	39.6	98	60	30.3	75	56
45	42.3	58	41.9	99	59	41.2	97	60	38.2	90	56
49	43.9	58	43.6	99	59	42.7	97	60	40.9	93	56
53	45.5	57	45.3	100	59	44.4	98	60	42.1	93	56
57	46.2	57	46.4	100	59	45.3	98	60	43.3	94	56
61	46.8	57	47.0	100	59	46.1	99	60	44.1	94	56
65	48.0	56	48.7	102	59	47.5	99	60	45.8	95	56
69[a]	48.7	46	49.8	102	49	48.3	99	50	46.8	96	56
73	49.8	44	51.3	103	49	49.6	100	49	48.0	96	56
77	50.2	43	52.6	105	49	51.0	102	48	49.2	98	55
81	50.6	43	52.1	103	49	50.7	100	47	48.7	96	55
85	50.9	42	52.6	103	48	50.7	100	46	49.0	96	53
89	50.3	42	52.1	104	48	50.6	101	46	48.1	96	50
93	51.2	42	53.8	105	46	51.2	100	46	49.5	97	48
97	51.6	42[b]	54.2	105	44	50.2	97	44	49.1	95	48[b]
101	49.4	41[b]	52.8	107	43	49.3	100	44	46.6	94	44[b]
104	47.0	38	49.9	106	43	47.4	101	43	44.4	95	43
Mean for weeks											
1-13	22.7		22.6	100		22.5	99		22.4	99	
14-52	37.3		36.9	99		36.6	98		34.4	92	
53-104	49.0		50.6	103		48.7	99		46.8	96	

[a] Interim evaluations occurred during week 13 for all exposure groups and during week 65 for the 0, 100, and 200 ppm groups.
[b] The number of animals weighed for this week is fewer than the number of animals surviving.

TABLE 14b
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Triamterene: Second Study

Week on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	16.7	60	16.5	99	60
3	19.2	60	19.1	100	60
4	20.1	60	20.0	100	60
5	21.0	60	20.8	99	60
6	22.4	60	22.4	100	60
7	22.9	60	22.9	100	60
8	23.4	60	23.7	101	60
9	23.9	60	23.9	100	60
10	25.6	60	25.2	98	60
11	25.9	60	25.5	99	60
12	26.6	60	26.4	99	60
13	27.2	60	27.0	99	60
17	30.4	60	30.2	99	60
21	32.9	60	32.5	99	60
25	35.5	60	35.0	99	60
29	37.5	60	37.2	99	60
33	39.5	60	39.2	99	60
37	40.0	60	39.8	100	60
41	42.1	60	41.4	98	60
45	43.3	60	42.9	99	60
49	45.0	60	44.5	99	60
53	45.6	60	44.8	98	60
57	45.8	60	45.1	99	60
61	47.7	60	46.9	98	59
65	47.7	60	47.0	99	59
69[a]	48.6	50	47.7	98	50
73	49.3	49	48.8	99	50
77	49.5	49	48.7	98	50
81	49.2	46	48.8	99	48
85	49.9	46	48.8	98	47
89	49.5	45	47.8	97	46
93	49.6	44	47.7	96	45
97	48.7	44	44.2	91	43
101	45.9	42	43.3	94	38
Mean for weeks					
1-13	22.9		22.8	100	
14-52	38.5		38.1	99	
53-101	48.2		46.9	97	

[a] Interim evaluation occurred during week 65.

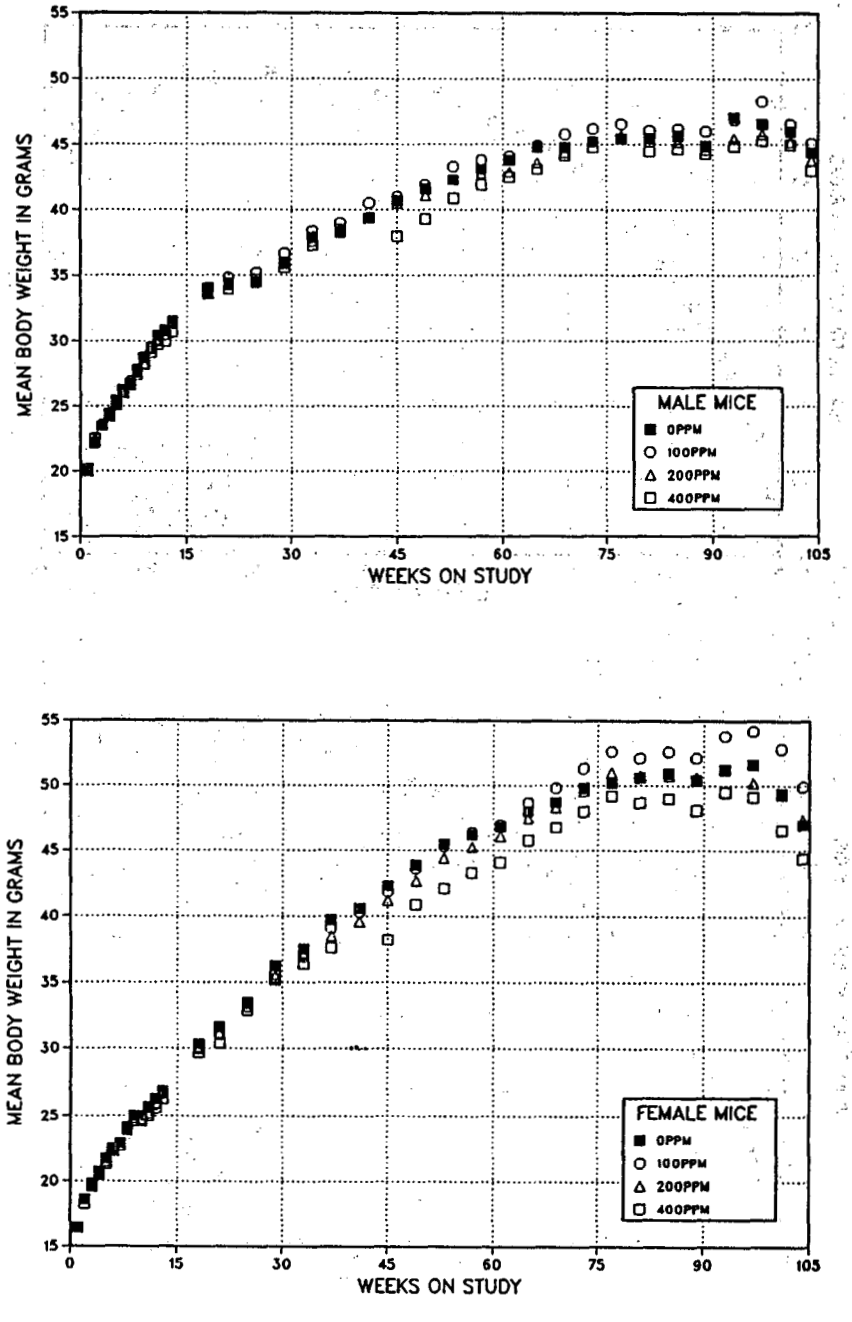
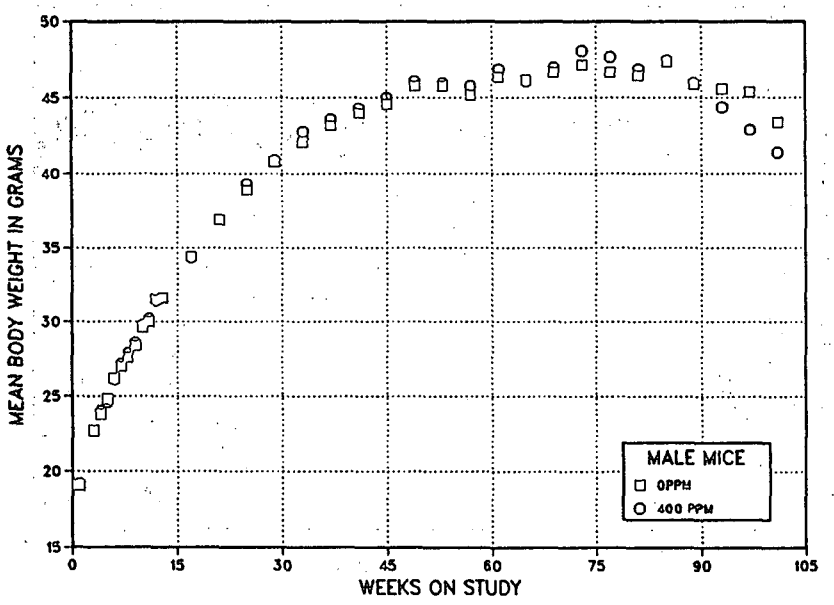


FIGURE 3
Growth Curves for Male and Female Mice Administered Triamterene in Feed for 2 Years: First Study



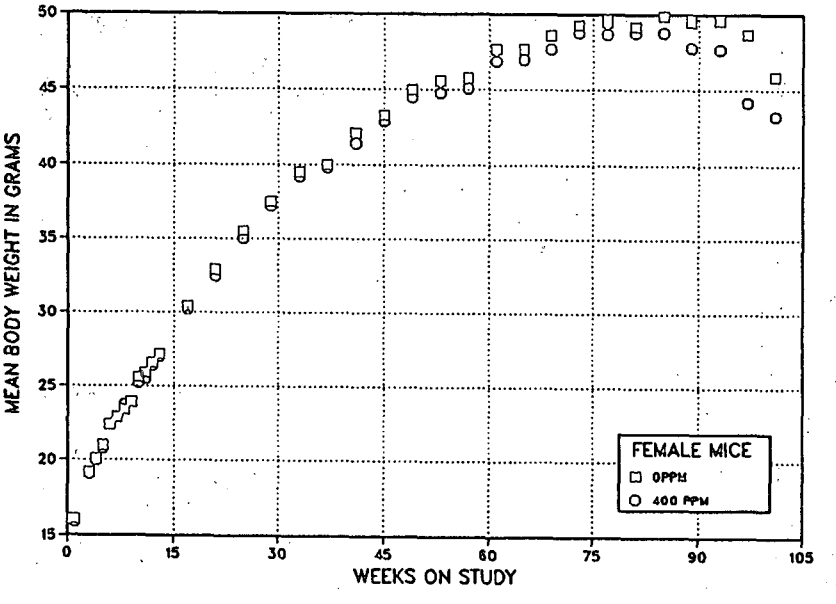


FIGURE 4
Growth Curves for Male and Female Mice Administered Triamterene in Feed for 2 Years: Second Study

TABLE 15
Survival of Mice in the 2-Year Feed Studies of Triamterene

	First Study				Second Study	
	0 ppm	100 ppm	200 ppm	400 ppm	0 ppm	400 ppm
Male						
Animals initially in study	70	70	70	70	60	60
3-Month interim evaluation[a]	10	10	10	10	0	0
15-Month interim evaluation[a]	10	10	10	0	10	10
Moribund	1	2	2	6	3	4
Natural deaths	2	3	2	8	4	7
Animals surviving to study termination	47	45	46	46	43[b]	39
Percent probability of survival at end of study[c]	94	90	92	77	86	78
Mean survival days[d]	723	715	724	638	674	667
Survival analysis[e]	P=0.004	P=0.685	P=0.997	P=0.021		P=0.415
Female						
Animals initially in study	70	70	70	70	60	60
3-Month interim evaluation[a]	10	10	10	10	0	0
15-Month interim evaluation[a]	10	10	10	0	10	9
Moribund	8	5	1	10	7	4
Natural deaths	4	2	6	7	3	9
Animals surviving to study termination	38	43	43	43	40	38
Percent probability of survival at end of study	76	86	86	72	80	75
Mean survival days	672	709	711	680	667	666
Survival analysis	P=0.361	P=0.285N	P=0.283N	P=0.776		P=0.643

[a] Censored from survival analyses
[b] Includes one animal that died the last day of the study.
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, terminal sacrifice)
[e] The result of the life table trend test (Tarone, 1975) is in the control column (first study), and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A lower mortality in an exposure group is indicated by N.

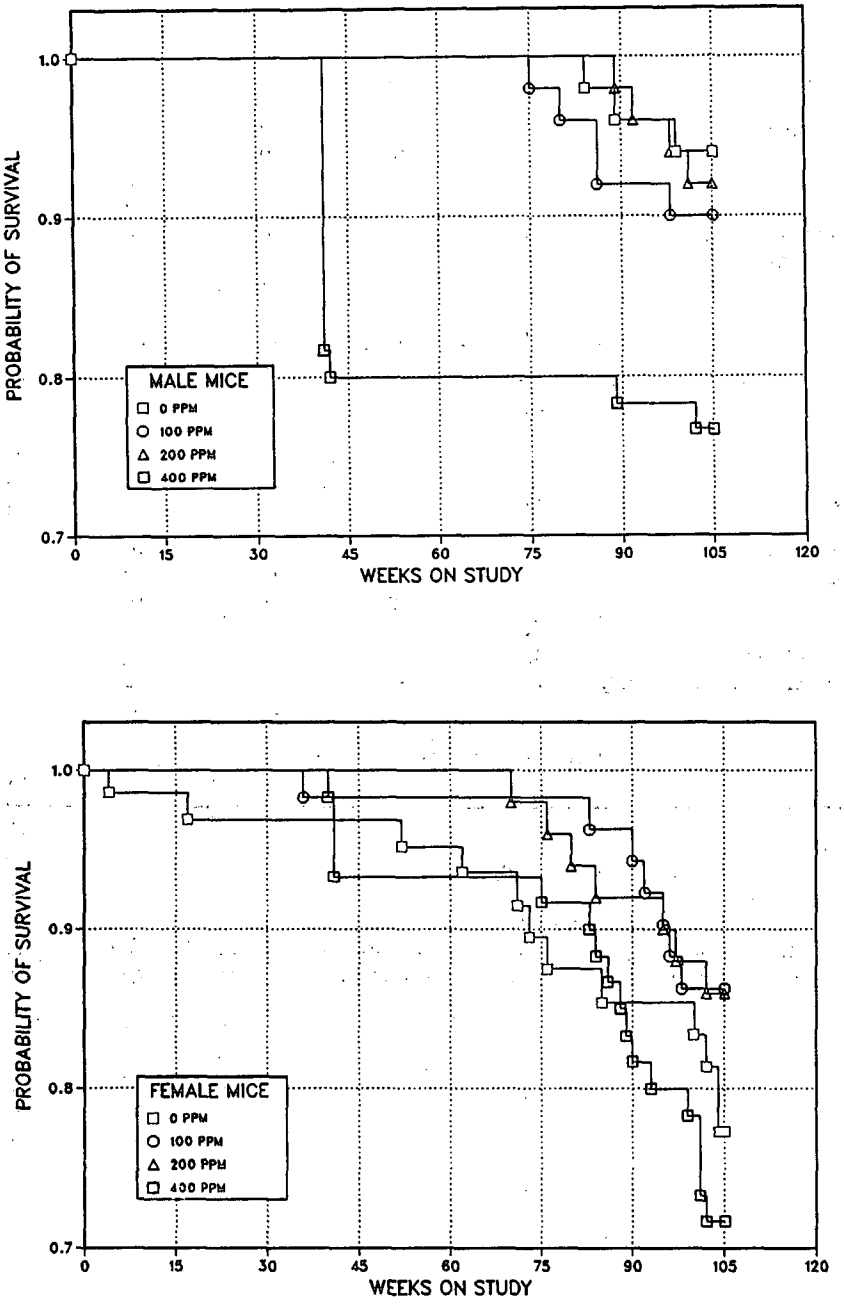


FIGURE 5
Kaplan-Meier Survival Curves for Male and Female Mice Administered Triamterene in Feed for 2 Years: First Study

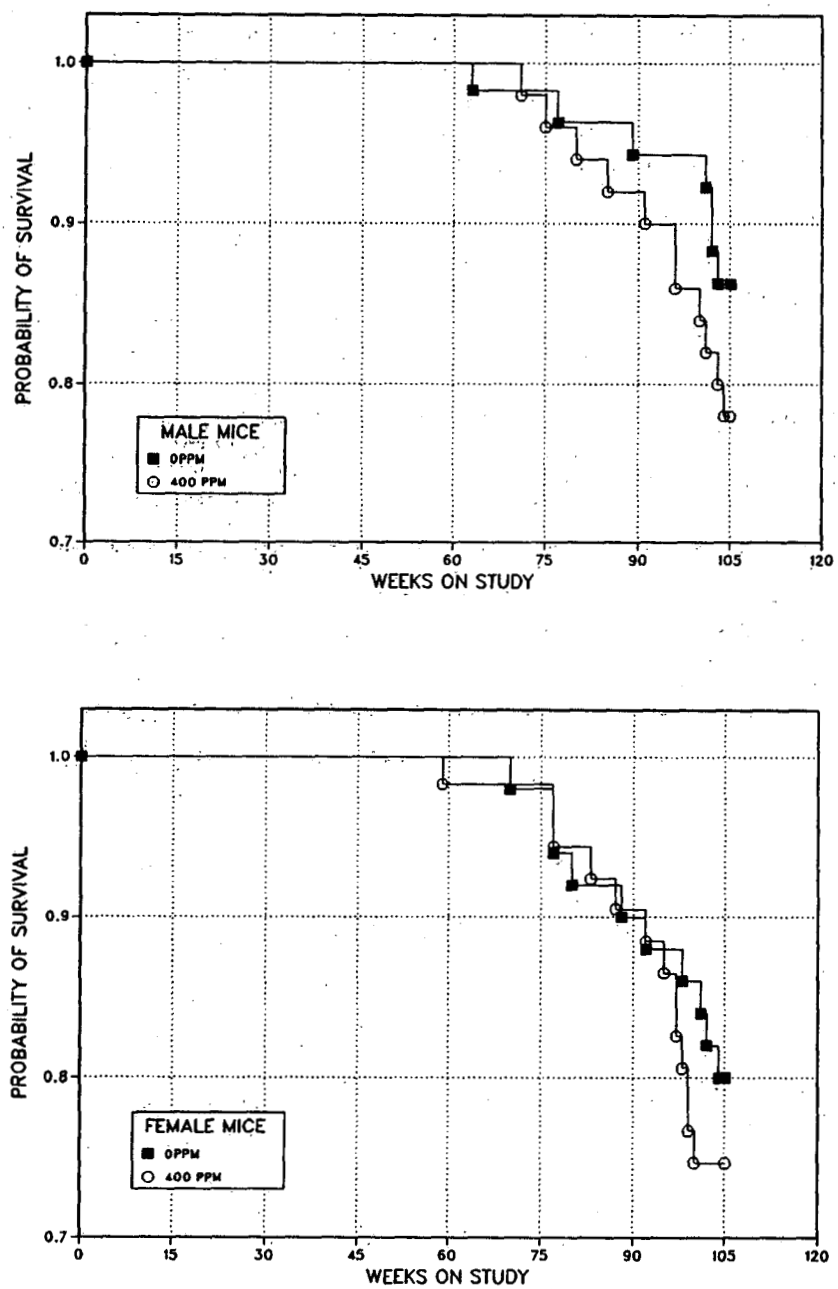


FIGURE 6
Kaplan-Meier Survival Curves for Male and Female Mice Administered Triamterene in Feed for 2 Years: Second Study

Pathology and Statistical Analyses of Results

Statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions in the liver, thyroid gland, kidney, harderian gland, and small intestine are described below. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendixes C for male mice and D for female mice.

Liver: The incidences of hepatocellular adenoma in exposed female mice in the first study occurred with a significant positive trend, and the incidences in the exposed groups were significantly greater than that of controls (Table 16a). Moreover, the incidences of multiple hepatocellular adenoma were increased in exposed females (Table D1a). The incidences of hepatocellular carcinoma in exposed and control females in the first study were similar. The overall incidences of hepatocellular foci (basophilic, eosinophilic, clear cell, or mixed cell) were also increased in exposed female mice. These findings were confirmed in the second study, where incidences of hepatocellular adenoma, multiple adenoma, and foci (any type) were significantly greater than those of controls (Table 16b).

In contrast, the incidences of hepatocellular adenoma in exposed and control males in the first study were similar, but the incidence of hepatocellular carcinoma in the 400 ppm males was marginally greater than that of controls (Table 16a). However, the incidences of multiple hepatocellular adenoma in exposed males were marginally increased (Table C1a). The overall incidences of hepatocellular foci (any type) in exposed and control groups were similar. In the second study, the incidence of hepatocellular adenoma in 400 ppm males was significantly greater than that of controls, as was the incidence of multiple adenoma, but the incidences of hepatocellular carcinoma were similar (Table 16b).

TABLE 16a
Incidences of Liver Lesions in Mice at the 15-Month Interim Evaluations and in the 2-Year Feed Studies of Triamterene: First Study[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Male				
15-Month interim evaluation				
Basophilic focus	0/10 (0%)	2/3 (67%)	1/10 (10%)	–[b]
2-Year study				
Basophilic focus	6/50 (12%)	4/50 (8%)	10/50 (20%)	5/60 (8%)
Clear cell focus	1/50 (2%)	9/50 (18%)**	4/50 (8%)	11/60 (18%)**
Eosinophilic focus	7/50 (14%)	12/50 (24%)	11/50 (22%)	3/60 (5%)
Focus (any type)	14/50 (28%)	18/50 (36%)	20/50 (40%)	18/60 (30%)
Hepatocellular Adenoma[c]				
15-Month interim evaluation				
Overall rates	1/10 (10%)	3/3 (100%)	2/10 (20%)	–
2-Year study				
Overall rates	17/50 (34%)	22/50 (44%)	19/50 (38%)	20/60 (33%)
Adjusted rates[d]	36.2%	48.9%	40.3%	42.6%
Terminal rates[e]	17/47 (36%)	22/45 (49%)	18/46 (39%)	19/46 (41%)
First incidence (days)	729 (T)	729 (T)	617	711
Logistic regression tests[f]	P=0.391	P=0.154	P=0.417	P=0.314

(continued)

TABLE 16a
Incidences of Liver Lesions in Mice at the 15-Month Interim Evaluations and in the 2-Year Feed Studies of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
Male (continued)				
Hepatocellular Carcinoma[g]				
Overall rates	5/50 (10%)	7/50 (14%)	3/50 (6%)	13/60 (22%)
Adjusted rates	10.6%	14.8%	6.5%	28.3%
Terminal rates	5/47 (11%)	5/45 (11%)	3/46 (7%)	13/46 (28%)
First incidence (days)	729 (T)	557	729 (T)	729 (T)
Logistic regression tests	P=0.022	P=0.448	P=0.368N	P=0.030
Hepatocellular Adenoma or Carcinoma[h]				
Overall rates	20/50 (40%)	26/50 (52%)	19/50 (38%)	29/60 (48%)
Adjusted rates	42.6%	55.3%	40.3%	61.7%
Terminal rates	20/47 (43%)	24/45 (53%)	18/46 (39%)	28/46 (61%)
First incidence (days)	729 (T)	557	617	711
Logistic regression tests	P=0.074	P=0.136	P=0.500N	P=0.043
Hepatoblastoma	0/50 (0%)	1/50 (2%)	1/50 (2%)	0/60 (0%)
Female				
15-Month interim evaluation				
Basophilic focus	2/10 (20%)	0/2 (0%)	0/10 (0%)	–
Eosinophilic focus	0/10 (0%)	0/2 (0%)	1/10 (10%)	–
2-Year study				
Basophilic focus	1/50 (2%)	6/50 (12%)	6/50 (12%)	11/60 (18%)**
Clear cell focus	0/50 (0%)	1/50 (2%)	4/50 (8%)	3/60 (5%)
Eosinophilic focus	7/50 (14%)	11/50 (22%)	19/50 (38%)*	7/60 (12%)
Mixed focus	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/60 (2%)
Focus (any type)	8/50 (16%)	16/50 (32%)	24/50 (48%)**	19/60 (32%)*
Hepatocellular Adenoma[i]				
15-Month interim evaluation				
Overall rates	2/10 (20%)	2/2 (100%)	2/10 (20%)	–
2-Year study				
Overall rates	10/50 (20%)	22/50 (44%)	23/50 (46%)	36/60 (60%)
Adjusted rates	25.6%	51.2%	52.3%	78.1%
Terminal rates	9/38 (24%)	22/43 (51%)	22/43 (51%)	33/43 (77%)
First incidence (days)	723	729 (T)	712	579
Logistic regression tests	P<0.001	P=0.014	P=0.008	P<0.001
Hepatocellular Carcinoma[j]				
Overall rates	4/50 (8%)	4/50 (8%)	3/50 (6%)	8/60 (13%)
Adjusted rates	10.0%	9.3%	7.0%	18.6%
Terminal rates	3/38 (8%)	4/43 (9%)	3/43 (7%)	8/43 (19%)
First incidence (days)	589	729 (T)	729 (T)	729 (T)
Logistic regression tests	P=0.159	P=0.614N	P=0.472N	P=0.272

(continued)

TABLE 16a
Incidences of Liver Lesions in Mice at the 15-Month Interim Evaluations and in the 2-Year Feed Studies of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
Female (continued)				
Hepatocellular Adenoma or Carcinoma[k]				
Overall rates	13/50 (26%)	26/50 (52%)	25/50 (50%)	37/60 (62%)
Adjusted rates	32.3%	60.5%	56.8%	80.3%
Terminal rates	11/38 (29%)	26/43 (60%)	24/43 (56%)	34/43 (79%)
First incidence (days)	589	729 (T)	712	579
Logistic regression tests	P<0.001	P=0.014	P=0.022	P<0.001

° Significantly different (P≤0.05) from the control group by the logistic regression test
°° P≤0.01
(T)Terminal sacrifice
[a] Number of animals with lesion/number of animals with liver examined microscopically
[b] Interim evaluation not performed on animals receiving 400 ppm
[c] 2-Year historical incidence for untreated control groups in NTP feed studies (mean ± standard deviation): 145/865 (16.8% ± 8.2%); range 4%-38%
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. For all tests, a lower incidence in an exposure group is indicated by N.
[g] 2-Year historical incidence: 122/865 (14.1% ± 7.2%); range 3%-27%
[h] 2-Year historical incidence: 249/865 (28.8% ± 10.9%); range 17%-58%
[i] 2-Year historical incidence: 74/863 (8.6% ± 6.5%); range 0%-28%
[j] 2-Year historical incidence: 28/863 (3.2% ± 2.9%); range 0%-10%
[k] 2-Year historical incidence: 98/863 (11.4% ± 7.6%); range 3%-34%

TABLE 16b
Incidences of Liver Lesions in Mice at the 15-Month Interim Evaluations and in the 2-Year Feed Studies of Triamterene: Second Study[a]

	0 ppm	400 ppm
Male		
15-Month interim evaluation		
Basophilic focus	1/9 (11%)	0/10 (0%)
Clear cell focus	0/9 (0%)	1/10 (10%)
2-Year study		
Basophilic focus	0/50 (0%)	7/50 (14%)**
Clear cell focus	8/50 (16%)	4/50 (8%)
Eosinophilic focus	12/50 (24%)	10/50 (20%)
Focus (any type)	18/50 (36%)	16/50 (32%)
Hepatocellular Adenoma[b]		
15-Month interim evaluation		
Overall rates	0/9 (0%)	1/10 (10%)
2-Year study		
Overall rates	21/50 (42%)	36/50 (72%)
Adjusted rates[c]	44.7%	81.7%
Terminal rates[d]	17/43 (40%)	31/39 (79%)
First incidence (days)	701	522
Logistic regression tests[e]		P=0.001
Hepatocellular Carcinoma[f]		
Overall rates	9/50 (18%)	11/50 (22%)
Adjusted rates	19.3%	25.0%
Terminal rates	6/43 (14%)	7/39 (18%)
First incidence (days)	622	494
Logistic regression tests		P=0.422
Hepatocellular Adenoma or Carcinoma[g]		
Overall rates	25/50 (50%)	38/50 (76%)
Adjusted rates	52.1%	82.5%
Terminal rates	20/43 (47%)	31/39 (79%)
First incidence (days)	622	494
Logistic regression tests		P=0.005
Hepatoblastoma	0/50 (0%)	1/50 (2%)

(continued)

TABLE 16b
Incidences of Liver Lesions in Mice at the 15-Month Interim Evaluations and in the 2-Year Feed Studies of Triamterene: Second Study (continued)

	0 ppm	400 ppm
Female		
15-Month interim evaluation		
Basophilic focus	1/10 (10%)	1/9 (11%)
Eosinophilic focus	1/10 (10%)	0/9 (0%)
2-Year study		
Basophilic focus	0/50 (0%)	5/51 (10%)°
Clear cell focus	0/50 (0%)	4/51 (8%)
Eosinophilic focus	9/50 (18%)	16/51 (31%)
Mixed focus	1/50 (2%)	0/51 (0%)
Focus (any type)	10/50 (20%)	20/51 (39%)°
Hepatocellular Adenoma[h]		
Overall rates	7/50 (14%)	28/51 (55%)
Adjusted rates	17.5%	70.0%
Terminal rates	7/40 (18%)	26/38 (68%)
First incidence (days)	730 (T)	687
Logistic regression tests		P<0.001
Hepatocellular Carcinoma[i]		
15-Month interim evaluation		
Overall rates	1/10 (10%)	0/9 (0%)
2-Year study		
Overall rates	5/50 (10%)	11/51 (22%)
Adjusted rates	12.0%	28.0%
Terminal rates	4/40 (10%)	10/38 (26%)
First incidence (days)	616	676
Logistic regression tests		P=0.082
Hepatocellular Adenoma or Carcinoma[j]		
Overall rates	10/50 (20%)	31/51 (61%)
Adjusted rates	24.2%	75.6%
Terminal rates	9/40 (23%)	28/38 (74%)
First incidence (days)	616	676
Logistic regression tests		P<0.001

° Significantly different (P≤0.05) from the control group by the logistic regression test
°° P≤0.01
(T)Terminal sacrifice
[a] Number of animals with lesion/number of animals with liver examined microscopically
[b] 2-Year historical incidence for untreated control groups in NTP feed studies (mean ± standard deviation): 145/865 (16.8% ± 8.2%); range 4%-38%
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards these lesions as nonfatal.
[f] 2-Year historical incidence: 122/865 (14.1% ± 7.2%); range 3%-27%
[g] 2-Year historical incidence: 249/865 (28.8% ± 10.9%); range 17%-58%
[h] 2-Year historical incidence: 74/863 (8.6% ± 6.5%); range 0%-28%
[i] 2-Year historical incidence: 28/863 (3.2% ± 2.9%); range 0%-10%
[j] 2-Year historical incidence: 98/863 (11.4% ± 7.6%); range 3%-34%

Thyroid gland: In the first study, chemical-related increases in the incidences of follicular cell hyperplasia occurred, and the incidences were significantly greater than those of the controls in all but the 100 ppm males (Table 17). The incidences in the 400 ppm groups in the second study were also significantly greater than those of the controls. However, the average severity of hyperplasia was similar among exposed and control groups. The incidences of follicular cell adenoma in exposed and control mice were similar in both studies (Tables C1a,b and D1a,b).

Follicular cell hyperplasia was generally minimal to mild in severity. Minimal hyperplasia involved one to several individual follicles, occasionally with slightly dilated lumens, lined by enlarged epithelial cells that formed small projections into the follicular lumen. Mild lesions usually consisted of small clusters of follicles with lumens partially or totally filled by projections of enlarged epithelial cells (Plate 1). The follicular cell neoplasms were generally larger with more distinct borders and compressed or replaced the normal parenchyma.

TABLE 17
Incidences of Thyroid Gland Lesions in Mice in the 2-Year Feed Studies of Triamterene

	0 ppm	100 ppm	200 ppm	400 ppm
First Study				
Male				
Follicular cell, hyperplasia	3/50 (1.3)[a]	8/50 (1.4)	16/50** (1.4)	20/60** (1.5)
Female				
Follicular cell, hyperplasia	4/49 (2.3)	17/49** (1.4)	18/50** (1.4)	28/60** (1.5)
Second Study				
Male				
Follicular cell, hyperplasia	0/50			16/50** (1.6)
Female				
Follicular cell, hyperplasia	9/50 (1.2)			32/51** (1.6)

** Significantly different (P≤0.01) from the control group by the logistic regression test
[a] Average severity grade for affected animals: 1 = minimal; 2 = mild; 3 = moderate.

Kidney: The incidences (control, 28/50; 100 ppm, 36/50; 200 ppm, 43/50; 400 ppm, 49/60) and average severity (over all animals) (0.56, 0.80, 1.00, 1.07) of nephropathy in exposed females were greater than in controls in the first study (Table D5a). In the second study, however, the differences in incidences (control, 17/50; 400 ppm, 21/50) and severity (0.38, 0.55) of nephropathy between 400 ppm females and the controls were not as great (Table D5b). Thus, it is uncertain if these marginal changes are related to the ingestion of triamterene. In males, the incidences (first study: 49/50, 48/50, 49/50, 58/60; second study: 45/50, 43/50) and severity (first study: 1.7, 1.7, 1.6, 1.7; second study: 1.06, 1.16) of nephropathy were similar among exposed and control groups (Tables C5a,b).

Nephropathy was characterized by individual or clusters of cortical tubules with basophilic epithelial cells often surrounded by increased amounts of interstitial collagen and accumulations of small numbers of mononuclear inflammatory cells.

Harderian gland: Although the incidences of harderian gland neoplasms (adenoma or carcinoma) were similar among exposed and control male mice in the first study, the incidence of adenoma in the 400 ppm group in the second study was marginally greater than that of controls (first study: 1/50, 1/50, 3/50, 2/50; second study: 1/50, 6/50). No harderian gland adenomas were observed in male mice at the 3- or 15-month interim evaluations. The incidence of adenomas in the 400 ppm males in the second study was within the historical range for control male B6C3F$_1$ mice in recent NTP 2-year feed studies (48/872, 6%, range, 0%-20%). Hyperplasia occurred at low incidences in the control, 100 ppm, and 200 ppm males of the first study and in the control males of the second study; hyperplasia was not observed in the 400 ppm groups of the first or second study. The increased incidence of harderian gland adenomas in male mice was not considered to be chemical related because 1) it occurred only in the second study, 2) the incidence was within the range of historical controls, and 3) there was no supporting increase in hyperplasia (Tables C5a and C5b).

Small intestine: Adenocarcinomas of the small intestine occurred in two 400 ppm male mice in the first study; none were seen in other exposure groups or in groups in the second study (Tables C1a and C1b). Neoplasms of the small intestine are uncommon in male B6C3F$_1$ mice and have occurred in 3/872 (0.2%) NTP historical controls with a range of 0%-2%. Because this neoplasm occurred at low incidence in the first study and not in 400 ppm males in the second study, they were not considered to be chemical related.

Genetic Toxicology

Triamterene (10-10,000 μg/plate) was tested at two laboratories for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no induction of mutations was observed at either laboratory (Mortelmans *et al.*, 1986; Table E1). In cytogenetic tests with Chinese hamster ovary cells, triamterene induced sister chromatid exchanges with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table E2). Without S9, doses tested ranged from 0.5 to 40 μg/mL and 10 μg/mL was the lowest dose at which a positive response occurred. With S9, doses of 5 to 500 μg/mL were tested and the lowest effective dose was 160 μg/mL. Tests for induction of chromosomal aberrations in Chinese hamster ovary cells were negative, with and without S9 activation (Table E3). With S9, the first trial showed a significant increase in aberrations at the middle dose of 50 μg/mL, but this response was not repeated in a second trial.

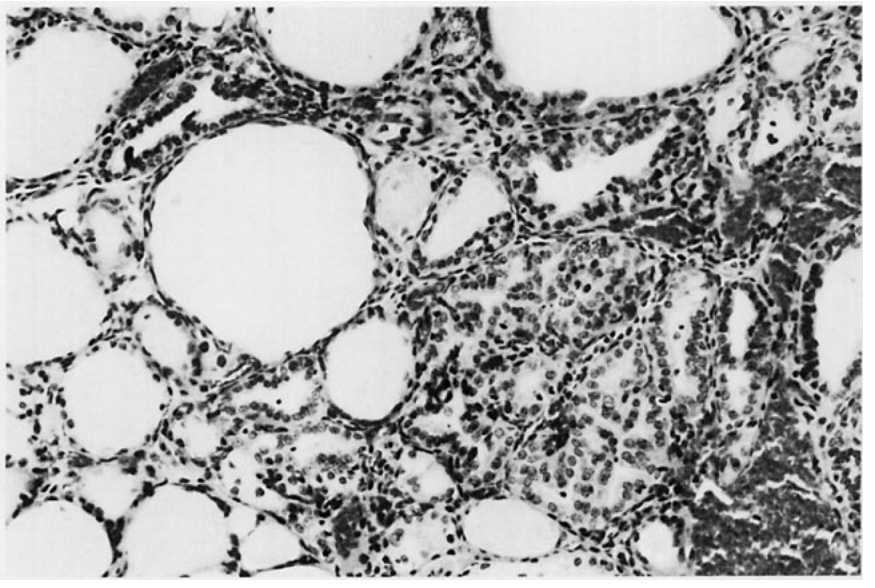


PLATE 1
Thyroid Gland: Follicular cell hyperplasia. Follicles are lined by large cells which have filled much of the lumens of some follicles. Female $B6C3F_1$ mouse given 400 ppm triamterene in the 2-year feed study. H&E ×150

DISCUSSION AND CONCLUSIONS

Triamterene is a widely used potassium-sparing diuretic which was first synthesized in 1954 and was made commercially available in the 1960's. Toxicology and carcinogenesis studies were conducted in F344/N rats and B6C3F$_1$ mice because there have been no previous long-term studies of this drug in animals.

The dietary admixtures were unpalatable at concentrations of 10,000 ppm or more in the NTP 15-day studies. Reduced feed consumption was also observed with dietary admixtures containing approximately 1,600 ppm (mice) or 2,400 ppm (rats) in the 13-week studies, but it was uncertain to what extent this was associated with palatability of the diet or with anorexia resulting from toxicity.

In the NTP 13-week studies, all rats receiving 2,400 ppm and all mice receiving 1,600 ppm died before the end of the studies. Most of the rats died during the third and fourth weeks, whereas mice died during the first week of the studies. Although renal lesions were observed in most of the rats that died, nutritional deficiencies associated with the reduced feed consumption may also have contributed to their deaths. In contrast to rats, renal lesions were not observed in mice. Moreover, there were no histological lesions in other organs of mice that could account for their deaths. In humans, an increase in serum potassium concentration (hyperkalemia) may result from the overdose of triamterene, resulting in ventricular tachycardia or fibrillation and death (Weiner 1990). Whether hyperkalemia and physiological alterations associated with the diuretic effects of triamterene contributed to the deaths of mice and rats in the 13-week studies was not determined.

In the NTP 13-week study, sand-like calculi were observed at necropsy in the renal pelvis of several male rats receiving 1,200 ppm, which is consistent with reports of abnormal urinary sediments and nephrolithiasis in humans as complications of triamterene therapy or as toxic effects from overdose (Sica and Gehr, 1989). The urine sediments of patients receiving therapeutic doses of triamterene contained pigmented brown casts and hyaline casts with birefringent crystals (Fairley *et al.*, 1986). Furthermore, renal calculi composed of triamterene and its primary metabolites, hydroxytriamterene and hydroxytriamterene sulfate ester, have been observed in patients receiving triamterene (Patel, 1981; Grunberg and Silberg, 1981; Werness *et al.*, 1982; Sörgel *et al.*, 1985a).

Although triamterene and its primary metabolites have been identified in urinary calculi (sometimes as a major constituent), the role of triamterene in the formation of calculi in humans has not been fully clarified. It has been proposed that triamterene may promote the growth of calculi in three different ways. First, the precipitation of triamterene and its metabolites in the urine may result in the formation of concretions composed almost entirely of the drug (Gault *et al.*, 1981). Second, the triamterene crystals may provide a nidus upon which other crystals are deposited, and third, triamterene may increase the size of existing calculi by being adsorbed to the protein matrix common to most renal or urinary calculi (Werness *et al.*, 1982; Sörgel *et al.*, 1985a). The formation of urinary calculi in male F344/N rats receiving triamterene may provide a model for studying this process.

Triamterene therapy also has been associated with transient declines in renal function and, less frequently, acute renal failure in humans. Several different causal mechanisms for these effects have been proposed, including interstitial nephritis from drug-induced hypersensitivity (Bailey *et al.*, 1982; Magil, 1983), intrarenal obstruction due to crystalline deposits in renal tubules and collecting ducts (Farge *et al.*, 1986), and hemodynamic events accompanying the administration of triamterene with nonsteroidal anti-inflammatory agents (Weinberg *et al.*, 1985; Mathews and Baille, 1986). The results of the NTP studies suggest that the intrinsic nephrotoxicity of triamterene or its metabolites may also play a role in these conditions.

Rats receiving 3,000 ppm in the 15-day study and 1,200 or 2,400 ppm in the 13-week study had moderately severe renal lesions involving the outer stripe of

the outer medulla and, to a lesser extent, cortical tubules or medullary collecting ducts. The epithelium of the straight portions of renal tubules in the outer stripe of the outer medulla exhibited increased cytoplasmic basophilia and enlarged nuclei with occasional cells in mitosis. These cytologic features are consistent with a rapid rate of cell turnover and are usually due to enhanced cell loss or necrosis. Individual necrotic cells were occasionally seen. Segments of convoluted tubules with similar features were also observed in the cortex, and occasionally segmental lesions involving the full thickness of the cortex were seen. Cellular degeneration and necrosis were more prominent features of the lesion in mice receiving 3,000 ppm in the 15-day study than in rats.

The particular segment or segments of the nephron affected is not entirely clear from these studies. The focal, segmental lesions involving the full thickness of the cortex clearly included the P1 and P2 segments of the proximal convoluted tubules. The outer stripe of the outer medulla, which seemed to be the most extensive region affected, contains the descending straight portion of the proximal tubules (P3), the thick ascending limb of the distal tubules, and collecting ducts. Ožegović *et al.* (1979) reported renal lesions in rats given triamterene. These authors described vacuolar degeneration and loss of PAS-staining of the brush border of the proximal convoluted tubule epithelium with focal karyolysis and cytolysis (necrosis) in male Fischer rats given 3 or 4.5 mg triamterene per 100 g body weight.

Necrosis of lymphocytes in the spleen, lymph nodes, and thymus was observed in mice receiving 800 or 1,600 ppm in the 13-week studies, and lymphoid depletion and bone marrow hypocellularity were seen in rats receiving 2,400 ppm. Although similar lesions are commonly associated with debilitation, malnutrition, and stress, there may be an alternative explanation for the lesions in rats and mice receiving triamterene. The molecular structure of triamterene consists of a pteridine nucleus like the antifolate drugs used in cancer chemotherapy. The antifolate drugs, such as methotrexate, bind to dihydrofolate reductase, an enzyme essential in the synthesis of DNA, and inhibit DNA synthesis and the growth of rapidly dividing cells. Since the bone marrow and lymphoid tissues have a relatively high rate of cell turnover, the lesions in these tissues in the 13-week studies might be related to the antifolate effects of triamterene. Although triamterene has been reported to be a weak antifolate compound *in vitro*, it has not exhibited antifolate activity *in vivo* (Maass *et al.*, 1967; Manson *et al.*, 1986).

The high dose selected for the 2-year study in rats was 600 ppm, one-half the lowest dose at which triamterene-related kidney lesions were observed in the 13-week study and one-fourth the dose at which all rats died in the 13-week study. Dietary concentrations greater than 600 ppm were considered too great, primarily because of the potential for triamterene-related kidney toxicity to exacerbate the spontaneous renal disease of aging rats and shorten their lifespan. At the end of the 2-year study, a slight but statistically significant increase in the severity of nephropathy was observed in high-dose female rats and in male rats receiving 300 ppm. The slight but consistent decrement in body weight between exposed and control rats in the second year of the study was also attributed to triamterene administration.

The high dose selected for the 2-year study in mice was 400 ppm, one-half the dose at which necrosis of lymphocytes was observed in lymph nodes, spleen, and thymus and one-fourth the dose at which all mice died in the 13-week study. Moreover, one female mouse receiving 800 ppm also died and the body weight gain of males in this exposure group was less than 50% of the controls. Thus, a dietary concentration of 800 ppm was considered too great for the 2-year study.

In the 2-year studies, the estimated amount of triamterene consumed was approximately 5, 10, or 25 mg/kg per day for rats fed 150, 300, or 600 ppm, and was approximately 10, 20, or 50 mg/kg per day for mice fed 100, 200, or 400 ppm. In humans, up to 5 mg/kg per day may be used in the treatment of edema from various causes.

In the 2-year rat and mouse studies, there were no drug-related effects on survival at the targeted concentrations, and there were no clinical findings of toxicity. An effect on survival was observed in the high-dose mice that received approximately four times the targeted concentration (approximately 1,600 ppm) of triamterene for 7 days at week 40. Because of the overdosing, 12 male and four female mice died during week 40 of treatment. However, the majority of the mice in the high-dose group survived, unlike the 13-week study in which all the mice fed 1,600 ppm died during the first week of

treatment. Since the older mice may consume less feed on a body weight basis, it is unknown if the apparent greater resistance is related to the amount of triamterene ingested or to some other factor. The surviving high-dose mice were kept in the 2-year study, but because of the uncertainty about what effect this one week of increased exposure would have on the outcome of the study, a second study was conducted with control and 400 ppm male and female mice.

Other than the slight increase in the severity of nephropathy in rats, the principal drug-related effects in rats and mice in the 2-year studies were observed in the liver. The incidences of mixed cell foci occurred with a significant positive trend in male and female rats and the incidences in the mid- and high-dose groups were significantly greater than in controls. Moreover, the incidence of eosinophilic foci in males and clear cell foci in females were marginally increased in the high-dose groups. The incidences of lesions classified as hyperplasia, which were morphologically similar to the various foci, were also increased in exposed male rats.

In hematoxylin and eosin stained sections, hepatocellular foci are typically categorized as basophilic, eosinophilic, clear, vacuolated, or mixed depending on the predominant staining properties of the cytoplasm. These staining properties are determined by the relative amounts of the various cytoplasmic constituents. Therefore, although convenient and necessary for making diagnoses, the descriptive categories of the various foci are not mutually exclusive. Consequently, all phenotypes must be considered when evaluating the biological significance of these lesions.

Hepatocellular foci can also be identified by a variety of histochemical and immunoperoxidase stains for various enzymes. The foci observed in this study and those described in aged rats by other investigators (Ogawa *et al.*, 1981; Ward, 1981) are morphologically and phenotypically similar to the foci induced by potent hepatocarcinogens (Williams, 1989). In short- and medium-term rat liver initiation/promotion carcinogenesis models, the analysis of hepatocellular foci is believed to provide a qualitative and quantitative measurement of a chemical's potential to induce liver cancer (Campbell *et al.*, 1982, 1986; Williams, 1989). Foci are rapidly induced by hepatocarcinogens, and the numbers of induced foci are related to the dose of the carcinogen (Emmelot and Scherer, 1980). Foci increase in number and size with continued carcinogen exposure or with time after cessation of exposure to certain carcinogens (Rabes and Szymkowiak, 1979; Barbason and Betz, 1981). Furthermore, hepatocellular neoplasms are believed to develop from some foci, even though the number of induced foci far exceeds the number of neoplasms that ultimately develop. The rate of progression of foci to neoplasms has been estimated to be on the order of 1 in 1,000 (Watanabe and Williams, 1978) to 1 in 2,500 (Pitot *et al.*, 1978) for certain carcinogens.

Based on these experimental considerations, the more frequent occurrences of mixed cell foci, eosinophilic foci, and hyperplasia in male rats and mixed cell and clear cell foci in female rats receiving triamterene may reflect early biochemical changes that could lead to the development of hepatocellular neoplasms. However, the incidences of hepatocellular neoplasms in exposed rats at the end of the 2-year study do not convincingly support this hypothesis. No hepatocellular carcinomas were observed in male or female rats. Although the incidence of hepatocellular adenomas in male rats in the 150 ppm group was significantly greater than that of concurrent controls and exceeded the range of historical controls, the incidences in males receiving twice (300 ppm) or four times that amount (600 ppm) of triamterene were not significantly greater than controls. Therefore, the data were considered to provide equivocal evidence of carcinogenic activity in male rats.

Hepatocellular adenomas were observed in two high-dose female rats, and none were seen in the lower exposure groups or in controls. While hepatocellular adenomas are relatively uncommon in untreated female rats, an incidence as high as 6% has been observed in a single control group. Therefore, it was concluded that there was no evidence of carcinogenic activity in female rats.

In contrast to rats, the incidences of hepatocellular neoplasms (adenoma or carcinoma) were significantly increased in female mice receiving diets containing 100, 200, or 400 ppm triamterene. The rates observed in the 400 ppm groups in both studies also fall outside the range of recent NTP historical control data. Moreover, the number of females with multiple liver neoplasms or with hepatocellular foci also increased in the exposed groups, providing further evidence that these lesions are related to the

ingestion of triamterene. The increased incidences of hepatocellular neoplasms in exposed female mice were due primarily to the more frequent occurrence of hepatocellular adenomas. Therefore, these findings were considered some evidence of carcinogenic activity rather than clear evidence.

In male mice, there were significant increases in the incidences of hepatocellular neoplasms in the groups receiving 400 ppm. In the first study, this was due primarily to an increased incidence of carcinomas, whereas in the second study it was due to an increased incidence of adenomas. As in females, the number of high-dose males with multiple liver neoplasms was greater than controls. In contrast to female mice, however, the overall incidences of hepatocellular foci were similar in exposed groups of male mice and controls. Because of the consistent finding of increased incidences of hepatocellular neoplasms in both the first and second studies and the increased incidence of multiple adenomas in the treated groups, these findings were considered to be some evidence of carcinogenic activity.

In addition to the treatment-related effects in the liver of exposed mice, there was an increase in the incidence of thyroid follicular cell hyperplasia. The reason for this thyroid effect is unknown.

The mechanism by which triamterene increased the incidences of hepatocellular foci in rats and liver neoplasms in mice is unknown. Liver toxicity is not reported as a common side effect from triamterene treatment in humans, although in older patients metabolism of the drug may be decreased and accumulation of the drug may contribute to liver and kidney disease (Knauf *et al.*, 1983). Results of *in vitro* genetic toxicity assays show that triamterene is not mutagenic in *Salmonella typhimurium*, but it does induce chromosomal aberrations, sister chromatid exchanges, and micronuclei formation in Chinese hamster lung cells (Kawachi *et al.*, 1980; Sasaki *et al.*, 1980; Ishidate *et al.*, 1981). On the other hand, triamterene did not induce chromosomal aberrations in bone marrow cells or dominant lethal mutations in germ cells of CD-1 mice (Manson *et al.*, 1986), nor did it induce chromosomal aberrations in bone marrow cells (Kawachi *et al.*, 1980) or unscheduled DNA synthesis in hepatocytes of male rats (Mirsalis *et al.*, 1983).

The NTP has evaluated the results of genetic toxicity tests and carcinogenicity studies of 114 chemicals (Zeiger *et al.*, 1990). In this group of chemicals, positive tests for the induction of chromosomal aberrations or sister chromatid exchanges were less predictive of carcinogenicity than positive tests for the induction of mutations in *Salmonella typhimurium*. That is, 73% of chemicals inducing chromosomal aberrations and 64% of chemicals inducing sister chromatid exchanges were carcinogenic in rodents, while 89% of the chemicals mutagenic in *S. typhimurium* were carcinogenic in rodents. Moreover, the specificity of tests for chromosomal aberrations and sister chromatid exchanges was less than tests for mutagenicity in *S. typhimurium*. The proportion of noncarcinogens that was negative in tests for chromosomal aberrations was 72% while the proportion that was negative in tests for sister chromatid exchanges was 45%, as compared with 91% for *S. typhimurium*. While a chemical mutagenic in *S. typhimurium* strongly implicates a mechanism of carcinogenicity involving DNA damage, the significance of tests for the induction of chromosomal aberrations or sister chromatid exchanges is less certain. Further study is necessary to determine how triamterene induces liver neoplasms in mice. In compilations of NCI and NTP rat and mouse carcinogenicity test results, the proportions of chemicals that induced neoplasms only in the liver of mice that were also mutagenic were 20% (Zeiger, 1987) and 39% (Ashby and Tennant, 1991).

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of triamterene in male F344/N rats based on a marginal increase in the incidence of hepatocellular adenoma. There was *no evidence of carcinogenic activity* of triamterene in female F344/N rats administered 150, 300, or 600 ppm. There was *some evidence of carcinogenic activity* of triamterene in male B6C3F$_1$ mice based on a marginal increase in the incidence of hepatocellular carcinoma in the first study and a significantly increased incidence of hepatocellular adenoma in the second study. There was *some evidence of carcinogenic activity* of triamterene in female B6C3F$_1$ mice based on significantly increased incidences of hepatocellular adenoma and of adenoma and carcinoma (combined).

Exposure to triamterene was associated with an increased incidence of hepatocellular foci, primarily mixed cell type, and an increase in the severity of nephropathy in female rats. In mice, exposure to triamterene was associated with an increased incidence of hepatocellular foci in females and an increased incidence of thyroid gland follicular cell hyperplasia in males and females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF TRIAMTERENE

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Triamterene[a]

	0 ppm	150 ppm	300 ppm	600 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation	10	10	10	10
2-Year study				
Early deaths				
Moribund	18	20	18	17
Natural deaths	4	5	13	6
Accidental deaths	3			
Survivors				
Terminal sacrifice	25	25	19	27
Animals examined microscopically	70	70	70	70
15-Month Interim Evaluation				
Alimentary System				
Mesentery			(1)	(2)
Lipoma			1 (100%)	
Cardiovascular System				
None				
Endocrine System				
Adrenal gland, medulla	(10)	(1)		(10)
Pheochromocytoma benign	1 (10%)			
Pituitary gland	(10)	(2)		(10)
Pars distalis, adenoma		1 (50%)		
Thyroid gland	(10)	(1)		(10)
C-cell, adenoma	1 (10%)			1 (10%)
General Body System				
None				
Genital System				
Preputial gland	(10)	(1)	(1)	(8)
Adenoma	2 (20%)		1 (100%)	
Testes	(10)	(1)	(6)	(10)
Bilateral, interstitial cell, adenoma	4 (40%)	1 (100%)	5 (83%)	6 (60%)
Interstitial cell, adenoma	6 (60%)		1 (17%)	4 (40%)
Hematopoietic System				
None				
Integumentary System				
None				

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

	0 ppm	150 ppm	300 ppm	600 ppm
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(1)	(2)	(10)
Liposarcoma		1 (100%)		
2-Year Study				
Alimentary System				
Intestine large, rectum	(49)	(47)	(49)	(47)
Adenocarcinoma				1 (2%)
Adenoma		1 (2%)		
Intestine small, jejunum	(48)	(49)	(49)	(47)
Adenoma		1 (2%)		
Liver	(50)	(50)	(50)	(49)
Cholangioma				1 (2%)
Fibrous histiocytoma, metastatic, skin			1 (2%)	
Hepatocellular adenoma		4 (8%)	4 (8%)	2 (4%)
Hepatocellular adenoma, multiple		2 (4%)		1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Mesentery	(4)	(4)	(3)	(8)
Pancreas	(50)	(50)	(50)	(48)
Stomach, forestomach	(50)	(50)	(50)	(49)
Papilloma squamous		1 (2%)		1 (2%)
Stomach, glandular	(50)	(50)	(50)	(48)
Tongue	(1)		(1)	(1)
Papilloma squamous			1 (100%)	
Squamous cell carcinoma				1 (100%)
Tooth		(1)	(1)	(1)
Gingiva, squamous cell carcinoma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Chemodectoma benign			1 (2%)	
Hemangiosarcoma				1 (2%)

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

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		
Adrenal gland, medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant	1 (2%)	2 (4%)		
Pheochromocytoma benign	7 (14%)	10 (20%)	7 (14%)	5 (10%)
Bilateral, pheochromocytoma benign	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	2 (4%)	1 (2%)	5 (10%)	1 (2%)
Parathyroid gland	(46)	(46)	(50)	(49)
Adenoma	1 (2%)			
Pituitary gland	(50)	(50)	(49)	(49)
Pars distalis, adenoma	8 (16%)	6 (12%)	7 (14%)	9 (18%)
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(50)	(49)	(50)	(49)
Bilateral, C-cell, adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
C-cell, adenoma	9 (18%)	6 (12%)	11 (22%)	8 (16%)
Follicle, adenoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
General Body System				
Tissue NOS			(1)	
Chemodectoma benign			1 (100%)	
Genital System				
Epididymis	(50)	(50)	(50)	(49)
Preputial gland	(50)	(50)	(50)	(49)
Adenoma	1 (2%)	2 (4%)	4 (8%)	3 (6%)
Prostate	(48)	(48)	(50)	(49)
Seminal vesicle	(49)	(48)	(50)	(49)
Testes	(50)	(50)	(50)	(49)
Bilateral, interstitial cell, adenoma	39 (78%)	42 (84%)	43 (86%)	43 (88%)
Interstitial cell, adenoma	3 (6%)	5 (10%)	6 (12%)	4 (8%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(50)	(50)	(50)	(50)
Pancreatic, pheochromocytoma malignant, metastatic, adrenal gland	1 (2%)			
Lymph node, mandibular	(50)	(49)	(50)	(50)
Lymph node, mesenteric	(48)	(47)	(47)	(48)
Spleen	(50)	(50)	(50)	(50)
Leiomyosarcoma	2 (4%)			
Thymus	(42)	(46)	(46)	(41)
Squamous cell carcinoma, metastatic, lung		1 (2%)		

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

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(36)	(37)	(35)	(42)
Fibroadenoma				1 (2%)
Skin	(49)	(50)	(50)	(49)
Basal cell adenoma		1 (2%)	1 (2%)	
Basal cell carcinoma		1 (2%)		
Basosquamous tumor malignant	2 (4%)			
Basosquamous tumor benign			1 (2%)	1 (2%)
Keratoacanthoma	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Papilloma squamous	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Subcutaneous tissue, fibrous histiocytoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma		1 (2%)	1 (2%)	1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland			1 (2%)	
Granular cell tumor benign	1 (2%)			
Oligodendroglioma benign	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)			
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)	
Carcinoma, metastatic, Zymbal's gland			1 (2%)	
Fibrous histiocytoma, metastatic, skin			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal gland		1 (2%)		
Squamous cell carcinoma		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Papilloma squamous			1 (2%)	
Special Senses System				
Ear	(2)			(1)
Middle ear, papilloma squamous	1 (50%)			
Pinna, fibrosarcoma				1 (100%)
Pinna, papilloma squamous	1 (50%)			
Zymbal's gland		(1)	(2)	
Adenoma		1 (100%)		
Carcinoma			2 (100%)	

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

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	
Urinary bladder	(49)	(47)	(50)	(47)
Adenoma				1 (2%)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Leukemia mononuclear	22 (44%)	23 (46%)	19 (38%)	18 (36%)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant mixed	1 (2%)			
Mesothelioma malignant		2 (4%)		1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	10	3	8	10
2-Year study	45	49	50	50
Total primary neoplasms				
15-Month interim evaluation	14	3	8	11
2-Year study	114	124	128	114
Total animals with benign neoplasms				
15-Month interim evaluation	10	2	8	10
2-Year study	44	48	50	48
Total benign neoplasms				
15-Month interim evaluation	14	2	8	11
2-Year study	86	93	103	89
Total animals with malignant neoplasms				
15-Month interim evaluation		1		
2-Year study	26	28	24	23
Total malignant neoplasms				
15-Month interim evaluation		1		
2-Year study	28	31	25	25
Total animals with metastatic neoplasms				
2-Year study	1	3	3	
Total metastatic neoplasms				
2-Year study	1	3	4	
Total animals with malignant neoplasms uncertain primary site				
2-Year study		1		

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were found at the 3-month interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 0 ppm

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 0 5 3	0 0 7 5	0 0 8 2	0 1 0 2	0 1 0 3	0 1 3 4	0 1 4 2	0 1 4 3	0 0 1 1	0 0 1 3	0 0 3 5	0 0 5 1	0 0 6 3	0 0 6 4	0 0 6 1	0 0 7 3	0 0 7 3	0 0 8 3	0 0 8 4	0 0 9 1	0 1 1 2	0 1 1 5	0 1 2 1	0 1 2 3	0 1 2 5	0 1 4 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																		+								4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue		+																								1
Cardiovascular System																										
Blood vessel			+																							1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																						X				1
Pheochromocytoma benign			X	X						X				X											X	7
Bilateral, pheochromocytoma benign		X					X																			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															2
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma														X												1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X			X			X												X				X	8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																X										1
C-cell, adenoma		X	X				X		X				X													9
Follicle, adenoma			X																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	0 8 3	0 8 3	0 8 3	3 3 6	4 7 0	4 8 4	4 8 8	5 0 8	5 3 0	5 3 9	5 3 4	6 8 7	6 1 4	6 2 4	6 4 5	6 5 3	6 5 5	6 5 9	6 7 5	6 8 1	7 0 2	7 0 9	7 1 4	7 1 9	7 2 5	7 2 6
Carcass ID Number	0 0 9 2	0 0 9 3	0 0 9 4	0 3 3 5	0 3 3 1	0 6 3 2	0 5 3 1	0 3 1 5	0 1 1 1	0 1 4 2	0 0 3 4	0 1 4 4	0 0 2 5	0 0 1 5	0 0 5 5	0 1 4 2	0 0 5 5	0 1 4 4	0 1 0 4	0 0 1 2	0 0 3 2	0 1 3 3	0 0 4 3	0 0 2 1	0 1 1 3	0 0 4 1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X				
Prostate	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X	X			X	X	X	X	X	X	X	X			X	X	X	X	X	X
Interstitial cell, adenoma																			X							
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic, pheochromocytoma malignant, metastatic, adrenal gland																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																										
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	M	+	+	M	M	M	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant														X												
Keratoacanthoma														X												
Papilloma squamous																										
Subcutaneous tissue, fibroma																						X				
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																										X
Oligodendroglioma benign						X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 0 5 3	0 0 7 5	0 0 8 2	0 1 0 2	0 1 0 3	0 1 3 4	0 1 4 2	0 1 4 3	0 0 1 1	0 0 3 3	0 0 5 5	0 0 6 1	0 0 6 3	0 0 6 4	0 0 7 1	0 0 7 3	0 0 8 3	0 0 8 4	0 0 9 1	0 1 1 2	0 1 1 5	0 1 2 1	0 1 2 3	0 1 2 5	0 1 4 1	**Total Tissues/ Tumors**
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	39
Interstitial cell, adenoma							X				X														3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreatic, pheochromocytoma malignant, metastatic, adrenal gland																				X					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma			X																					X	2
Thymus	M	+	M	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	42
Integumentary System																									
Mammary gland	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	36
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor malignant												X													2
Keratoacanthoma																X									2
Papilloma squamous															X										1
Subcutaneous tissue, fibroma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign																									1
Oligodendroglioma benign																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	0	0	0	3	4	4	4	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	
	8	8	8	3	7	8	8	0	3	3	8	1	2	4	5	5	5	7	8	0	0	1	1	2	2
	3	3	3	6	0	4	8	8	0	9	4	7	4	5	3	5	9	5	1	2	9	4	9	5	6
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	1	0	1	0	0	1	0	0	1	0
	9	9	9	3	3	6	5	3	1	4	3	4	2	1	5	4	1	0	1	3	3	4	2	1	4
	2	3	4	5	1	2	1	5	1	2	4	4	5	5	2	5	4	4	2	2	3	3	1	3	1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear															+										
Middle ear, papilloma squamous																									
Pinna, papilloma squamous															X										
Eye														+							+				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X		X	X	X		X	X	X	X		X		X	X		
Lymphoma malignant mixed																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 0 5 3	0 0 7 5	0 0 8 2	0 1 0 2	0 1 0 3	0 1 3 4	0 1 4 2	0 1 4 3	0 0 1 1	0 0 1 3	0 0 3 5	0 0 6 1	0 0 6 3	0 0 6 4	0 0 7 1	0 0 7 3	0 0 8 3	0 0 8 4	0 0 9 1	0 1 1 2	0 1 1 5	0 1 2 1	0 2 2 3	0 2 2 5	0 4 1	**Total Tissues/ Tumors**
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X							X			2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Ear															+										2
Middle ear, papilloma squamous															X										1
Pinna, papilloma squamous																									1
Eye							+																		3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X		X	X							X					X	X				X	X	22
Lymphoma malignant mixed																			X							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 150 ppm

Number of Days on Study	3 2 4	3 6 6	5 3 9	5 4 2	6 1 0	6 1 0	6 1 1	6 1 1	6 1 7	6 1 9	6 4 0	6 5 2	6 5 3	6 5 5	6 5 9	6 6 0	6 7 4	7 7 4	7 8 3	7 0 2	7 0 2	7 1 0	7 1 3	7 1 5	7 2 2
Carcass ID Number	0 1 9 5	0 2 4 1	0 2 1 3	0 2 0 1	0 1 6 2	0 2 0 5	0 1 7 3	0 2 0 2	0 2 8 2	0 2 1 4	0 2 4 5	0 2 5 3	0 2 8 5	0 1 9 3	0 2 2 4	0 2 0 3	0 1 5 5	0 1 7 4	0 2 7 3	0 1 7 1	0 1 8 5	0 2 6 4	0 1 5 2	0 1 5 1	0 1 5 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Adenoma																									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																							X		
Hepatocellular adenoma, multiple						X																			
Sarcoma, metastatic, uncertain primary site															X										
Mesentery				+																+					+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel																						+	+		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																	X		X		X				
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 6 3	0 1 6 5	0 1 7 2	0 1 7 5	0 2 0 4	0 2 3 5	0 2 4 2	0 2 7 5	0 2 1 1	0 1 8 2	0 1 8 2	0 1 9 1	0 1 9 2	0 2 2 2	0 2 2 3	0 2 2 5	0 2 3 2	0 2 3 3	0 3 3 4	0 3 5 2	0 3 7 1	0 3 7 2	0 3 7 4	0 3 8 1	0 3 8 3	0 3 8 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma												X														1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X																		1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X										X												X		4
Hepatocellular adenoma, multiple																				X						2
Sarcoma, metastatic, uncertain primary site																										1
Mesentery					+																					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous												X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+																									1
Cardiovascular System																										
Blood vessel							+																			3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant						X				X																2
Pheochromocytoma benign									X	X		X		X				X	X			X				10
Bilateral, pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	3 2 4	3 6 6	5 3 9	5 4 2	6 1 0	6 1 0	6 1 1	6 1 1	6 1 7	6 1 9	6 4 0	6 5 2	6 5 3	6 5 5	6 5 9	6 6 0	6 7 4	6 7 4	6 8 3	7 0 2	7 0 2	7 1 0	7 1 3	7 1 5	7 2 2
Carcass ID Number	0 1 9 5	0 2 4 1	0 2 1 3	0 2 0 1	0 1 6 2	0 2 0 5	0 1 7 3	0 2 0 2	0 2 8 2	0 2 1 4	0 2 4 5	0 2 5 3	0 2 8 5	0 1 9 3	0 2 2 4	0 2 0 3	0 1 5 5	0 1 7 4	0 2 7 3	0 1 7 1	0 1 8 5	0 2 6 4	0 1 5 2	0 1 5 1	0 1 5 3
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X							X				X	
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma					X				X	X															
Follicle, adenoma												X													
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
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												
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung																		X							
Integumentary System																									
Mammary gland	+	+	+	M	M	+	+	M	+	+	+	+	M	M	+	+	+	+	+	M	M	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									
Keratoacanthoma																									
Papilloma squamous												X													
Subcutaneous tissue, fibroma								X																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 6 3	0 1 6 5	0 1 7 2	0 1 7 5	0 2 0 4	0 2 3 5	0 2 4 2	0 2 7 5	0 1 8 1	0 1 8 2	0 1 9 1	0 1 9 2	0 2 2 2	0 2 2 3	0 2 2 5	0 2 3 2	0 2 3 3	0 2 3 4	0 2 5 2	0 2 7 1	0 2 7 2	0 2 7 4	0 2 8 1	0 2 8 3	0 2 8 4	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X					X													X				6
Pars intermedia, adenoma																							X			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma																	X									1
C-cell, adenoma	X			X																					X	6
Follicle, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															2
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	42
Interstitial cell, adenoma									X				X													5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	37
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																					X					1
Basal cell carcinoma													X													1
Keratoacanthoma						X			X																	2
Papilloma squamous																										1
Subcutaneous tissue, fibroma																	X									2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	3	3	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7		
	2	6	3	4	1	1	1	1	1	1	4	5	5	5	5	6	7	7	8	0	0	1	1	1	2	
	4	6	9	2	0	0	1	1	7	9	0	2	3	5	9	0	4	4	3	2	2	0	3	5	2	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	2	2	2	1	2	1	2	2	2	2	2	2	1	2	2	1	1	2	1	1	2	1	1	1	
	9	4	1	0	6	0	7	0	8	1	4	5	8	9	2	0	5	7	7	7	8	6	5	5	5	
	5	1	3	1	2	5	3	2	2	4	5	3	5	3	4	3	5	4	3	1	5	4	2	1	3	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Osteosarcoma		X																								
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spinal cord		+																								
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar carcinoma																										
Pheochromocytoma malignant, metastatic, adrenal gland																										
Squamous cell carcinoma																		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye														+										+		
Zymbal's gland							+																			
Adenoma							X																			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear			X	X	X	X			X	X	X	X	X	X		X	X				X				X		
Mesothelioma malignant				X																						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 6 3	0 1 6 5	0 1 7 2	0 1 7 5	0 2 0 4	0 2 3 5	0 2 4 2	0 2 7 5	0 1 8 1	0 1 8 2	0 1 9 1	0 1 9 2	0 2 2 2	0 2 2 3	0 2 2 5	0 2 3 2	0 2 3 3	0 2 3 4	0 2 5 2	0 2 7 1	0 2 7 2	0 2 7 4	0 2 8 1	0 2 8 3	0 2 8 4	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																						X				1
Pheochromocytoma malignant, metastatic, adrenal gland						X																				1
Squamous cell carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Zymbal's gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X						X	X	X					X			X	X		X			X	23
Mesothelioma malignant					X																					2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 300 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	7 0 2	7 0 5	7 1 3	7 1 8	7 1 9	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 3 8 4	0 2 9 1	0 3 7 3	0 3 0 2	0 3 6 1	0 3 3 2	0 3 0 3	0 3 0 4	0 3 1 1	0 3 2 3	0 3 3 4	0 3 4 2	0 3 9 5	0 3 2 4	0 3 2 5	0 3 4 5	0 3 4 3	0 3 4 4	0 3 5 1	0 3 5 5	0 3 7 2	0 4 1 1	0 4 1 2	0 4 1 5	0 4 2 1	0 4 2 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Hepatocellular adenoma																		X			X					4
Mesentery						+																				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Papilloma squamous																										1
Tooth					+																					1
Cardiovascular System																										
Blood vessel		+																								3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chemodectoma benign																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign														X					X				X			7
Bilateral, pheochromocytoma benign						X																				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma									X					X												7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma												X														1
C-cell, adenoma	X				X		X		X														X	X		11
Follicle, adenoma			X																		X					2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	
	3	3	4	5	7	9	1	2	2	3	4	6	6	7	7	7	8	8	9	9	9	9	9	0	0
	1	9	1	2	2	2	7	6	6	5	9	6	8	0	1	2	0	8	1	3	3	4	8	1	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	4	4	3	3	3	3	3	3	4	3	4	3	4	3	3	2	4	3	3	3	4	3	4	3
	2	0	2	0	7	1	2	3	4	2	9	0	7	1	5	9	9	0	3	0	9	1	6	0	8
	2	3	4	1	4	3	1	1	1	5	4	1	5	4	4	3	3	2	3	5	2	3	5	4	2
General Body System																									
Tissue NOS																						+			
Chemodectoma benign																						X			
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																					+				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X					X			X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X
Interstitial cell, adenoma		X																			X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	
Integumentary System																									
Mammary gland	M	+	+	M	+	M	+	+	M	M	M	M	+	+	M	M	+	+	M	+	+	+	+	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basosquamous tumor benign																									
Keratoacanthoma							X																		
Papilloma squamous																					X				
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrous histiocytoma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																				X					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																		X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	7 0 2	7 0 5	7 1 3	7 1 8	7 1 9	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 3 8 4	0 2 9 1	0 3 7 3	0 3 0 2	0 3 6 1	0 3 3 2	0 3 0 3	0 3 0 4	0 3 1 1	0 3 2 3	0 3 3 4	0 3 4 2	0 3 9 5	0 3 2 4	0 3 2 5	0 3 4 3	0 3 4 4	0 3 5 1	0 3 5 5	0 3 7 2	0 4 1 1	0 4 1 2	0 4 1 5	0 4 1 1	0 4 2 2	0 4 2 1	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Chemodectoma benign																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	43
Interstitial cell, adenoma	X		X					X				X														6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	35
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																X										1
Basosquamous tumor benign										X																1
Keratoacanthoma																										1
Papilloma squamous																										1
Subcutaneous tissue, fibroma				X															X							3
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	5 3 1	5 3 9	5 4 1	5 5 2	5 7 2	5 9 2	6 1 7	6 2 6	6 2 6	6 3 5	6 4 9	6 6 6	6 6 8	6 7 0	6 7 1	6 7 2	6 8 0	6 8 8	6 9 1	6 9 3	6 9 3	6 9 4	6 9 8	7 0 1	7 0 2
Carcass ID Number	0 3 2 2	0 4 0 3	0 4 2 4	0 3 0 1	0 3 7 4	0 3 1 3	0 3 2 1	0 3 3 1	0 3 4 1	0 4 2 5	0 3 9 4	0 4 0 1	0 3 7 5	0 4 1 4	0 3 5 4	0 3 9 3	0 2 9 3	0 4 0 2	0 3 3 3	0 3 0 5	0 3 9 2	0 4 1 3	0 3 6 5	0 4 0 4	0 3 8 2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma							X																		
Carcinoma, metastatic, Zymbal's gland																									
Fibrous histiocytoma, metastatic, skin																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																		+							
Zymbal's gland																		+							
Carcinoma																		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X				X	X	X		X	X	X	X				X	X	X				
Lymphoma malignant histiocytic																						X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	7 0 2	7 0 5	7 1 3	7 1 8	7 1 9	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 3 8 4	0 2 9 1	0 3 7 3	0 3 0 2	0 3 6 1	0 3 3 2	0 3 0 3	0 3 0 4	0 3 1 1	0 3 2 3	0 3 3 4	0 3 4 2	0 3 9 5	0 3 2 4	0 3 2 5	0 3 4 3	0 3 4 4	0 3 5 1	0 3 5 5	0 3 7 2	0 4 1 1	0 4 1 2	0 4 1 5	0 4 2 1	0 4 2 2	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, Zymbal's gland																		X								1
Fibrous histiocytoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland																		+								2
Carcinoma																		X								2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X			X	X			X	X	X														19
Lymphoma malignant histiocytic																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 600 ppm

Number of Days on Study	3 6 8	5 0 8	5 1 9	5 2 2	5 4 2	5 5 8	5 8 9	5 9 2	6 1 6	6 3 4	6 4 5	6 5 3	6 6 8	6 7 4	6 7 5	6 8 0	6 8 7	6 9 5	7 0 2	7 0 3	7 0 9	7 1 2	7 1 5	7 2 9	7 2 9
Carcass ID Number	0 5 4 1	0 4 5 4	0 5 1 5	0 4 5 5	0 4 5 3	0 4 7 1	0 4 3 5	0 5 3 1	0 5 3 2	0 4 8 5	0 4 9 1	0 5 3 3	0 5 1 2	0 5 4 4	0 5 2 4	0 4 3 4	0 4 7 4	0 5 6 2	0 5 6 1	0 4 7 3	0 4 4 4	0 4 5 1	0 4 4 1	0 5 1 3	0 4 3 3	0 4 4 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Adenocarcinoma																									X
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangioma																X									
Hepatocellular adenoma		X																							
Hepatocellular adenoma, multiple																									
Mesentery			+	+								+													+
Pancreas	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	A	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue										+															
Squamous cell carcinoma										X															
Tooth										+															
Gingiva, squamous cell carcinoma										X															
Cardiovascular System																									
Blood vessel														+											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									X
Bilateral, pheochromocytoma benign																						X			
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 4 4 3	0 4 8 1	0 4 9 2	0 5 0 5	0 5 2 2	0 5 6 4	0 5 6 5	0 4 8 4	0 4 9 3	0 4 9 4	0 4 9 5	0 5 2 2	0 5 0 3	0 5 0 4	0 5 0 4	0 5 1 1	0 5 2 2	0 4 6 5	0 5 3 4	0 5 3 5	0 5 4 3	0 5 4 5	0 5 5 2	0 5 5 3	0 5 5 4	0 5 5 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Adenocarcinoma																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangioma																										1
Hepatocellular adenoma																		X								2
Hepatocellular adenoma, multiple			X																							1
Mesentery				+									+			+		+								8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Squamous cell carcinoma																										1
Tooth																										1
Gingiva, squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pheochromocytoma benign										X			X										X		X		5
Bilateral, pheochromocytoma benign			X																							2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	3 6 8	5 0 8	5 1 9	5 2 2	5 4 2	5 5 8	5 8 9	5 9 2	6 1 6	6 3 4	6 4 5	6 5 3	6 6 8	6 7 4	6 7 5	6 8 0	6 8 7	6 9 5	7 0 2	7 0 3	7 0 9	7 1 2	7 1 5	7 2 9	7 2 9
Carcass ID Number	0 5 4 1	0 4 5 4	0 5 1 5	0 4 5 5	0 4 5 3	0 4 7 1	0 4 4 5	0 5 3 1	0 5 3 2	0 4 8 5	0 4 9 1	0 5 3 3	0 5 1 2	0 5 4 4	0 5 2 4	0 5 3 4	0 4 7 4	0 4 6 2	0 5 6 1	0 4 7 3	0 4 4 4	0 4 5 1	0 5 1 3	0 4 3 3	0 4 3 5
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X												X	X								X
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																	X								
C-cell, adenoma			X									X													
Follicle, adenoma																			X						
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma															X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Keratoacanthoma																									
Subcutaneous tissue, fibroma						X						X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 4 4 3	0 4 8 1	0 4 9 2	0 5 0 5	0 5 2 2	0 5 6 4	0 5 6 5	0 4 8 4	0 4 9 3	0 4 9 4	0 4 9 5	0 5 0 2	0 5 0 3	0 5 0 4	0 5 1 4	0 5 1 2	0 4 6 1	0 5 3 5	0 5 3 4	0 5 4 5	0 5 4 3	0 5 5 5	0 5 2 2	0 5 3 3	0 5 4 4	0 5 5 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X				X		X													X				9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma																										1
C-cell, adenoma				X			X						X		X				X				X			8
Follicle, adenoma																		X								2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X											X	X						3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X		43
Interstitial cell, adenoma									X													X			X	4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	M	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	M	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
Fibroadenoma																	X									1
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor benign																X										1
Keratoacanthoma																									X	1
Subcutaneous tissue, fibroma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	3	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	
	6	0	1	2	4	5	8	9	1	3	4	5	6	7	7	8	8	9	0	0	0	1	1	2	
	8	8	9	2	2	8	9	2	6	4	5	3	8	4	5	0	7	5	2	3	9	2	5	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	4	5	4	4	4	4	5	5	4	4	5	5	5	5	4	4	5	5	4	4	4	5	4	4
	4	5	1	5	5	7	4	3	3	8	9	3	1	4	2	3	7	6	6	7	4	5	1	3	3
	1	4	5	5	3	1	5	1	2	5	1	3	2	4	4	4	4	2	1	3	4	1	3	3	5
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, fibrosarcoma																									
Eye				+																				+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X			X	X	X			X														
Mesothelioma malignant																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 4 4 3	0 4 8 1	0 4 9 2	0 5 0 5	0 5 2 2	0 5 6 4	0 5 6 5	0 4 8 4	0 4 9 3	0 4 9 4	0 4 9 5	0 5 0 2	0 5 0 3	0 5 0 4	0 5 1 4	0 5 2 1	0 4 6 5	0 5 3 4	0 5 3 5	0 5 4 3	0 5 4 5	0 5 5 2	0 5 5 3	0 5 5 4	0 5 5 5	**Total Tissues/ Tumors**
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Ear													+												1
Pinna, fibrosarcoma													X												1
Eye																									2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																									1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X		X	X	X		X				X			X			X	X			X	18
Mesothelioma malignant																									1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Triamterene

	0 ppm	150 ppm	300 ppm	600 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	9/50 (18%)	11/50 (22%)	8/50 (16%)	7/49 (14%)
Adjusted rates[b]	32.6%	38.1%	29.0%	25.7%
Terminal rates[c]	7/25 (28%)	8/25 (32%)	3/19 (16%)	6/26 (23%)
First incidence (days)	659	674	668	712
Life table tests[d]	P=0.238N	P=0.403	P=0.556	P=0.359N
Logistic regression tests[d]	P=0.227N	P=0.431	P=0.469N	P=0.368N
Cochran-Armitage test[d]	P=0.270N			
Fisher exact test[d]		P=0.402	P=0.500N	P=0.410N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rates	10/50 (20%)	12/50 (24%)	8/50 (16%)	7/49 (14%)
Adjusted rates	36.4%	41.8%	29.0%	25.7%
Terminal rates	8/25 (32%)	9/25 (36%)	3/19 (16%)	6/26 (23%)
First incidence (days)	659	674	668	712
Life table tests	P=0.158N	P=0.405	P=0.561N	P=0.263N
Logistic regression tests	P=0.145N	P=0.431	P=0.368N	P=0.271N
Cochran-Armitage test	P=0.182N			
Fisher exact test		P=0.405	P=0.398N	P=0.314N
Liver: Hepatocellular Adenoma				
Overall rates	0/50 (0%)	6/50 (12%)	4/50 (8%)	3/49 (6%)
Adjusted rates	0.0%	20.9%	15.6%	9.3%
Terminal rates	0/25 (0%)	4/25 (16%)	2/19 (11%)	2/27 (7%)
First incidence (days)	-[e]	610	668	508
Life table tests	P=0.368	P=0.020	P=0.054	P=0.140
Logistic regression tests	P=0.355	P=0.021	P=0.069	P=0.108
Cochran-Armitage test	P=0.320			
Fisher exact test		P=0.013	P=0.059	P=0.117
Pancreatic Islets: Adenoma				
Overall rates	2/50 (4%)	1/50 (2%)	5/50 (10%)	1/49 (2%)
Adjusted rates	6.5%	4.0%	14.8%	2.1%
Terminal rates	1/25 (4%)	1/25 (4%)	1/19 (5%)	0/27 (0%)
First incidence (days)	624	729 (T)	572	522
Life table tests	P=0.490N	P=0.494N	P=0.221	P=0.469N
Logistic regression tests	P=0.565N	P=0.478N	P=0.216	P=0.551N
Cochran-Armitage test	P=0.532N			
Fisher exact test		P=0.500N	P=0.218	P=0.508N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	8/50 (16%)	6/50 (12%)	7/49 (14%)	9/49 (18%)
Adjusted rates	26.6%	20.2%	22.1%	28.9%
Terminal rates	5/25 (20%)	3/25 (12%)	2/19 (11%)	6/26 (23%)
First incidence (days)	539	653	626	522
Life table tests	P=0.409	P=0.378N	P=0.562N	P=0.551
Logistic regression tests	P=0.393	P=0.336N	P=0.468N	P=0.541
Cochran-Armitage test	P=0.350			
Fisher exact test		P=0.387N	P=0.517N	P=0.482

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

	0 ppm	150 ppm	300 ppm	600 ppm
Preputial Gland: Adenoma				
Overall rates	1/50 (2%)	2/50 (4%)	4/50 (8%)	3/49 (6%)
Adjusted rates	3.3%	6.1%	11.3%	11.1%
Terminal rates	0/25 (0%)	1/25 (4%)	1/19 (5%)	3/27 (11%)
First incidence (days)	709	610	531	729 (T)
Life table tests	P=0.248	P=0.515	P=0.181	P=0.327
Logistic regression tests	P=0.212	P=0.517	P=0.150	P=0.319
Cochran-Armitage test	P=0.213			
Fisher exact test		P=0.500	P=0.181	P=0.301
Skin: Keratoacanthoma, Basal Cell Adenoma, or Carcinoma				
Overall rates	3/50 (6%)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rates	10.5%	18.2%	10.4%	3.7%
Terminal rates	2/25 (8%)	4/25 (16%)	1/19 (5%)	1/27 (4%)
First incidence (days)	645	652	617	729 (T)
Life table tests	P=0.147N	P=0.366	P=0.613	P=0.279N
Logistic regression tests	P=0.137N	P=0.389	P=0.633N	P=0.277N
Cochran-Armitage test	P=0.157N			
Fisher exact test		P=0.357	P=0.661N	P=0.309N
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	1/50 (2%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rates	3.3%	6.2%	12.4%	4.7%
Terminal rates	0/25 (0%)	1/25 (4%)	1/19 (5%)	0/27 (0%)
First incidence (days)	709	611	691	558
Life table tests	P=0.423	P=0.510	P=0.245	P=0.523
Logistic regression tests	P=0.409	P=0.517	P=0.313	P=0.482
Cochran-Armitage test	P=0.404			
Fisher exact test		P=0.500	P=0.309	P=0.500
Testes: Adenoma				
Overall rates	42/50 (84%)	47/50 (94%)	49/50 (98%)	47/49 (96%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	25/25 (100%)	25/25 (100%)	19/19 (100%)	27/27 (100%)
First incidence (days)	488	539	531	508
Life table tests	P=0.431	P=0.308	P=0.038	P=0.453
Logistic regression tests	P=0.212	P=0.564	P=0.425	P=0.390
Cochran-Armitage test	P=0.026			
Fisher exact test		P=0.100	P=0.015	P=0.049
Thyroid Gland (C-cell): Adenoma				
Overall rates	10/50 (20%)	7/49 (14%)	12/50 (24%)	9/49 (18%)
Adjusted rates	32.1%	21.7%	41.5%	27.9%
Terminal rates	6/25 (24%)	4/25 (16%)	5/19 (26%)	6/27 (22%)
First incidence (days)	488	610	552	519
Life table tests	P=0.512N	P=0.282N	P=0.282	P=0.424N
Logistic regression tests	P=0.539N	P=0.282N	P=0.464	P=0.465N
Cochran-Armitage test	P=0.510			
Fisher exact test		P=0.314N	P=0.405	P=0.520N

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

	0 ppm	150 ppm	300 ppm	600 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rates	22/50 (44%)	23/50 (46%)	19/50 (38%)	18/50 (36%)
Adjusted rates	57.6%	55.9%	50.0%	49.3%
Terminal rates	10/25 (40%)	9/25 (36%)	4/19 (21%)	11/27 (41%)
First incidence (days)	508	539	541	368
Life table tests	P=0.163N	P=0.552	P=0.463N	P=0.208N
Logistic regression tests	P=0.176N	P=0.567	P=0.279N	P=0.240N
Cochran-Armitage test	P=0.178N			
Fisher exact test		P=0.500	P=0.342N	P=0.270N
All Organs: Benign Neoplasms				
Overall rates	44/50 (88%)	48/50 (96%)	50/50 (100%)	48/50 (96%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	25/25 (100%)	25/25 (100%)	19/19 (100%)	27/27 (100%)
First incidence (days)	484	539	531	508
Life table tests	P=0.486	P=0.378	P=0.061	P=0.529
Logistic regression tests	P=0.620	P=0.792	P=0.676	P=0.688
Cochran-Armitage test	P=0.077			
Fisher exact test		P=0.134	P=0.013	P=0.134
All Organs: Malignant Neoplasms				
Overall rates	26/50 (52%)	29/50 (58%)	24/50 (48%)	23/50 (46%)
Adjusted rates	67.0%	66.9%	59.0%	59.0%
Terminal rates	13/25 (52%)	12/25 (48%)	5/19 (26%)	13/27 (48%)
First incidence (days)	508	366	541	368
Life table tests	P=0.188N	P=0.434	P=0.560N	P=0.256N
Logistic regression tests	P=0.202N	P=0.418	P=0.321N	P=0.292N
Cochran-Armitage test	P=0.208N			
Fisher exact test		P=0.344	P=0.421N	P=0.345N
All Organs: Benign or Malignant Neoplasms				
Overall rates	45/50 (90%)	49/50 (98%)	50/50 (100%)	50/50 (100%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	25/25 (100%)	25/25 (100%)	19/19 (100%)	27/27 (100%)
First incidence (days)	484	366	531	368
Life table tests	P=0.437	P=0.386	P=0.084	P=0.475
Logistic regression tests	P=0.138	P=0.366	P=0.638	P=0.266
Cochran-Armitage test	P=0.009			
Fisher exact test		P=0.102	P=0.028	P=0.028

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

TABLE A4
Historical Incidence of Liver Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratory			
2,4-Dichlorophenol	4/50	3/50	5/50
5,5-Diphenylhydantoin	0/50	0/50	0/50
Ethylene thiourea	0/50	0/50	0/50
Polybrominated biphenyls (Firemaster FF-1®)	1/50	0/50	1/50
Overall Historical Incidence			
Total	19/799 (2.4%)	7/799 (0.9%)	24/799 (3.0%)
Standard deviation	2.9%	1.8%	3.4%
Range	0%-8%	0%-6%	0%-10%

[a] Data as of 3 April 1991

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene[a]

	0 ppm	150 ppm	300 ppm	600 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
2-Year study				
Early deaths				
Moribund	18	20	18	17
Natural deaths	4	5	13	6
Accidental deaths	3			
Survivors				
Terminal sacrifice	25	25	19	27
Animals examined microscopically	70	70	70	70
3-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)			(10)
Parasite metazoan	2 (20%)			1 (10%)
Liver	(10)			(10)
Periportal, inflammation, chronic	2 (20%)			
Pancreas	(10)			(10)
Acinus, atrophy				1 (10%)
Salivary glands	(10)			(10)
Acinus, parotid gland, cytoplasmic alteration, focal				1 (10%)
Acinus, parotid gland, vacuolization cytoplasmic, focal				1 (10%)
Stomach, forestomach	(10)		(1)	(10)
Inflammation, focal, chronic	1 (10%)			
Inflammation, subacute, focal	1 (10%)			
Epithelium, acanthosis, focal	2 (20%)			
Epithelium, hyperkeratosis, focal	2 (20%)		1 (100%)	
Stomach, glandular	(10)			(10)
Inflammation, subacute, focal	1 (10%)			
Mucosa, hyperplasia, focal	1 (10%)			
Cardiovascular System				
Blood vessel				(1)
Aorta, inflammation, focal, chronic				1 (100%)
Heart	(10)			(10)
Myocardium, inflammation, multifocal, chronic	9 (90%)			3 (30%)
Endocrine System				
Adrenal gland, cortex	(10)			(10)
Hyperplasia, nodular	1 (10%)			
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
3-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(10)			(10)
Inflammation, chronic				1 (10%)
Testes	(10)			(10)
Right, interstitial cell, hyperplasia				1 (10%)
Right, seminiferous tubule, atrophy				1 (10%)
Hematopoietic System				
Lymph node, mandibular	(10)			(10)
Infiltration cellular, histiocyte	2 (20%)			
Lymph node, mesenteric	(10)			(9)
Infiltration cellular, histiocyte	7 (70%)			5 (56%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)			(10)
Alveolus, hemorrhage, multifocal				1 (10%)
Artery, mineralization, focal				1 (10%)
Bronchus, foreign body, single	1 (10%)			
Bronchus, epithelium, hyperplasia, multifocal	1 (10%)			
Interstitium, inflammation, focal, chronic				1 (10%)
Peribronchial, inflammation, focal, chronic				1 (10%)
Peribronchiolar, inflammation, multifocal, chronic	4 (40%)			
Nose	(10)			(10)
Sinus, inflammation, chronic active	1 (10%)			
Special Senses System				
Harderian gland	(2)			(1)
Inflammation, multifocal, chronic	2 (100%)			1 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
3-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)			(10)
Interstitial tissue, inflammation, multifocal, chronic	4 (40%)			
Urinary bladder	(10)			(10)
Lumen, hemorrhage	2 (20%)			3 (30%)
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(1)		(10)
Parasite metazoan	1 (10%)			1 (10%)
Liver	(10)	(6)	(5)	(10)
Basophilic focus		3 (50%)	2 (40%)	4 (40%)
Clear cell focus		1 (17%)	1 (20%)	4 (40%)
Degeneration, cystic		1 (17%)		
Eosinophilic focus				1 (10%)
Hepatodiaphragmatic nodule		2 (33%)	1 (20%)	
Inflammation, granulomatous	3 (30%)		2 (40%)	
Mixed cell focus			1 (20%)	2 (20%)
Necrosis, coagulative		1 (17%)		
Mesentery		(1)	(2)	
Inflammation, chronic				2 (100%)
Pancreas	(10)	(1)		(10)
Acinus, atrophy	2 (20%)			1 (10%)
Duct, ectasia				1 (10%)
Stomach, glandular	(10)	(1)		(10)
Mucosa, mineralization	1 (10%)			
Cardiovascular System				
Blood vessel				(1)
Aorta, inflammation, chronic				1 (100%)
Heart	(10)	(10)	(10)	(10)
Coronary artery, inflammation, chronic		1 (10%)		
Myocardium, degeneration, multifocal	6 (60%)	7 (70%)	6 (60%)	10 (100%)
Endocrine System				
Adrenal gland, cortex	(10)	(1)		(10)
Angiectasis		1 (100%)		
Pituitary gland	(10)	(2)		(10)
Pars distalis, cyst				1 (10%)
Pars distalis, hyperplasia, nodular				1 (10%)
Thyroid gland	(10)	(1)		(10)
C-cell, hyperplasia	10 (100%)			8 (80%)
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(10)	(1)	(1)	(8)
Hyperplasia		1 (100%)		
Inflammation, chronic	5 (50%)	1 (100%)		5 (63%)
Prostate	(10)	(1)		(10)
Inflammation, chronic	5 (50%)			1 (10%)
Testes	(10)	(1)	(6)	(10)
Seminiferous tubule, hypoplasia	1 (10%)			
Hematopoietic System				
Lymph node	(10)	(1)		(10)
Mediastinal, pigmentation, hemosiderin	1 (10%)			
Lymph node, mandibular	(10)	(1)		(10)
Hyperplasia, lymphoid	1 (10%)			
Sinus, ectasia				2 (20%)
Lymph node, mesenteric	(10)	(1)		(10)
Infiltration cellular, mononuclear cell		1 (100%)		
Spleen	(10)	(1)		(10)
Fibrosis				1 (10%)
Hematopoietic cell proliferation		1 (100%)		
Thymus	(10)	(1)		(10)
Atrophy		1 (100%)		
Arteriole, giant cell				1 (10%)
Integumentary System				
None				
Musculoskeletal System				
Bone	(10)	(1)		(10)
Femur, osteopetrosis				1 (10%)
Nervous System				
None				
Respiratory System				
Lung	(10)	(1)		(10)
Interstitium, inflammation, chronic				1 (10%)
Special Senses System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(1)	(2)	(10)
Cyst			1 (50%)	
Nephropathy, multifocal	10 (100%)	1 (100%)	2 (100%)	10 (100%)
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Dilatation			1 (2%)	
Intestine large, cecum	(49)	(48)	(49)	(47)
Edema		1 (2%)		
Inflammation, chronic	1 (2%)			
Parasite metazoan			2 (4%)	
Ulcer	1 (2%)			1 (2%)
Intestine large, colon	(50)	(50)	(48)	(48)
Edema				1 (2%)
Mineralization	1 (2%)			
Parasite metazoan		1 (2%)	5 (10%)	
Intestine large, rectum	(49)	(47)	(49)	(47)
Edema	1 (2%)	1 (2%)		
Mineralization	1 (2%)			
Parasite metazoan	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Intestine small, duodenum	(50)	(49)	(50)	(48)
Ulcer		1 (2%)	1 (2%)	
Intestine small, ileum	(49)	(49)	(48)	(46)
Mineralization	1 (2%)			
Intestine small, jejunum	(48)	(49)	(49)	(47)
Ulcer		1 (2%)		
Liver	(50)	(50)	(50)	(49)
Angiectasis, focal		2 (4%)		1 (2%)
Bacterium	1 (2%)		1 (2%)	
Basophilic focus	16 (32%)	10 (20%)	3 (6%)	19 (39%)
Clear cell focus	4 (8%)	5 (10%)	4 (8%)	7 (14%)
Degeneration, cystic	10 (20%)	6 (12%)	10 (20%)	8 (16%)
Eosinophilic focus	2 (4%)	3 (6%)	2 (4%)	8 (16%)
Fatty change		2 (4%)		
Fibrosis, focal				1 (2%)
Hepatodiaphragmatic nodule		2 (4%)	3 (6%)	3 (6%)
Hyperplasia		3 (6%)	5 (10%)	10 (20%)
Inflammation, granulomatous	4 (8%)		3 (6%)	2 (4%)
Mixed cell focus		6 (12%)	8 (16%)	12 (24%)
Necrosis, coagulative	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Sinusoid, congestion		1 (2%)		
Mesentery	(4)	(4)	(3)	(8)
Inflammation, chronic	1 (25%)			
Pigmentation, hemosiderin				1 (13%)
Fat, necrosis	3 (75%)	2 (50%)	3 (100%)	5 (63%)
Pancreas	(50)	(50)	(50)	(48)
Ectopic tissue			1 (2%)	1 (2%)
Acinus, atrophy	14 (28%)	19 (38%)	17 (34%)	15 (31%)
Artery, inflammation, chronic	14 (28%)	6 (12%)	11 (22%)	12 (25%)
Salivary glands	(50)	(49)	(50)	(50)
Periductular, fibrosis			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(49)
Acanthosis			3 (6%)	4 (8%)
Hyperkeratosis			3 (6%)	4 (8%)
Inflammation, chronic		2 (4%)	1 (2%)	2 (4%)
Mineralization	2 (4%)		1 (2%)	
Ulcer	2 (4%)	6 (12%)	2 (4%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)	(48)
Inflammation, chronic	4 (8%)		1 (2%)	
Ulcer	8 (16%)	6 (12%)	4 (8%)	3 (6%)
Mucosa, mineralization	6 (12%)	3 (6%)	7 (14%)	4 (8%)
Tongue	(1)		(1)	(1)
Acanthosis	1 (100%)			
Hyperkeratosis	1 (100%)			
Tooth	(1)	(1)	(1)	
Peridontal tissue, inflammation, chronic		1 (100%)		
Pulp, inflammation, suppurative		1 (100%)		
Cardiovascular System				
Blood vessel	(1)	(3)	(3)	(1)
Aorta, mineralization	1 (100%)	3 (100%)	3 (100%)	1 (100%)
Heart	(50)	(50)	(50)	(50)
Atrium, dilatation	1 (2%)			
Atrium, thrombus	1 (2%)		1 (2%)	
Myocardium, degeneration	34 (68%)	44 (88%)	42 (84%)	36 (72%)
Myocardium, inflammation, suppurative	1 (2%)			
Myocardium, mineralization	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Valve, inflammation, chronic active	1 (2%)			
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Ectopic tissue		1 (2%)		
Hemorrhage	1 (2%)			
Hyperplasia	8 (16%)	14 (28%)	18 (36%)	14 (28%)
Adrenal gland, medulla	(50)	(50)	(50)	(49)
Hyperplasia	12 (24%)	14 (28%)	16 (32%)	6 (12%)
Infarct	1 (2%)	1 (2%)		
Parathyroid gland	(46)	(46)	(50)	(49)
Hyperplasia	4 (9%)	3 (7%)	11 (22%)	8 (16%)
Pituitary gland	(50)	(50)	(49)	(49)
Abscess			1 (2%)	
Pars distalis, cyst		2 (4%)		
Pars distalis, hyperplasia	10 (20%)	5 (10%)	7 (14%)	6 (12%)
Pars intermedia, cyst		1 (2%)		
Thyroid gland	(50)	(49)	(50)	(49)
C-cell, hyperplasia	33 (66%)	32 (65%)	28 (56%)	36 (73%)
Follicle, dilatation	3 (6%)	2 (4%)		1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(49)
Granuloma sperm		1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)	
Inflammation, suppurative		1 (2%)		
Preputial gland	(50)	(50)	(50)	(49)
Hyperplasia		2 (4%)	3 (6%)	
Inflammation, chronic	39 (78%)	38 (76%)	40 (80%)	41 (84%)
Duct, dilatation		1 (2%)		
Prostate	(48)	(48)	(50)	(49)
Cyst			1 (2%)	
Inflammation, suppurative	23 (48%)	17 (35%)	13 (26%)	22 (45%)
Seminal vesicle	(49)	(48)	(50)	(49)
Inflammation, suppurative	1 (2%)	2 (4%)		
Testes	(50)	(50)	(50)	(49)
Necrosis, coagulative	1 (2%)			
Interstitial cell, hyperplasia	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Seminiferous tubule, atrophy	12 (24%)	15 (30%)	12 (24%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia, histiocytic				1 (2%)
Lymph node	(50)	(50)	(50)	(50)
Mediastinal, pigmentation, hemosiderin			1 (2%)	
Mediastinal, sinus, ectasia	1 (2%)	1 (2%)		1 (2%)
Renal, ectasia			2 (4%)	
Renal, sinus, ectasia		1 (2%)		
Lymph node, mandibular	(50)	(49)	(50)	(50)
Hyperplasia, plasma cell	1 (2%)	2 (4%)	1 (2%)	
Sinus, ectasia		1 (2%)		
Lymph node, mesenteric	(48)	(47)	(47)	(48)
Hyperplasia, plasma cell		1 (2%)		
Infiltration cellular, histiocyte			1 (2%)	
Sinus, ectasia		3 (6%)	1 (2%)	1 (2%)
Spleen	(50)	(50)	(50)	(50)
Depletion lymphoid	1 (2%)			
Fibrosis	4 (8%)	6 (12%)	4 (8%)	7 (14%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Infarct	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Inflammation, granulomatous			1 (2%)	
Thymus	(42)	(46)	(46)	(41)
Ectopic parathyroid gland		1 (2%)		
Ectopic thyroid		1 (2%)		
Inflammation, chronic		1 (2%)		
Artery, mineralization			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(36)	(37)	(35)	(42)
Hyperplasia, cystic	17 (47%)	5 (14%)	5 (14%)	8 (19%)
Skin	(49)	(50)	(50)	(49)
Abscess	1 (2%)	2 (4%)	1 (2%)	
Cyst epithelial inclusion		3 (6%)		1 (2%)
Hemorrhage				1 (2%)
Ulcer		1 (2%)	1 (2%)	
Epidermis, acanthosis		1 (2%)		1 (2%)
Epidermis, hyperkeratosis		1 (2%)		1 (2%)
Hair follicle, hyperkeratosis		1 (2%)		
Sebaceous gland, hyperplasia		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis				1 (2%)
Femur, fibrous osteodystrophy	4 (8%)	3 (6%)	5 (10%)	2 (4%)
Synovial tissue, inflammation, suppurative	1 (2%)			1 (2%)
Tarsal, fracture healed				1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Gliosis	1 (2%)			
Hydrocephalus				1 (2%)
Infarct	3 (6%)	1 (2%)	6 (12%)	2 (4%)
Inflammation, suppurative				1 (2%)
Hypothalamus, compression	4 (8%)	4 (8%)	2 (4%)	3 (6%)
Spinal cord		(1)		
Lumbar, atrophy		1 (100%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Inflammation, granulomatous				1 (2%)
Alveolus, inflammation, subacute			1 (2%)	2 (4%)
Interstitium, inflammation, chronic	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Interstitium, mineralization	2 (4%)	2 (4%)	2 (4%)	
Nose	(50)	(50)	(50)	(50)
Fungus	1 (2%)			1 (2%)
Nares, foreign body			1 (2%)	
Nares, inflammation, suppurative	3 (6%)		2 (4%)	2 (4%)
Trachea	(50)	(50)	(50)	(50)
Inflammation, subacute			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Special Senses System				
Ear	(2)			(1)
Middle ear, abscess	1 (50%)			
Eye	(3)	(2)	(1)	(2)
Phthisis bulbi	1 (33%)			
Cornea, inflammation, necrotizing			1 (100%)	
Cornea, mineralization	1 (33%)			1 (50%)
Lens, cataract	1 (33%)	1 (50%)		1 (50%)
Sclera, mineralization		1 (50%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hydronephrosis	1 (2%)			
Inflammation, suppurative	1 (2%)			
Nephropathy	47 (94%)	49 (98%)	50 (100%)	49 (98%)
Urinary bladder	(49)	(47)	(50)	(47)
Ectasia			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, necrotizing	1 (2%)			
Inflammation, suppurative	1 (2%)			

[a] Number of animals examined microscopically at site and number of animals with lesion

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF TRIAMTERENE

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Triamterene[a]

	0 ppm	150 ppm	300 ppm	600 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation	10	10	10	10
2-Year study				
Early deaths				
Moribund	17	11	12	18
Natural deaths	4	5	4	3
Survivors				
Terminal sacrifice	29	34	34	29
Animals examined microscopically	70	70	70	70
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(3)	(2)	(10)
Pars distalis, adenoma	1 (10%)	1 (33%)		
General Body System				
None				
Genital System				
Uterus	(10)	(1)		(10)
Polyp stromal	1 (10%)	1 (100%)		
Hematopoietic System				
None				
Integumentary System				
Mammary gland	(9)			(9)
Fibroadenoma	1 (11%)			
Musculoskeletal System				
None				
Nervous System				
None				

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

	0 ppm	150 ppm	300 ppm	600 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
Ear				(1)
Pinna, schwannoma malignant				1 (100%)
Urinary System				
None				
2-Year Study				
Alimentary System				
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma				1 (2%)
Hepatocellular adenoma, multiple				1 (2%)
Mesentery	(3)	(2)	(3)	(1)
Pancreas	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma	2 (4%)		1 (2%)	
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)		
Pheochromocytoma benign		1 (2%)		1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)		2 (4%)	1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	21 (42%)	20 (40%)	25 (50%)	28 (56%)
Pars distalis, carcinoma		1 (2%)		
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	5 (10%)	11 (22%)	5 (10%)	10 (20%)
C-cell, adenoma, multiple			1 (2%)	
C-cell, carcinoma			1 (2%)	
Follicle, adenocarcinoma			1 (2%)	
Follicle, adenoma			1 (2%)	1 (2%)
General Body System				
Tissue NOS	(1)			
Chemodectoma malignant	1 (100%)			

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

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Genital System				
Clitoral gland	(42)	(49)	(50)	(48)
Adenoma	3 (7%)	3 (6%)	4 (8%)	2 (4%)
Carcinoma	1 (2%)			
Bilateral, adenoma				1 (2%)
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor malignant	1 (2%)			
Granulosa cell tumor benign				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Leiomyoma				2 (4%)
Polyp stromal	4 (8%)	6 (12%)	5 (10%)	5 (10%)
Cervix, squamous cell carcinoma	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(50)	(50)	(50)	(50)
Lymph node, mandibular	(48)	(50)	(49)	(50)
Lymph node, mesenteric	(48)	(48)	(50)	(48)
Spleen	(50)	(50)	(50)	(50)
Thymus	(44)	(46)	(46)	(45)
Mediastinum, schwannoma malignant	1 (2%)			
Integumentary System				
Mammary gland	(48)	(49)	(49)	(47)
Adenoma	4 (8%)		4 (8%)	1 (2%)
Fibroadenoma	15 (31%)	11 (22%)	14 (29%)	12 (26%)
Fibroadenoma, multiple	4 (8%)	5 (10%)	2 (4%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Keratoacanthoma				1 (2%)
Subcutaneous tissue, fibroma		2 (4%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Subcutaneous tissue, neurofibrosarcoma				1 (2%)
Musculoskeletal System				
Skeletal muscle	(1)			
Sarcoma	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Peripheral nerve	(1)		(1)	
Sciatic, schwannoma malignant	1 (100%)			

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

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, thyroid gland			1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)		1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Granulosa cell tumor malignant, metastatic, ovary	1 (2%)			
Mediastinum, schwannoma malignant	1 (2%)			
Special Senses System				
Ear				(1)
Pinna, fibroma			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(49)	(49)	(50)	(50)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Leukemia mononuclear	8 (16%)	11 (22%)	7 (14%)	9 (18%)
Mesothelioma malignant	1 (2%)			
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	3	2		1
2-Year study	46	43	42	41
Total primary neoplasms				
15-Month interim evaluation	3	2		1
2-Year study	81	75	74	80
Total animals with benign neoplasms				
15-Month interim evaluation	3	2		
2-Year study	40	37	40	37
Total benign neoplasms				
15-Month interim evaluation	3	2		
2-Year study	62	62	65	70
Total animals with malignant neoplasms				
15-Month interim evaluation				1
2-Year study	16	13	9	9
Total malignant neoplasms				
15-Month interim evaluation				1
2-Year study	19	13	9	10
Total animals with metastatic neoplasms				
2-Year study	1		2	
Total metastatic neoplasms				
2-Year study	1		2	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were found at the 3-month interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 0 ppm

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 6 1 2	0 6 2 2	0 6 2 3	0 6 2 4	0 6 3 3	0 6 4 1	0 6 4 3	0 6 4 4	0 6 5 4	0 6 6 1	0 6 6 2	0 6 6 5	0 6 7 1	0 6 7 2	0 6 8 1	0 5 8 3	0 5 9 1	0 6 7 4	0 6 9 2	0 6 9 3	0 6 9 4	0 6 9 5	0 7 0 1	0 7 0 4	0 7 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+																	3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X		X																						2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X				X		X	X	X		X		X	X			X	X		X		21
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X	X										X	X						X				5
General Body System																										
Tissue NOS																										1
Chemodectoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	4 5 5 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 5 3 5 7 7 9 6 7 7 7 7 8 9 0 0 0 0 0 0 1 2 2 2 2 2 1 4 4 1 3 6 0 1 3 6 6 0 8 4 4 4 5 7 8 5 5 9 9 9 9
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 6 6 7 6 6 6 5 6 5 6 6 6 6 5 6 6 6 5 5 6 6 5 5 5 6 5 2 0 3 7 0 7 5 9 2 6 8 3 8 4 5 1 8 7 3 1 8 8 9 0 3 1 2 2 5 5 5 5 2 5 4 4 4 2 2 2 3 1 2 5 5 4 5 4 1
Genital System	
Clitoral gland	+ + + + + M + M M M M + + + + + + + + + + + + + +
Adenoma	X
Carcinoma	X
Ovary	+ +
Granulosa cell tumor malignant	
Uterus	+ +
Polyp stromal	X X X
Cervix, squamous cell carcinoma	
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, mandibular	+ + + + + + + + + + + + + M + + + + + + + + + + M +
Lymph node, mesenteric	+ +
Spleen	+ +
Thymus	+ + + + M + + + + + + + + + + + + M + + M + + + M
Mediastinum, schwannoma malignant	X
Integumentary System	
Mammary gland	+ + + + + + + + + + + + + + + + + M + + + + + + + +
Adenoma	X X X X
Fibroadenoma	X X X X X X X X
Fibroadenoma, multiple	X X
Skin	+ +
Subcutaneous tissue, fibrosarcoma	
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Sarcoma	X
Nervous System	
Brain	+ +
Peripheral nerve	+
Sciatic, schwannoma malignant	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 6 1 2	0 6 2 2	0 6 2 3	0 6 2 4	0 6 3 3	0 6 4 1	0 6 4 3	0 6 4 4	0 6 4 4	0 6 5 4	0 6 6 1	0 6 6 2	0 6 6 5	0 6 7 1	0 6 7 2	0 6 8 1	0 6 8 3	0 5 9 1	0 5 9 4	0 6 7 2	0 6 9 2	0 6 9 3	0 6 9 4	0 6 9 5	0 7 0 1	0 7 0 4	0 7 0 5	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	42
Adenoma										X										X							3
Carcinoma																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant															X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal												X															4
Cervix, squamous cell carcinoma															X												1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Mediastinum, schwannoma malignant																											1
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																						X					4
Fibroadenoma			X				X						X				X				X				X	X	15
Fibroadenoma, multiple																		X	X								4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma							X																				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											1
Sarcoma																											1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																											1
Sciatic, schwannoma malignant																											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	4	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	
	5	3	5	7	7	9	6	7	7	7	7	8	9	0	0	0	0	0	0	1	2	2	2	2	2	
	1	4	4	1	3	6	0	1	3	6	6	0	8	4	4	4	5	7	8	5	5	9	9	9	9	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	6	7	6	6	6	5	6	5	6	6	6	6	5	6	6	6	5	5	6	6	5	5	5	6	
	5	2	0	3	7	0	7	5	9	2	6	8	3	8	4	5	1	8	7	3	1	8	8	9	0	
	3	1	2	2	5	5	5	5	2	5	4	4	4	2	2	2	3	1	2	5	5	4	5	4	1	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																										
Granulosa cell tumor malignant, metastatic, ovary																										
Mediastinum, schwannoma malignant			X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye											+															
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear		X					X	X				X					X	X	X						
Mesothelioma malignant																					X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 6 1 2	0 6 2 2	0 6 2 3	0 6 2 4	0 6 3 3	0 6 4 1	0 6 4 3	0 6 4 4	0 6 5 4	0 6 6 1	0 6 6 2	0 6 6 5	0 6 7 1	0 6 7 2	0 6 8 1	0 5 8 3	0 5 9 1	0 6 7 4	0 6 9 2	0 6 9 3	0 6 9 4	0 6 9 5	0 7 0 1	0 7 0 4	0 7 0 5	**Total Tissues/ Tumors**
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X														1
Granulosa cell tumor malignant, metastatic, ovary														X											1
Mediastinum, schwannoma malignant																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Eye																					+				2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X																			8
Mesothelioma malignant																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 150 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 6 2	0 7 6 3	0 7 7 1	0 7 7 2	0 7 8 2	0 7 8 4	0 7 8 5	0 7 9 1	0 7 9 2	0 7 9 4	0 8 0 1	0 8 0 2	0 8 0 3	0 8 0 4	0 7 2 5	0 7 7 4	0 8 1 3	0 8 1 5	0 8 2 1	0 8 2 4	0 8 2 5	0 8 3 4	0 8 4 1	0 8 4 2	0 8 4 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+																			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																				X						1
Pheochromocytoma benign											X															1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X		X	X			X					X	X			X		X			X	20
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X					X				X						X		X				X				11
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	4 7 6	5 2 2	5 9 2	6 0 0	6 1 1	6 4 3	6 6 2	6 6 6	6 7 6	7 0 0	7 0 1	7 0 8	7 0 8	7 1 5	7 1 5	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 7 4 1	0 8 3 1	0 7 6 4	0 8 3 5	0 7 2 2	0 8 2 3	0 7 8 1	0 7 2 3	0 7 9 5	0 8 3 2	0 7 3 2	0 7 3 1	0 8 1 2	0 7 6 5	0 7 7 3	0 7 5 5	0 7 1 1	0 7 1 4	0 7 1 5	0 7 2 1	0 7 2 4	0 7 5 1	0 7 5 2	0 7 5 3	0 7 6 1
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal														X											
Vagina					+																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							X							X											X
Fibroadenoma, multiple												X							X		X	X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Lacrimal gland																		+							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 6 2	0 7 6 3	0 7 7 1	0 7 7 2	0 7 8 2	0 7 8 4	0 7 8 5	0 7 9 1	0 7 9 2	0 7 9 4	0 7 8 1	0 8 0 2	0 8 0 3	0 8 0 4	0 7 2 5	0 7 7 4	0 8 1 3	0 8 1 5	0 8 2 1	0 8 2 4	0 8 2 5	0 8 3 4	0 8 4 1	0 8 4 2	0 8 4 4	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X														X								3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X					X	X						X			X								6
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Fibroadenoma			X	X			X					X		X	X	X			X							11
Fibroadenoma, multiple																								X		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																			X							2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																					2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																1
Lacrimal gland																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1		
Carcass ID Number	0 7 6 2	0 7 6 3	0 7 7 1	0 7 7 2	0 7 8 2	0 7 8 4	0 7 8 5	0 7 9 1	0 7 9 2	0 7 9 4	0 7 8 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 0 5	0 7 2 5	0 7 7 4	0 8 1 3	0 8 1 5	0 8 2 1	0 8 2 4	0 8 2 5	0 8 3 4	0 8 4 1	0 8 4 2	0 8 4 4	**Total Tissues/ Tumors**
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear		X	X	X		X	X	X		X			X			X									X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 150 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 6 2	0 7 6 3	0 7 7 1	0 7 7 2	0 7 8 2	0 7 8 4	0 7 8 5	0 7 9 1	0 7 9 2	0 7 9 4	0 7 9 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 0 5	0 7 2 4	0 7 7 5	0 8 1 3	0 8 1 5	0 8 2 1	0 8 2 4	0 8 2 5	0 8 3 4	0 8 4 1	0 8 4 2	0 8 4 4	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X															11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 300 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 9 3	0 9 0 5	0 9 1 1	0 9 1 3	0 9 1 5	0 9 2 3	0 9 3 3	0 9 3 4	0 9 3 5	0 9 4 1	0 9 4 5	0 9 5 1	0 9 5 2	0 8 5 5	0 9 5 5	0 9 6 1	0 9 6 4	0 9 6 5	0 9 7 1	0 9 7 4	0 9 8 1	0 9 8 2	0 9 8 3	0 9 8 4	0 9 8 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																		+						+		3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																				+						1
Tooth																							+			2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X														X					2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X			X	X	X	X	X			X	X				X	X		X	X		25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X		X													5
C-cell, adenoma, multiple																				X						1
C-cell, carcinoma										X																1
Follicle, adenocarcinoma																										1
Follicle, adenoma																X										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	378	383	397	619	628	635	652	662	680	682	689	699	696	704	707	723	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	00975	00931	00811	00855	00992	00910	00883	00874	00972	00925	00993	00973	00972	00943	00863	00901	00885	00553	00664	00771	00833	00755	00888	00814	00844	00885
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X												X										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																X										
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X							X											
Fibroadenoma		X					X							X											X	
Fibroadenoma, multiple																	X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve															+											
Spinal cord															+											
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, thyroid gland																				X						
Carcinoma, metastatic, thyroid gland																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 9 3	0 9 0 5	0 9 1 1	0 9 1 3	0 9 1 5	0 9 2 3	0 9 3 3	0 9 3 4	0 9 3 5	0 9 4 1	0 9 4 5	0 9 5 1	0 9 5 2	0 8 5 5	0 9 5 5	0 9 6 1	0 9 6 4	0 9 6 5	0 9 7 1	0 9 7 4	0 9 8 1	0 9 8 2	0 9 8 3	0 9 8 4	0 9 9 5	**Total Tissues/ Tumors**
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X														X								4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X					X							X					X	5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adenoma												X			X										4
Fibroadenoma	X	X		X	X		X	X		X				X	X					X					14
Fibroadenoma, multiple						X																			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																									1
Spinal cord																									1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, thyroid gland																									1
Carcinoma, metastatic, thyroid gland										X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	3 7 8	3 8 3	3 9 7	6 1 9	6 2 8	6 3 5	6 5 2	6 6 2	6 8 0	6 8 2	6 8 9	6 8 9	6 9 6	7 0 4	7 0 7	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 9 7 5	0 9 3 1	0 8 9 1	0 8 6 5	0 9 1 2	0 9 0 2	0 8 8 3	0 8 7 4	0 9 7 2	0 9 7 2	0 9 2 5	0 9 5 3	0 9 7 3	0 9 2 2	0 9 4 3	0 8 6 3	0 9 0 1	0 8 5 1	0 8 5 3	0 8 6 4	0 8 7 1	0 8 7 3	0 8 7 5	0 8 8 1	0 8 8 4	0 8 8 5
Special Senses System																										
Ear																										
Pinna, fibroma																										
Eye																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X				X	X			X			X										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 300 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 9 3	0 9 0 5	0 9 1 1	0 9 1 3	0 9 1 5	0 9 2 3	0 9 3 3	0 9 3 4	0 9 3 5	0 9 4 1	0 9 4 5	0 9 5 1	0 9 5 2	0 9 5 5	0 8 5 5	0 9 5 5	0 9 6 1	0 9 6 4	0 9 6 5	0 9 7 1	0 9 7 4	0 9 8 1	0 9 8 2	0 9 8 3	0 9 8 4	0 9 8 5	**Total Tissues/ Tumors**
Special Senses System																											
Ear																						+					1
Pinna, fibroma																						X					1
Eye							+						+				+										3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																									X		7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 600 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 0 3 2	1 0 3 3	1 0 4 4	1 0 5 1	1 0 5 3	1 0 4 1	1 0 4 2	1 0 6 3	1 0 6 4	1 0 7 1	1 0 7 2	1 0 7 3	1 0 7 4	1 0 8 1	1 0 8 5	1 0 9 2	1 0 5 2	1 0 6 1	1 0 7 5	1 0 9 3	1 1 1 1	1 1 2 2	1 1 2 4	1 1 2 5	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X															1
Hepatocellular adenoma, multiple																									1
Mesentery																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X			X				X	X	X		X			X	28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X	X							X					X						X				X	10
Follicle, adenoma																				X					1
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	4 6 6	5 0 9	5 3 0	5 4 1	5 4 2	5 8 9	6 1 9	6 2 0	6 2 0	6 3 4	6 4 7	6 4 8	6 4 8	6 8 5	6 9 5	6 9 8	6 9 8	7 0 7	7 0 7	7 0 9	7 1 5	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 1 0 2	1 0 1 2	1 0 5 5	1 1 0 5	1 0 5 4	1 0 6 5	0 9 9 2	1 0 2 3	1 0 9 1	1 1 2 1	1 0 1 2	1 0 8 4	1 0 3 5	0 9 3 1	9 1 9 3	1 0 2 1	1 0 3 2	1 0 6 3	1 0 4 3	1 0 0 3	1 0 1 3	1 0 4 5	1 0 0 1	1 0 0 3	1 0 0 4	1 0 2 5
Genital System																										
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X			
Bilateral, adenoma				X																						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma							X																			
Polyp stromal														X									X		X
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Adenoma																										
Fibroadenoma	X	X						X		X		X							X					X	X	
Fibroadenoma, multiple																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																	X									
Subcutaneous tissue, neurofibrosarcoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 0 3 2	1 0 3 3	1 0 4 4	1 0 5 1	1 0 5 3	1 0 4 1	1 0 4 2	1 0 6 3	1 0 6 4	1 0 7 1	1 0 7 2	1 0 7 3	1 0 7 4	1 0 8 1	1 0 8 5	1 0 9 2	1 0 5 2	1 0 6 1	1 0 7 5	1 0 7 3	1 0 9 1	1 1 1 2	1 1 2 2	1 1 2 4	1 1 2 5	Total Tissues/ Tumors
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Adenoma													X													2
Bilateral, adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																					X					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma										X																2
Polyp stromal													X					X								5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Adenoma		X																								1
Fibroadenoma					X									X			X		X							12
Fibroadenoma, multiple										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Subcutaneous tissue, neurofibrosarcoma	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	4 6 6	5 0 9	5 3 0	5 4 1	5 4 2	5 8 9	6 1 9	6 2 0	6 2 0	6 3 4	6 4 7	6 4 8	6 4 8	6 8 5	6 9 5	6 9 8	6 9 8	7 0 7	7 0 7	7 0 9	7 1 5	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	1 1 0 2	1 0 1 2	1 0 5 5	1 1 0 5	1 0 5 4	1 0 6 5	0 9 9 2	1 0 2 3	1 0 9 1	1 1 2 1	1 0 8 2	1 0 3 4	1 0 3 5	0 9 9 1	1 1 2 3	1 0 3 1	1 0 6 2	1 0 4 3	1 1 0 3	1 0 1 3	1 0 4 5	1 0 0 1	1 0 0 3	1 0 0 4	1 0 2 5	
Special Senses System																										
Eye										+	+															
Harderian gland															+											
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X		X							X				X	X	X				X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Triamterene: 600 ppm (continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	
Carcass ID Number	10033	10034	10045	10051	10053	10041	10042	10063	10064	10071	10072	10073	10074	10081	10085	10092	10052	10061	10075	10093	10111	10122	10124	10125	10131	**Total Tissues/ Tumors**
Special Senses System																										
Eye																	+									3
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																					X				9

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Triamterene

	0 ppm	150 ppm	300 ppm	600 ppm
Clitoral Gland: Adenoma				
Overall rates[a]	3/42 (7%)	3/49 (6%)	4/50 (8%)	3/48 (6%)
Adjusted rates[b]	11.5%	8.3%	10.5%	9.1%
Terminal rates[c]	3/26 (12%)	2/34 (6%)	2/34 (6%)	2/28 (7%)
First incidence (days)	729 (T)	708	619	541
Life table tests[d]	P=0.555	P=0.540N	P=0.619	P=0.636N
Logistic regression tests[d]	P=0.554N	P=0.564N	P=0.593	P=0.604N
Cochran-Armitage test[d]	P=0.543N			
Fisher exact test[d]		P=0.585N	P=0.598	P=0.596N
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	4/42 (10%)	3/49 (6%)	4/50 (8%)	3/48 (6%)
Adjusted rates	14.4%	8.3%	10.5%	9.1%
Terminal rates	3/26 (12%)	2/34 (6%)	2/34 (6%)	2/28 (7%)
First incidence (days)	715	708	619	541
Life table tests	P=0.469N	P=0.369N	P=0.524N	P=0.475N
Logistic regression tests	P=0.417N	P=0.391N	P=0.547N	P=0.434N
Cochran-Armitage test	P=0.405N			
Fisher exact test		P=0.413N	P=0.541N	P=0.425N
Mammary Gland: Fibroadenoma				
Overall rates	19/50 (38%)	16/50 (32%)	16/50 (32%)	13/50 (26%)
Adjusted rates	47.9%	42.8%	42.5%	34.6%
Terminal rates	10/29 (34%)	13/34 (38%)	13/34 (38%)	7/29 (24%)
First incidence (days)	571	662	383	466
Life table tests	P=0.184N	P=0.211N	P=0.227N	P=0.197N
Logistic regression tests	P=0.139N	P=0.299N	P=0.339N	P=0.136N
Cochran-Armitage test	P=0.130N			
Fisher exact test		P=0.338N	P=0.338N	P=0.142N
Mammary Gland: Adenoma				
Overall rates	4/50 (8%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rates	10.9%	0.0%	10.6%	3.4%
Terminal rates	1/29 (3%)	0/34 (0%)	2/34 (6%)	1/29 (3%)
First incidence (days)	451	-[e]	662	729 (T)
Life table tests	P=0.285N	P=0.055N	P=0.597N	P=0.194N
Logistic regression tests	P=0.252N	P=0.072N	P=0.635N	P=0.162N
Cochran-Armitage test	P=0.263N			
Fisher exact test		P=0.059N	P=0.643N	P=0.181N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	22/50 (44%)	16/50 (32%)	19/50 (38%)	14/50 (28%)
Adjusted rates	53.2%	42.8%	48.0%	37.6%
Terminal rates	11/29 (38%)	13/34 (38%)	14/34 (41%)	8/29 (28%)
First incidence (days)	451	662	383	466
Life table tests	P=0.147N	P=0.086N	P=0.231N	P=0.120N
Logistic regression tests	P=0.096N	P=0.140N	P=0.343N	P=0.064N
Cochran-Armitage test	P=0.093N			
Fisher exact test		P=0.151N	P=0.342N	P=0.072N

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

	0 ppm	150 ppm	300 ppm	600 ppm
Pancreatic Islets: Adenoma				
Overall rates	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rates	9.0%	0.0%	5.9%	3.4%
Terminal rates	2/29 (7%)	0/34 (0%)	2/34 (6%)	1/29 (3%)
First incidence (days)	660	-	729 (T)	729 (T)
Life table tests	P=0.353N	P=0.105N	P=0.444N	P=0.322N
Logistic regression tests	P=0.357N	P=0.118N	P=0.491N	P=0.321N
Cochran-Armitage test	P=0.337N			
Fisher exact test		P=0.121N	P=0.500N	P=0.309N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	21/50 (42%)	20/50 (40%)	25/50 (50%)	28/50 (56%)
Adjusted rates	55.7%	50.6%	60.4%	73.1%
Terminal rates	13/29 (45%)	15/34 (44%)	18/34 (53%)	19/29 (66%)
First incidence (days)	451	522	635	466
Life table tests	P=0.044	P=0.305N	P=0.487	P=0.126
Logistic regression tests	P=0.036	P=0.470N	P=0.274	P=0.084
Cochran-Armitage test	P=0.057			
Fisher exact test		P=0.500N	P=0.274	P=0.115
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	21/50 (42%)	21/50 (42%)	25/50 (50%)	28/50 (56%)
Adjusted rates	55.7%	53.2%	60.4%	73.1%
Terminal rates	13/29 (45%)	16/34 (47%)	18/34 (53%)	19/29 (66%)
First incidence (days)	451	522	635	466
Life table tests	P=0.050	P=0.368N	P=0.487	P=0.126
Logistic regression tests	P=0.042	P=0.549N	P=0.274	P=0.084
Cochran-Armitage test	P=0.066			
Fisher exact test		P=0.580N	P=0.274	P=0.115
Thyroid Gland (C-cell): Adenoma				
Overall rates	5/50 (10%)	11/50 (22%)	6/50 (12%)	10/50 (20%)
Adjusted rates	17.2%	30.1%	17.1%	29.7%
Terminal rates	5/29 (17%)	9/34 (26%)	5/34 (15%)	7/29 (24%)
First incidence (days)	729 (T)	666	723	634
Life table tests	P=0.178	P=0.146	P=0.611	P=0.122
Logistic regression tests	P=0.166	P=0.113	P=0.593	P=0.110
Cochran-Armitage test	P=0.217			
Fisher exact test		P=0.086	P=0.500	P=0.131
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	5/50 (10%)	11/50 (22%)	7/50 (14%)	10/50 (20%)
Adjusted rates	17.2%	30.1%	20.0%	29.7%
Terminal rates	5/29 (17%)	9/34 (26%)	6/34 (18%)	7/29 (24%)
First incidence (days)	729 (T)	666	723	634
Life table tests	P=0.171	P=0.146	P=0.494	P=0.122
Logistic regression tests	P=0.159	P=0.113	P=0.472	P=0.110
Cochran-Armitage test	P=0.210			
Fisher exact test		P=0.086	P=0.380	P=0.131

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

	0 ppm	150 ppm	300 ppm	600 ppm
Uterus: Stromal Polyp				
Overall rates	4/50 (8%)	6/50 (12%)	5/50 (10%)	5/50 (10%)
Adjusted rates	11.4%	17.0%	14.3%	16.1%
Terminal rates	2/29 (7%)	5/34 (15%)	4/34 (12%)	4/29 (14%)
First incidence (days)	573	715	723	685
Life table tests	P=0.468	P=0.460	P=0.577	P=0.489
Logistic regression tests	P=0.455	P=0.383	P=0.502	P=0.483
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.370	P=0.500	P=0.500
All Organs: Mononuclear Cell Leukemia				
Overall rates	8/50 (16%)	11/50 (22%)	7/50 (14%)	9/50 (18%)
Adjusted rates	19.8%	23.8%	16.2%	24.5%
Terminal rates	1/29 (3%)	2/34 (6%)	1/34 (3%)	3/29 (10%)
First incidence (days)	534	522	619	589
Life table tests	P=0.499	P=0.392	P=0.454N	P=0.471
Logistic regression tests	P=0.487N	P=0.239	P=0.484N	P=0.517
Cochran-Armitage test	P=0.538N			
Fisher exact test		P=0.306	P=0.500N	P=0.500
All Organs: Benign Neoplasms				
Overall rates	40/50 (80%)	37/50 (74%)	40/50 (80%)	37/50 (74%)
Adjusted rates	88.7%	85.8%	88.8%	83.8%
Terminal rates	24/29 (83%)	28/34 (82%)	29/34 (85%)	22/29 (76%)
First incidence (days)	451	476	383	466
Life table tests	P=0.522N	P=0.117N	P=0.268N	P=0.431N
Logistic regression tests	P=0.409N	P=0.285N	P=0.571	P=0.358N
Cochran-Armitage test	P=0.345N			
Fisher exact test		P=0.318N	P=0.598N	P=0.318N
All Organs: Malignant Neoplasms				
Overall rates	16/50 (32%)	13/50 (26%)	9/50 (18%)	9/50 (18%)
Adjusted rates	36.5%	28.6%	21.3%	24.5%
Terminal rates	3/29 (10%)	4/34 (12%)	3/34 (9%)	3/29 (10%)
First incidence (days)	534	522	619	589
Life table tests	P=0.097N	P=0.264N	P=0.081N	P=0.130N
Logistic regression tests	P=0.040N	P=0.401N	P=0.075N	P=0.068N
Cochran-Armitage test	P=0.054N			
Fisher exact test		P=0.330N	P=0.083N	P=0.083N
All Organs: Benign or Malignant Neoplasms				
Overall rates	46/50 (92%)	43/50 (86%)	42/50 (84%)	41/50 (82%)
Adjusted rates	93.8%	87.7%	89.3%	87.1%
Terminal rates	26/29 (90%)	28/34 (82%)	29/34 (85%)	23/29 (79%)
First incidence (days)	451	476	383	466
Life table tests	P=0.373N	P=0.125N	P=0.105N	P=0.328N
Logistic regression tests	P=0.119N	P=0.306N	P=0.191N	P=0.118N
Cochran-Armitage test	P=0.107N			
Fisher exact test		P=0.262N	P=0.178N	P=0.117N

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

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

TABLE B4
Historical Incidence of Liver Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratory			
2,4-Dichlorophenol	0/50	0/50	0/50
5,5-Diphenylhydantoin	0/50	0/50	0/50
Ethylene thiourea	0/50	0/50	0/50
Polybrominated biphenyls (Firemaster FF-1®)	0/50	0/50	0/50
Overall Historical Incidence			
Total	3/800 (0.4%)	1/800 (0.1%)	4/800 (0.5%)
Standard deviation	1.5%	0.5%	1.6%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 3 April 1991

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Triamterene[a]

	0 ppm	150 ppm	300 ppm	600 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
2-Year study				
Early deaths				
Moribund	17	11	12	18
Natural deaths	4	5	4	3
Survivors				
Terminal sacrifice	29	34	34	29
Animals examined microscopically	70	70	70	70
3-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)			(10)
Parasite metazoan	1 (10%)			
Intestine large, rectum	(10)			(10)
Parasite metazoan				1 (10%)
Liver	(10)	(1)	(3)	(10)
Inflammation, granulomatous	1 (10%)	1 (100%)	3 (100%)	3 (30%)
Periportal, inflammation, chronic	1 (10%)			1 (10%)
Pancreas	(10)			(10)
Acinus, atrophy	1 (10%)			
Stomach, forestomach	(10)			(10)
Epithelium, acanthosis, diffuse				1 (10%)
Epithelium, hyperkeratosis, diffuse				1 (10%)
Cardiovascular System				
Heart	(10)			(10)
Myocardium, inflammation, multifocal, chronic	1 (10%)			
Endocrine System				
None				
General Body System				
None				
Genital System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Triamterene
(continued)

	0 ppm	150 ppm	300 ppm	600 ppm
3-Month Interim Evaluation (continued)				
Hematopoietic System				
Bone marrow	(10)			(10)
Femoral, hyperplasia, RE cell	10 (100%)			9 (90%)
Lymph node, mesenteric	(10)			(10)
Infiltration cellular, histiocyte	9 (90%)			10 (100%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)			(10)
Peribronchiolar, inflammation, multifocal, chronic	1 (10%)			
Peribronchiolar, inflammation, multifocal, chronic active				1 (10%)
Special Senses System				
Harderian gland	(8)			(2)
Inflammation, focal, chronic				2 (100%)
Inflammation, multifocal, chronic	7 (88%)			
Inflammation, multifocal, chronic active	1 (13%)			
Urinary System				
Kidney	(10)			(10)
Renal tubule, mineralization, multifocal	2 (20%)			
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(8)	(10)
Angiectasis, focal		2 (20%)		
Basophilic focus	5 (50%)	9 (90%)	3 (38%)	4 (40%)
Hepatodiaphragmatic nodule		1 (10%)		2 (20%)
Inflammation, granulomatous	5 (50%)	6 (60%)	8 (100%)	5 (50%)
Vacuolization cytoplasmic, focal		1 (10%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
15-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Mesentery	(1)		(1)	
Inflammation, chronic	1 (100%)		1 (100%)	
Pancreas	(10)			(10)
Acinus, atrophy	3 (30%)			2 (20%)
Cardiovascular System				
Blood vessel	(1)			
Aorta, inflammation, chronic	1 (100%)			
Heart	(10)			(10)
Myocardium, degeneration, multifocal	3 (30%)			3 (30%)
Endocrine System				
Adrenal gland, cortex	(10)			(10)
Hyperplasia, nodular	1 (10%)			
Pituitary gland	(10)	(3)	(2)	(10)
Pars distalis, angiectasis	1 (10%)			
Pars distalis, degeneration, cystic				1 (10%)
Pars distalis, hyperplasia	1 (10%)	2 (67%)	2 (100%)	1 (10%)
Thyroid gland	(10)			(10)
C-cell, hyperplasia	9 (90%)			8 (80%)
General Body System				
None				
Genital System				
Clitoral gland	(10)			(10)
Inflammation, chronic	1 (10%)			
Inflammation, suppurative	1 (10%)			
Uterus	(10)	(1)		(10)
Dilatation				1 (10%)
Hematopoietic System				
Bone marrow	(10)			(10)
Femoral, atrophy	1 (10%)			
Lymph node, mandibular	(10)	(1)		(10)
Sinus, ectasia		1 (100%)		1 (10%)
Integumentary System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats and in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
Bone	(10)			(10)
Femur, osteopetrosis	2 (20%)			1 (10%)
Nervous System				
None				
Respiratory System				
Lung	(10)			(10)
Interstitium, inflammation, chronic				1 (10%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy, multifocal	7 (70%)	8 (80%)	5 (50%)	8 (80%)
2-Year Study				
Alimentary System				
Intestine large, cecum	(50)	(47)	(50)	(50)
Ulcer		1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(49)
Parasite metazoan	1 (2%)	6 (12%)	3 (6%)	4 (8%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	2 (4%)			
Intestine small, duodenum	(50)	(50)	(50)	(50)
Ulcer		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis, focal	1 (2%)	3 (6%)		
Basophilic focus	37 (74%)	36 (72%)	34 (68%)	34 (68%)
Clear cell focus	3 (6%)	3 (6%)	4 (8%)	9 (18%)
Degeneration, cystic				1 (2%)
Eosinophilic focus			1 (2%)	3 (6%)
Fatty change	1 (2%)		1 (2%)	3 (6%)
Hepatodiaphragmatic nodule	2 (4%)	6 (12%)	1 (2%)	5 (10%)
Hyperplasia	1 (2%)	3 (6%)	3 (6%)	2 (4%)
Hyperplasia, histiocytic, lymphoid	1 (2%)			
Inflammation, granulomatous	17 (34%)	8 (16%)	11 (22%)	6 (12%)
Mixed cell focus	2 (4%)	2 (4%)	8 (16%)	13 (26%)
Necrosis, coagulative	1 (2%)	2 (4%)		1 (2%)
Serosa, hemorrhage				1 (2%)
Mesentery	(3)	(2)	(3)	(1)
Inflammation, chronic		1 (50%)		
Fat, necrosis	3 (100%)		2 (67%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			
Acinus, atrophy	12 (24%)	6 (12%)	11 (22%)	13 (26%)
Artery, inflammation, chronic	1 (2%)	1 (2%)		1 (2%)
Salivary glands	(49)	(50)	(49)	(50)
Inflammation, acute				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Acanthosis	2 (4%)			
Cyst		1 (2%)		
Hyperkeratosis	2 (4%)			
Inflammation, chronic				2 (4%)
Ulcer	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			1 (2%)
Ulcer	3 (6%)	3 (6%)	3 (6%)	3 (6%)
Mucosa, mineralization			2 (4%)	
Tongue	(1)		(1)	
Acanthosis	1 (100%)		1 (100%)	
Hyperkeratosis	1 (100%)		1 (100%)	
Tooth			(2)	
Peridontal tissue, inflammation, chronic			2 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Atrium, thrombus		2 (4%)		
Endothelium, hyperplasia	1 (2%)			
Myocardium, degeneration	32 (64%)	39 (78%)	30 (60%)	27 (54%)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	13 (26%)	18 (36%)	10 (20%)	16 (32%)
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	6 (12%)	6 (12%)		5 (10%)
Pituitary gland	(50)	(50)	(50)	(50)
Necrosis, liquefactive			1 (2%)	
Pars distalis, angiectasis		3 (6%)	1 (2%)	
Pars distalis, cyst	6 (12%)	1 (2%)	4 (8%)	6 (12%)
Pars distalis, hyperplasia	11 (22%)	10 (20%)	7 (14%)	13 (26%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	43 (86%)	32 (64%)	37 (74%)	35 (70%)
Follicle, dilatation		2 (4%)	2 (4%)	2 (4%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Triamterene
(continued)

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
General Body System				
None				
Genital System				
Clitoral gland	(42)	(49)	(50)	(48)
Inflammation, chronic	15 (36%)	17 (35%)	28 (56%)	22 (46%)
Ovary	(50)	(50)	(50)	(50)
Cyst	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, granulomatous	1 (2%)			
Follicle, cyst			2 (4%)	
Uterus	(50)	(50)	(50)	(50)
Dilatation		2 (4%)	1 (2%)	
Hemorrhage			1 (2%)	
Cervix, epithelium, hyperplasia	2 (4%)			
Endometrium, hyperplasia, cystic	2 (4%)	2 (4%)	1 (2%)	
Vagina	(1)			
Infiltration cellular, polymorphonuclear		1 (100%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Femoral, myelofibrosis				1 (2%)
Lymph node	(50)	(50)	(50)	(50)
Inguinal, sinus, ectasia	1 (2%)			
Lumbar, sinus, ectasia				1 (2%)
Mediastinal, sinus, ectasia	2 (4%)		1 (2%)	
Pancreatic, hematopoietic cell proliferation				1 (2%)
Pancreatic, hyperplasia, plasma cell			1 (2%)	
Pancreatic, infiltration cellular, histiocyte				1 (2%)
Lymph node, mandibular	(48)	(50)	(49)	(50)
Hyperplasia, plasma cell		2 (4%)	1 (2%)	
Sinus, ectasia		1 (2%)	2 (4%)	
Lymph node, mesenteric	(48)	(48)	(50)	(48)
Sinus, ectasia	3 (6%)		1 (2%)	4 (8%)
Spleen	(50)	(50)	(50)	(50)
Depletion lymphoid	1 (2%)		1 (2%)	
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	4 (8%)	1 (2%)		3 (6%)
Hyperplasia, lymphoid	1 (2%)			
Infarct	2 (4%)	2 (4%)		
Inflammation, granulomatous	1 (2%)		2 (4%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Triamterene (continued)

	0 ppm	150 ppm	300 ppm	600 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(48)	(49)	(49)	(47)
Hyperplasia, cystic	17 (35%)	25 (51%)	22 (45%)	24 (51%)
Skin	(50)	(50)	(50)	(50)
Ulcer				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis	1 (2%)	5 (10%)	1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Infarct	3 (6%)	2 (4%)	1 (2%)	
Hypothalamus, compression	10 (20%)	7 (14%)	11 (22%)	14 (28%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Abscess				1 (2%)
Foreign body			1 (2%)	1 (2%)
Inflammation, granulomatous			2 (4%)	
Alveolus, inflammation, subacute		2 (4%)	1 (2%)	1 (2%)
Interstitium, inflammation, chronic	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Nares, inflammation, suppurative		1 (2%)		3 (6%)
Special Senses System				
Eye	(2)	(1)	(3)	(3)
Hemorrhage			1 (33%)	
Lens, cataract	1 (50%)	1 (100%)	2 (67%)	1 (33%)
Harderian gland				(1)
Inflammation, suppurative				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst			1 (2%)	
Hydronephrosis				1 (2%)
Nephropathy	38 (76%)	45 (90%)	45 (90%)	45 (90%)
Urinary bladder	(49)	(49)	(50)	(50)
Transitional epithelium, hyperplasia				1 (2%)

[a] Number of animals examined microscopically at site and number of animals with lesion

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF TRIAMTERENE

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TABLE C1a
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation	10	10	10	0
2-Year study				
Early deaths				
Moribund	1	2	2	6
Natural deaths	2	3	2	8
Survivors				
Terminal sacrifice	47	45	46	46
Animals examined microscopically	70	70	70	70
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(3)	(10)	
Hepatocellular adenoma	1 (10%)	3 (100%)	2 (20%)	
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
None				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

TABLE C1a
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(1)	(10)	
Alveolar/bronchiolar adenoma	2 (20%)	1 (100%)		
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Gallbladder	(48)	(46)	(50)	(54)
Intestine large, cecum	(50)	(50)	(50)	(54)
Intestine large, colon	(50)	(49)	(50)	(57)
Intestine small, duodenum	(50)	(50)	(49)	(55)
Adenocarcinoma				1 (2%)
Intestine small, ileum	(49)	(49)	(50)	(55)
Intestine small, jejunum	(50)	(50)	(49)	(55)
Adenocarcinoma				1 (2%)
Liver	(50)	(50)	(50)	(60)
Hemangiosarcoma	1 (2%)	1 (2%)	3 (6%)	
Hepatoblastoma		1 (2%)	1 (2%)	
Hepatocellular carcinoma	4 (8%)	7 (14%)	3 (6%)	13 (22%)
Hepatocellular carcinoma, multiple	1 (2%)			
Hepatocellular adenoma	13 (26%)	11 (22%)	11 (22%)	9 (15%)
Hepatocellular adenoma, multiple	4 (8%)	11 (22%)	8 (16%)	11 (18%)
Mesentery	(3)	(3)	(4)	(2)
Pancreas	(50)	(50)	(50)	(60)
Stomach, forestomach	(49)	(50)	(50)	(58)
Papilloma squamous				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(59)
Cardiovascular System				
None				
Endocrine System				
Adrenal gland	(50)	(50)	(50)	(59)
Capsule, adenoma	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(48)	(60)
Pheochromocytoma malignant		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(60)
C-cell, adenoma			1 (2%)	
Follicular cell, adenoma		1 (2%)	1 (2%)	2 (3%)

TABLE C1a
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(60)
Prostate	(50)	(50)	(50)	(60)
Seminal vesicle	(50)	(50)	(50)	(60)
Testes	(50)	(50)	(50)	(60)
Interstitial cell, adenoma		1 (2%)		1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(60)
Lymph node	(50)	(50)	(50)	(60)
Lymph node, mandibular	(47)	(48)	(49)	(60)
Lymph node, mesenteric	(46)	(46)	(44)	(45)
Spleen	(50)	(50)	(50)	(60)
Hemangioma			1 (2%)	
Hemangiosarcoma		1 (2%)	2 (4%)	
Thymus	(36)	(40)	(37)	(39)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (3%)		
Integumentary System				
Skin	(49)	(50)	(49)	(60)
Subcutaneous tissue, fibroma	1 (2%)			
Subcutaneous tissue, hemangioma		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(59)
Femur, hemangiosarcoma, metastatic, spleen			1 (2%)	
Skeletal muscle	(1)	(2)	(1)	
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (50%)		
Nervous System				
Brain	(50)	(50)	(50)	(60)
Respiratory System				
Lung	(50)	(50)	(50)	(60)
Adenocarcinoma, metastatic, harderian gland	1 (2%)			
Alveolar/bronchiolar adenoma	3 (6%)	9 (18%)	9 (18%)	9 (15%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	4 (8%)	1 (2%)	4 (8%)	4 (7%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Nose	(50)	(50)	(50)	(60)

TABLE C1a
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study
(continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Special Senses System				
Harderian gland	(3)	(3)	(6)	(2)
Adenocarcinoma	1 (33%)			1 (50%)
Adenoma		1 (33%)	3 (50%)	1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(60)
Urinary bladder	(50)	(50)	(49)	(60)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(60)
Lymphoma malignant histiocytic			1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)			
Lymphoma malignant mixed	5 (10%)	3 (6%)	4 (8%)	4 (7%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	3	4	2	
2-Year study	32	38	35	38
Total primary neoplasms				
15-Month interim evaluation	3	4	2	
2-Year study	41	52	55	60
Total animals with benign neoplasms				
15-Month interim evaluation	3	4	2	
2-Year study	21	26	29	27
Total benign neoplasms				
15-Month interim evaluation	3	4	2	
2-Year study	22	35	35	34
Total animals with malignant neoplasms				
2-Year study	17	17	16	22
Total malignant neoplasms				
2-Year study	19	17	20	26
Total animals with metastatic neoplasms				
2-Year study	1	1	1	
Total metastatic neoplasms				
2-Year study	1	2	1	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were found at the 3-month interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C1b
Summmary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study[a]

	0 ppm	400 ppm
Disposition Summary		
Animals initially in study	60	60
15-Month interim evaluation	10	10
2-Year study		
Early deaths		
Moribund	3	4
Natural deaths	4	7
Survivors		
Died last week of study	1	
Terminal sacrifice	42	39
Animals examined microscopically	60	60
15-Month Interim Evaluation		
Alimentary System		
Liver	(9)	(10)
Hepatocellular adenoma		1 (10%)
Cardiovascular System		
None		
Endocrine System		
Islets, pancreatic	(10)	(10)
Adenoma	1 (10%)	
General Body System		
None		
Genital System		
None		
Hematopoietic System		
None		
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		

TABLE C1b
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study
(continued)

	0 ppm	400 ppm
15-Month Interim Evaluation (continued)		
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
None		
2-Year Study		
Alimentary System		
Gallbladder	(48)	(48)
Intestine large, cecum	(49)	(50)
Fibrosarcoma	1 (2%)	
Intestine large, colon	(48)	(50)
Intestine large, rectum	(49)	(50)
Intestine small, duodenum	(47)	(50)
Intestine small, jejunum	(49)	(49)
Liver	(50)	(50)
Hemangiosarcoma	2 (4%)	
Hemangiosarcoma, multiple		1 (2%)
Hepatoblastoma		1 (2%)
Hepatocellular carcinoma	8 (16%)	8 (16%)
Hepatocellular carcinoma, multiple	1 (2%)	3 (6%)
Hepatocellular adenoma	10 (20%)	12 (24%)
Hepatocellular adenoma, multiple	11 (22%)	24 (48%)
Mesentery	(2)	(1)
Adenocarcinoma	1 (50%)	
Fibrosarcoma, metastatic, skeletal muscle	1 (50%)	
Pancreas	(48)	(50)
Fibrosarcoma, metastatic, skeletal muscle	1 (2%)	
Salivary glands	(50)	(50)
Stomach, forestomach	(49)	(50)
Stomach, glandular	(49)	(50)
Cardiovascular System		
Heart	(50)	(50)
Fibrosarcoma, metastatic, skeletal muscle	1 (2%)	
Hepatocellular carcinoma, metastatic, liver		1 (2%)

TABLE C1b
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Endocrine System		
Adrenal gland, cortex	(50)	(50)
Spindle cell, adenoma		1 (2%)
Adrenal gland, medulla	(50)	(50)
Islets, pancreatic	(47)	(49)
Carcinoma	1 (2%)	
Pituitary gland	(50)	(48)
Pars distalis, adenoma		1 (2%)
Thyroid gland	(50)	(50)
Follicular cell, adenoma	1 (2%)	
General Body System		
None		
Genital System		
Epididymis	(50)	(50)
Prostate	(50)	(50)
Seminal vesicle	(50)	(50)
Testes	(50)	(50)
Hematopoietic System		
Bone marrow	(50)	(50)
Hemangiosarcoma	1 (2%)	
Lymph node	(50)	(50)
Fibrosarcoma, metastatic, lymph node	1 (2%)	
Lymph node, mandibular	(50)	(50)
Lymph node, mesenteric	(41)	(44)
Spleen	(47)	(50)
Hemangiosarcoma	2 (4%)	
Thymus	(40)	(43)
Fibrosarcoma, metastatic, skeletal muscle	1 (3%)	
Integumentary System		
Skin	(50)	(50)
Osteosarcoma, metastatic, bone	1 (2%)	
Subcutaneous tissue, hemangioma		1 (2%)
Musculoskeletal System		
Bone	(50)	(50)
Maxilla, fibrosarcoma	1 (2%)	
Vertebra, coccygeal, osteosarcoma	1 (2%)	
Skeletal muscle	(1)	(2)
Hindlimb, fibrosarcoma	1 (100%)	

TABLE C1b
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study
(continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Nervous System		
Brain	(50)	(50)
Respiratory System		
Lung	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)
Alveolar/bronchiolar carcinoma	7 (14%)	5 (10%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)
Fibrosarcoma, metastatic, skeletal muscle	1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	3 (6%)
Hepatocellular carcinoma, metastatic, multiple		1 (2%)
Special Senses System		
Ear	(1)	
Fibrosarcoma	1 (100%)	
Harderian gland	(4)	(6)
Adenoma	1 (25%)	6 (100%)
Urinary System		
Kidney	(50)	(50)
Carcinoma	1 (2%)	
Fibrosarcoma, metastatic, skeletal muscle	1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	
Artery, hepatocellular carcinoma, metastatic		1 (2%)
Urinary bladder	(50)	(50)
Papilloma		1 (2%)
Systemic Lesions		
Multiple organs[b]	(50)	(50)
Lymphoma malignant histiocytic		1 (2%)
Lymphoma malignant mixed	5 (10%)	8 (16%)
Neoplasm Summary		
Total animals with primary neoplasms[c]		
15-Month interim evaluation	1	1
2-Year study	37	44
Total primary neoplasms		
15-Month interim evaluation	1	1
2-Year study	63	84
Total animals with benign neoplasms		
15-Month interim evaluation	1	1
2-Year study	25	39

TABLE C1b
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
Neoplasm Summary (continued)		
Total benign neoplasms		
15-Month interim evaluation	1	1
2-Year study	29	56
Total animals with malignant neoplasms		
2-Year study	25	26
Total malignant neoplasms		
2-Year study	34	28
Total animals with metastatic neoplasms		
2-Year study	4	4
Total metastatic neoplasms		
2-Year study	10	6

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm

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

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

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 3 5 1	0 3 6 1	0 3 9 1	0 4 1 1	0 4 3 1	0 4 4 1	0 4 6 1	0 4 7 1	0 4 8 1	0 4 9 1	0 5 3 1	0 5 4 1	0 5 5 1	0 5 6 1	0 5 7 1	0 5 8 1	0 5 9 1	0 6 1 1	0 6 2 1	0 6 5 1	0 6 6 1	0 6 7 1	0 6 8 1	0 6 9 1	0 7 0 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma				X											X		X									4
Hepatocellular carcinoma, multiple										X																1
Hepatocellular adenoma	X	X									X									X				X		13
Hepatocellular adenoma, multiple						X				X																4
Mesentery			+																							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	5 8 5	6 2 3	6 9 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 6 4 1	0 6 0 1	0 0 6 1	0 0 3 1	0 0 4 1	0 0 5 1	0 0 8 1	0 0 9 1	0 1 0 1	0 1 2 1	0 1 3 1	0 1 5 1	0 1 6 1	0 1 7 1	0 1 8 1	0 1 9 1	0 2 3 1	0 2 4 1	0 2 5 1	0 2 6 1	0 2 7 1	0 2 8 1	0 3 1 1	0 3 3 1	0 3 4 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland				+													+						+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	M	I	+	+	+	+	+	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																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland	X																								
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma		X							X		X	X													
Alveolar/bronchiolar carcinoma, multiple																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 3 5 1	0 3 6 1	0 3 9 1	0 4 1 1	0 4 3 1	0 4 4 1	0 4 6 1	0 4 7 1	0 4 8 1	0 4 9 1	0 5 3 1	0 5 4 1	0 5 5 1	0 5 6 1	0 5 7 1	0 5 8 1	0 5 9 1	0 6 1 1	0 6 2 1	0 6 5 1	0 6 6 1	0 6 7 1	0 6 8 1	0 6 9 1	0 7 0 1	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis											+															1
Preputial gland				+		+		+		+			+			+	+							+		11
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	M	M	M	+	+	+	+	M	+	36
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma											X															1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																										1
Alveolar/bronchiolar adenoma																		X							X	3
Alveolar/bronchiolar carcinoma																										4
Alveolar/bronchiolar carcinoma, multiple											X															2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	8	2	9	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3
	5	3	0	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	6	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	
	4	0	6	3	4	5	8	9	0	2	3	5	6	7	8	9	3	4	5	6	7	8	1	3	4	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Special Senses System																										
Harderian gland	+																								+	
Adenocarcinoma	X																									
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant lymphocytic											X															
Lymphoma malignant mixed			X		X										X											

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 3 5 1	0 3 6 1	0 3 9 1	0 4 1 1	0 4 3 1	0 4 4 1	0 4 6 1	0 4 7 1	0 4 8 1	0 4 9 1	0 5 3 1	0 5 4 1	0 5 5 1	0 5 6 1	0 5 7 1	0 5 8 1	0 5 9 1	0 6 1 1	0 6 2 1	0 6 5 1	0 6 6 1	0 6 7 1	0 6 8 1	0 6 9 1	0 7 0 1	**Total Tissues/ Tumors**
Special Senses System																										
Harderian gland														+												3
Adenocarcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed		X										X														5

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm

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

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 0 5 1	1 0 6 1	1 1 0 1	1 1 1 1	1 1 2 1	1 1 4 1	1 1 5 1	1 1 7 1	1 1 8 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 5 1	1 2 6 1	1 2 7 1	1 3 0 1	1 3 1 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 6 1	1 3 7 1	1 3 9 1	1 4 0 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma																										1
Hepatocellular carcinoma			X			X																		X		7
Hepatocellular adenoma		X						X					X		X											11
Hepatocellular adenoma, multiple						X			X		X			X										X		11
Mesentery														+												3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	5 2 2	5 5 7	5 9 9	6 0 1	6 8 1	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 9 0 1	1 1 9 1	1 0 7 1	0 9 5 1	1 3 8 1	0 7 1 1	0 7 3 1	0 7 4 1	0 7 5 1	0 7 6 1	0 7 7 1	0 7 8 1	0 7 9 1	0 8 0 1	0 8 1 1	0 8 3 1	0 8 6 1	0 8 7 1	0 8 8 1	0 8 9 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 7 1	0 9 0 1	1 0 1 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+		+	+					+							+					+			+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma											X														
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	+	M	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung			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, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+		+																				
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X	X			X		X	X		X				X				
Alveolar/bronchiolar carcinoma	X																								
Alveolar/bronchiolar carcinoma, multiple			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 0 5 1	1 0 6 1	1 1 0 1	1 1 1 1	1 1 2 1	1 1 4 1	1 1 5 1	1 1 7 1	1 1 8 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 5 1	1 2 6 1	1 2 7 1	1 3 0 1	1 3 1 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 6 1	1 3 7 1	1 3 9 1	1 4 0 1	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland					+				+			+									+	+				12
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								1
Thymus	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	40
Alveolar/bronchiolar carcinoma, metastatic, lung																										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, hemangioma						X																				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X	X														9
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, multiple																			X							2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	5	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	5	9	0	8	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3
	2	7	9	1	1	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0
Carcass ID Number	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	9	1	0	9	3	7	7	7	7	7	7	7	7	8	8	8	8	8	8	8	9	9	9	9	0
	0	9	7	5	8	1	3	4	5	6	7	8	9	0	1	3	6	7	8	9	1	2	3	7	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Special Senses System																									
Harderian gland																		+							
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene:
First Study: 100 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 0 5 1	1 0 6 1	1 1 0 1	1 1 1 1	1 1 2 1	1 1 4 1	1 1 5 1	1 1 7 1	1 1 8 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 5 1	1 2 6 1	1 2 7 1	1 3 0 1	1 3 1 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 6 1	1 3 7 1	1 3 9 1	1 4 0 1	**Total Tissues/ Tumors**
Special Senses System																										
Harderian gland																						+	+			3
Adenoma																							X			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed				X			X															X				3

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm

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

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene:
First Study: 200 ppm (continued)

Number of Days on Study	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 7 4 1	1 7 5 1	1 7 6 1	1 7 7 1	1 8 0 1	1 8 1 1	1 8 2 1	1 8 3 1	1 8 4 1	1 8 6 1	1 8 7 1	1 9 0 1	1 9 1 1	1 9 4 1	1 9 5 1	1 9 6 1	1 9 8 1	1 9 9 1	2 0 1 1	2 0 2 1	2 0 3 1	2 0 5 1	2 0 6 1	2 0 7 1	2 0 1 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X			X																		3
Hepatoblastoma																										1
Hepatocellular carcinoma								X			X			X												3
Hepatocellular adenoma		X		X		X					X			X	X		X								11
Hepatocellular adenoma, multiple								X													X	X			X	8
Mesentery								+		+											+					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
Follicular cell, adenoma														X												1
General Body System																										
None																										

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	6 1 7	6 4 1	6 8 2	7 0 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 7 8 1	1 6 0 1	1 4 1 1	1 8 5 1	1 4 2 1	1 4 3 1	1 4 5 1	1 4 6 1	1 4 7 1	1 4 8 1	1 4 9 1	1 5 1 1	1 5 2 1	1 5 3 1	1 5 4 1	1 5 5 1	1 5 8 1	1 5 9 1	1 6 4 1	1 6 5 1	1 6 7 1	1 6 9 1	1 7 0 1	1 7 1 1	1 7 2 1
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								
Preputial gland	+	+				+		+	+	+	+			+				+		+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Blood																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma													X											
Hemangiosarcoma												X												X
Thymus	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, hemangiosarcoma, metastatic, spleen												X												
Skeletal muscle		+																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X				X		X							X	
Alveolar/bronchiolar adenoma, multiple																						X		
Alveolar/bronchiolar carcinoma			X																					
Alveolar/bronchiolar carcinoma, multiple																				X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 7 4 1	1 7 5 1	1 7 6 1	1 7 7 1	1 8 0 1	1 8 1 1	1 8 2 1	1 8 3 1	1 8 4 1	1 8 6 1	1 8 7 1	1 9 0 1	1 9 1 1	1 9 4 1	1 9 5 1	1 9 6 1	1 9 8 1	1 9 9 1	1 0 1 1	2 0 2 1	2 0 3 1	2 0 5 1	2 0 6 1	2 0 7 1	2 1 0 1	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																								+		1
Preputial gland						+		+	+				+			+		+			+		+		+	23
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Blood			+																							1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										2
Thymus	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	37
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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, hemangiosarcoma, metastatic, spleen																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X						X		X							X	X	9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma		X		X																	X					4
Alveolar/bronchiolar carcinoma, multiple	X																									2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	6 1 7	6 4 1	6 8 2	7 0 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 7 8 1	1 6 0 1	1 4 1 1	1 8 5 1	1 4 2 1	1 4 3 1	1 4 5 1	1 4 6 1	1 4 7 1	1 4 8 1	1 4 9 1	1 5 1 1	1 5 2 1	1 5 3 1	1 5 4 1	1 5 5 1	1 5 8 1	1 5 9 1	1 6 4 1	1 6 5 1	1 6 7 1	1 6 9 1	1 7 0 1	1 7 1 1	1 7 2 1
Special Senses System																									
Eye																							+		
Harderian gland			+										+			+							+		
Adenoma			X																				X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic		X																							
Lymphoma malignant mixed																									

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	730	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	17741	17751	17761	17771	17881	17891	17901	17911	17921	17931	17941	17961	17971	17991	18011	18041	18051	18061	18081	18091	18201	18221	18231	18251	18261	18271	**Total Tissues/ Tumors**
Special Senses System																											
Eye																											1
Harderian gland					+																			+			6
Adenoma																								X			3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																											1
Lymphoma malignant mixed					X	X					X									X							4

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm

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

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	732	732	732	732	732	732	732	732	732	733	733
Carcass ID Number	22511	22711	22811	22911	23011	23311	23411	23711	24011	24111	24211	24311	24411	24511	24611	24811	24911	25011	25111	25311	25511	25911	26211	26311	26511
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X																							
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma					X																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma	X		X			X																X		X	
Hepatocellular adenoma		X											X										X		X
Hepatocellular adenoma, multiple					X		X	X			X						X							X	
Mesentery																						+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous									X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
General Body System																									
None																									

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 6 7 1	2 6 9 1	2 7 0 1	2 7 1 1	2 7 4 1	2 7 5 1	2 7 6 1	2 7 7 1	2 7 9 1	2 8 0 1	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	M	+	+	+	+	54
Intestine large	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	57
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine small	+	+	+	+	+	+	+	+	+	+	57
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	55
Adenocarcinoma											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	55
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	55
Adenocarcinoma											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma							X	X		X	13
Hepatocellular adenoma	X										9
Hepatocellular adenoma, multiple			X		X						11
Mesentery											2
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	58
Papilloma squamous											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	59
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	56
Pituitary gland	+	+	+	+	+	+	+	+	+	+	58
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma											2
General Body System											
None											

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	2 8 3	2 8 4	2 8 4	2 8 4	2 8 4	2 8 5	2 8 5	2 8 5	2 8 6	2 8 6	2 8 6	2 8 8	2 8 0	6 2 1	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 3 4 1	2 1 9 1	2 4 7 1	2 5 4 1	2 5 7 1	2 5 2 1	2 6 0 1	2 7 3 1	2 3 5 1	2 3 9 1	2 5 8 1	2 2 4 1	2 5 6 1	2 6 1 1	2 1 1 1	2 1 2 1	2 1 3 1	2 1 4 1	2 1 5 1	2 1 6 1	2 1 8 1	2 2 0 1	2 2 1 1	2 2 2 1	2 2 3 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland															+	+			+	+			+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	A	+	+	M	M	+	+	+	+	+	+	M	M	+	M	M	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma															X	X									
Alveolar/bronchiolar carcinoma, multiple																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenocarcinoma																									
Adenoma																									

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	22251	22271	22281	22291	23301	23311	23321	23331	23371	24411	24421	24431	24441	24451	24461	24481	24491	25501	25511	25531	25551	25591	26621	26631	26651
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland				+					+				+	+	+		+			+	+	+			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																				X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X	X				X				X						X	X								
Alveolar/bronchiolar carcinoma																		X							
Alveolar/bronchiolar carcinoma, multiple																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland							+																		
Adenocarcinoma							X																		
Adenoma																									

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene:
First Study: 400 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 6 7 1	2 6 9 1	2 7 0 1	2 7 1 1	2 7 4 1	2 7 5 1	2 7 6 1	2 7 7 1	2 7 9 1	2 8 0 1	**Total Tissues/ Tumors**
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Preputial gland									+		15
Prostate	+	+	+	+	+	+	+	+	+	+	60
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	60
Interstitial cell, adenoma											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mesenteric	+	+	+	+	+	M	M	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	60
Thymus	M	+	+	M	+	+	+	M	+	M	39
Integumentary System											
Mammary gland	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	60
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	59
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma	X								X		9
Alveolar/bronchiolar carcinoma		X									4
Alveolar/bronchiolar carcinoma, multiple											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Harderian gland									+		2
Adenocarcinoma											1
Adenoma									X		1

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

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

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene:
First Study: 400 ppm (continued)

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

TABLE C2a
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	7 7 7 7 7 7 7 7 7 7 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 6 6 7 7 7 7 7 7 7 8 7 9 0 1 4 5 6 7 9 0 1 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Urinary System		
Kidney	+ + + + + + + + + +	60
Urinary bladder	+ + + + + + + + + +	60
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	60
Lymphoma malignant histiocytic	X	1
Lymphoma malignant mixed	X	4

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm

Number of Days on Study	4 4 0	5 3 4	6 2 2	7 0 1	7 0 9	7 1 2	7 1 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 9 1 1	6 3 1 1	6 2 6 1	6 1 5 1	6 3 4 1	6 1 0 1	6 1 9 1	5 9 2 1	5 9 3 1	5 9 5 1	5 9 6 1	5 9 7 1	5 9 8 1	5 9 9 1	6 0 1 1	6 0 2 1	6 0 3 1	6 0 4 1	6 0 5 1	6 0 7 1	6 0 8 1	6 0 9 1	6 1 1 1	6 1 3 1	6 1 6 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																						X			
Intestine large, colon	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X					X						
Hepatocellular carcinoma			X		X								X							X			X		X
Hepatocellular carcinoma, multiple				X																					
Hepatocellular adenoma					X		X									X				X					
Hepatocellular adenoma, multiple				X		X							X	X			X				X				X
Mesentery			+																						
Adenocarcinoma																									
Fibrosarcoma, metastatic, skeletal muscle			X																						
Pancreas	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Fibrosarcoma, metastatic, skeletal muscle			X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skeletal muscle			X																						

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

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene:
Second Study: 0 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	61811	62011	62211	62211	62211	62211	62211	62211	62211	62211	62211	63011	63211	63511	63611	63711	63811	63911	64011	64211	64411	64611	64711	64811	64911	65011	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											2
Hepatocellular carcinoma							X														X						8
Hepatocellular carcinoma, multiple																											1
Hepatocellular adenoma		X			X									X			X						X	X			10
Hepatocellular adenoma, multiple	X		X			X														X							11
Mesentery	+																										2
Adenocarcinoma	X																										1
Fibrosarcoma, metastatic, skeletal muscle																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skeletal muscle																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skeletal muscle																											1

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm (continued)

Number of Days on Study	4 4 0	5 3 4	6 2 2	7 0 1	7 0 9	7 1 2	7 1 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 9 1 1	6 3 1 1	6 2 6 1	6 1 5 1	6 3 4 1	6 1 0 1	6 1 9 1	5 9 2 1	5 9 3 1	5 9 5 1	5 9 6 1	5 9 7 1	5 9 8 1	5 9 9 1	5 9 0 1	6 0 1 1	6 0 2 1	6 0 3 1	6 0 4 1	6 0 5 1	6 0 7 1	6 0 8 1	6 0 9 1	6 1 1 1	6 1 3 1	6 1 6 1
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Carcinoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+	+			+	+	+	+	+	+	+		+	+		+	+	+	+		+	+	+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, lymph node			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M
Spleen	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Hemangiosarcoma																									
Thymus	+	M	+	M	+	+	+	M	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M
Fibrosarcoma, metastatic, skeletal muscle			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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																				X					

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	6 1 8 1 1	6 2 0 1 1	6 2 1 1 1	6 2 2 1 1	6 2 3 1 1	6 2 4 1 1	6 2 5 1 1	6 2 7 1 1	6 2 8 1 1	6 2 9 1 1	6 3 0 1 1	6 3 2 1 1	6 3 5 1 1	6 3 6 1 1	6 3 7 1 1	6 3 8 1 1	6 3 9 1 1	6 4 0 1 1	6 4 2 1 1	6 4 5 1 1	6 4 6 1 1	6 4 7 1 1	6 4 8 1 1	6 4 9 1 1	6 5 0 1 1	**Total Tissues/ Tumors**
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																		X								1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma							X																			1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+		+	+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	40
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																	X									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																	X				X					2
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	40
Fibrosarcoma, metastatic, skeletal muscle																										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
Osteosarcoma, metastatic, bone																										1

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm (continued)

Number of Days on Study	4 4 0	5 3 4	6 2 2	7 0 1	7 0 9	7 1 2	7 1 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 9 1 1	6 3 1 1	6 2 6 1	6 1 5 1	6 3 4 1	6 1 0 1	6 1 9 1	5 9 2 1	5 9 3 1	5 9 5 1	5 9 6 1	5 9 7 1	5 9 8 1	5 9 9 1	6 0 1 1	6 0 2 1	6 0 3 1	6 0 4 1	6 0 5 1	6 0 7 1	6 0 8 1	6 0 9 1	6 1 1 1	6 1 3 1	6 1 6 1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, fibrosarcoma																									
Vertebra, coccygeal, osteosarcoma																				X					
Skeletal muscle			+																						
Hindlimb, fibrosarcoma			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma		X						X					X									X			
Fibrosarcoma, metastatic, skeletal muscle			X																						
Hepatocellular carcinoma, metastatic, liver				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear															+							M			
Fibrosarcoma															X										
Eye																									
Harderian gland																				+					
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibrosarcoma, metastatic, skeletal muscle			X																						
Hepatocellular carcinoma, metastatic, liver					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed	X					X	X																		

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	6 1 8 1 1	6 2 0 1 1	6 2 2 1 1	6 2 2 1 1	6 2 2 1 1	6 2 2 1 1	6 2 2 1 1	6 2 2 1 1	6 2 2 1 1	6 2 2 1 1	6 2 3 1 1	6 3 3 1 1	6 3 3 1 1	6 3 3 1 1	6 3 3 1 1	6 3 3 1 1	6 3 3 1 1	6 4 4 1 1	6 4 4 1 1	6 4 4 1 1	6 4 4 1 1	6 4 4 1 1	6 4 4 1 1	6 4 5 1 1	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Maxilla, fibrosarcoma										X																1
Vertebra, coccygeal, osteosarcoma																										1
Skeletal muscle																										1
Hindlimb, fibrosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X				X	X				X												X		6
Alveolar/bronchiolar carcinoma													X							X		X				7
Fibrosarcoma, metastatic, skeletal muscle																										1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Fibrosarcoma																										1
Eye							+																			1
Harderian gland					+						+									+						4
Adenoma					X																					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma										X																1
Fibrosarcoma, metastatic, skeletal muscle																										1
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed										X								X								5

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm

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

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	6 6 9 1	6 7 0 1	6 7 1 1	6 7 2 1	6 7 3 1	6 7 4 1	6 7 8 1	6 7 9 1	6 8 0 1	6 8 6 1	6 8 7 1	6 8 8 1	6 9 2 1	6 9 6 1	6 9 8 1	7 0 1 1	7 0 2 1	7 0 3 1	7 0 4 1	7 0 5 1	7 0 6 1	7 0 7 1	7 0 8 1	7 0 9 1	7 1 0 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																										1
Hepatoblastoma																										1
Hepatocellular carcinoma		X								X						X				X			X			8
Hepatocellular carcinoma, multiple																									X	3
Hepatocellular adenoma		X		X			X	X	X											X						12
Hepatocellular adenoma, multiple	X		X			X				X	X	X	X			X	X		X				X	X	X	24
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver		X																								1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm (continued)

Number of Days on Study	4	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	9	2	5	9	3	6	7	9	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	4	2	4	3	3	6	1	4	1	8	4	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	6	6	6	6	6	6	6	6	6	6	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	9	7	5	8	6	9	9	9	8	9	0	5	5	5	5	5	5	6	6	6	6	6	6	6	6
	5	6	3	4	4	1	0	7	1	9	0	2	4	5	6	7	8	9	0	1	3	5	6	7	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+	+	+	+				+		+			+	+	+	+	+		+			+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+	+														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene:
Second Study: 400 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	66911	67011	67711	67811	67911	68011	68111	68211	68311	68611	68711	68811	68911	69211	69611	69911	70111	70211	70311	70411	70511	70611	70711	70811	70911	71011	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+			+	+	+	+			37
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	43
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	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																X											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											2
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm (continued)

Number of Days on Study	4 9 4	5 2 2	5 5 4	5 9 3	6 3 3	6 6 6	6 7 1	6 9 4	7 0 1	7 1 8	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 9 5 1	6 7 6 1	6 5 3 1	6 8 4 1	6 6 4 1	6 9 1 1	6 9 0 1	6 9 7 1	6 8 1 1	6 9 9 1	7 0 0 1	6 5 2 1	6 5 4 1	6 5 5 1	6 5 6 1	6 5 7 1	6 5 8 1	6 5 9 1	6 6 0 1	6 6 1 1	6 6 3 1	6 6 5 1	6 6 6 1	6 6 7 1	6 6 8 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X											X			X			X							
Alveolar/bronchiolar adenoma, multiple																									X
Alveolar/bronchiolar carcinoma																							X		
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, multiple									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																			M						
Eye																									
Harderian gland															+	+							+		
Adenoma															X	X							X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Artery, hepatocellular carcinoma, metastatic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																							X		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																	X								
Lymphoma malignant mixed		X	X	X			X			X	X													X	

TABLE C2b
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	66911	67011	67711	67721	67731	67741	67781	67791	68001	68061	68071	68081	68291	68261	68111	70121	70011	70031	70041	70051	70061	70071	70081	70091	70101	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X		X							X			X				X		9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma			X	X												X			X							5
Alveolar/bronchiolar carcinoma, multiple													X													1
Hepatocellular carcinoma, metastatic, liver		X																		X				X		3
Hepatocellular carcinoma, metastatic, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear		M																								
Eye					+																					1
Harderian gland					+			+		+																6
Adenoma					X			X		X																6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Artery, hepatocellular carcinoma, metastatic		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed												X														8

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study

	0 ppm	100 ppm	200 ppm	400 ppm
Harderian Gland: Adenoma				
Overall rates[a]	0/50 (0%)	1/50 (2%)	3/50 (6%)	1/60 (2%)
Adjusted rates[b]	0.0%	2.2%	6.3%	2.2%
Terminal rates[c]	0/47 (0%)	1/45 (2%)	2/46 (4%)	1/46 (2%)
First incidence (days)	–[e]	729 (T)	682	729 (T)
Life table tests[d]	P=0.350	P=0.491	P=0.121	P=0.496
Logistic regression tests[d]	P=0.357	P=0.491	P=0.115	P=0.496
Cochran-Armitage test[d]	P=0.416			
Fisher exact test[d]		P=0.500	P=0.121	P=0.545
Harderian Gland: Adenoma or Carcinoma				
Overall rates	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/60 (3%)
Adjusted rates	2.0%	2.2%	6.3%	4.3%
Terminal rates	0/47 (0%)	1/45 (2%)	2/46 (4%)	2/46 (4%)
First incidence (days)	585	729 (T)	682	729 (T)
Life table tests	P=0.323	P=0.751	P=0.304	P=0.490
Logistic regression tests	P=0.381	P=0.667N	P=0.238	P=0.560
Cochran-Armitage test	P=0.400			
Fisher exact test		P=0.753N	P=0.309	P=0.569
Liver: Hemangiosarcoma				
Overall rates	1/50 (2%)	1/50 (2%)	3/50 (6%)	0/60 (0%)
Adjusted rates	2.1%	2.2%	6.5%	0.0%
Terminal rates	1/47 (2%)	1/45 (2%)	3/46 (7%)	0/46 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	–
Life table tests	P=0.413N	P=0.752	P=0.298	P=0.504N
Logistic regression tests	P=0.413N	P=0.752	P=0.298	P=0.504N
Cochran-Armitage test	P=0.351N			
Fisher exact test		P=0.753N	P=0.309	P=0.455N
Liver: Hepatocellular Adenoma				
Overall rates	17/50 (34%)	22/50 (44%)	19/50 (38%)	20/60 (33%)
Adjusted rates	36.2%	48.9%	40.3%	42.6%
Terminal rates	17/47 (36%)	22/45 (49%)	18/46 (39%)	19/46 (41%)
First incidence (days)	729 (T)	729 (T)	617	711
Life table tests	P=0.387	P=0.154	P=0.388	P=0.310
Logistic regression tests	P=0.391	P=0.154	P=0.417	P=0.314
Cochran-Armitage test	P=0.359N			
Fisher exact test		P=0.206	P=0.418	P=0.550N
Liver: Hepatocellular Carcinoma				
Overall rates	5/50 (10%)	7/50 (14%)	3/50 (6%)	13/60 (22%)
Adjusted rates	10.6%	14.8%	6.5%	28.3%
Terminal rates	5/47 (11%)	5/45 (11%)	3/46 (7%)	13/46 (28%)
First incidence (days)	729 (T)	557	729 (T)	729 (T)
Life table tests	P=0.019	P=0.353	P=0.368N	P=0.030
Logistic regression tests	P=0.022	P=0.448	P=0.368N	P=0.030
Cochran-Armitage test	P=0.055			
Fisher exact test		P=0.380	P=0.357N	P=0.081

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rates	5/50 (10%)	8/50 (16%)	4/50 (8%)	13/60 (22%)
Adjusted rates	10.6%	16.6%	8.7%	28.3%
Terminal rates	5/47 (11%)	5/45 (11%)	4/46 (9%)	13/46 (28%)
First incidence (days)	729 (T)	557	729 (T)	729 (T)
Life table tests	P=0.027	P=0.256	P=0.513N	P=0.030
Logistic regression tests	P=0.031	P=0.346	P=0.513N	P=0.030
Cochran-Armitage test	P=0.072			
Fisher exact test		P=0.277	P=0.500N	P=0.081
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	20/50 (40%)	26/50 (52%)	19/50 (38%)	29/60 (48%)
Adjusted rates	42.6%	55.3%	40.3%	61.7%
Terminal rates	20/47 (43%)	24/45 (53%)	18/46 (39%)	28/46 (61%)
First incidence (days)	729 (T)	557	617	711
Life table tests	P=0.077	P=0.116	P=0.533N	P=0.043
Logistic regression tests	P=0.074	P=0.136	P=0.500N	P=0.043
Cochran-Armitage test	P=0.343			
Fisher exact test		P=0.158	P=0.500N	P=0.248
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	3/50 (6%)	9/50 (18%)	10/50 (20%)	9/60 (15%)
Adjusted rates	6.4%	20.0%	21.7%	19.6%
Terminal rates	3/47 (6%)	9/45 (20%)	10/46 (22%)	9/46 (20%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.095	P=0.053	P=0.034	P=0.057
Logistic regression tests	P=0.095	P=0.053	P=0.034	P=0.057
Cochran-Armitage test	P=0.205			
Fisher exact test		P=0.061	P=0.036	P=0.114
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	6/50 (12%)	3/50 (6%)	6/50 (12%)	5/60 (8%)
Adjusted rates	12.5%	6.2%	12.7%	10.9%
Terminal rates	5/47 (11%)	1/45 (2%)	5/46 (11%)	5/46 (11%)
First incidence (days)	623	522	682	729 (T)
Life table tests	P=0.554	P=0.267N	P=0.606	P=0.516N
Logistic regression tests	P=0.469N	P=0.115N	P=0.613	P=0.499N
Cochran-Armitage test	P=0.430N			
Fisher exact test		P=0.243N	P=0.620N	P=0.373N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	9/50 (18%)	12/50 (24%)	16/50 (32%)	14/60 (23%)
Adjusted rates	18.7%	25.4%	34.0%	30.4%
Terminal rates	8/47 (17%)	10/45 (22%)	15/46 (33%)	14/46 (30%)
First incidence (days)	623	522	682	729 (T)
Life table tests	P=0.140	P=0.281	P=0.079	P=0.158
Logistic regression tests	P=0.157	P=0.376	P=0.083	P=0.159
Cochran-Armitage test	P=0.325			
Fisher exact test		P=0.312	P=0.083	P=0.328

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
All Organs: Hemangiosarcoma				
Overall rates	1/50 (2%)	2/50 (4%)	4/50 (8%)	0/60 (0%)
Adjusted rates	2.1%	4.4%	8.7%	0.0%
Terminal rates	1/47 (2%)	2/45 (4%)	4/46 (9%)	0/46 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	-
Life table tests	P=0.377N	P=0.485	P=0.174	P=0.504N
Logistic regression tests	P=0.377N	P=0.485	P=0.174	P=0.504N
Cochran-Armitage test	P=0.307N			
Fisher exact test		P=0.500	P=0.181	P=0.455N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	1/50 (2%)	3/50 (6%)	5/50 (10%)	0/60 (0%)
Adjusted rates	2.1%	6.7%	10.9%	0.0%
Terminal rates	1/47 (2%)	3/45 (7%)	5/46 (11%)	0/46 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	-
Life table tests	P=0.348N	P=0.290	P=0.099	P=0.504N
Logistic regression tests	P=0.348N	P=0.290	P=0.099	P=0.504N
Cochran-Armitage test	P=0.272N			
Fisher exact test		P=0.309	P=0.102	P=0.455N
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rates	6/50 (12%)	3/50 (6%)	5/50 (10%)	5/60 (8%)
Adjusted rates	12.5%	6.7%	10.6%	10.6%
Terminal rates	5/47 (11%)	3/45 (7%)	4/46 (9%)	4/46 (9%)
First incidence (days)	690	729 (T)	641	620
Life table tests	P=0.554N	P=0.268N	P=0.512N	P=0.515N
Logistic regression tests	P=0.520N	P=0.257N	P=0.507N	P=0.488N
Cochran-Armitage test	P=0.419N			
Fisher exact test		P=0.243N	P=0.500N	P=0.373N
All Organs: Benign Neoplasms				
Overall rates	21/50 (42%)	26/50 (52%)	29/50 (58%)	27/60 (45%)
Adjusted rates	44.7%	57.8%	60.4%	57.4%
Terminal rates	21/47 (45%)	26/45 (58%)	27/46 (59%)	26/46 (57%)
First incidence (days)	729 (T)	729 (T)	617	711
Life table tests	P=0.138	P=0.149	P=0.068	P=0.133
Logistic regression tests	P=0.137	P=0.149	P=0.080	P=0.135
Cochran-Armitage test	P=0.510			
Fisher exact test		P=0.212	P=0.081	P=0.451
All Organs: Malignant Neoplasms				
Overall rates	17/50 (34%)	17/50 (34%)	16/50 (32%)	22/60 (37%)
Adjusted rates	34.0%	34.0%	33.3%	46.8%
Terminal rates	14/47 (30%)	12/45 (27%)	14/46 (30%)	21/46 (46%)
First incidence (days)	585	522	641	620
Life table tests	P=0.165	P=0.522	P=0.524N	P=0.192
Logistic regression tests	P=0.239	P=0.460N	P=0.500N	P=0.207
Cochran-Armitage test	P=0.414			
Fisher exact test		P=0.583N	P=0.500N	P=0.465

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rates	32/50 (64%)	38/50 (76%)	35/50 (70%)	38/60 (63%)
Adjusted rates	64.0%	76.0%	71.4%	79.2%
Terminal rates	29/47 (62%)	33/45 (73%)	32/46 (70%)	36/46 (78%)
First incidence (days)	585	522	617	620
Life table tests	P=0.185	P=0.112	P=0.306	P=0.124
Logistic regression tests	P=0.203	P=0.168	P=0.345	P=0.106
Cochran-Armitage test	P=0.328N			
Fisher exact test		P=0.138	P=0.335	P=0.551N

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

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study

	0 ppm	400 ppm
Harderian Gland: Adenoma		
Overall rates[a]	1/50 (2%)	6/50 (12%)
Adjusted rates[b]	2.3%	15.4%
Terminal rates[c]	1/43 (2%)	6/39 (15%)
First incidence (days)	729 (T)	729 (T)
Life table tests[d]		P=0.044
Logistic regression tests[d]		P=0.044
Fisher exact test[d]		P=0.056
Liver: Hepatocellular Adenoma		
Overall rates	21/50 (42%)	36/50 (72%)
Adjusted rates	44.7%	81.7%
Terminal rates	17/43 (40%)	31/39 (79%)
First incidence (days)	701	522
Life table tests		P=0.001
Logistic regression tests		P=0.001
Fisher exact test		P=0.002
Liver: Hepatocellular Carcinoma		
Overall rates	9/50 (18%)	11/50 (22%)
Adjusted rates	19.3%	25.0%
Terminal rates	6/43 (14%)	7/39 (18%)
First incidence (days)	622	494
Life table tests		P=0.329
Logistic regression tests		P=0.422
Fisher exact test		P=0.402
Liver: Hepatoblastoma or Hepatocellular Carcinoma		
Overall rates	9/50 (18%)	12/50 (24%)
Adjusted rates	19.3%	26.7%
Terminal rates	6/43 (14%)	7/39 (18%)
First incidence (days)	622	494
Life table tests		P=0.254
Logistic regression tests		P=0.338
Fisher exact test		P=0.312
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rates	25/50 (50%)	38/50 (76%)
Adjusted rates	52.1%	82.5%
Terminal rates	20/43 (47%)	31/39 (79%)
First incidence (days)	622	494
Life table tests		P=0.004
Logistic regression tests		P=0.005
Fisher exact test		P=0.006
Lung: Alveolar/bronchiolar Adenoma		
Overall rates	6/50 (12%)	10/50 (20%)
Adjusted rates	14.0%	24.6%
Terminal rates	6/43 (14%)	9/39 (23%)
First incidence (days)	729 (T)	494
Life table tests		P=0.154
Logistic regression tests		P=0.201
Fisher exact test		P=0.207

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
Lung: Alveolar/bronchiolar Carcinoma		
Overall rates	7/50 (14%)	6/50 (12%)
Adjusted rates	15.7%	15.4%
Terminal rates	6/43 (14%)	6/39 (15%)
First incidence (days)	534	729 (T)
Life table tests		P=0.570N
Logistic regression tests		P=0.505N
Fisher exact test		P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rates	13/50 (26%)	16/50 (32%)
Adjusted rates	29.4%	39.7%
Terminal rates	12/43 (28%)	15/39 (38%)
First incidence (days)	534	494
Life table tests		P=0.231
Logistic regression tests		P=0.321
Fisher exact test		P=0.330
All Organs: Hemangiosarcoma		
Overall rates	4/50 (8%)	1/50 (2%)
Adjusted rates	9.3%	2.6%
Terminal rates	4/43 (9%)	1/39 (3%)
First incidence (days)	729 (T)	729 (T)
Life table tests		P=0.210N
Logistic regression tests		P=0.210N
Fisher exact test		P=0.181N
All Organs: Hemangioma or Hemangisarcoma		
Overall rates	4/50 (8%)	2/50 (4%)
Adjusted rates	9.3%	5.1%
Terminal rates	4/43 (9%)	2/39 (5%)
First incidence (days)	729 (T)	729 (T)
Life table tests		P=0.383N
Logistic regression tests		P=0.383N
Fisher exact test		P=0.339N
All Organs: Malignant Lymphoma (Histiocytic or Mixed)		
Overall rates	5/50 (10%)	9/50 (18%)
Adjusted rates	10.7%	19.4%
Terminal rates	2/43 (5%)	3/39 (8%)
First incidence (days)	440	522
Life table tests		P=0.177
Logistic regression tests		P=0.247
Fisher exact test		P=0.194
All Organs: Malignant Lymphoma or Histiocytic Sarcoma		
Overall rates	5/50 (10%)	9/50 (18%)
Adjusted rates	10.7%	19.4%
Terminal rates	2/43 (5%)	3/39 (8%)
First incidence (days)	440	522
Life table tests		P=0.177
Logistic regression tests		P=0.247
Fisher exact test		P=0.194

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
All Organs: Benign Neoplasms		
Overall rates	25/50 (50%)	39/50 (78%)
Adjusted rates	53.2%	86.5%
Terminal rates	21/43 (49%)	33/39 (85%)
First incidence (days)	701	494
Life table tests		P=0.001
Logistic regression tests		P=0.002
Fisher exact test		P=0.003
All Organs: Malignant Neoplasms		
Overall rates	25/50 (50%)	26/50 (52%)
Adjusted rates	50.0%	52.0%
Terminal rates	18/43 (42%)	15/39 (38%)
First incidence (days)	440	494
Life table tests		P=0.369
Logistic regression tests		P=0.465N
Fisher exact test		P=0.500
All Organs: Benign or Malignant Neoplasms		
Overall rates	37/50 (74%)	44/50 (88%)
Adjusted rates	74.0%	88.0%
Terminal rates	30/43 (70%)	33/39 (85%)
First incidence (days)	440	494
Life table tests		P=0.048
Logistic regression tests		P=0.093
Fisher exact test		P=0.062

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the exposure group is indicated by N.

TABLE C4
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma	Hepatoblastoma
Historical Incidence at Battelle Columbus Laboratory				
2,4-Dichlorophenol	4/50	7/50	10/50	0/50
5,5-Diphenylhydantoin	19/50	13/50	29/50	0/50
Dowicide EC-7 pentachlorophenol	5/35	1/35	6/35	0/35
Ethylene thiourea	11/49	13/49	20/49	0/49
Polybrominated biphenyls (Firemaster FF-1®)	9/50	8/50	16/50	0/50
Technical grade pentachlorophenol	5/32	2/32	7/32	0/32
Overall Historical Incidence				
Total	145/865 (16.8%)	122/865 (14.1%)	249/865 (28.8%)	0/865 (0.0%)
Standard deviation	8.2%	7.2%	10.9%	
Range	4%-38%	3%-27%	17%-58%	

[a] Data as of 3 April 1991

TABLE C5a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Triamterene: First Study[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	0
2-Year study				
Early deaths				
Moribund	1	2	2	6
Natural deaths	2	3	2	8
Survivors				
Terminal sacrifice	47	45	46	46
Animals examined microscopically	70	70	70	70
3-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Testes	10		(10)	
Bilateral, seminiferous tubule, atrophy, focal	2 (20%)		1 (10%)	
Seminiferous tubule, atrophy, focal	4 (40%)		7 (70%)	
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

TABLE C5a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
3-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(4)	(1)	(10)
Nephropathy	1 (10%)	4 (100%)	1 (100%)	1 (10%)
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(3)	(10)	
Basophilic focus		2 (67%)	1 (10%)	
Vacuolization cytoplasmic	3 (30%)	1 (33%)	1 (10%)	
Pancreas	(10)		(10)	
Acinus, necrosis, acute	1 (10%)			
Cardiovascular System				
None				
Endocrine System				
Parathyroid gland	(9)		(10)	
Cyst			1 (10%)	
Thyroid gland	(10)		(10)	
Cyst			1 (10%)	
General Body System				
None				
Genital System				
Preputial gland	(1)	(2)	(1)	
Dilatation	1 (100%)	2 (100%)	1 (100%)	
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE C5a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	
Nephropathy	8 (80%)	9 (90%)	9 (90%)	
2-Year Study				
Alimentary System				
Gallbladder	(48)	(46)	(50)	(54)
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Intestine small, ileum	(49)	(49)	(50)	(55)
Inflammation, acute			1 (2%)	
Peyer's patch, necrosis				1 (2%)
Liver	(50)	(50)	(50)	(60)
Basophilic focus	6 (12%)	3 (6%)	10 (20%)	5 (8%)
Basophilic focus, multiple		1 (2%)		
Clear cell focus	1 (2%)	9 (18%)	4 (8%)	10 (17%)
Clear cell focus, multiple				1 (2%)
Eosinophilic focus	7 (14%)	12 (24%)	11 (22%)	3 (5%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)		
Necrosis, acute		1 (2%)		
Bile duct, cyst				1 (2%)
Bile duct, inflammation		1 (2%)		
Mesentery	(3)	(3)	(4)	(2)
Ectopic tissue				1 (50%)
Inflammation, chronic active	1 (33%)	1 (33%)		
Fat, necrosis	2 (67%)	2 (67%)	3 (75%)	1 (50%)
Pancreas	(50)	(50)	(50)	(60)
Inflammation, chronic active	1 (2%)	1 (2%)		
Acinus, atrophy	1 (2%)			
Duct, ectasia				1 (2%)
Stomach, forestomach	(49)	(50)	(50)	(58)
Acanthosis		1 (2%)	3 (6%)	3 (5%)
Diverticulum		1 (2%)		
Inflammation, acute				4 (7%)
Stomach, glandular	(50)	(50)	(50)	(59)
Inflammation, acute	1 (2%)		2 (4%)	1 (2%)
Inflammation, chronic active	1 (2%)			

TABLE C5a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(50)	(50)	(60)
Inflammation, chronic active	1 (2%)			
Thrombus			1 (2%)	
Endocrine System				
Adrenal gland	(50)	(50)	(50)	(59)
Capsule, hyperplasia	10 (20%)	6 (12%)	3 (6%)	5 (8%)
Adrenal gland, cortex	(50)	(50)	(50)	(60)
Angiectasis	1 (2%)			
Hyperplasia	1 (2%)	2 (4%)		
Hypertrophy	26 (52%)	16 (32%)	7 (14%)	16 (27%)
Infarct		1 (2%)		
Adrenal gland, medulla	(50)	(50)	(48)	(60)
Infarct		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(60)
Hyperplasia	1 (2%)	6 (12%)	1 (2%)	
Inflammation, acute	1 (2%)			
Pituitary gland	(49)	(48)	(44)	(58)
Pars distalis, cyst	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Pars intermedia, hypertrophy				1 (2%)
Thyroid gland	(50)	(50)	(50)	(60)
Ultimobranchial cyst		1 (2%)		
Follicular cell, hyperplasia	3 (6%)	8 (16%)	16 (32%)	20 (33%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(60)
Granuloma sperm			1 (2%)	
Inflammation, chronic active			1 (2%)	
Preputial gland	(11)	(12)	(23)	(15)
Dilatation	8 (73%)	10 (83%)	21 (91%)	13 (87%)
Inflammation, chronic active	3 (27%)	3 (25%)	2 (9%)	2 (13%)
Seminal vesicle	(50)	(50)	(50)	(60)
Dilatation	1 (2%)			
Hyperplasia			1 (2%)	
Inflammation, chronic active	1 (2%)			
Testes	(50)	(50)	(50)	(60)
Atrophy			1 (2%)	
Degeneration	5 (10%)	2 (4%)	2 (4%)	5 (8%)
Granuloma sperm, multiple	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(60)
Myelofibrosis			3 (6%)	
Lymph node	(50)	(50)	(50)	(60)
Mediastinal, infiltration cellular, histiocyte		1 (2%)		

TABLE C5a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(47)	(48)	(49)	(60)
Necrosis				1 (2%)
Lymph node, mesenteric	(46)	(46)	(44)	(45)
Congestion				1 (2%)
Infiltration cellular, histiocyte			1 (2%)	
Necrosis				1 (2%)
Spleen	(50)	(50)	(50)	(60)
Fibrosis				1 (2%)
Hematopoietic cell proliferation		2 (4%)		
Necrosis				4 (7%)
Thymus	(36)	(40)	(37)	(39)
Necrosis				7 (18%)
Integumentary System				
Skin	(49)	(50)	(49)	(60)
Alopecia	2 (4%)	3 (6%)	1 (2%)	4 (7%)
Inflammation, chronic active		1 (2%)		
Ulcer		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(59)
Rib, cartilage, fracture healed		1 (2%)		
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(60)
Hemorrhage			1 (2%)	
Inflammation, chronic			1 (2%)	
Thrombus		1 (2%)		
Alveolar epithelium, hyperplasia	4 (8%)	3 (6%)	2 (4%)	1 (2%)
Bronchiole, epithelium, hyperplasia				1 (2%)
Nose	(50)	(50)	(50)	(60)
Angiectasis				2 (3%)
Inflammation, acute			1 (2%)	2 (3%)
Special Senses System				
Eye			(1)	
Cornea, angiectasis			1 (100%)	
Harderian gland	(3)	(3)	(6)	(2)
Hyperplasia	2 (67%)	2 (67%)	4 (67%)	
Inflammation			1 (17%)	

TABLE C5a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(60)
Cyst			2 (4%)	3 (5%)
Infarct	2 (4%)			1 (2%)
Inflammation, acute			1 (2%)	
Nephropathy	49 (98%)	48 (96%)	49 (98%)	58 (97%)
Pigmentation		1 (2%)		

[a] Number of animals examined microscopically at site and number of animals with lesion

TABLE C5b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice at the 15-Month Interim Evaluation and in the 2-Year Feed Study of Triamterene: Second Study[a]

	0 ppm	400 ppm
Disposition Summary		
Animals initially in study	60	60
15-Month interim evaluation	10	10
2-Year study		
Early deaths		
Moribund	3	4
Natural deaths	4	7
Survivors		
Died last week of study	1	
Terminal sacrifice	42	39
Animals examined microscopically	60	60
15-Month Interim Evaluation		
Alimentary System		
Liver	(9)	(10)
Basophilic focus	1 (11%)	
Clear cell focus		1 (10%)
Vacuolization cytoplasmic		2 (20%)
Cardiovascular System		
None		
Endocrine System		
Pituitary gland	(10)	(9)
Pars distalis, hyperplasia	1 (10%)	1 (11%)
General Body System		
None		
Genital System		
Epididymis	(10)	(10)
Inflammation, chronic active		1 (10%)
Preputial gland	(1)	
Dilatation	1 (100%)	
Testes	(10)	(10)
Degeneration	1 (10%)	
Hematopoietic System		
None		

TABLE C5b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice at the 15-Month Interim Evaluation and in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
15-Month Interim Evaluation (continued)		
Integumentary System		
Skin	(10)	(10)
Subcutaneous tissue, abscess		1 (10%)
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
Harderian gland	(1)	
Hyperplasia	1 (100%)	
Urinary System		
Kidney	(10)	(10)
Nephropathy	10 (100%)	10 (100%)
2-Year Study		
Alimentary System		
Intestine small, duodenum	(47)	(50)
Ulcer		1 (2%)
Intestine small, jejunum	(49)	(49)
Peyer's patch, infiltration cellular, histiocyte		1 (2%)
Liver	(50)	(50)
Basophilic focus		7 (14%)
Clear cell focus	7 (14%)	4 (8%)
Clear cell focus, multiple	1 (2%)	
Congestion		2 (4%)
Eosinophilic focus	11 (22%)	10 (20%)
Eosinophilic focus, multiple	1 (2%)	
Hematopoietic cell proliferation	1 (2%)	
Infarct	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)	
Regeneration		1 (2%)
Hepatocyte, necrosis		1 (2%)
Mesentery	(2)	(1)
Fat, necrosis		1 (100%)

TABLE C5b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice at the 15-Month Interim Evaluation and in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Alimentary System (continued)		
Pancreas	(48)	(50)
Acinus, atrophy	2 (4%)	4 (8%)
Duct, cyst		1 (2%)
Stomach, forestomach	(49)	(50)
Acanthosis	2 (4%)	2 (4%)
Inflammation, chronic active		1 (2%)
Stomach, glandular	(49)	(50)
Inflammation, acute	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)	
Mucosa, mineralization	1 (2%)	
Cardiovascular System		
Heart	(50)	(50)
Inflammation, chronic active	1 (2%)	
Endocrine System		
Adrenal gland	(50)	(50)
Capsule, hyperplasia	8 (16%)	1 (2%)
Adrenal gland, cortex	(50)	(50)
Hypertrophy	19 (38%)	8 (16%)
Islets, pancreatic	(47)	(49)
Hyperplasia	2 (4%)	2 (4%)
Pituitary gland	(50)	(48)
Pars distalis, cyst	1 (2%)	
Pars distalis, hyperplasia		2 (4%)
Thyroid gland	(50)	(50)
Follicular cell, hyperplasia		16 (32%)
General Body System		
None		
Genital System		
Epididymis	(50)	(50)
Granuloma sperm		1 (2%)
Inflammation, chronic	1 (2%)	2 (4%)
Preputial gland	(40)	(37)
Dilatation	35 (88%)	37 (100%)
Inflammation, acute	1 (3%)	
Inflammation, chronic active	3 (8%)	1 (3%)
Seminal vesicle	(50)	(50)
Inflammation, acute	1 (2%)	
Testes	(50)	(50)
Degeneration	2 (4%)	2 (4%)

TABLE C5b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice at the 15-Month Interim Evaluation and in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Hematopoietic System		
Bone marrow	(50)	(50)
Myelofibrosis	1 (2%)	
Lymph node, mesenteric	(41)	(44)
Congestion	2 (5%)	2 (5%)
Hematopoietic cell proliferation	1 (2%)	
Inflammation, granulomatous		2 (5%)
Spleen	(47)	(50)
Hematopoietic cell proliferation	3 (6%)	1 (2%)
Integumentary System		
Skin	(50)	(50)
Subcutaneous tissue, abscess	1 (2%)	
Musculoskeletal System		
None		
Nervous System		
Brain	(50)	(50)
Compression	1 (2%)	
Hemorrhage	1 (2%)	
Respiratory System		
Lung	(50)	(50)
Alveolar epithelium, hyperplasia	1 (2%)	2 (4%)
Nose	(50)	(50)
Concretion	1 (2%)	
Inflammation, acute	4 (8%)	2 (4%)
Special Senses System		
Ear	(1)	
Inflammation, acute	1 (100%)	
Eye	(1)	(1)
Cornea, inflammation, chronic active		1 (100%)
Harderian gland	(4)	(6)
Hyperplasia	3 (75%)	
Urinary System		
Kidney	(50)	(50)
Inflammation, suppurative	1 (2%)	
Nephropathy	45 (90%)	43 (86%)
Urinary bladder	(50)	(50)
Inflammation, acute	1 (2%)	

[a] Number of animals examined microscopically at site and number of animals with lesion

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF TRIAMTERENE

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TABLE D1a
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation	10	10	10	
2-Year study				
Early deaths				
Moribund	8	5	1	10
Natural deaths	4	2	6	7
Survivors				
Died last week of study	1	2	1	
Terminal sacrifice	37	41	42	43
Animals examined microscopically	70	70	70	70
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(2)	(10)	
Hepatocellular adenoma	2 (20%)	2 (100%)	2 (20%)	
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
None				
Hematopoietic System				
Spleen	(10)		(9)	
Lymphoma malignant histiocytic			1 (11%)	
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

TABLE D1a
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)		(10)	
Alveolar/bronchiolar adenoma	1 (10%)			
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[c]	(10)	(10)	(10)	
Lymphoma malignant histiocytic			1 (10%)	
2-Year Study				
Alimentary System				
Gallbladder	(48)	(47)	(49)	(55)
Intestine large, cecum	(47)	(50)	(50)	(60)
Intestine small, ileum	(47)	(49)	(49)	(57)
Intestine small, jejunum	(47)	(48)	(48)	(59)
Adenocarcinoma	1 (2%)			
Liver	(50)	(50)	(50)	(60)
Hemangiosarcoma	1 (2%)		1 (2%)	
Hepatocellular carcinoma	3 (6%)	3 (6%)	3 (6%)	6 (10%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)		2 (3%)
Hepatocellular adenoma	6 (12%)	10 (20%)	12 (24%)	22 (37%)
Hepatocellular adenoma, multiple	4 (8%)	12 (24%)	11 (22%)	14 (23%)
Hepatocholangiocarcinoma	1 (2%)			
Osteosarcoma, metastatic, bone			1 (2%)	
Serosa, adenocarcinoma, metastatic, ovary		1 (2%)		
Mesentery	(8)	(10)	(8)	(5)
Adenocarcinoma, metastatic, ovary		1 (10%)		
Hemangiosarcoma	1 (13%)			
Hepatocholangiocarcinoma, metastatic, uterus	1 (13%)			
Osteosarcoma, metastatic, uncertain primary site				1 (20%)
Pancreas	(49)	(50)	(50)	(60)
Adenocarcinoma, metastatic, ovary		1 (2%)		
Hepatocholangiocarcinoma, metastatic, uterus	1 (2%)			
Salivary glands	(49)	(49)	(50)	(60)
Stomach, forestomach	(49)	(50)	(50)	(60)
Papilloma squamous			1 (2%)	1 (2%)
Squamous cell carcinoma			1 (2%)	

TABLE D1a
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study
(continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(50)	(50)	(60)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(60)
Spindle cell, adenoma	3 (6%)		3 (6%)	2 (3%)
Islets, pancreatic	(49)	(49)	(50)	(59)
Adenoma		1 (2%)		
Pituitary gland	(49)	(47)	(48)	(58)
Pars distalis, adenoma	7 (14%)	5 (11%)	3 (6%)	5 (9%)
Pars intermedia, adenoma			2 (4%)	1 (2%)
Thyroid gland	(49)	(49)	(50)	(60)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Ovary	(48)	(50)	(50)	(59)
Adenocarcinoma		1 (2%)		
Cystadenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Granulosa cell tumor benign			1 (2%)	
Hemangiosarcoma			1 (2%)	
Hepatocholangiocarcinoma, metastatic, uterus	1 (2%)			
Mixed tumor benign				1 (2%)
Teratoma	1 (2%)			
Uterus	(48)	(50)	(50)	(60)
Adenoma		2 (4%)		
Hemangiosarcoma			1 (2%)	
Polyp stromal		1 (2%)	2 (4%)	2 (3%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(60)
Hemangiosarcoma		1 (2%)	1 (2%)	1 (2%)
Lymph node	(49)	(50)	(50)	(60)
Axillary, liposarcoma, metastatic, skin		1 (2%)		
Inguinal, squamous cell carcinoma, metastatic, skin				1 (2%)
Mediastinal, hepatocellular carcinoma, metastatic, liver			1 (2%)	
Mediastinal, hepatocholangiocarcinoma, metastatic, uterus	1 (2%)			
Renal, hepatocholangiocarcinoma, metastatic, uterus	1 (2%)			

TABLE D1a
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(46)	(49)	(50)	(58)
Adenocarcinoma, metastatic, ovary		1 (2%)		
Lymph node, mesenteric	(43)	(45)	(46)	(54)
Hepatocholangiocarcinoma, metastatic, uterus	1 (2%)			
Spleen	(49)	(50)	(49)	(60)
Hemangiosarcoma	1 (2%)		3 (6%)	1 (2%)
Thymus	(38)	(44)	(44)	(50)
Integumentary System				
Mammary gland	(36)	(43)	(46)	(51)
Skin	(50)	(49)	(49)	(60)
Basal cell carcinoma				1 (2%)
Squamous cell carcinoma				1 (2%)
Subcutaneous tissue, fibrosarcoma	3 (6%)		1 (2%)	3 (5%)
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Subcutaneous tissue, liposarcoma		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(60)
Vertebra, osteosarcoma		1 (2%)	1 (2%)	
Skeletal muscle	(1)	(1)		
Adenocarcinoma, metastatic, ovary		1 (100%)		
Hepatocholangiocarcinoma, metastatic, uterus	1 (100%)			
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(60)
Adenocarcinoma, metastatic, ovary		1 (2%)		
Alveolar/bronchiolar adenoma	4 (8%)	5 (10%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		3 (5%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)	1 (2%)	
Hepatocholangiocarcinoma, metastatic, uterus	1 (2%)			
Liposarcoma, metastatic, multiple, skin		1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)	1 (2%)	
Osteosarcoma, metastatic, uncertain primary site				1 (2%)
Special Senses System				
Harderian gland	(1)	(3)	(3)	(2)
Adenoma	1 (100%)	3 (100%)	2 (67%)	

TABLE D1a
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study
(continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(60)
Capsule, adenocarcinoma, metastatic, ovary		1 (2%)		
Urinary bladder	(48)	(49)	(49)	(60)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(60)
Lymphoma malignant histiocytic	1 (2%)	3 (6%)	4 (8%)	3 (5%)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)		2 (3%)
Lymphoma malignant mixed	9 (18%)	5 (10%)	9 (18%)	6 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	3	2	3	
2-Year study	34	40	40	46
Total primary neoplasms				
15-Month interim evaluation	3	2	3	
2-Year study	53	60	67	81
Total animals with benign neoplasms				
15-Month interim evaluation	3	2	2	
2-Year study	22	31	28	36
Total benign neoplasms				
15-Month interim evaluation	3	2	2	
2-Year study	28	42	41	51
Total animals with malignant neoplasms				
15-Month interim evaluation			1	
2-Year study	20	17	21	25
Total malignant neoplasms				
15-Month interim evaluation			1	
2-Year study	25	18	26	30
Total animals with metastatic neoplasms				
2-Year study	2	4	2	2
Total metastatic neoplasms				
2-Year study	9	11	4	3
Total animals with malignant neoplasms uncertain primary site				
2-Year study				1

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were found at the 3-month interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D1b
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study[a]

	0 ppm	400 ppm
Disposition Summary		
Animals initially in study	60	60
15-Month interim evaluation	10	9
2-Year study		
Early deaths		
Moribund	7	4
Natural deaths	3	9
Survivors		
Terminal sacrifice	40	38
Animals examined microscopically	60	60
15-Month Interim Evaluation		
Alimentary System		
Liver	(10)	(9)
Hepatocellular carcinoma	1 (10%)	
Lymphoma malignant mixed		1 (11%)
Pancreas	(10)	(9)
Lymphoma malignant mixed		1 (11%)
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
None		
Hematopoietic System		
Lymph node	(10)	(9)
Renal, lymphoma malignant mixed		1 (11%)
Lymph node, mandibular	(10)	(9)
Lymphoma malignant mixed		1 (11%)
Lymph node, mesenteric	(10)	(9)
Lymphoma malignant mixed		1 (11%)
Spleen	(10)	(9)
Lymphoma malignant mixed		2 (22%)
Thymus	(9)	(9)
Lymphoma malignant mixed		1 (11%)

TABLE D1b
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study
(continued)

	0 ppm	400 ppm
15-Month Interim Evaluation (continued)		
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
Kidney	(10)	(9)
Lymphoma malignant mixed		1 (11%)
Systemic Lesions		
Multiple organs[b]	(10)	(9)
Lymphoma malignant mixed		2 (22%)
2-Year Study		
Alimentary System		
Gallbladder	(50)	(50)
Intestine large, cecum	(49)	(51)
Intestine large, colon	(50)	(51)
Fibrosarcoma, metastatic, uterus		1 (2%)
Intestine large, rectum	(50)	(50)
Intestine small, ileum	(49)	(51)
Intestine small, jejunum	(49)	(51)
Liver	(50)	(51)
Hepatocellular carcinoma	5 (10%)	9 (18%)
Hepatocellular carcinoma, multiple		2 (4%)
Hepatocellular adenoma	4 (8%)	9 (18%)
Hepatocellular adenoma, multiple	3 (6%)	19 (37%)
Pancreas	(49)	(50)
Salivary glands	(50)	(51)
Stomach, forestomach	(50)	(51)
Papilloma squamous		1 (2%)
Stomach, glandular	(50)	(51)

TABLE D1b
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Cardiovascular System		
Heart	(50)	(51)
Endocrine System		
Adrenal gland, cortex	(50)	(51)
Spindle cell, adenoma	2 (4%)	2 (4%)
Adrenal gland, medulla	(49)	(51)
Islets, pancreatic	(49)	(48)
Adenoma	1 (2%)	
Pituitary gland	(49)	(47)
Adenoma	1 (2%)	1 (2%)
Pars distalis, adenoma		2 (4%)
Pars distalis, carcinoma		1 (2%)
General Body System		
None		
Genital System		
Clitoral gland	(7)	(4)
Hemangiosarcoma	1 (14%)	
Ovary	(50)	(49)
Granulosa cell tumor benign		1 (2%)
Teratoma benign		1 (2%)
Uterus	(50)	(51)
Adenocarcinoma	1 (2%)	
Fibrosarcoma		1 (2%)
Hemangiosarcoma	1 (2%)	
Leiomyosarcoma	1 (2%)	
Sarcoma stromal	1 (2%)	
Hematopoietic System		
Lymph node	(50)	(51)
Lymph node, mandibular	(50)	(51)
Mast cell tumor malignant		1 (2%)
Lymph node, mesenteric	(47)	(47)
Spleen	(49)	(51)
Hemangiosarcoma	3 (6%)	
Thymus	(47)	(43)
Fibrosarcoma, metastatic, bone	1 (2%)	

TABLE D1b
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study
(continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Integumentary System		
Skin	(50)	(51)
Subcutaneous tissue, mast cell tumor malignant		1 (2%)
Subcutaneous tissue, myxosarcoma	1 (2%)	
Subcutaneous tissue, neurofibrosarcoma	1 (2%)	
Musculoskeletal System		
Bone	(50)	(51)
Fibrosarcoma	2 (4%)	
Nervous System		
Brain	(50)	(51)
Respiratory System		
Lung	(50)	(51)
Alveolar/bronchiolar adenoma	2 (4%)	
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	4 (8%)
Special Senses System		
Harderian gland	(4)	(4)
Adenoma		3 (75%)
Urinary System		
Kidney	(50)	(51)
Urinary bladder	(50)	(50)
Fibrosarcoma, metastatic, uterus		1 (2%)
Systemic Lesions		
Multiple organs	(50)	(51)
Lymphoma malignant histiocytic		3 (6%)
Lymphoma malignant lymphocytic	1 (2%)	2 (4%)
Lymphoma malignant mixed	8 (16%)	10 (20%)
Lymphoma malignant undifferentiated cell		1 (2%)

TABLE D1b
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
Neoplasm Summary		
Total animals with primary neoplasms[c]		
15-Month interim evaluation	1	2
2-Year study	29	43
Total primary neoplasms		
15-Month interim evaluation	1	2
2-Year study	40	71
Total animals with benign neoplasms		
2-Year study	12	31
Total benign neoplasms		
2-Year study	13	39
Total animals with malignant neoplasms		
15-Month interim evaluation	1	2
2-Year study	23	28
Total malignant neoplasms		
15-Month interim evaluation	1	2
2-Year study	27	32
Total animals with metastatic neoplasms		
2-Year study	2	5
Total metastatic neoplasms		
2-Year study	2	6

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm

Number of Days on Study	0 2 3	1 1 4	3 6 2	4 3 1	4 9 4	5 0 9	5 3 0	5 8 9	6 9 6	7 1 1	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 4 3 1	3 1 6 1	3 0 1 1	3 1 8 1	3 2 7 1	2 8 6 1	3 4 9 1	3 3 4 1	2 9 5 1	3 0 6 1	2 8 9 1	3 4 5 1	2 8 1 1	2 8 3 1	2 8 8 1	2 9 3 1	2 9 4 1	2 9 6 1	2 9 7 1	2 9 8 1	3 0 2 1	3 2 0 1	3 0 5 1	3 0 7 1	3 0 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, jejunum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Hepatocellular carcinoma								X																	
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma														X			X								
Hepatocellular adenoma, multiple											X														
Hepatocholangiocarcinoma											X														
Mesentery				+							+	+													
Hemangiosarcoma																									
Hepatocholangiocarcinoma, metastatic, uterus											X														
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, uterus											X														
Salivary glands	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma											X				X										
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M

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

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
First Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 0 9 1	3 1 0 1	3 1 3 1	3 1 5 1	3 1 7 1	3 1 9 1	3 2 1 1	3 2 3 1	3 2 5 1	3 2 8 1	3 2 9 1	3 3 0 1	3 3 1 1	3 3 2 1	3 3 3 1	3 3 6 1	3 3 7 1	3 3 8 1	3 3 9 1	3 4 1 1	3 4 2 1	3 4 4 1	3 4 6 1	3 4 7 1	3 4 8 1	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma											X														1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Hepatocellular carcinoma				X																			X		3
Hepatocellular carcinoma, multiple								X																	1
Hepatocellular adenoma																X		X				X		X	6
Hepatocellular adenoma, multiple	X							X											X						4
Hepatocholangiocarcinoma																									1
Mesentery								+			+					+			+						8
Hemangiosarcoma																X									1
Hepatocholangiocarcinoma, metastatic, uterus																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, uterus																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma												X													3
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	41

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	0 2 3	1 1 4	3 6 2	4 3 1	4 9 4	5 0 9	5 3 0	5 8 9	6 9 6	7 1 1	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 4 3 1	3 1 6 1	3 0 1 1	3 1 8 1	3 2 7 1	2 8 6 1	3 4 9 1	3 3 4 1	2 9 5 1	3 0 6 1	2 8 9 1	3 4 5 1	2 8 1 1	2 8 3 1	2 8 8 1	2 9 3 1	2 9 4 1	2 9 6 1	2 9 7 1	2 9 8 1	3 0 2 1	3 2 0 1	3 0 5 1	3 0 7 1	3 0 8 1
Endocrine System (continued)																									
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X						X			X		
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma															X										
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS		+																							
Genital System																									
Clitoral gland																								+	
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Hepatocholangiocarcinoma, metastatic, uterus											X														
Teratoma		X																							
Uterus	+	+	A	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, hepatocholangiocarcinoma, metastatic, uterus											X														
Renal, hepatocholangiocarcinoma, metastatic, uterus											X														
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, uterus											X														
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	M	M	M	M	+	M	+	M	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	M	+	+	+	+	M	+	+	+	M	+	+	M	M	M	+	+	M	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X		X															X	

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 0 9 1	3 1 0 1	3 1 3 1	3 1 5 1	3 1 7 1	3 1 9 1	3 2 1 1	3 2 3 1	3 2 5 1	3 2 8 1	3 2 9 1	3 3 0 1	3 3 1 1	3 3 2 1	3 3 3 1	3 3 6 1	3 3 7 1	3 3 8 1	3 3 9 1	3 4 1 1	3 4 2 1	3 4 4 1	3 4 6 1	3 4 7 1	3 4 8 1	**Total Tissues/ Tumors**
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X		X										X				X						7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																									1
Follicular cell, carcinoma																X									1
General Body System																									
Tissue NOS									+																2
Genital System																									
Clitoral gland																									1
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma																						X			1
Hepatocholangiocarcinoma, metastatic, uterus																									1
Teratoma																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinal, hepatocholangiocarcinoma, metastatic, uterus																									1
Renal, hepatocholangiocarcinoma, metastatic, uterus																									1
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Hepatocholangiocarcinoma, metastatic, uterus																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																X									1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	38
Integumentary System																									
Mammary gland	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	36
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																									3

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	0213	1414	3622	4131	4494	5904	5930	5898	6396	7011	7223	7225	7229	7299	7299	7299	7299	7299	7299	7299	7299	7300	7300	7300
Carcass ID Number	3411	3611	3011	3811	3271	2769	3491	3431	2951	3061	2891	3451	2881	2813	2881	2991	2991	2991	2991	3002	3220	3005	3071	3081
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+													
Hepatocholangiocarcinoma, metastatic, uterus											X													
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X				
Hepatocellular carcinoma, metastatic, liver								X																
Hepatocholangiocarcinoma, metastatic, uterus											X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X																	
Lymphoma malignant lymphocytic													X											
Lymphoma malignant mixed									X		X	X			X	X			X		X			

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 0 9 1	3 1 0 1	3 1 3 1	3 1 5 1	3 1 7 1	3 1 9 1	3 2 1 1	3 2 3 1	3 2 5 1	3 2 8 1	3 2 9 1	3 3 0 1	3 3 1 1	3 3 2 1	3 3 3 1	3 3 6 1	3 3 7 1	3 3 8 1	3 3 9 1	3 4 1 1	3 4 2 1	3 4 4 1	3 4 6 1	3 4 7 1	3 4 8 1	**Total Tissues/ Tumors**
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									1
Hepatocholangiocarcinoma, metastatic, uterus																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X									X				X								4
Hepatocellular carcinoma, metastatic, liver																									1
Hepatocholangiocarcinoma, metastatic, uterus																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Harderian gland																	+								1
Adenoma																	X								1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																									1
Lymphoma malignant lymphocytic																				X					2
Lymphoma malignant mixed									X															X	9

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm

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

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 8 6 1	3 8 9 1	3 9 1 1	3 9 2 1	3 9 4 1	3 9 7 1	3 9 8 1	3 9 9 1	4 0 0 1	4 0 1 1	4 0 2 1	4 0 3 1	4 0 4 1	4 0 5 1	4 0 6 1	4 0 7 1	4 2 0 1	4 0 8 1	4 0 9 1	4 1 0 1	4 1 1 1	4 1 5 1	4 1 7 1	4 1 8 1	4 1 9 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																X	X							X		3
Hepatocellular carcinoma, multiple									X																	1
Hepatocellular adenoma							X	X		X	X			X							X					10
Hepatocellular adenoma, multiple	X			X		X							X					X	X	X						12
Serosa, adenocarcinoma, metastatic, ovary																										1
Mesentery						+	+						+							+						10
Adenocarcinoma, metastatic, ovary																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, ovary																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	41
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma			X														X		X							5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																	X									1

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	2 5 0	5 7 9	6 2 9	6 3 9	6 6 4	6 7 0	6 8 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 8 3 1	3 9 0 1	4 1 2 1	4 1 4 1	3 6 4 1	3 6 2 1	3 5 8 1	3 5 2 1	3 5 4 1	3 5 6 1	3 5 7 1	3 5 9 1	3 6 1 1	3 6 3 1	3 6 5 1	3 6 6 1	3 6 7 1	3 6 8 1	3 7 2 1	3 7 7 1	3 7 8 1	3 7 9 1	3 8 1 1	3 8 2 1	3 8 5 1
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X																		
Cystadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, liposarcoma, metastatic, skin																									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, ovary							X																		
Lymph node, mesenteric	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Skin	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, liposarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma	X																								
Skeletal muscle							+																		
Adenocarcinoma, metastatic, ovary							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+																								
Spinal cord	+																								

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 8 6 1	3 8 9 1	3 9 1 1	3 9 2 1	3 9 4 1	3 9 7 1	3 9 8 1	3 9 9 1	4 0 0 1	4 0 1 1	4 0 2 1	4 0 3 1	4 0 4 1	4 0 5 1	4 0 6 1	4 0 7 1	4 2 0 1	4 0 8 1	4 0 9 1	4 1 0 1	4 1 1 1	4 1 5 1	4 1 7 1	4 1 8 1	4 1 9 1	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Cystadenoma		X																								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									2
Polyp stromal		X																								1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, liposarcoma, metastatic, skin																	X									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, ovary																										1
Lymph node, mesenteric	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	44
Integumentary System																										
Mammary gland	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	43
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, hemangioma																						X				1
Subcutaneous tissue, liposarcoma																	X									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1
Skeletal muscle																										1
Adenocarcinoma, metastatic, ovary																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 100 ppm (continued)

Number of Days on Study	2 5 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	5 7 2 3 6 7 8 2 2 2 2 2 2 2 2 2 2 2 3 3 3 3 3 3 3
	0 9 9 9 4 0 3 9 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 0 0
Carcass ID Number	3 3 4 4 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
	8 9 1 1 6 6 5 5 5 5 5 5 6 6 6 6 6 6 7 7 7 7 8 8 8
	3 0 2 4 4 2 8 2 4 6 7 9 1 3 5 6 7 8 2 7 8 9 1 2 5
	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Respiratory System	
Lung	+ +
Adenocarcinoma, metastatic, ovary	X
Alveolar/bronchiolar adenoma	X
Alveolar/bronchiolar carcinoma	
Hepatocellular carcinoma, metastatic, liver	
Liposarcoma, metastatic, multiple, skin	
Osteosarcoma, metastatic, bone	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+
Harderian gland	+
Adenoma	X
Urinary System	
Kidney	+ +
Capsule, adenocarcinoma, metastatic, ovary	X
Urinary bladder	+ + + + + M + + + + + + + + + + + + + + + + + + +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant histiocytic	X X X
Lymphoma malignant lymphocytic	
Lymphoma malignant mixed	X

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
First Study: 100 ppm (continued)

Number of Days on Study	730	730	730	730	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	
Carcass ID Number	38611	38911	39111	39211	39411	39711	39811	39911	40011	40111	40211	40311	40411	40511	40611	40711	41011	41211	41811	42011	42111	42511	42711	43111	43911	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, ovary																										1
Alveolar/bronchiolar adenoma			X							X	X				X											5
Alveolar/bronchiolar carcinoma																									X	1
Hepatocellular carcinoma, metastatic, liver																X										1
Liposarcoma, metastatic, multiple, skin																	X									1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland							+										+									3
Adenoma							X										X									3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenocarcinoma, metastatic, ovary																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic				X																						1
Lymphoma malignant mixed						X	X							X							X					5

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm

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

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
First Study: 200 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	4 5 1 1	4 5 2 1	4 5 6 1	4 5 8 1	4 5 9 1	4 6 1 1	4 6 4 1	4 6 5 1	4 6 6 1	4 6 8 1	4 7 0 1	4 7 2 1	4 7 3 1	4 7 4 1	4 7 5 1	4 7 6 1	4 7 7 1	4 7 8 1	4 7 9 1	4 8 2 1	4 8 4 1	4 8 5 1	4 8 8 1	4 8 9 1	4 9 0 1	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Hepatocellular carcinoma															X	X									3
Hepatocellular adenoma				X	X			X							X			X		X	X		X			12
Hepatocellular adenoma, multiple	X						X		X	X	X	X													X		11
Osteosarcoma, metastatic, bone																											1
Mesentery										+	+		+														8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Papilloma squamous																											1
Squamous cell carcinoma						X																					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spindle cell, adenoma																					X						3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+		43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Pars distalis, adenoma			X					X	X																		3
Pars intermedia, adenoma	X									X																	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Follicular cell, adenoma																											1

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	4 9 0	5 2 8	5 6 0	5 8 6	6 6 0	6 7 7	7 1 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 5 4 1	4 7 1 1	4 3 5 1	4 6 9 1	4 3 7 1	4 4 7 1	4 4 5 1	4 2 1 1	4 2 5 1	4 2 6 1	4 2 7 1	4 2 8 1	4 3 2 1	4 3 4 1	4 3 6 1	4 3 8 1	4 4 0 1	4 4 1 1	4 6 2 1	4 4 2 1	4 4 3 1	4 4 6 1	4 4 8 1	4 4 9 1	4 5 0 1
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																						X			
Hemangiosarcoma																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Polyp stromal											X														
Hematopoietic System																									
Blood							+																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, hepatocellular carcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hemangiosarcoma											X	X	X												
Thymus	+	+	+	M	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	4 5 1 1	4 5 2 1	4 5 6 1	4 5 8 1	4 5 9 1	4 6 1 1	4 6 4 1	4 6 5 1	4 6 6 1	4 6 8 1	4 7 0 1	4 7 2 1	4 7 3 1	4 7 4 1	4 7 5 1	4 7 6 1	4 7 7 1	4 7 8 1	4 7 9 1	4 8 2 1	4 8 4 1	4 8 5 1	4 8 8 1	4 8 9 1	4 9 0 1	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																						X				1
Granulosa cell tumor benign																										1
Hemangiosarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Polyp stromal									X																	2
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, hepatocellular carcinoma, metastatic, liver																X										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	4 9 0	5 2 8	5 6 0	5 8 6	6 6 0	6 7 7	7 1 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 5 4 1	4 7 1 1	4 3 5 1	4 6 9 1	4 3 7 1	4 4 7 1	4 4 5 1	4 2 1 1	4 2 5 1	4 2 6 1	4 2 7 1	4 2 8 1	4 3 2 1	4 3 4 1	4 3 6 1	4 3 8 1	4 4 0 1	4 4 1 1	4 6 2 1	4 4 2 1	4 4 3 1	4 4 6 1	4 4 8 1	4 4 9 1	4 5 0 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																		X					
Hepatocellular carcinoma, metastatic, liver																									
Osteosarcoma, metastatic, bone			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X	X	X													X						
Lymphoma malignant mixed									X						X	X	X			X		X			

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 200 ppm (continued)

Number of Days on Study	730	730	730	730	730	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	45111	45211	45611	45811	45911	46111	46411	46511	46611	46811	47011	47711	47911	48111	48411	48611	48711	48911	49211	49411	49511	49811	49911	49011		**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma																										2
Hepatocellular carcinoma, metastatic, liver																X										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																										
Harderian gland						+				+						+										3
Adenoma										X						X										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant histiocytic																										4
Lymphoma malignant mixed																X			X				X			9

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm

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

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
First Study: 400 ppm (continued)

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	50051	50071	50081	50091	50101	50121	50161	50181	50191	50221	50241	50251	50261	50281	50291	50311	50325	50361	50371	50381	50433	50451	50461	50471
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X															X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma			X		X	X						X	X	X	X			X				X	X		
Hepatocellular adenoma, multiple				X			X			X	X					X		X							X
Mesentery					+														+			+			
Osteosarcoma, metastatic, uncertain primary site																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous			X																						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma										X															
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X									X					X						
Pars intermedia, adenoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 4 8 1	5 4 9 1	5 5 1 1	5 5 2 1	5 5 3 1	5 5 4 1	5 5 5 1	5 5 6 1	5 5 8 1	5 5 9 1	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	M	+	+	+	+	+	+	55
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine small	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	M	+	+	+	57
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	59
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma	X	X			X						6
Hepatocellular carcinoma, multiple											2
Hepatocellular adenoma	X	X			X	X		X	X		22
Hepatocellular adenoma, multiple				X							14
Mesentery						+					5
Osteosarcoma, metastatic, uncertain primary site											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Papilloma squamous											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Spindle cell, adenoma											2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	59
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	53
Pituitary gland	+	+	+	+	+	+	+	+	+	+	58
Pars distalis, adenoma				X							5
Pars intermedia, adenoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma											1

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	2 8 0	2 8 3	2 8 4	2 8 5	5 2 2	5 7 9	5 8 5	6 0 0	6 1 3	6 2 3	6 2 9	6 4 5	6 9 0	7 0 3	7 0 4	7 0 5	7 1 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 1 5 1	5 0 2 1	5 4 2 1	5 4 0 1	4 9 1 1	5 4 1 1	5 3 9 1	5 5 7 1	5 2 1 1	4 9 4 1	4 9 3 1	5 3 4 1	5 4 4 1	5 3 3 1	5 5 0 1	5 6 0 1	4 1 7 1	4 9 2 1	4 9 5 1	4 9 6 1	4 9 8 1	4 9 9 1	5 0 1 1	5 0 1 1	5 0 3 1
General Body System																								
None																								
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Mixed tumor benign																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, squamous cell carcinoma, metastatic, skin																	X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X														
Thymus	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	M	+	+
Integumentary System																								
Mammary gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																								
Squamous cell carcinoma																	X							
Subcutaneous tissue, fibrosarcoma					X						X		X											
Subcutaneous tissue, hemangiosarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	732	732	732	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	50571	50071	50881	50991	50101	51121	51161	51181	51191	52211	52241	52251	52261	52281	52391	52411	52531	52551	52671	52781	53391	54451	54461	54471	54481	54491	54501	54511
General Body System																												
None																												
Genital System																												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																												X
Mixed tumor benign										X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal											X	X																
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, squamous cell carcinoma, metastatic, skin																												
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																												
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	M	+			
Integumentary System																												
Mammary gland	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Basal cell carcinoma																												X
Squamous cell carcinoma																												
Subcutaneous tissue, fibrosarcoma																												
Subcutaneous tissue, hemangiosarcoma										X																		
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
First Study: 400 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 4 8 1	5 4 9 1	5 5 1 1	5 5 2 1	5 5 3 1	5 5 4 1	5 5 5 1	5 5 6 1	5 5 8 1	5 5 9 1	Total Tissues/ Tumors
General Body System											
None											
Genital System											
Ovary	+	+	+	+	+	+	+	M	+	+	59
Cystadenoma											1
Mixed tumor benign											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Polyp stromal											2
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Inguinal, squamous cell carcinoma, metastatic, skin											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	58
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	54
Spleen	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Thymus	+	+	+	+	+	+	+	+	+	M	50
Integumentary System											
Mammary gland	+	M	M	+	+	+	+	+	+	+	51
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell carcinoma											1
Squamous cell carcinoma											1
Subcutaneous tissue, fibrosarcoma											3
Subcutaneous tissue, hemangiosarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	2	2	2	2	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	8	8	8	8	2	7	8	0	1	2	2	4	9	0	0	0	1	2	2	2	2	2	2	2	2
	0	3	4	5	2	9	5	0	3	3	9	5	0	3	4	5	2	9	9	9	9	9	9	9	9
Carcass ID Number	5	5	5	5	4	5	5	5	5	4	4	5	5	5	5	5	5	4	4	4	4	4	5	5	5
	1	0	4	4	9	4	3	5	2	9	9	3	4	3	5	6	1	9	9	9	9	9	0	0	0
	5	2	2	0	1	1	9	7	1	4	3	4	4	3	0	0	7	2	5	6	8	9	0	1	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic, uncertain primary site																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic												X			X										
Lymphoma malignant lymphocytic											X			X											
Lymphoma malignant mixed									X							X			X						

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
First Study: 400 ppm (continued)

Number of Days on Study	729	729	729	730	700	700	700	700	700	700	700	700	700	700	700	702	702	702	702	702	702	702	702	702	702	702
Carcass ID Number	50511	50711	50811	50911	50111	50211	50611	50811	50911	51211	51411	51511	51611	51811	52211	52311	52411	52511	52611	52711	52811	53311	53411	53511	53611	53711
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																						
Alveolar/bronchiolar carcinoma				X												X										
Osteosarcoma, metastatic, uncertain primary site																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland																				+						
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																										
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed		X		X							X															

TABLE D2a
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: First Study: 400 ppm (continued)

Number of Days on Study	7 7 7 7 7 7 7 7 7 7 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	
Carcass ID Number	5 5 5 5 5 5 5 5 5 5 4 4 5 5 5 5 5 5 5 5 8 9 1 2 3 4 5 6 8 9 1 1 1 1 1 1 1 1 1 1	**Total Tissues/ Tumors**
Respiratory System		
Lung	+ + + + + + + + + +	60
Alveolar/bronchiolar adenoma		1
Alveolar/bronchiolar carcinoma	X	3
Osteosarcoma, metastatic, uncertain primary site		1
Nose	+ + + + + + + + + +	60
Trachea	+ + + + + + + + + +	60
Special Senses System		
Harderian gland		2
Urinary System		
Kidney	+ + + + + + + + + +	60
Urinary bladder	+ + + + + + + + + +	60
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	60
Lymphoma malignant histiocytic	X	3
Lymphoma malignant lymphocytic		2
Lymphoma malignant mixed		6

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm

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

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

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	7 3 8 1	7 3 9 1	7 4 0 1	7 4 1 1	7 4 3 1	7 4 4 1	7 4 6 1	7 4 7 1	7 4 9 1	7 5 0 1	7 5 1 1	7 5 3 1	7 5 4 1	7 5 5 1	7 5 6 1	7 5 7 1	7 5 8 1	7 5 9 1	7 6 0 1	7 6 2 1	7 6 3 1	7 6 4 1	7 6 5 1	7 6 6 1	7 6 7 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma										X							X									5
Hepatocellular adenoma				X					X														X			4
Hepatocellular adenoma, multiple										X																3
Mesentery																								+		2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma																X									X	2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm (continued)

Number of Days on Study	4 8 8	5 3 4	5 3 9	5 5 5	6 1 6	6 4 2	6 8 3	7 0 1	7 1 2	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	7 6 8 1	7 7 0 1	7 3 0 1	7 2 0 1	7 1 7 1	7 3 5 1	7 6 1 1	7 5 2 1	7 2 1 1	7 4 8 1	1 1 2 1	1 1 3 1	1 1 4 1	1 1 5 1	1 1 8 1	1 2 9 1	2 2 3 1	2 2 5 1	2 2 8 1	2 2 9 1	3 3 1 1	3 3 3 1	3 3 7 1
Genital System																									
Clitoral gland										+								+		+					
Hemangiosarcoma																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Hemangiosarcoma				X																					
Leiomyosarcoma																									
Sarcoma stromal																				X					
Hematopoietic System																									
Blood				+																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X								X						X							
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, bone																		X							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, myxosarcoma										X															
Subcutaneous tissue, neurofibrosarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma																								X	
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
Second Study: 0 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	7 3 8 1	7 3 9 1	7 4 0 1	7 4 1 1	7 4 3 1	7 4 4 1	7 4 6 1	7 4 7 1	7 4 9 1	7 5 0 1	7 5 1 1	7 5 3 1	7 5 4 1	7 5 5 1	7 5 6 1	7 5 7 1	7 5 8 1	7 5 9 1	7 6 0 1	7 6 2 1	7 6 3 1	7 6 4 1	7 6 5 1	7 6 6 1	7 6 7 1	Total Tissues/ Tumors
Genital System																										
Clitoral gland		+																		+		+		+		7
Hemangiosarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma						X																				1
Hemangiosarcoma																										1
Leiomyosarcoma																			X							1
Sarcoma stromal																										1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										3
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma, metastatic, bone																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, myxosarcoma																										1
Subcutaneous tissue, neurofibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																						X				2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										2
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver										X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 0 ppm (continued)

Number of Days on Study	4	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	8	3	3	5	1	4	8	0	1	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	8	4	9	5	6	2	3	1	2	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	7	3	2	1	3	6	5	2	4	1	1	1	1	1	1	1	2	2	2	2	2	3	3	3	
	8	0	0	0	7	5	1	2	1	8	1	2	3	4	5	8	9	2	3	5	8	9	1	3	7	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Special Senses System																										
Harderian gland											+										+		+			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed		X	X				X	X													X					

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
Second Study: 0 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	738	739	740	741	743	744	746	747	749	750	751	753	754	755	756	757	758	759	760	762	763	764	765	766	767	**Total Tissues/ Tumors**
	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	111	
Special Senses System																										
Harderian gland																								+		4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																							X			1
Lymphoma malignant mixed			X														X								X	8

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm

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

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
Second Study: 400 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	7 8 9 1 1	7 9 1 1	7 9 2 1	7 9 4 1	7 9 5 1	7 9 6 1	7 9 8 1	8 0 0 1	8 0 1 1	8 0 3 1	8 0 4 1	8 0 6 1	8 0 8 1	8 0 9 1	8 1 0 1	8 1 1 1	8 1 2 1	8 1 6 1	8 1 7 1	8 2 2 1	8 2 5 1	8 2 6 1	8 2 7 1	8 2 8 1	8 3 0 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrosarcoma, metastatic, uterus																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma						X				X	X						X	X		X						9
Hepatocellular carcinoma, multiple									X																	2
Hepatocellular adenoma							X					X			X	X					X					9
Hepatocellular adenoma, multiple			X			X		X	X	X			X	X			X			X				X		19
Mesentery						+																		+		7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spindle cell, adenoma													X									X				2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Adenoma														X												1
Pars distalis, adenoma			X																							2
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm (continued)

Number of Days on Study	4 1 2	5 3 4	5 3 4	5 7 8	6 0 5	6 3 9	6 6 3	6 7 3	6 7 6	6 8 2	6 8 7	6 8 7	6 9 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	7 9 3 1	7 9 0 1	8 2 3 1	7 7 4 1	8 1 4 1	7 9 9 1	8 1 8 1	8 2 4 1	7 8 5 1	8 1 5 1	8 1 9 1	8 2 1 1	8 2 0 1	7 7 2 1	7 7 3 1	7 7 5 1	7 7 6 1	7 7 7 1	7 7 8 1	7 7 9 1	7 8 0 1	8 8 1 1	8 8 2 1	8 8 3 1	8 8 4 1	8 8 8 1
General Body System																									
None																									
Genital System																									
Clitoral gland																				+		+			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																		X							
Teratoma benign																				X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma			X																						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									
Lymph node, mesenteric	+	+	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, mast cell tumor malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver									X														X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene:
Second Study: 400 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	7 8 9 1 1	7 9 1 1 1	7 9 2 1 1	7 9 4 1 1	7 9 5 1 1	7 9 6 1 1	7 9 8 1 1	8 0 0 1 1	8 0 1 1 1	8 0 3 1 1	8 0 4 1 1	8 0 6 1 1	8 0 8 1 1	8 0 9 1 1	8 1 0 1 1	8 1 1 1 1	8 1 2 1 1	8 1 6 1 1	8 1 7 1 1	8 2 2 1 1	8 2 5 1 1	8 2 6 1 1	8 2 7 1 1	8 2 8 1 1	8 3 0 1 1	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland															+									+	4
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Granulosa cell tumor benign																										1
Teratoma benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mast cell tumor malignant								X																		1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	M	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, mast cell tumor malignant								X																		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar carcinoma																								X		1
Hepatocellular carcinoma, metastatic, liver						X											X									4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm (continued)

Number of Days on Study	4 1 2	5 3 4	5 3 4	5 7 8	6 0 5	6 3 9	6 6 3	6 7 3	6 7 6	6 8 2	6 8 7	6 8 7	6 9 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	7 9 3 1	7 9 0 1	8 2 3 1	7 7 4 1	8 1 4 1	7 9 9 1	8 1 8 1	8 2 4 1	7 8 5 1	8 1 5 1	8 1 9 1	8 2 1 1	8 2 0 1	7 7 2 1	7 7 3 1	7 7 5 1	7 7 6 1	7 7 7 1	7 7 8 1	7 7 9 1	7 8 0 1	7 8 1 1	7 8 2 1	7 8 3 1	7 8 4 1	7 8 8 1
Special Senses System																									
Harderian gland											+		+												
Adenoma											X		X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibrosarcoma, metastatic, uterus			X																						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic								X		X	X														
Lymphoma malignant lymphocytic										X															
Lymphoma malignant mixed				X	X	X	X															X		X	
Lymphoma malignant undifferentiated cell type																									

TABLE D2b
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Triamterene: Second Study: 400 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	7 8 9 1	7 9 1 1	7 9 2 1	7 9 4 1	7 9 5 1	7 9 6 1	7 9 8 1	8 0 0 1	8 0 1 1	8 0 3 1	8 0 4 1	8 0 6 1	8 0 8 1	8 0 9 1	8 1 0 1	8 1 1 1	8 1 2 1	8 1 6 1	8 1 7 1	8 2 2 1	8 2 5 1	8 2 6 1	8 2 7 1	8 2 8 1	8 3 0 1	**Total Tissues/ Tumors**
Special Senses System																										
Harderian gland					+												+									4
Adenoma					X																					3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, uterus																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic											X															2
Lymphoma malignant mixed					X		X					X								X						10
Lymphoma malignant undifferentiated cell type																							X			1

TABLE D3a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study

	0 ppm	100 ppm	200 ppm	400 ppm
Adrenal Cortex: Adenoma				
Overall rates[a]	3/50 (6%)	0/50 (0%)	3/50 (6%)	2/60 (3%)
Adjusted rates[b]	7.6%	0.0%	7.0%	4.7%
Terminal rates[c]	2/38 (5%)	0/43 (0%)	3/43 (7%)	2/43 (5%)
First incidence (days)	723	-[e]	729 (T)	729 (T)
Life table tests[d]	P=0.559N	P=0.105N	P=0.608N	P=0.449N
Logistic regression tests[d]	P=0.557N	P=0.107N	P=0.628N	P=0.449N
Cochran-Armitage test[d]	P=0.514N			
Fisher exact test[d]		P=0.121N	P=0.661N	P=0.414N
Harderian Gland: Adenoma				
Overall rates	1/50 (2%)	3/50 (6%)	2/50 (4%)	0/60 (0%)
Adjusted rates	2.6%	7.0%	4.7%	0.0%
Terminal rates	1/38 (3%)	3/43 (7%)	2/43 (5%)	0/43 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	-
Life table tests	P=0.214N	P=0.350	P=0.543	P=0.475N
Logistic regression tests	P=0.214N	P=0.350	P=0.543	P=0.475N
Cochran-Armitage test	P=0.196N			
Fisher exact test		P=0.309	P=0.500	P=0.455N
Liver: Hepatocellular Adenoma				
Overall rates	10/50 (20%)	22/50 (44%)	23/50 (46%)	36/60 (60%)
Adjusted rates	25.6%	51.2%	52.3%	78.1%
Terminal rates	9/38 (24%)	22/43 (51%)	22/43 (51%)	33/43 (77%)
First incidence (days)	723	729 (T)	712	579
Life table tests	P<0.001	P=0.022	P=0.015	P<0.001
Logistic regression tests	P<0.001	P=0.014	P=0.008	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.009	P=0.005	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rates	4/50 (8%)	4/50 (8%)	3/50 (6%)	8/60 (13%)
Adjusted rates	10.0%	9.3%	7.0%	18.6%
Terminal rates	3/38 (8%)	4/43 (9%)	3/43 (7%)	8/43 (19%)
First incidence (days)	589	729 (T)	729 (T)	729 (T)
Life table tests	P=0.136	P=0.575N	P=0.438N	P=0.248
Logistic regression tests	P=0.159	P=0.614N	P=0.472N	P=0.272
Cochran-Armitage test	P=0.183			
Fisher exact test		P=0.643N	P=0.500N	P=0.281
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	13/50 (26%)	26/50 (52%)	25/50 (50%)	37/60 (62%)
Adjusted rates	32.3%	60.5%	56.8%	80.3%
Terminal rates	11/38 (29%)	26/43 (60%)	24/43 (56%)	34/43 (79%)
First incidence (days)	589	729 (T)	712	579
Life table tests	P<0.001	P=0.021	P=0.035	P<0.001
Logistic regression tests	P<0.001	P=0.014	P=0.022	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.007	P=0.011	P<0.001

TABLE D3a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	4/50 (8%)	5/50 (10%)	2/50 (4%)	1/60 (2%)
Adjusted rates	10.5%	11.6%	4.3%	2.3%
Terminal rates	4/38 (11%)	5/43 (12%)	1/43 (2%)	1/43 (2%)
First incidence (days)	729 (T)	729 (T)	528	729 (T)
Life table tests	P=0.060N	P=0.578	P=0.285N	P=0.144N
Logistic regression tests	P=0.053N	P=0.578	P=0.330N	P=0.144N
Cochran-Armitage test	P=0.053N			
Fisher exact test		P=0.500	P=0.339N	P=0.130N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/60 (5%)
Adjusted rates	0.0%	2.3%	0.0%	7.0%
Terminal rates	0/38 (0%)	1/43 (2%)	0/43 (0%)	3/43 (7%)
First incidence (days)	-	729 (T)	-	729 (T)
Life table tests	P=0.050	P=0.525	-	P=0.144
Logistic regression tests	P=0.050	P=0.525	-	P=0.144
Cochran-Armitage test	P=0.065			
Fisher exact test		P=0.500	-	P=0.159
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	4/50 (8%)	6/50 (12%)	2/50 (4%)	3/60 (5%)
Adjusted rates	10.5%	14.0%	4.3%	7.0%
Terminal rates	4/38 (11%)	6/43 (14%)	1/43 (2%)	3/43 (7%)
First incidence (days)	729 (T)	729 (T)	528	729 (T)
Life table tests	P=0.228N	P=0.449	P=0.285N	P=0.432N
Logistic regression tests	P=0.202N	P=0.449	P=0.330N	P=0.432N
Cochran-Armitage test	P=0.196N			
Fisher exact test		P=0.370	P=0.339N	P=0.399N
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma				
Overall rates	7/49 (14%)	5/47 (11%)	3/48 (6%)	5/58 (9%)
Adjusted rates	18.4%	12.2%	7.1%	11.6%
Terminal rates	7/38 (18%)	5/41 (12%)	3/42 (7%)	5/43 (12%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.249N	P=0.325N	P=0.120N	P=0.294N
Logistic regression tests	P=0.249N	P=0.325N	P=0.120N	P=0.294N
Cochran-Armitage test	P=0.214N			
Fisher exact test		P=0.410N	P=0.167N	P=0.268N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rates	3/50 (6%)	0/50 (0%)	1/50 (2%)	3/60 (5%)
Adjusted rates	7.1%	0.0%	2.3%	5.8%
Terminal rates	1/38 (3%)	0/43 (0%)	1/43 (2%)	0/43 (0%)
First incidence (days)	530	-	729 (T)	522
Life table tests	P=0.480	P=0.109N	P=0.275N	P=0.581N
Logistic regression tests	P=0.492	P=0.133N	P=0.324N	P=0.592N
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.121N	P=0.309N	P=0.570N

TABLE D3a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
Spleen: Hemangiosarcoma				
Overall rates	1/49 (2%)	0/50 (0%)	3/49 (6%)	1/60 (2%)
Adjusted rates	2.6%	0.0%	7.1%	2.0%
Terminal rates	1/38 (3%)	0/43 (0%)	3/42 (7%)	0/43 (0%)
First incidence (days)	729 (T)	-	729 (T)	623
Life table tests	P=0.505	P=0.475N	P=0.342	P=0.725N
Logistic regression tests	P=0.533	P=0.475N	P=0.342	P=0.717N
Cochran-Armitage test	P=0.539			
Fisher exact test		P=0.495N	P=0.309	P=0.699N
All Organs: Hemangiosarcoma				
Overall rates	2/50 (4%)	1/50 (2%)	5/50 (10%)	2/60 (3%)
Adjusted rates	5.0%	2.3%	11.6%	4.2%
Terminal rates	1/38 (3%)	1/43 (2%)	5/43 (12%)	1/43 (2%)
First incidence (days)	711	729 (T)	729 (T)	623
Life table tests	P=0.504	P=0.466N	P=0.267	P=0.646N
Logistic regression tests	P=0.537	P=0.471N	P=0.248	P=0.626N
Cochran-Armitage test	P=0.548			
Fisher exact test		P=0.500N	P=0.218	P=0.619N
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rates	12/50 (24%)	9/50 (18%)	13/50 (26%)	11/60 (18%)
Adjusted rates	28.4%	19.8%	28.2%	22.1%
Terminal rates	8/38 (21%)	7/43 (16%)	10/43 (23%)	5/43 (12%)
First incidence (days)	530	629	586	613
Life table tests	P=0.441N	P=0.229N	P=0.553N	P=0.372N
Logistic regression tests	P=0.353N	P=0.265N	P=0.558	P=0.306N
Cochran-Armitage test	P=0.346N			
Fisher exact test		P=0.312N	P=0.500	P=0.310N
All Organs: Benign Neoplasms				
Overall rates	22/50 (44%)	31/50 (62%)	28/50 (56%)	36/60 (60%)
Adjusted rates	54.8%	70.4%	62.2%	78.1%
Terminal rates	20/38 (53%)	30/43 (70%)	26/43 (60%)	33/43 (77%)
First incidence (days)	114	664	528	579
Life table tests	P=0.029	P=0.154	P=0.341	P=0.027
Logistic regression tests	P=0.081	P=0.100	P=0.238	P=0.061
Cochran-Armitage test	P=0.123			
Fisher exact test		P=0.054	P=0.159	P=0.069
All Organs: Malignant Neoplasms				
Overall rates	20/50 (40%)	17/50 (34%)	21/50 (42%)	25/60 (42%)
Adjusted rates	45.5%	36.0%	44.6%	47.1%
Terminal rates	14/38 (37%)	13/43 (30%)	17/43 (40%)	15/43 (35%)
First incidence (days)	530	250	560	522
Life table tests	P=0.252	P=0.223N	P=0.477N	P=0.430
Logistic regression tests	P=0.354	P=0.304N	P=0.579N	P=0.517
Cochran-Armitage test	P=0.360			
Fisher exact test		P=0.339N	P=0.500	P=0.507

TABLE D3a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rates	34/50 (68%)	40/50 (80%)	40/50 (80%)	46/60 (77%)
Adjusted rates	75.5%	83.3%	81.6%	85.2%
Terminal rates	27/38 (71%)	35/43 (81%)	34/43 (79%)	35/43 (81%)
First incidence (days)	114	250	528	522
Life table tests	P=0.109	P=0.443	P=0.446	P=0.155
Logistic regression tests	P=0.243	P=0.199	P=0.217	P=0.218
Cochran-Armitage test	P=0.266			
Fisher exact test		P=0.127	P=0.127	P=0.211

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

TABLE D3b
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study

	0 ppm	400 ppm
Harderian Gland: Adenoma		
Overall rates[a]	0/50 (0%)	3/51 (6%)
Adjusted rates[b]	0.0%	7.4%
Terminal rates[c]	0/40 (0%)	1/38 (3%)
First incidence (days)	_[e]	687
Life table tests[d]		P=0.113
Logistic regression tests[d]		P=0.124
Fisher exact test[d]		P=0.125
Liver: Hepatocellular Adenoma		
Overall rates	7/50 (14%)	28/51 (55%)
Adjusted rates	17.5%	70.0%
Terminal rates	7/40 (18%)	26/38 (68%)
First incidence (days)	730 (T)	687
Life table tests		P<0.001
Logistic regression tests		P<0.001
Fisher exact test		P<0.001
Liver: Hepatocellular Carcinoma		
Overall rates	5/50 (10%)	11/51 (22%)
Adjusted rates	12.0%	28.0%
Terminal rates	4/40 (10%)	10/38 (26%)
First incidence (days)	616	676
Life table tests		P=0.073
Logistic regression tests		P=0.082
Fisher exact test		P=0.093
Liver: Hepatoblastoma or Hepatocellular Carcinoma		
Overall rates	5/50 (10%)	11/51 (22%)
Adjusted rates	12.0%	28.0%
Terminal rates	4/40 (10%)	10/38 (26%)
First incidence (days)	616	676
Life table tests		P=0.073
Logistic regression tests		P=0.082
Fisher exact test		P=0.093
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rates	10/50 (20%)	31/51 (61%)
Adjusted rates	24.2%	75.6%
Terminal rates	9/40 (23%)	28/38 (74%)
First incidence (days)	616	676
Life table tests		P<0.001
Logistic regression tests		P<0.001
Fisher exact test		P<0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rates	3/50 (6%)	1/51 (2%)
Adjusted rates	7.5%	2.6%
Terminal rates	3/40 (8%)	1/38 (3%)
First incidence (days)	730 (T)	730 (T)
Life table tests		P=0.324N
Logistic regression tests		P=0.324N
Fisher exact test		P=0.301N

TABLE D3b
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma		
Overall rates	1/49 (2%)	3/47 (6%)
Adjusted rates	2.6%	8.6%
Terminal rates	1/39 (3%)	3/35 (9%)
First incidence (days)	730 (T)	730 (T)
Life table tests		P=0.267
Logistic regression tests		P=0.267
Fisher exact test		P=0.293
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma or Carcinoma		
Overall rates	1/49 (2%)	4/47 (9%)
Adjusted rates	2.6%	11.4%
Terminal rates	1/39 (3%)	4/35 (11%)
First incidence (days)	730 (T)	730 (T)
Life table tests		P=0.148
Logistic regression tests		P=0.148
Fisher exact test		P=0.168
Spleen: Hemangiosarcoma		
Overall rates	3/49 (6%)	0/51 (0%)
Adjusted rates	7.0%	0.0%
Terminal rates	2/40 (5%)	0/38 (0%)
First incidence (days)	555	-
Life table tests		P=0.128N
Logistic regression tests		P=0.101N
Fisher exact test		P=0.114N
All Organs: Hemangiosarcoma		
Overall rates	3/50 (6%)	0/51 (0%)
Adjusted rates	7.0%	0.0%
Terminal rates	2/40 (5%)	0/38 (0%)
First incidence (days)	555	-
Life table tests		P=0.128N
Logistic regression tests		P=0.107N
Fisher exact test		P=0.118N
All Organs: Hemangioma or Hemangisarcoma		
Overall rates	3/50 (6%)	0/51 (0%)
Adjusted rates	7.0%	0.0%
Terminal rates	2/40 (5%)	0/38 (0%)
First incidence (days)	555	-
Life table tests		P=0.128N
Logistic regression tests		P=0.107N
Fisher exact test		P=0.118N
All Organs: Malignant Lymphoma or Histiocytic Sarcoma		
Overall rates	9/50 (18%)	15/51 (29%)
Adjusted rates	19.9%	32.6%
Terminal rates	5/40 (13%)	8/38 (21%)
First incidence (days)	534	578
Life table tests		P=0.124
Logistic regression tests		P=0.146
Fisher exact test		P=0.133

TABLE D3b
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
All Organs: Benign Neoplasms		
Overall rates	12/50 (24%)	31/51 (61%)
Adjusted rates	30.0%	75.6%
Terminal rates	12/40 (30%)	28/38 (74%)
First incidence (days)	730 (T)	687
Life table tests		P<0.001
Logistic regression tests		P<0.001
Fisher exact test		P<0.001
All Organs: Malignant Neoplasms		
Overall rates	23/50 (46%)	28/51 (55%)
Adjusted rates	47.8%	59.2%
Terminal rates	15/40 (38%)	19/38 (50%)
First incidence (days)	534	534
Life table tests		P=0.202
Logistic regression tests		P=0.259
Fisher exact test		P=0.243
All Organs: Benign or Malignant Neoplasms		
Overall rates	29/50 (58%)	43/51 (84%)
Adjusted rates	60.3%	87.8%
Terminal rates	21/40 (53%)	32/38 (84%)
First incidence (days)	534	534
Life table tests		P=0.008
Logistic regression tests		P=0.003
Fisher exact test		P=0.003

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

TABLE D4
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma	Hepatoblastoma
Historical Incidence at Battelle Columbus Laboratory				
2,4-Dichlorophenol	0/50	2/50	2/50	0/50
5,5-Diphenylhydantoin	5/48	0/48	5/48	0/48
Dowicide EC-7 pentachlorophenol	1/34	0/34	1/34	0/34
Ethylene thiourea	2/50	2/50	4/50	0/50
Polybrominated biphenyls (Firemaster FF-1®)	4/50	1/50	5/50	0/50
Technical grade pentachlorophenol	3/33	0/33	3/33	0/33
Overall Historical Incidence				
Total	74/863 (8.6%)	28/863 (3.2%)	98/863 (11.4%)	1/863 (0.1%)
Standard deviation	6.5%	2.9%	7.6%	0.5%
Range	0%-28%	0%-10%	3%-34%	0%-2%

[a] Data as of 3 April 1991

TABLE D5a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: First Study[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	
2-Year study				
Early deaths				
Moribund	8	5	1	10
Natural deaths	4	2	6	7
Survivors				
Died last week of study	1	2	1	
Terminal sacrifice	37	41	42	43
Animals examined microscopically	70	70	70	70
3-Month Interim Evaluation				
Alimentary System				
Stomach, forestomach	(7)			(8)
Mucosa, hyperplasia, papillary, diffuse	1 (14%)			
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Ovary	(7)	(1)		(8)
Cyst		1 (100%)		
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

TABLE D5a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
3-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(2)	(10)	
Basophilic focus	2 (20%)			
Eosinophilic focus			1 (10%)	
Infiltration cellular, lymphocyte			1 (10%)	
Inflammation, necrotizing, acute			4 (40%)	
Vacuolization cytoplasmic		1 (50%)	2 (20%)	
Pancreas	(10)		(10)	
Acinus, cytoplasmic alteration	2 (20%)			
Stomach, glandular	(10)		(10)	
Inflammation, subacute			1 (10%)	
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Ovary	(10)	(3)	(10)	
Angiectasis			1 (10%)	
Cyst	5 (50%)	3 (100%)	1 (10%)	
Uterus	(10)	(4)	(10)	
Dilatation	3 (30%)	4 (100%)	5 (50%)	
Hematopoietic System				
None				
Integumentary System				
None				

TABLE D5a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	
Nephropathy	7 (70%)	2 (20%)	4 (40%)	
2-Year Study				
Alimentary System				
Gallbladder	(48)	(47)	(49)	(55)
Inflammation, chronic active		1 (2%)		
Intestine large, colon	(48)	(50)	(49)	(59)
Inflammation, acute				1 (2%)
Intestine small, duodenum	(47)	(50)	(50)	(59)
Inflammation, acute				1 (2%)
Ulcer		1 (2%)		
Intestine small, jejunum	(47)	(48)	(48)	(59)
Diverticulum, single				1 (2%)
Liver	(50)	(50)	(50)	(60)
Basophilic focus	1 (2%)	6 (12%)	6 (12%)	10 (17%)
Basophilic focus, multiple				1 (2%)
Clear cell focus		1 (2%)	4 (8%)	3 (5%)
Eosinophilic focus	7 (14%)	11 (22%)	17 (34%)	7 (12%)
Eosinophilic focus, multiple			2 (4%)	
Inflammation, chronic active	1 (2%)			
Mixed cell focus			1 (2%)	1 (2%)
Necrosis, acute	1 (2%)			1 (2%)
Regeneration			2 (4%)	
Thrombus		1 (2%)		1 (2%)
Mesentery	(8)	(10)	(8)	(5)
Angiectasis			1 (13%)	
Ectopic tissue	1 (13%)			
Inflammation, chronic active	2 (25%)		1 (13%)	
Fat, necrosis	2 (25%)	9 (90%)	6 (75%)	3 (60%)
Pancreas	(49)	(50)	(50)	(60)
Inflammation, chronic active		1 (2%)		
Vacuolization cytoplasmic	1 (2%)			
Acinus, atrophy	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Duct, ectasia		2 (4%)		

TABLE D5a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(50)	(60)
Acanthosis	2 (4%)	2 (4%)	2 (4%)	7 (12%)
Inflammation, acute		1 (2%)		3 (5%)
Inflammation, chronic active			1 (2%)	
Stomach, glandular	(49)	(50)	(50)	(60)
Inflammation, acute		1 (2%)	1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(60)
Inflammation, chronic active			1 (2%)	
Mineralization			1 (2%)	
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(60)
Angiectasis	1 (2%)			
Cyst	1 (2%)		1 (2%)	
Hyperplasia		2 (4%)		
Hypertrophy	3 (6%)	3 (6%)	1 (2%)	4 (7%)
Mineralization				1 (2%)
Adrenal gland, medulla	(47)	(50)	(50)	(59)
Angiectasis	1 (2%)			
Mineralization				1 (2%)
Islets, pancreatic	(49)	(49)	(50)	(59)
Hyperplasia	1 (2%)	2 (4%)		
Pituitary gland	(49)	(47)	(48)	(58)
Pars distalis, cyst	1 (2%)		1 (2%)	3 (5%)
Pars distalis, hyperplasia	7 (14%)	3 (6%)	6 (13%)	9 (16%)
Pars intermedia, cyst		1 (2%)		
Pars intermedia, hyperplasia		2 (4%)	1 (2%)	1 (2%)
Pars intermedia, hypertrophy				2 (3%)
Thyroid gland	(49)	(49)	(50)	(60)
Inflammation, chronic active		1 (2%)		1 (2%)
Follicular cell, hyperplasia	4 (8%)	17 (35%)	18 (36%)	28 (47%)
General Body System				
None				
Genital System				
Ovary	(48)	(50)	(50)	(59)
Angiectasis	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Cyst	13 (27%)	17 (34%)	18 (36%)	26 (44%)
Hemorrhage	1 (2%)			
Thrombus	1 (2%)			
Uterus	(48)	(50)	(50)	(60)
Angiectasis			1 (2%)	1 (2%)
Dilatation				4 (7%)
Hyperplasia, glandular, cystic	38 (79%)	44 (88%)	47 (94%)	53 (88%)
Thrombus		1 (2%)		

TABLE D5a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(60)
Myelofibrosis	20 (40%)	19 (38%)	19 (38%)	17 (28%)
Lymph node, mandibular	(46)	(49)	(50)	(58)
Infiltration cellular, histiocyte		1 (2%)		
Necrosis				1 (2%)
Lymphatic, ectasia			1 (2%)	
Lymph node, mesenteric	(43)	(45)	(46)	(54)
Cyst			1 (2%)	
Necrosis				1 (2%)
Thrombus		1 (2%)		
Spleen	(49)	(50)	(49)	(60)
Hematopoietic cell proliferation	2 (4%)	4 (8%)	5 (10%)	1 (2%)
Necrosis				2 (3%)
Thymus	(38)	(44)	(44)	(50)
Necrosis	2 (5%)			4 (8%)
Integumentary System				
Mammary gland	(36)	(43)	(46)	(51)
Hyperplasia				1 (2%)
Skin	(50)	(49)	(49)	(60)
Alopecia	3 (6%)	1 (2%)	1 (2%)	5 (8%)
Hemorrhage	1 (2%)			
Inflammation, chronic active	1 (2%)			
Ulcer	2 (4%)	1 (2%)		1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(60)
Bilateral, tarsal, hyperostosis		1 (2%)		
Femur, cyst			1 (2%)	
Nervous System				
Peripheral nerve		(1)		
Degeneration		1 (100%)		
Spinal cord		(1)		
Degeneration		1 (100%)		
Respiratory System				
Lung	(50)	(50)	(50)	(60)
Alveolar epithelium, hyperplasia	2 (4%)	1 (2%)		4 (7%)
Nose	(50)	(50)	(50)	(60)
Inflammation, acute	2 (4%)	2 (4%)		7 (12%)
Trachea	(50)	(50)	(50)	(60)
Inflammation, acute			1 (2%)	
Special Senses System				
Harderian gland	(1)	(3)	(3)	(2)
Hyperplasia			1 (33%)	2 (100%)

TABLE D5a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: First Study (continued)

	0 ppm	100 ppm	200 ppm	400 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(60)
Atrophy	1 (2%)			
Cyst				1 (2%)
Infarct			1 (2%)	
Nephropathy	28 (56%)	36 (72%)	43 (86%)	49 (82%)
Pigmentation		1 (2%)		

[a] Number of animals examined microscopically at site and number of animals with lesion

TABLE D5b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: Second Study[a]

	0 ppm	400 ppm
Disposition Summary		
Animals initially in study	60	60
15-Month interim evaluation	10	9
2-Year study		
Early deaths		
Moribund	7	4
Natural deaths	3	9
Survivors		
Terminal sacrifice	40	38
Animals examined microscopically	60	60
15-Month Interim Evaluation		
Alimentary System		
Liver	(10)	(9)
Basophilic focus	1 (10%)	1 (11%)
Eosinophilic focus	1 (10%)	
Pancreas	(10)	(9)
Inflammation, chronic active		1 (11%)
Cardiovascular System		
None		
Endocrine System		
Pituitary gland	(10)	(9)
Pars distalis, hyperplasia	3 (30%)	2 (22%)
Thyroid gland	(10)	(9)
Cyst	1 (10%)	1 (11%)
Follicular cell, hyperplasia		1 (11%)
General Body System		
None		
Genital System		
Ovary	(10)	(9)
Cyst	1 (10%)	2 (22%)
Uterus	(10)	(9)
Hyperplasia, cystic, glandular	10 (100%)	7 (78%)
Hematopoietic System		
Bone marrow	(10)	(8)
Myelofibrosis		1 (13%)
Integumentary System		
Skin	(10)	(9)
Alopecia	1 (10%)	

TABLE D5b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
15-Month Interim Evaluation (continued)		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
Kidney	(10)	(9)
Nephropathy	3 (30%)	3 (33%)
2-Year Study		
Alimentary System		
Esophagus	(50)	(51)
Ulcer	1 (2%)	
Muscularis, degeneration	1 (2%)	
Gallbladder	(50)	(50)
Mucosa, hyperplasia		1 (2%)
Intestine small, ileum	(49)	(51)
Peyer's patch, inflammation, granulomatous		1 (2%)
Liver	(50)	(51)
Angiectasis		1 (2%)
Basophilic focus		5 (10%)
Clear cell focus		4 (8%)
Eosinophilic focus	9 (18%)	16 (31%)
Infarct		1 (2%)
Infiltration cellular, lymphocyte	1 (2%)	
Inflammation, acute		1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)
Mixed cell focus	1 (2%)	
Necrosis, acute		1 (2%)
Vacuolization cytoplasmic		1 (2%)
Mesentery	(2)	(7)
Ectopic tissue	1 (50%)	
Artery, inflammation, chronic active		1 (14%)
Fat, necrosis	1 (50%)	6 (86%)
Pancreas	(49)	(50)
Cyst		1 (2%)
Acinus, atrophy	3 (6%)	1 (2%)
Duct, ectasia	2 (4%)	1 (2%)

TABLE D5b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Alimentary System (continued)		
Stomach, forestomach	(50)	(51)
Acanthosis	1 (2%)	1 (2%)
Stomach, glandular	(50)	(51)
Dysplasia		1 (2%)
Cardiovascular System		
Heart	(50)	(51)
Degeneration	2 (4%)	
Mineralization	1 (2%)	1 (2%)
Endocrine System		
Adrenal gland, cortex	(50)	(51)
Hypertrophy	3 (6%)	2 (4%)
Adrenal gland, medulla	(49)	(51)
Hyperplasia		1 (2%)
Islets, pancreatic	(49)	(48)
Hyperplasia		1 (2%)
Pituitary gland	(49)	(47)
Pars distalis, cyst	1 (2%)	
Pars distalis, hyperplasia	22 (45%)	16 (34%)
Thyroid gland	(50)	(51)
Follicular cell, hyperplasia	9 (18%)	32 (63%)
General Body System		
None		
Genital System		
Clitoral gland	(7)	(4)
Dilatation	5 (71%)	4 (100%)
Inflammation	1 (14%)	
Ovary	(50)	(49)
Cyst	14 (28%)	14 (29%)
Cyst, multiple		1 (2%)
Uterus	(50)	(51)
Hemorrhage	1 (2%)	
Hyperplasia, cystic, glandular	42 (84%)	40 (78%)
Hematopoietic System		
Bone marrow	(50)	(51)
Myelofibrosis	19 (38%)	18 (35%)
Lymph node	(50)	(51)
Lumbar, cyst	1 (2%)	
Mediastinal, inflammation, granulomatous		1 (2%)
Lymph node, mandibular	(50)	(51)
Infiltration cellular, histiocyte		1 (2%)
Pigmentation		1 (2%)

TABLE D5b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Triamterene: Second Study (continued)

	0 ppm	400 ppm
2-Year Study (continued)		
Hematopoietic System (continued)		
Lymph node, mesenteric	(47)	(47)
Congestion	1 (2%)	
Cyst		1 (2%)
Infiltration cellular, histiocyte	2 (4%)	1 (2%)
Spleen	(49)	(51)
Hematopoietic cell proliferation	1 (2%)	5 (10%)
Hemorrhage		1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)
Lymphoid follicle, hyperplasia	1 (2%)	
Integumentary System		
Mammary gland	(49)	(50)
Ectasia		1 (2%)
Hyperplasia	2 (4%)	2 (4%)
Skin	(50)	(51)
Cyst epithelial inclusion	1 (2%)	
Inflammation, chronic active	1 (2%)	
Musculoskeletal System		
None		
Nervous System		
Brain	(50)	(51)
Compression		1 (2%)
Cyst epithelial inclusion	1 (2%)	
Arteriole, infiltration cellular, lymphocyte	1 (2%)	
Respiratory System		
Lung	(50)	(51)
Hemorrhage	1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)
Pleura, infiltration cellular, lymphocyte	1 (2%)	
Nose	(50)	(51)
Inflammation, acute	2 (4%)	3 (6%)
Special Senses System		
Harderian gland	(4)	(4)
Hyperplasia	4 (100%)	1 (25%)
Urinary System		
Kidney	(50)	(51)
Nephropathy	17 (34%)	21 (41%)
Artery, inflammation, chronic active		1 (2%)

[a] Number of animals examined microscopically at site and number of animals with lesion

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

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

Each trial consisted of triplicate plates of concurrent positive and solvent (dimethylsulfoxide) controls and of at least five doses of triamterene. High dose was limited by solubility and did not exceed 10,000 μg/plate. All assays were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987). Triamterene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of triamterene; the high dose was limited by toxicity.

In the SCE test without S9, CHO cells were incubated for 26 hours with triamterene in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing triamterene was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 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 triamterene, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no triamterene and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining was the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with triamterene for 8.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with triamterene and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 10 to 12 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.

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 scored for frequency of SCEs per cell from each dose level; 100 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. 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. A single increased dose was considered weak evidence of a positive response two increased doses were sufficient to evaluate the trial as positive. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive (Galloway *et al.*, 1987).

RESULTS

Triamterene (10 to 10,000 μg/plate) was tested in two laboratories for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with a preincubation protocol in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no induction of mutations was observed in either laboratory (Table E1; Mortelmans *et al.*, 1986). In cytogenetic tests with Chinese hamster ovary cells, triamterene induced sister chromatid exchanges with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table E2). Without S9, doses tested ranged from 0.5 to 40 μg/mL; 10 μg/mL was the lowest dose at which a positive response occurred. With S9, doses of 5 to 500 μg/mL were tested and the lowest effective dose was 160 μg/mL. Tests for induction of chromosomal aberrations in CHO cells were negative, with and without S9 activation. With S9, the first trial showed a significant increase in aberrations at 50 μg/mL, but this response was not repeated in a subsequent trial (Table E3).

TABLE E1
Mutagenicity of Triamterene in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at EG&G Mason Research Institute							
TA100							
	0	102 ± 0.9	103 ± 2.0	120 ± 9.0	94 ± 5.2	122 ± 8.1	83 ± 7.5
	10	93 ± 3.4					
	33	97 ± 4.0	85 ± 1.5	123 ± 8.6	83 ± 4.6	114 ± 6.7	92 ± 11.6
	100	114 ± 9.0	97 ± 1.2	136 ± 4.6	97 ± 6.7	131 ± 12.5	89 ± 4.3
	333	96 ± 4.0	102 ± 7.3	134 ± 5.5	102 ± 4.6	113 ± 3.2	90 ± 7.0
	1,000	101 ± 10.4	48 ± 0.7	106 ± 16.3	68 ± 7.4	107 ± 8.1	74 ± 7.6
	2,000			25 ± 2.6[c]	12 ± 1.9[c]	67 ± 9.5[c]	25 ± 9.6[c]
	3,333		9 ± 2.5[c]				
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		2,140 ± 29.7	1,338 ± 99.7	1,443 ± 42.4	946 ± 33.3	2,051 ± 101.1	1,234 ± 16.4
TA1535							
	0	14 ± 2.6	28 ± 5.0	9 ± 1.8	7 ± 2.0	9 ± 1.9	8 ± 1.7
	10	9 ± 1.7					
	33	12 ± 2.7	17 ± 3.3	11 ± 1.2	9 ± 1.9	10 ± 1.2	9 ± 1.5
	100	12 ± 1.8	19 ± 1.0	8 ± 2.5	9 ± 1.9	9 ± 0.3	8 ± 0.6
	333	13 ± 2.3	14 ± 1.8	9 ± 1.2	9 ± 2.3	13 ± 2.5	8 ± 1.7
	1,000	5 ± 1.5	3 ± 1.0	8 ± 0.9	7 ± 1.5	8 ± 0.7	5 ± 0.6
	2,000			6 ± 0.7[c]		6 ± 1.2[c]	
	3,333		1 ± 0.0[c]		0 ± 0.0[c]		1 ± 0.7[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,537 ± 42.2	978 ± 131.0	107 ± 6.4	115 ± 7.4	128 ± 3.5	111 ± 9.6
TA1537							
	0	7 ± 1.5	4 ± 1.2	9 ± 1.5	6 ± 0.3	9 ± 1.2	5 ± 1.5
	10	8 ± 1.5					
	33	4 ± 1.8	7 ± 0.3	10 ± 0.9	7 ± 0.7	13 ± 3.5	5 ± 0.9
	100	10 ± 1.5	3 ± 1.2	12 ± 0.7	7 ± 0.7	8 ± 1.5	5 ± 1.9
	333	6 ± 1.2	6 ± 1.8	7 ± 1.9	7 ± 0.7	10 ± 0.3	4 ± 0.3
	1,000	5 ± 0.9	2 ± 1.5	6 ± 1.3	3 ± 1.2	9 ± 2.0	4 ± 1.7
	2,000			4 ± 1.2[c]		7 ± 2.3[c]	
	3,333		0 ± 0.0[c]		0 ± 0.3[c]		2 ± 0.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		461 ± 51.1	105 ± 9.8	166 ± 9.7	85 ± 2.3	209 ± 10.7	142 ± 3.2
TA98							
	0	19 ± 2.3	17 ± 1.5	32 ± 2.0	27 ± 2.1	31 ± 1.0	29 ± 1.2
	10	16 ± 2.8					
	33	16 ± 1.5	15 ± 0.9	29 ± 1.8	26 ± 3.0	34 ± 2.5	30 ± 2.0
	100	18 ± 1.2	13 ± 1.5	22 ± 3.2	28 ± 2.5	39 ± 4.1	25 ± 2.7
	333	14 ± 1.8	15 ± 1.5	30 ± 2.6	27 ± 5.3	40 ± 0.9	27 ± 2.7
	1,000	17 ± 2.6	15 ± 0.9	20 ± 2.3	18 ± 1.5	28 ± 5.4	21 ± 1.2
	2,000			19 ± 3.0[c]		24 ± 3.4[c]	
	3,333		9 ± 2.3[c]		14 ± 1.0[c]		9 ± 3.0[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		2,805 ± 16.7	1,166 ± 54.5	954 ± 24.8	520 ± 12.7	1,277 ± 21.8	730 ± 54.0

TABLE E1
Mutagenicity of Triamterene in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at Case Western Reserve University							
TA100							
	0	134 ± 7.3	104 ± 6.8	178 ± 9.0	125 ± 24.8	176 ± 4.3	117 ± 18.0
	100	106 ± 5.2	111 ± 7.4	167 ± 10.9	107 ± 9.6	126 ± 16.8	132 ± 11.2
	333	116 ± 6.0	94 ± 1.5	167 ± 7.9	133 ± 7.2	151 ± 15.6	160 ± 6.8
	1,000	108 ± 2.3	107 ± 6.0[c]	157 ± 5.0	133 ± 5.2[c]	122 ± 19.4	130 ± 4.7[c]
	3,333	91 ± 5.4[c]	93 ± 5.9[c]	104 ± 3.7[c]	142 ± 5.2[c]	77 ± 3.8[c]	94 ± 14.0[c]
	10,000	63 ± 12.3[c]	55 ± 4.2[c]	104 ± 7.0[c]	108 ± 9.8[c]	99 ± 6.5[c]	63 ± 12.7[c]
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control	1,058 ± 172.1	1,533 ± 44.4	1,740 ± 159.2	1,936 ± 152.5	1,468 ± 152.6	2,471 ± 176.8
TA1535							
	0	26 ± 0.9	28 ± 5.4	19 ± 2.0	23 ± 4.0	21 ± 0.9	26 ± 1.5
	100	27 ± 1.7	25 ± 5.2	12 ± 2.3	18 ± 0.9	20 ± 2.6	23 ± 3.2
	333	29 ± 1.5	29 ± 2.8	16 ± 1.5	29 ± 2.6	17 ± 1.2	27 ± 3.2
	1,000	26 ± 3.2	31 ± 4.1[c]	20 ± 1.2	17 ± 4.0[c]	10 ± 0.3	17 ± 0.6[c]
	3,333	10 ± 1.2[c]	22 ± 3.6[c]	8 ± 0.6[c]	16 ± 0.9[c]	4 ± 2.1[c]	18 ± 0.9[c]
	10,000	8 ± 1.2[c]	15 ± 1.5[c]	5 ± 0.6[c]	13 ± 1.8[c]	8 ± 0.6[c]	12 ± 0.9[c]
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control	1,264 ± 245.1	1,837 ± 143.4	418 ± 24.6	439 ± 14.4	222 ± 15.7	418 ± 35.9
TA1537							
	0	15 ± 3.1	14 ± 1.2	30 ± 1.2	23 ± 2.1	22 ± 1.9	19 ± 2.6
	100	10 ± 3.3	13 ± 0.9	28 ± 1.3	19 ± 2.5	27 ± 4.3	15 ± 1.2
	333	10 ± 1.8	10 ± 0.9	14 ± 2.0	17 ± 1.8	18 ± 5.2	16 ± 2.0
	1,000	11 ± 2.6	10 ± 1.5[c]	15 ± 2.1[c]	18 ± 2.0[c]	15 ± 1.0[c]	12 ± 0.6[c]
	3,333	6 ± 2.0[c]	9 ± 0.7[c]	9 ± 2.2[c]	10 ± 1.2[c]	6 ± 1.5[c]	9 ± 0.7[c]
	10,000	4 ± 0.0[c]	7 ± 0.9[c]	6 ± 1.5[c]	5 ± 1.2[c]	7 ± 2.4[c]	4 ± 0.9[c]
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control	984 ± 55.2	1,000 ± 124.5	209 ± 28.6	486 ± 16.1	393 ± 45.5	800 ± 40.5
TA98							
	0	37 ± 3.4	42 ± 3.4	47 ± 2.3	46 ± 2.7	37 ± 2.7	38 ± 3.2
	100	34 ± 3.5	40 ± 2.2	37 ± 3.3	39 ± 2.1	38 ± 3.7	45 ± 6.4
	333	32 ± 1.8	42 ± 2.3	43 ± 3.5	46 ± 7.5	37 ± 3.7	46 ± 2.6
	1,000	28 ± 6.0	37 ± 5.7[c]	18 ± 4.5[c]	34 ± 1.5[c]	33 ± 3.1[c]	31 ± 5.3[c]
	3,333	16 ± 1.7[c]	31 ± 5.2[c]	18 ± 1.3[c]	23 ± 2.6[c]	22 ± 2.4[c]	22 ± 4.7[c]
	10,000	13 ± 0.9[c]	26 ± 0.6[c]	10 ± 0.3[c]	17 ± 2.0[c]	13 ± 3.5[c]	14 ± 0.9[c]
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control	171 ± 11.0	444 ± 30.5	692 ± 85.2	1,681 ± 148.0	636 ± 59.0	1,997 ± 90.0

[a] The detailed protocol and these data are presented in Mortelmans *et al.* (1986). 0 μg/plate dose is the solvent control.
[b] Revertants are presented as mean ± the standard error from three plates.
[c] Precipitate on plate
[d] 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Triamterene[a]

Compound	Dose μg/mL	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,039	451	0.43	9.0	26.0	
Mitomycin-C	0.005	50	1,039	1,581	1.52	31.6	26.0	250.55
Triamterene	0.5	50	1,046	414	0.39	8.3	26.0	-8.82
	1.6	50	1,034	520	0.50	10.4	26.0	15.86
	5.0	50	1,038	503	0.48	10.1	26.0	11.64
	16.0	50	1,019	738	0.72	14.8	26.0	66.85*
								P<0.001[c]
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,033	411	0.39	8.2	26.0	
Mitomycin-C	0.005	50	1,050	1,393	1.32	27.9	26.0	233.44
	0.010	50	1,045	2,049	1.96	41.0	26.0	392.81
Triamterene	5.0	50	1,046	497	0.47	9.9	26.0	19.42
	10.0	50	1,039	641	0.61	12.8	26.0	55.06*
	20.0	50	1,037	1,017	0.98	20.3	26.0	146.49*
	40.0	0						
								P<0.001

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Triamterene (continued)

Compound	Dose μg/mL	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/Chromosome	SCEs/Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)
+S9								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		50	1,034	573	0.55	11.5	26.0	
Cyclophosphamide	2.0	50	1,039	3,005	2.89	60.1	26.0	421.92
Triamterene	5.0	50	1,034	522	0.50	10.4	26.0	-8.90
	16.0	50	1,017	437	0.42	8.7	26.0	-22.46
	50.0	50	1,028	661	0.64	13.2	26.0	16.03
	160.0	50	1,025	590	0.57	11.8	26.0	3.87
	500.0	0					26.0	
								P=0.007
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,046	434	0.41	8.7	26.0	
Cyclophosphamide	1.5	50	1,044	1,894	1.81	37.9	26.0	337.24
	2.0	50	1,049	3,083	2.93	61.7	26.0	608.34
Triamterene	5.0	50	1,048	424	0.40	8.5	26.0	-2.49
	16.0	50	1,051	437	0.41	8.7	26.0	0.21
	50.0	50	1,044	485	0.46	9.7	26.0	11.96
	160.0	50	1,047	696	0.66	13.9	26.0	60.22*
	500.0	50	1,036	909	0.87	18.2	26.0	111.47*
								P<0.001

* Significant increase (P<0.01)
[a] Study performed at Environmental Health Research & Testing, Inc. SCE=sister chromatid exchange; BrdU=bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1985, 1987).
[b] SCEs/chromosome of culture exposed to triamterene relative to those of culture exposed to solvent.
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Triamterene[a]

-S9					+S9				
Dose µg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose µg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Trial 1 - Harvest time: 10.5 hours Summary: Negative					**Trial 1** - Harvest time: 12.0 hours Summary: Questionable				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	1	0.01	1.0		100	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.250	100	23	0.23	18.0	50.0	100	117	1.17	67.0
Triamterene					Triamterene				
1.6	100	1	0.01	1.0	5.0	100	1	0.01	1.0
5.0	100	0	0.00	0.0	16.0	100	4	0.04	3.0
16.0	100	0	0.00	0.0	50.0	100	8	0.08	7.0*
50.0	100	0	0.00	0.0	160.0	100	1	0.01	1.0
					500.0	100	2	0.02	2.0
				P=0.933[b]					P=0.134
					Trial 2 - Harvest time: 14.0 hours Summary: Negative				
					Dimethylsulfoxide				
						100	0	0.00	0.0
					Cyclophosphamide				
					50.0	100	133	1.33	61.0
					Triamterene				
					25.0	100	0	0.00	0.0
					50.0	100	2	0.02	2.0
					100.0	100	1	0.01	1.0
					200.0	100	0	0.00	0.0
					600.0	100	0	0.00	0.0
									P=0.587

* Significant increase ($P<0.05$)
[a] Study performed at Environmental Health Research & Testing, Inc. Abs=aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985, 1987).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

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

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TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 15-Day Feed Study of Triamterene[a]

Organ	0 ppm	1,000 ppm	3,000 ppm
Male			
n	5	5	4
Necropsy body wt	243 ± 4	244 ± 6	125 ± 4**
Brain			
Absolute	1.764 ± 0.018	1.758 ± 0.015	1.625 ± 0.025**
Relative	7.26 ± 0.14	7.24 ± 0.24	13.03 ± 0.63**
Heart			
Absolute	0.863 ± 0.005	0.812 ± 0.015*	0.451 ± 0.020**
Relative	3.55 ± 0.07	3.33 ± 0.06	3.60 ± 0.12
R. Kidney			
Absolute	1.053 ± 0.019	1.063 ± 0.040	0.666 ± 0.026**
Relative	4.33 ± 0.11	4.36 ± 0.06	5.35 ± 0.38**
Liver			
Absolute	12.839 ± 0.269	13.972 ± 0.508	5.744 ± 0.278**
Relative	52.85 ± 1.47	57.25 ± 0.73	46.11 ± 3.17
Lungs			
Absolute	1.579 ± 0.155	1.386 ± 0.151	0.755 ± 0.119**
Relative	6.50 ± 0.66	5.64 ± 0.49	6.09 ± 1.05
R. Testis			
Absolute	1.273 ± 0.031	1.280 ± 0.040	0.963 ± 0.026**
Relative	5.23 ± 0.08	5.25 ± 0.03	7.70 ± 0.05**
Thymus			
Absolute	0.418 ± 0.017	0.367 ± 0.016*	0.038 ± 0.004**[b]
Relative	1.72 ± 0.09	1.51 ± 0.06	0.30 ± 0.03**[b]

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 15-Day Feed Study of Triamterene (continued)

Organ	0 ppm	1,000 ppm	3,000 ppm
Female			
n	5	5	3
Necropsy body wt	163 ± 8	161 ± 3	106 ± 12**
Brain			
Absolute	1.735 ± 0.030	1.664 ± 0.027	1.580 ± 0.040**
Relative	10.63 ± 0.20	10.34 ± 0.13	15.27 ± 1.62**
Heart			
Absolute	0.657 ± 0.027	0.600 ± 0.021	0.408 ± 0.031**
Relative	4.02 ± 0.16	3.72 ± 0.06	3.89 ± 0.23
R. Kidney			
Absolute	0.759 ± 0.015	0.738 ± 0.036	0.563 ± 0.033**
Relative	4.65 ± 0.08	4.58 ± 0.16	5.39 ± 0.38*
Liver			
Absolute	8.196 ± 0.180	8.330 ± 0.457	7.530 ± 0.703
Relative	50.17 ± 0.51	51.64 ± 2.27	71.57 ± 4.15**
Lungs			
Absolute	1.152 ± 0.052	1.070 ± 0.044	0.796 ± 0.089**
Relative	7.04 ± 0.21	6.63 ± 0.16	7.52 ± 0.19
Thymus			
Absolute	0.349 ± 0.014	0.340 ± 0.014	0.036 ± 0.003**
Relative	2.13 ± 0.07	2.11 ± 0.08	0.34 ± 0.02**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for the 10,000, 30,000, and 60,000 ppm groups due to 100% mortality.
[b] n=2

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Triamterene[a]

Organ	0 ppm	150 ppm	600 ppm	1,200 ppm
Male				
n	10	10	10	10
Necropsy body weight	364 ± 7	356 ± 10	351 ± 7	332 ± 16*
Brain				
Absolute	2.05 ± 0.03	2.01 ± 0.04	2.07 ± 0.03	1.90 ± 0.03**
Relative	5.65 ± 0.10	5.69 ± 0.17	5.89 ± 0.10	5.82 ± 0.24
Heart				
Absolute	1.34 ± 0.07[b]	1.34 ± 0.04[b]	1.31 ± 0.06	1.22 ± 0.04
Relative	3.73 ± 0.18[b]	3.72 ± 0.14[b]	3.73 ± 0.13	3.75 ± 0.19
R. Kidney				
Absolute	1.43 ± 0.04	1.37 ± 0.04	1.34 ± 0.04	1.19 ± 0.03**
Relative	3.93 ± 0.11	3.85 ± 0.09	3.83 ± 0.06	3.64 ± 0.18
Liver				
Absolute	12.55 ± 0.45	12.08 ± 0.50	12.44 ± 0.35	11.95 ± 0.44
Relative	34.5 ± 1.0	34.0 ± 1.1	35.4 ± 0.7	36.5 ± 1.6
Lungs				
Absolute	1.47 ± 0.06	1.48 ± 0.04	1.47 ± 0.05	1.38 ± 0.05
Relative	4.05 ± 0.14	4.17 ± 0.06	4.17 ± 0.09	4.24 ± 0.22
R. Testis				
Absolute	1.49 ± 0.02	1.45 ± 0.03	1.44 ± 0.03	1.48 ± 0.02
Relative	4.10 ± 0.07	4.09 ± 0.06	4.12 ± 0.09	4.52 ± 0.16**
Thymus[c]				
Absolute	270.0 ± 13.0	280.0 ± 14.6	300.1 ± 16.2	237.9 ± 10.4
Relative	0.74 ± 0.03	0.79 ± 0.04	0.85 ± 0.04	0.73 ± 0.04

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Triamterene (continued)

Organ	0 ppm	150 ppm	600 ppm	1,200 ppm
Female				
n	10	10	10	10
Necropsy body weight	197 ± 2	196 ± 2	191 ± 3	183 ± 11
Brain				
Absolute	1.89 ± 0.03	1.78 ± 0.03*	1.90 ± 0.03	1.78 ± 0.03*
Relative	9.58 ± 0.16	9.06 ± 0.19	9.97 ± 0.17	9.93 ± 0.44
Heart				
Absolute	0.86 ± 0.02[b]	0.79 ± 0.02	0.81 ± 0.02	0.73 ± 0.03**
Relative	4.36 ± 0.13[b]	4.03 ± 0.09	4.27 ± 0.08	4.09 ± 0.24
R. Kidney				
Absolute	0.78 ± 0.02	0.76 ± 0.01	0.75 ± 0.02	0.66 ± 0.01**
Relative	3.95 ± 0.11	3.85 ± 0.03	3.92 ± 0.06	3.70 ± 0.16
Liver				
Absolute	6.78 ± 0.15	6.81 ± 0.13	6.88 ± 0.16	6.26 ± 0.23
Relative	34.5 ± 1.0	34.8 ± 0.9	36.0 ± 0.6	35.0 ± 1.8
Lungs				
Absolute	1.11 ± 0.04	1.11 ± 0.03	1.05 ± 0.04	0.98 ± 0.03*
Relative	5.66 ± 0.19	5.65 ± 0.13	5.52 ± 0.24	5.46 ± 0.19
Thymus[c]				
Absolute	254.9 ± 15.1	242.7 ± 15.4	228.0 ± 9.6	209.2 ± 3.3*
Relative	1.30 ± 0.08	1.23 ± 0.07	1.20 ± 0.05	1.17 ± 0.06

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams unless otherwise specified; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for the 2,400 ppm group due to 100% mortality.
[b] n=9
[c] Weights are given in milligrams.

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of Triamterene[a]

Organ	0 ppm	150 ppm	300 ppm	600 ppm
Male				
n	10	10	10	10
Necropsy body wt	350 ± 8	331 ± 5	336 ± 7	349 ± 5
Brain				
Absolute	1.98 ± 0.02	1.93 ± 0.02	1.96 ± 0.02	1.99 ± 0.02
Relative	5.67 ± 0.11	5.83 ± 0.11	5.84 ± 0.12	5.73 ± 0.07
L. Kidney				
Absolute	1.20 ± 0.03	1.08 ± 0.02**	1.13 ± 0.02	1.14 ± 0.03
Relative	3.43 ± 0.06	3.25 ± 0.06*	3.35 ± 0.04	3.26 ± 0.06*
R. Kidney				
Absolute	1.17 ± 0.03	1.08 ± 0.02*	1.10 ± 0.02	1.15 ± 0.02
Relative	3.35 ± 0.08	3.28 ± 0.06	3.27 ± 0.02	3.29 ± 0.04
Liver				
Absolute	10.77 ± 0.37	10.17 ± 0.19	10.67 ± 0.29	11.48 ± 0.36
Relative	30.8 ± 0.7	30.7 ± 0.4	31.7 ± 0.5	32.9 ± 0.8*
Female				
n	10	10	10	10
Necropsy body wt	194 ± 3	186 ± 3	183 ± 3*	182 ± 4*
Brain				
Absolute	1.83 ± 0.02	1.80 ± 0.07	1.80 ± 0.01	1.82 ± 0.02
Relative	9.47 ± 0.15	9.70 ± 0.32	9.85 ± 0.14	10.05 ± 0.18
L. Kidney				
Absolute	0.67 ± 0.01	0.64 ± 0.01	0.62 ± 0.01*	0.63 ± 0.01*
Relative	3.48 ± 0.07	3.44 ± 0.04	3.38 ± 0.07	3.46 ± 0.05
R. Kidney				
Absolute	0.67 ± 0.02	0.65 ± 0.02	0.62 ± 0.01*	0.63 ± 0.02*
Relative	3.47 ± 0.08	3.50 ± 0.06	3.36 ± 0.06	3.48 ± 0.07
Liver				
Absolute	5.32 ± 0.12	5.08 ± 0.20	5.14 ± 0.11	5.21 ± 0.15
Relative	27.5 ± 0.5	27.4 ± 0.8	28.0 ± 0.5	28.7 ± 0.6

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene[a]

Organ	0 ppm	150 ppm	300 ppm	600 ppm
Male				
n	10	10	10	10
Necropsy body weight	471 ± 8	493 ± 10	462 ± 10	471 ± 6
Brain				
Absolute	2.06 ± 0.02	2.07 ± 0.02	2.11 ± 0.02	2.11 ± 0.02
Relative	4.38 ± 0.10	4.20 ± 0.08	4.58 ± 0.08	4.49 ± 0.05
L. Kidney				
Absolute	1.49 ± 0.03	1.56 ± 0.04[b]	1.51 ± 0.04	1.51 ± 0.03
Relative	3.16 ± 0.04	3.14 ± 0.08[b]	3.27 ± 0.05	3.22 ± 0.05
R. Kidney				
Absolute	1.45 ± 0.03	1.56 ± 0.04	1.52 ± 0.05	1.50 ± 0.03
Relative	3.09 ± 0.06	3.18 ± 0.08	3.28 ± 0.06	3.19 ± 0.05
Liver				
Absolute	14.80 ± 0.45	16.22 ± 0.34*	15.78 ± 0.36	15.71 ± 0.42
Relative	31.4 ± 0.6	32.9 ± 0.6	34.2 ± 0.4**	33.3 ± 0.6**
Female				
n	10	10	10	10
Necropsy body weight	295 ± 5	287 ± 6	295 ± 3	281 ± 10
Brain				
Absolute	1.91 ± 0.02	1.89 ± 0.02	1.89 ± 0.03	1.93 ± 0.02
Relative	6.48 ± 0.12	6.61 ± 0.14	6.40 ± 0.09	6.95 ± 0.25
L. Kidney				
Absolute	0.93 ± 0.02	0.90 ± 0.02	0.88 ± 0.02	0.91 ± 0.03
Relative	3.15 ± 0.05	3.16 ± 0.06	2.98 ± 0.07	3.27 ± 0.09
R. Kidney				
Absolute	0.94 ± 0.02	0.90 ± 0.02	0.87 ± 0.01	0.93 ± 0.03
Relative	3.18 ± 0.05	3.14 ± 0.07	2.96 ± 0.04*	3.32 ± 0.07
Liver				
Absolute	8.94 ± 0.21	8.43 ± 0.21	8.59 ± 0.19	9.12 ± 0.29
Relative	30.3 ± 0.4	29.4 ± 0.6	29.1 ± 0.7	32.7 ± 1.1

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 15-Day Feed Study of Triamterene[a]

Organ	0 ppm	300 ppm	1,000 ppm
Male			
n	5	5	5
Necropsy body wt	25.3 ± 0.7	24.6 ± 0.5	25.8 ± 0.8
Brain			
Absolute	0.440 ± 0.016	0.422 ± 0.008	0.440 ± 0.013
Relative	17.44 ± 0.82	17.16 ± 0.33	17.09 ± 0.29
Heart			
Absolute	0.160 ± 0.006	0.165 ± 0.007	0.133 ± 0.013
Relative	6.31 ± 0.20	6.71 ± 0.27	5.14 ± 0.39*
R. Kidney			
Absolute	0.277 ± 0.007	0.259 ± 0.008	0.251 ± 0.013
Relative	10.96 ± 0.45	10.53 ± 0.19	9.71 ± 0.24*
Liver			
Absolute	1.499 ± 0.054	1.562 ± 0.065	1.660 ± 0.091
Relative	59.15 ± 0.93	63.33 ± 1.41	64.31 ± 1.86*
Lungs			
Absolute	0.197 ± 0.008	0.190 ± 0.001	0.199 ± 0.008
Relative	7.77 ± 0.30	7.72 ± 0.16	7.71 ± 0.19
R. Testis			
Absolute	0.102 ± 0.002	0.106 ± 0.006	0.099 ± 0.004
Relative	4.06 ± 0.17	4.30 ± 0.23	3.85 ± 0.14
Thymus			
Absolute	0.041 ± 0.005	0.040 ± 0.002	0.031 ± 0.005
Relative	1.63 ± 0.21	1.65 ± 0.10	1.23 ± 0.19

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 15-Day Feed Study of Triamterene (continued)

Organ	0 ppm	300 ppm	1,000 ppm
Female			
n	5	5	5
Necropsy body wt	20.7 ± 0.3	19.6 ± 0.6	21.3 ± 0.3
Brain			
Absolute	0.452 ± 0.007	0.432 ± 0.014	0.445 ± 0.004
Relative	21.84 ± 0.31	22.08 ± 0.25	20.89 ± 0.42
Heart			
Absolute	0.151 ± 0.014	0.133 ± 0.009	0.109 ± 0.007*
Relative	7.30 ± 0.75	6.79 ± 0.35	5.13 ± 0.37*
R. Kidney			
Absolute	0.194 ± 0.008	0.174 ± 0.007	0.177 ± 0.007
Relative	9.34 ± 0.26	8.86 ± 0.20	8.30 ± 0.27*
Liver			
Absolute	1.317 ± 0.024	1.213 ± 0.047	1.238 ± 0.020
Relative	63.57 ± 0.99	61.91 ± 1.41	58.09 ± 0.73**
Lungs			
Absolute	0.190 ± 0.008	0.196 ± 0.008	0.195 ± 0.004
Relative	9.16 ± 0.25	10.02 ± 0.39	9.16 ± 0.15
Thymus			
Absolute	0.054 ± 0.004	0.051 ± 0.004	0.049 ± 0.003
Relative	2.58 ± 0.17	2.64 ± 0.24	2.32 ± 0.15

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for the 3,000, 10,000, and 30,000 ppm groups due to 100% mortality.

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Triamterene[a]

Organ	0 ppm	100 ppm	400 ppm	800 ppm
Male				
n	10	6	10	10
Necropsy body weight	26.8 ± 0.9	25.3 ± 0.9	25.5 ± 0.8	24.4 ± 0.6*
Brain				
Absolute	0.44 ± 0.01	0.46 ± 0.03	0.43 ± 0.01	0.41 ± 0.01
Relative	16.5 ± 0.6	18.2 ± 0.8	16.9 ± 0.5	17.0 ± 0.5
Heart				
Absolute	0.16 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.14 ± 0.01
Relative	5.82 ± 0.12	6.04 ± 0.20	5.84 ± 0.23	5.90 ± 0.23
R. Kidney				
Absolute	0.23 ± 0.01	0.22 ± 0.01	0.24 ± 0.01	0.20 ± 0.01
Relative	8.71 ± 0.41	8.87 ± 0.23	9.36 ± 0.20	8.09 ± 0.19
Liver				
Absolute	1.16 ± 0.03	1.15 ± 0.04	1.13 ± 0.04	1.07 ± 0.04
Relative	43.5 ± 1.0	45.4 ± 0.8	44.5 ± 1.2	43.6 ± 1.1
Lungs				
Absolute	0.17 ± 0.01	0.17 ± 0.01[b]	0.15 ± 0.00	0.16 ± 0.01
Relative	6.52 ± 0.25	6.64 ± 0.14[b]	6.05 ± 0.15	6.65 ± 0.17
R. Testis				
Absolute	0.12 ± 0.00	0.10 ± 0.01	0.11 ± 0.00	0.11 ± 0.00
Relative	4.34 ± 0.14	3.95 ± 0.47	4.38 ± 0.24	4.71 ± 0.15
Thymus[c]				
Absolute	33.60 ± 3.25	23.50 ± 5.19	34.00 ± 4.20	19.30 ± 2.13**
Relative	1.26 ± 0.13	0.94 ± 0.22	1.32 ± 0.13	0.79 ± 0.09*

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Triamterene (continued)

Organ	0 ppm	100 ppm	400 ppm	800 ppm
Female				
n	10	10	10	8
Necropsy body weight	20.0 ± 0.4	19.3 ± 0.5	19.1 ± 0.3	19.6 ± 0.4
Brain				
Absolute	0.45 ± 0.02	0.46 ± 0.01	0.47 ± 0.02	0.47 ± 0.01
Relative	22.6 ± 0.9	23.9 ± 1.1	24.6 ± 0.9	24.2 ± 0.5
Heart				
Absolute	0.15 ± 0.02	0.13 ± 0.01	0.13 ± 0.00	0.12 ± 0.00
Relative	7.27 ± 0.96	6.86 ± 0.60	6.68 ± 0.12	5.87 ± 0.16
R. Kidney				
Absolute	0.18 ± 0.01	0.17 ± 0.01	0.17 ± 0.00[d]	0.15 ± 0.01
Relative	8.94 ± 0.47	8.75 ± 0.49	8.67 ± 0.13[d]	7.60 ± 0.41*
Liver				
Absolute	0.97 ± 0.03	0.94 ± 0.04	0.90 ± 0.02	0.93 ± 0.03
Relative	48.6 ± 1.2	48.5 ± 1.2	46.9 ± 0.7	47.6 ± 0.5
Lungs				
Absolute	0.16 ± 0.01	0.14 ± 0.00[d]	0.15 ± 0.00	0.16 ± 0.01
Relative	7.83 ± 0.38	7.41 ± 0.25[d]	7.68 ± 0.13	8.13 ± 0.34
Thymus[c]				
Absolute	35.40 ± 5.86	32.90 ± 3.44	29.50 ± 2.14	28.63 ± 3.82
Relative	1.75 ± 0.27	1.71 ± 0.18	1.55 ± 0.12	1.44 ± 0.17

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ and body weights are given in grams unless otherwise specified; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for the 1,600 ppm group due to 100% mortality.
[b] n=5
[c] Weights are given in milligrams.
[d] n=9

TABLE F7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of Triamterene[a]

Organ	0 ppm	100 ppm	200 ppm	400 ppm
Male				
n	10	10	10	10
Necropsy body wt	28.3 ± 0.5	27.9 ± 0.9	28.4 ± 0.6	26.2 ± 0.8
Brain				
Absolute	0.45 ± 0.00	0.46 ± 0.01	0.46 ± 0.01	0.45 ± 0.00
Relative	16.1 ± 0.3	16.5 ± 0.6	16.3 ± 0.4	17.2 ± 0.5
L. Kidney				
Absolute	0.23 ± 0.00	0.22 ± 0.01	0.23 ± 0.01	0.21 ± 0.00**
Relative	8.16 ± 0.13	7.96 ± 0.29	8.19 ± 0.22	8.05 ± 0.26
R. Kidney				
Absolute	0.24 ± 0.00	0.24 ± 0.00	0.25 ± 0.01	0.22 ± 0.01
Relative	8.35 ± 0.10	8.52 ± 0.24	8.66 ± 0.22	8.57 ± 0.27
Liver				
Absolute	1.10 ± 0.02	1.07 ± 0.01	1.10 ± 0.02	1.02 ± 0.02**
Relative	38.7 ± 0.5	38.5 ± 1.0	38.7 ± 0.6	39.0 ± 0.7
Female				
n	10	10	10	10
Necropsy body wt	22.5 ± 0.5	23.1 ± 0.5	23.2 ± 0.5	22.6 ± 0.6
Brain				
Absolute	0.47 ± 0.00	0.47 ± 0.00	0.47 ± 0.01	0.46 ± 0.00
Relative	20.8 ± 0.5	20.2 ± 0.5	20.5 ± 0.3	20.7 ± 0.5
L. Kidney				
Absolute	0.16 ± 0.00	0.15 ± 0.00	0.16 ± 0.01	0.16 ± 0.00
Relative	6.97 ± 0.19	6.54 ± 0.13	7.10 ± 0.17	7.09 ± 0.15
R. Kidney				
Absolute	0.17 ± 0.00	0.16 ± 0.00	0.17 ± 0.00	0.17 ± 0.00
Relative	7.36 ± 0.17	6.89 ± 0.15	7.31 ± 0.16	7.56 ± 0.14
Liver				
Absolute	0.97 ± 0.02	0.95 ± 0.01	0.99 ± 0.03	0.98 ± 0.02
Relative	43.1 ± 0.4	41.3 ± 0.8	42.6 ± 0.8	43.7 ± 0.5

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene: First Study[a]

Organ	0 ppm	100 ppm	200 ppm
Male			
n	10	10	10
Necropsy body wt	40.8 ± 1.1	37.5 ± 1.1	38.7 ± 1.0
Brain			
Absolute	0.47 ± 0.00	0.46 ± 0.00	0.47 ± 0.01
Relative	11.7 ± 0.4	12.5 ± 0.4	12.3 ± 0.4
L. Kidney			
Absolute	0.320 ± 0.007	0.310 ± 0.006	0.305 ± 0.007
Relative	7.89 ± 0.19	8.31 ± 0.18	7.93 ± 0.28
R. Kidney			
Absolute	0.34 ± 0.01	0.33 ± 0.01	0.32 ± 0.01
Relative	8.43 ± 0.17	8.81 ± 0.16	8.38 ± 0.25
Liver			
Absolute	1.46 ± 0.06	1.40 ± 0.09	1.34 ± 0.03
Relative	35.8 ± 1.0	37.2 ± 1.8	34.6 ± 0.7
Female			
n	10	10	10
Necropsy body wt	46.8 ± 1.5	45.1 ± 1.7	47.0 ± 2.1
Brain			
Absolute	0.48 ± 0.00	0.48 ± 0.00	0.48 ± 0.01
Relative	10.4 ± 0.3	10.7 ± 0.4	10.5 ± 0.6
L. Kidney			
Absolute	0.233 ± 0.004	0.226 ± 0.009	0.225 ± 0.006
Relative	5.02 ± 0.10	5.03 ± 0.14	4.85 ± 0.15
R. Kidney			
Absolute	0.24 ± 0.00	0.24 ± 0.01	0.25 ± 0.01
Relative	5.22 ± 0.15	5.25 ± 0.11	5.42 ± 0.16
Liver			
Absolute	1.52 ± 0.06	1.43 ± 0.06	1.50 ± 0.06
Relative	32.6 ± 0.9	31.7 ± 0.6	32.1 ± 0.8

[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F9
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene: Second Study[a]

Organ	0 ppm	400 ppm
Male		
n	10	10
Necropsy body weight	45.3 ± 1.2	46.2 ± 1.0
Brain		
Absolute	0.46 ± 0.01	0.48 ± 0.00**
Relative	10.2 ± 0.3	10.4 ± 0.2
L. Kidney		
Absolute	0.34 ± 0.01	0.33 ± 0.01
Relative	7.41 ± 0.16	7.10 ± 0.16
R. Kidney		
Absolute	0.35 ± 0.01	0.35 ± 0.01
Relative	7.81 ± 0.16	7.60 ± 0.16
Liver		
Absolute	2.01 ± 0.09	2.02 ± 0.09
Relative	44.3 ± 1.1	43.5 ± 1.0
Female		
n	10	9
Necropsy body weight	48.1 ± 1.2	48.2 ± 2.1
Brain		
Absolute	0.48 ± 0.01	0.49 ± 0.01
Relative	10.0 ± 0.3	10.3 ± 0.4
L. Kidney		
Absolute	0.23 ± 0.01	0.27 ± 0.06
Relative	4.71 ± 0.18	5.71 ± 1.24
R. Kidney		
Absolute	0.23 ± 0.01	0.24 ± 0.01
Relative	4.86 ± 0.14	5.07 ± 0.24
Liver		
Absolute	1.73 ± 0.04	1.79 ± 0.07
Relative	36.0 ± 0.6	37.3 ± 1.0

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS

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TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Triamterene[a]

Analysis	0 ppm	150 ppm	600 ppm	1,200 ppm
Male				
n	10	10	9	10
Hematology				
Hematocrit (%)	45.2 ± 0.4	45.9 ± 0.4	45.1 ± 0.9	47.3 ± 0.6*
Hemoglobin (g/dL)	17.8 ± 0.2	17.8 ± 0.1	17.5 ± 0.4	18.5 ± 0.2*
Erythrocytes ($10^6/\mu L$)	8.99 ± 0.05	9.07 ± 0.06	8.91 ± 0.16	9.20 ± 0.11
Mean cell volume (fL)	50.1 ± 0.3	50.6 ± 0.2	50.4 ± 0.3	51.3 ± 0.2**
Mean cell hemoglobin (pg)	19.8 ± 0.1	19.7 ± 0.1	19.6 ± 0.1	20.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	39.4 ± 0.3	38.9 ± 0.3	38.8 ± 0.3	39.0 ± 0.2
Leukocytes ($10^3/\mu L$)	8.70 ± 0.72	7.48 ± 0.64	6.36 ± 0.38*	7.22 ± 0.43
Segmented neutrophils ($10^3/\mu L$)	2.03 ± 0.24	1.65 ± 0.16	1.51 ± 0.15	1.39 ± 0.13*
Lymphocytes ($10^3/\mu L$)	6.31 ± 0.48	5.47 ± 0.53	4.59 ± 0.26*	5.62 ± 0.34
Monocytes ($10^3/\mu L$)	0.20 ± 0.02[b]	0.23 ± 0.03	0.16 ± 0.03[c]	0.18 ± 0.03[c]
Eosinophils ($10^3/\mu L$)	0.17 ± 0.04[d]	0.14 ± 0.04[b]	0.20 ± 0.08[e]	0.12 ± 0.02[b]
n	10	10	10	10
Clinical chemistry				
Creatinine (mg/dL)	0.63 ± 0.03	0.63 ± 0.04	0.64 ± 0.03	0.67 ± 0.03
Sodium (mEq/L)	151 ± 1	152 ± 1	150 ± 1	149 ± 1
Potassium (mEq/L)	6.7 ± 0.1	7.4 ± 0.1*	6.8 ± 0.2	7.0 ± 0.2
Chloride (mEq/L)	106 ± 1	107 ± 0	106 ± 0	105 ± 0*
Calcium (mg/dL)	11.92 ± 0.12	11.93 ± 0.17	11.58 ± 0.19	11.84 ± 0.20
Phosphorus (mg/dL)	8.4 ± 0.4	8.4 ± 0.3	8.1 ± 0.4	7.7 ± 0.2
n	10	10	10	10
Urinalysis				
Urine volume (mL/24 hr)	7 ± 1	7 ± 1	9 ± 2	11 ± 1*
Specific gravity	1.038 ± 0.004	1.038 ± 0.002	1.035 ± 0.004	1.026 ± 0.003*

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Triamterene (continued)

Analysis	0 ppm	150 ppm	600 ppm	1,200 ppm
Female				
n	10	10	9	9
Hematology				
Hematocrit (%)	43.8 ± 0.4	44.9 ± 0.5	43.9 ± 0.4	44.7 ± 0.9
Hemoglobin (g/dL)	16.9 ± 0.2	17.5 ± 0.2	16.9 ± 0.2	17.2 ± 0.3
Erythrocytes ($10^6/\mu L$)	8.04 ± 0.07	8.24 ± 0.09	8.00 ± 0.09	8.07 ± 0.17
Mean cell volume (fL)	54.5 ± 0.2	54.7 ± 0.2	54.8 ± 0.2	55.6 ± 0.2**
Mean cell hemoglobin (pg)	21.0 ± 0.1	21.2 ± 0.1	21.1 ± 0.1	21.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	38.6 ± 0.3	39.0 ± 0.3	38.5 ± 0.2	38.4 ± 0.2
Leukocytes ($10^3/\mu L$)	4.54 ± 0.26	5.39 ± 0.54	4.86 ± 0.41	4.84 ± 0.26
Segmented neutrophils ($10^3/\mu L$)	1.08 ± 0.13	1.11 ± 0.19	1.23 ± 0.22	1.02 ± 0.10
Lymphocytes ($10^3/\mu L$)	3.28 ± 0.19	4.12 ± 0.39	3.48 ± 0.24	3.64 ± 0.30
Monocytes ($10^3/\mu L$)	0.13 ± 0.02[c]	0.14 ± 0.02[d]	0.14 ± 0.02[c]	0.13 ± 0.03
Eosinophils ($10^3/\mu L$)	0.11 ± 0.01[d]	0.13 ± 0.03[d]	0.10 ± 0.00[f]	0.10 ± 0.03[e]
n	10	10	10	10
Clinical chemistry				
Creatinine (mg/dL)	0.62 ± 0.02	0.66 ± 0.02	0.61 ± 0.02	0.59 ± 0.02
Sodium (mEq/L)	149 ± 1	150 ± 1	149 ± 1	149 ± 1
Potassium (mEq/L)	6.5 ± 0.1	6.7 ± 0.2	6.6 ± 0.2	6.9 ± 0.2
Chloride (mEq/L)	108 ± 1	108 ± 0	108 ± 1	108 ± 0
Calcium (mg/dL)	11.73 ± 0.17	12.00 ± 0.13	11.57 ± 0.20	11.38 ± 0.16
Phosphorus (mg/dL)	7.1 ± 0.3	7.1 ± 0.4	6.7 ± 0.3	7.4 ± 0.3
n	10	10	10	10
Urinalysis				
Urine volume (mL/24 hr)	10 ± 1	10 ± 1	11 ± 1	6 ± 1*
Specific gravity	1.021 ± 0.003	1.019 ± 0.003	1.018 ± 0.003	1.030 ± 0.004

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[c] n=8
[d] n=7
[e] n=5
[f] n=6

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of Triamterene[a]

Analysis	0 ppm	150 ppm	300 ppm	600 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	43.6 ± 0.7	43.8 ± 0.4	44.1 ± 0.4	44.4 ± 0.5
Hemoglobin (g/dL)	15.4 ± 0.2	15.4 ± 0.1	15.5 ± 0.1	15.7 ± 0.1
Erythrocytes ($10^6/\mu L$)	9.33 ± 0.09	9.23 ± 0.09	9.36 ± 0.07	9.39 ± 0.09
Mean cell volume (fL)	46.9 ± 0.6	47.7 ± 0.4	47.2 ± 0.3	47.3 ± 0.2
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.7 ± 0.1	16.6 ± 0.1	16.7 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.2 ± 0.4	35.0 ± 0.2	35.1 ± 0.2	35.4 ± 0.2
Platelets ($10^3/\mu L$)	689.5 ± 27.4	710.2 ± 16.2	708.7 ± 13.9	686.1 ± 50.0
Reticulocytes ($10^6/\mu L$)	1.44 ± 0.18	1.61 ± 0.13	1.30 ± 0.13	1.56 ± 0.11
Leukocytes ($10^3/\mu L$)	5.93 ± 0.31	5.40 ± 0.13	5.30 ± 0.17	5.78 ± 0.19
Segmented neutrophils ($10^3/\mu L$)	1.77 ± 0.16	1.36 ± 0.08	1.59 ± 0.12	1.59 ± 0.14
Lymphocytes ($10^3/\mu L$)	4.14 ± 0.31	3.90 ± 0.15	3.57 ± 0.18	4.11 ± 0.19
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.07 ± 0.02	0.05 ± 0.02	0.03 ± 0.02
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.10 ± 0.03	0.13 ± 0.02*	0.05 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.30 ± 0.15	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00*
n	10	10	10	10
Clinical chemistry				
Urea nitrogen (mg/dL)	14.9 ± 0.4	14.8 ± 0.5	14.8 ± 0.6	15.6 ± 0.3
Creatinine (IU/L)	0.47 ± 0.03	0.43 ± 0.03	0.44 ± 0.05	0.51 ± 0.06
Sodium (mEq/L)	144 ± 1	144 ± 1	144 ± 1	145 ± 1
Potassium (mEq/L)	4.0 ± 0.2	4.1 ± 0.1	4.1 ± 0.2	4.2 ± 0.3
Chloride (mEq/L)	102 ± 0	102 ± 1	103 ± 1	102 ± 0
Calcium (mg/dL)	5.20 ± 0.18	5.10 ± 0.08	5.16 ± 0.17	4.98 ± 0.05
Phosphorus (mg/dL)	5.8 ± 0.2	6.1 ± 0.2	6.2 ± 0.1	6.6 ± 0.2*
Bicarbonate (mEq/L)	29.75 ± 0.29	29.75 ± 0.22	28.83 ± 0.58	28.84 ± 0.28
Total bilirubin (mg/dL)	0.3 ± 0.0	0.4 ± 0.0	0.3 ± 0.1	0.3 ± 0.0
pH	7.39 ± 0.00	7.38 ± 0.01	7.39 ± 0.01	7.36 ± 0.01*
n	10	10	10	10
Urinalysis				
Urine volume (mL/16 hr)	7 ± 0	8 ± 1	8 ± 1	10 ± 1
Specific gravity	1.031 ± 0.004	1.031 ± 0.005	1.029 ± 0.004	1.026 ± 0.003

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of Triamterene (continued)

Analysis	0 ppm	150 ppm	300 ppm	600 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	43.9 ± 0.5	44.3 ± 0.7	44.9 ± 0.5	42.9 ± 0.8
Hemoglobin (g/dL)	15.4 ± 0.1	15.4 ± 0.1	15.7 ± 0.1	15.0 ± 0.3
Erythrocytes ($10^6/\mu L$)	8.69 ± 0.08	8.72 ± 0.07	8.81 ± 0.10	8.46 ± 0.10
Mean cell volume (fL)	50.5 ± 0.4	50.9 ± 0.6	51.1 ± 0.4	50.8 ± 0.7
Mean cell hemoglobin (pg)	17.8 ± 0.2	17.7 ± 0.2	17.8 ± 0.1	17.7 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.2 ± 0.4	34.9 ± 0.6	34.9 ± 0.4	35.0 ± 0.4
Platelets ($10^3/\mu L$)	697.3 ± 19.8[b]	730.9 ± 25.4[b]	742.2 ± 15.2	689.8 ± 31.8
Reticulocytes ($10^6/\mu L$)	1.51 ± 0.15	1.43 ± 0.11	1.45 ± 0.13	1.50 ± 0.11
Leukocytes ($10^3/\mu L$)	4.47 ± 0.18	4.46 ± 0.22	4.51 ± 0.23	5.04 ± 0.35
Segmented neutrophils ($10^3/\mu L$)	0.96 ± 0.07	0.94 ± 0.07	1.01 ± 0.12	1.07 ± 0.07
Lymphocytes ($10^3/\mu L$)	3.46 ± 0.17	3.44 ± 0.18	3.40 ± 0.17	3.90 ± 0.34
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.06 ± 0.02	0.05 ± 0.03	0.06 ± 0.02	0.06 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.10 ± 0.10	0.30 ± 0.15	0.20 ± 0.13	0.00 ± 0.00
n	10	10	9	10
Clinical chemistry				
Urea nitrogen (mg/dL)	16.1 ± 0.7	14.4 ± 0.5	15.2 ± 0.3	14.8 ± 0.7
Creatinine (IU/L)	0.38 ± 0.02	0.44 ± 0.03	0.44 ± 0.03	0.54 ± 0.04**
Sodium (mEq/L)	143 ± 1	145 ± 1	145 ± 1	144 ± 1
Potassium (mEq/L)	3.7 ± 0.1	3.7 ± 0.2	3.8 ± 0.1	4.3 ± 0.3
Chloride (mEq/L)	105 ± 1	106 ± 1	106 ± 1	105 ± 1
Calcium (mg/dL)	4.78 ± 0.08	4.75 ± 0.06	4.62 ± 0.16	4.88 ± 0.13
Phosphorus (mg/dL)	6.3 ± 0.2	5.9 ± 0.3	6.3 ± 0.3	6.2 ± 0.4
Bicarbonate (mEq/L)	27.89 ± 0.31	27.19 ± 0.29	27.87 ± 0.49	27.80 ± 0.36
Total bilirubin (mg/dL)	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.1
pH	7.37 ± 0.01	7.36 ± 0.02	7.38 ± 0.01	7.35 ± 0.02
n	10	10	10	10
Urinalysis				
Urine volume (mL/16 hr)	7 ± 1	10 ± 1	11 ± 1*	8 ± 1
Specific gravity	1.019 ± 0.003	1.012 ± 0.001	1.011 ± 0.002*	1.014 ± 0.002

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene[a]

Analysis	0 ppm	150 ppm	300 ppm	600 ppm
Male				
n	9	8	9	9
Hematology				
Hematocrit (%)	50.7 ± 2.3	51.5 ± 0.9	53.3 ± 1.1	55.8 ± 1.5
Hemoglobin (g/dL)	14.3 ± 0.6	14.6 ± 0.1	15.2 ± 0.3	15.6 ± 0.3
Erythrocytes ($10^6/\mu L$)	9.53 ± 0.40	9.57 ± 0.12	9.95 ± 0.18	10.24 ± 0.22
Mean cell volume (fL)	53.3 ± 0.4	53.8 ± 0.8	53.9 ± 0.6	54.6 ± 0.4
Mean cell hemoglobin (pg)	15.1 ± 0.1	15.3 ± 0.2	15.3 ± 0.2	15.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.3 ± 0.4	28.4 ± 0.3	28.4 ± 0.3	27.9 ± 0.3
Platelets ($10^3/\mu L$)	836.3 ± 86.7	766.8 ± 41.7	798.6 ± 24.3	824.9 ± 66.1
Reticulocytes (%)	1.55 ± 0.17[b]	1.20 ± 0.12	1.33 ± 0.15	1.19 ± 0.12
Leukocytes ($10^3/\mu L$)	5.48 ± 0.45	5.45 ± 0.38	5.36 ± 0.55	5.72 ± 0.33
Segmented neutrophils (%)	2.01 ± 0.34	1.75 ± 0.29	2.01 ± 0.37	2.06 ± 0.24
Lymphocytes ($10^3/\mu L$)	3.36 ± 0.23	3.58 ± 0.21	3.21 ± 0.29	3.52 ± 0.36
Monocytes ($10^3/\mu L$)	0.05 ± 0.03	0.03 ± 0.01	0.04 ± 0.02	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.06 ± 0.02	0.09 ± 0.02	0.09 ± 0.03	0.13 ± 0.02**
Nucleated erythrocytes (/100 leukocytes)	0.778 ± 0.278	0.000 ± 0.000	0.778 ± 0.662	0.556 ± 0.294
n	10	10	10	10
Clinical chemistry				
Urea nitrogen (mg/dL)	17.1 ± 1.4	17.7 ± 1.6[c]	18.3 ± 1.2	15.9 ± 1.3
Creatinine (mg/dL)	0.40 ± 0.03	0.38 ± 0.03[c]	0.43 ± 0.04	0.40 ± 0.04
Sodium (mEq/L)	148 ± 2	149 ± 4	147 ± 2	152 ± 2
Potassium (mEq/L)	4.9 ± 0.3	5.1 ± 0.5	4.9 ± 0.3	5.2 ± 0.3
Chloride (mEq/L)	104 ± 2	112 ± 2*	109 ± 2	109 ± 2
Calcium (mg/dL)	4.35 ± 0.11	4.82 ± 0.47	4.48 ± 0.18	4.48 ± 0.09
Phosphorus (mg/dL)	5.5 ± 0.5	5.6 ± 0.2	6.1 ± 0.3	5.8 ± 0.3
Bicarbonate (mEq/L)	31 ± 0	29 ± 1	30 ± 0	31 ± 0
Total bilirubin (mg/dL)	0.3 ± 0.0	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.0
pH	7.26 ± 0.03	7.31 ± 0.02	7.27 ± 0.03	7.23 ± 0.03
n	10	10	10	10
Urinalysis				
Urine volume (mL/16 hr)	7 ± 1	6 ± 1	6 ± 0	9 ± 1[c]
Specific gravity	1.042 ± 0.004	1.044 ± 0.005	1.041 ± 0.003	1.034 ± 0.003

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene (continued)

Analysis	0 ppm	150 ppm	300 ppm	600 ppm
Female				
n	9	10	10	9
Hematology				
Hematocrit (%)	49.3 ± 0.9	50.7 ± 0.9	51.8 ± 0.4	50.1 ± 1.0
Hemoglobin (g/dL)	14.4 ± 0.2	14.6 ± 0.2	14.8 ± 0.1	14.4 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.58 ± 0.11	8.89 ± 0.08	8.97 ± 0.06*	8.73 ± 0.16
Mean cell volume (fL)	57.4 ± 0.5	56.9 ± 0.8	57.5 ± 0.4	57.1 ± 0.5
Mean cell hemoglobin (pg)	16.8 ± 0.1	16.4 ± 0.1	16.5 ± 0.1	16.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	29.2 ± 0.3	28.9 ± 0.5	28.6 ± 0.3	28.8 ± 0.3
Platelets ($10^3/\mu L$)	605.3 ± 24.9	669.6 ± 14.6[c]	659.6 ± 11.5	628.6 ± 33.9
Reticulocytes (%)	1.60 ± 0.17	1.53 ± 0.10	1.59 ± 0.12	1.56 ± 0.20
Leukocytes ($10^3/\mu L$)	3.08 ± 0.22	2.53 ± 0.17	2.61 ± 0.14	3.52 ± 0.25
Segmented neutrophils ($10^3/\mu L$)	0.90 ± 0.09	0.87 ± 0.08	0.84 ± 0.06	1.13 ± 0.17
Lymphocytes ($10^3/\mu L$)	2.12 ± 0.20	1.62 ± 0.14	1.72 ± 0.15	2.32 ± 0.20
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.05 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.07 ± 0.02
Nucleated erythrocytes (/100 leukocytes)	1.56 ± 0.50	0.80 ± 0.42	0.80 ± 0.42	1.89 ± 1.11
n	10	10	10	10
Clinical chemistry				
Urea nitrogen (mg/dL)	19.7 ± 0.9	17.5 ± 1.5	14.8 ± 1.5	18.4 ± 1.2
Creatinine (mg/dL)	0.47 ± 0.05	0.42 ± 0.02	0.42 ± 0.02	0.46 ± 0.03
Sodium (mEq/L)	144 ± 1	147 ± 3	147 ± 3	144 ± 2
Potassium (mEq/L)	5.2 ± 0.3	5.1 ± 0.3	5.0 ± 0.2	5.7 ± 0.3
Chloride (mEq/L)	109 ± 2	109 ± 2	111 ± 1	108 ± 2
Calcium (mg/dL)	4.56 ± 0.10	4.40 ± 0.13	4.36 ± 0.12	4.77 ± 0.11
Phosphorus (mg/dL)	6.1 ± 0.7	5.8 ± 0.3	6.2 ± 0.2	7.3 ± 0.6
Bicarbonate (mEq/L)	28 ± 1[c]	29 ± 0	29 ± 0[c]	29 ± 1
Total bilirubin (mg/dL)	0.6 ± 0.1	0.4 ± 0.0	0.4 ± 0.0	0.5 ± 0.1
pH	7.20 ± 0.03[c]	7.22 ± 0.03	7.27 ± 0.02[c]	7.17 ± 0.05
n	10	10	10	10
Urinalysis				
Urine volume (mL/16 hr)	6 ± 1[b]	6 ± 1[b]	6 ± 1	6 ± 1
Specific gravity	1.025 ± 0.004	1.026 ± 0.003	1.026 ± 0.002	1.029 ± 0.002

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error
[b] n=8
[c] n=9

TABLE G4
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Triamterene[a]

Analysis	0 ppm	100 ppm	400 ppm	800 ppm
Male				
n	10	6	10	10
Hematology				
Hematocrit (%)	37.2 ± 1.0	35.9 ± 1.2	38.0 ± 0.4	36.2 ± 1.0
Hemoglobin (g/dL)	15.1 ± 0.4	14.7 ± 0.5	15.6 ± 0.2	14.8 ± 0.4
Erythrocytes ($10^6/\mu L$)	7.40 ± 0.19	7.15 ± 0.24	7.63 ± 0.09	7.15 ± 0.24
Mean cell volume (fL)	50.1 ± 0.3	50.2 ± 0.5	49.9 ± 0.2	50.6 ± 0.4
Mean cell hemoglobin (pg)	20.4 ± 0.1	20.6 ± 0.2	20.5 ± 0.1	20.7 ± 0.1
Mean cell hemoglobin concentration (g/dL)	40.7 ± 0.2	41.0 ± 0.2	41.1 ± 0.3	40.9 ± 0.1
Leukocytes ($10^3/\mu L$)	4.05 ± 0.40	3.35 ± 0.49	3.38 ± 0.29	2.78 ± 0.33*[b]
Segmented neutrophils ($10^3/\mu L$)	0.70 ± 0.07	0.50 ± 0.07	0.65 ± 0.09	0.63 ± 0.17[b]
Lymphocytes ($10^3/\mu L$)	3.25 ± 0.33	2.77 ± 0.42	2.71 ± 0.25	2.07 ± 0.25*[b]
Monocytes ($10^3/\mu L$)	0.14 ± 0.02[c]	0.10 ± 0.00[d]	0.10 ± 0.00[d]	0.12 ± 0.02[c]
n	10	6	10	9
Clinical chemistry				
Sodium (mEq/L)	158 ± 2	159 ± 1	157 ± 3	162 ± 3
Potassium (mEq/L)	8.5 ± 0.4	8.4 ± 0.5	8.2 ± 0.4	8.7 ± 0.4
Chloride (mEq/L)	123 ± 1	123 ± 1	123 ± 2	124 ± 1
Calcium (mg/dL)	11.61 ± 0.27[e]	11.48 ± 0.49[f]	11.08 ± 0.25[g]	11.57 ± 0.58[h]
Phosphorus (mg/dL)	10.2 ± 1.2[e]	13.6 ± 2.4[f]	13.1 ± 1.1	10.1 ± 2.2[g]
n	10	6	10	9
Urinalysis				
Urine volume (mL/24 hr)	2 ± 0	2 ± 0	2 ± 0[e]	1 ± 0
Specific gravity	1.031 ± 0.005	1.032 ± 0.004	1.016 ± 0.003	1.028 ± 0.005

TABLE G4
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Triamterene (continued)

Analysis	0 ppm	100 ppm	400 ppm	800 ppm
Female				
n	10	9	9	8
Hematology				
Hematocrit (%)	38.7 ± 0.7	38.8 ± 0.5	39.2 ± 0.5	39.0 ± 0.5
Hemoglobin (g/dL)	15.8 ± 0.3	15.7 ± 0.2	15.8 ± 0.2	15.7 ± 0.2
Erythrocytes ($10^6/\mu L$)	7.64 ± 0.12	7.67 ± 0.10	7.67 ± 0.08	7.58 ± 0.10
Mean cell volume (fL)	50.7 ± 0.2	50.7 ± 0.2	51.1 ± 0.3	51.4 ± 0.3
Mean cell hemoglobin (pg)	20.6 ± 0.1	20.4 ± 0.1	20.6 ± 0.2	20.7 ± 0.1
Mean cell hemoglobin concentration (g/dL)	40.8 ± 0.2	40.4 ± 0.2	40.3 ± 0.2	40.4 ± 0.2
Leukocytes ($10^3/\mu L$)	3.76 ± 0.39	2.46 ± 0.45*	2.08 ± 0.19**	2.21 ± 0.41**
Segmented neutrophils ($10^3/\mu L$)	0.66 ± 0.05	0.44 ± 0.06	0.61 ± 0.08	0.51 ± 0.11
Lymphocytes ($10^3/\mu L$)	3.01 ± 0.35	1.91 ± 0.39*	1.46 ± 0.20**	1.66 ± 0.36**
Monocytes ($10^3/\mu L$)	0.13 ± 0.02[g]	0.10 ± 0.03[g]	0.07 ± 0.03[h]	0.13 ± 0.03[h]
n	9	10	10	8
Clinical chemistry				
Sodium (mEq/L)	152 ± 2	156 ± 1	157 ± 2	154 ± 1
Potassium (mEq/L)	7.5 ± 0.3	7.3 ± 0.3	7.7 ± 0.4	8.0 ± 0.4
Chloride (mEq/L)	120 ± 2	121 ± 1	122 ± 2	119 ± 1
Calcium (mg/dL)	11.66 ± 0.38[i]	11.13 ± 0.32[i]	10.78 ± 0.43[b]	12.66 ± 0.57[c]
Phosphorus (mg/dL)	11.5 ± 0.6	11.1 ± 0.8[b]	13.1 ± 1.1	14.4 ± 1.0*
n	7	9	9	6
Urinalysis				
Urine volume (mL/24 hr)	0 ± 0[g]	3 ± 1[e]	0 ± 0[e]	1 ± 1
Specific gravity	1.008 ± 0.003	1.012 ± 0.006	1.020 ± 0.007	1.013 ± 0.005

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
a Mean ± standard error
b n=9
c n=5
d n=2
e n=7
f n=4
g n=6
h n=3
i n=8

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of Triamterene[a]

Analysis	0 ppm	100 ppm	200 ppm	400 ppm
Male				
n	9	10	10	10
Hematology				
Hematocrit (%)	44.2 ± 0.9	44.4 ± 0.9	44.5 ± 0.5	44.2 ± 0.6[b]
Hemoglobin (g/dL)	17.7 ± 0.3	17.5 ± 0.4	17.4 ± 0.2	17.2 ± 0.3[b]
Erythrocytes ($10^6/\mu L$)	11.19 ± 0.23	11.31 ± 0.20	11.27 ± 0.14	11.25 ± 0.16[b]
Mean cell volume (fL)	39.3 ± 0.3	39.2 ± 0.3	39.4 ± 0.2	39.4 ± 0.2[b]
Mean cell hemoglobin (pg)	15.8 ± 0.1	15.5 ± 0.1*	15.5 ± 0.2	15.3 ± 0.2*[b]
Mean cell hemoglobin concentration (g/dL)	40.1 ± 0.3	39.5 ± 0.4	39.2 ± 0.4	38.8 ± 0.4*[b]
Platelets ($10^3/\mu L$)	1,014.4 ± 108	1,043.8 ± 102	1,114.4 ± 59.4	863.6 ± 111[b]
Reticulocytes ($10^6/\mu L$)	2.23 ± 0.23	1.91 ± 0.15	1.86 ± 0.11	1.83 ± 0.16
Leukocytes ($10^3/\mu L$)	2.47 ± 0.26	1.60 ± 0.20*	1.76 ± 0.26	1.71 ± 0.16
Segmented neutrophils ($10^3/\mu L$)	0.46 ± 0.08	0.30 ± 0.04	0.36 ± 0.08	0.27 ± 0.06*
Lymphocytes ($10^3/\mu L$)	1.98 ± 0.23	1.30 ± 0.18*	1.41 ± 0.22	1.44 ± 0.14
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Nucleated erythrocytes ($10^3/\mu L$)	0.22 ± 0.15	0.00 ± 0.00	0.00 ± 0.00	0.10 ± 0.10
n	9	10	10	10
Clinical chemistry				
Urea nitrogen (mg/dL)	23.6 ± 0.7	24.1 ± 0.7	22.6 ± 0.7	23.1 ± 1.1
Creatinine (mg/dL)	0.63 ± 0.06	0.60 ± 0.07	0.70 ± 0.07	0.66 ± 0.08
Sodium (mEq/L)	156 ± 1[c]	156 ± 2	157 ± 1	159 ± 1
Potassium (mEq/L)	10.1 ± 1.3[c]	7.3 ± 0.6*	8.1 ± 1.2*	7.5 ± 0.8*
Chloride (mEq/L)	121 ± 1[c]	120 ± 2	121 ± 1	120 ± 1
Calcium (mg/dL)	4.68 ± 0.14	4.61 ± 0.13	4.64 ± 0.10	4.52 ± 0.13
Phosphorus (mg/dL)	14.6 ± 1.5	14.1 ± 1.3	15.3 ± 2.0	19.9 ± 2.9
Bicarbonate (mEq/L)	8.97 ± 1.27	9.78 ± 1.32	9.31 ± 1.09	8.54 ± 1.28
Total bilirubin (mg/dL)	0.5 ± 0.1	0.3 ± 0.0	0.4 ± 0.1[b]	0.4 ± 0.1
pH	6.89 ± 0.04	6.96 ± 0.06	6.96 ± 0.05	6.93 ± 0.08
n	9	10	10	10
Urinalysis				
Urine volume (mL/16 hr)	1 ± 0	1 ± 0	0 ± 0	1 ± 0
Specific gravity	1.045 ± 0.003	1.048 ± 0.004	1.041 ± 0.003	1.051 ± 0.013

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of Triamterene (continued)

Analysis	0 ppm	100 ppm	200 ppm	400 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	46.1 ± 0.8	45.5 ± 0.7	45.4 ± 0.8	45.9 ± 0.7
Hemoglobin (g/dL)	18.0 ± 0.2	17.6 ± 0.3	17.7 ± 0.3	17.6 ± 0.3
Erythrocytes ($10^6/\mu L$)	11.50 ± 0.20	11.26 ± 0.15	11.28 ± 0.13	11.35 ± 0.14
Mean cell volume (fL)	40.1 ± 0.4	40.1 ± 0.2	40.1 ± 0.3	40.4 ± 0.3
Mean cell hemoglobin (pg)	15.7 ± 0.2	15.7 ± 0.2	15.7 ± 0.2	15.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	39.1 ± 0.6	38.9 ± 0.4	39.1 ± 0.4	38.4 ± 0.4
Platelets ($10^3/\mu L$)	1,103 ± 47	1,098 ± 37	1,084 ± 85	1,098 ± 74[b]
Reticulocytes ($10^6/\mu L$)	1.70 ± 0.12	1.62 ± 0.18	1.50 ± 0.10	1.71 ± 0.12
Leukocytes ($10^3/\mu L$)	3.14 ± 0.40	3.54 ± 0.40	2.82 ± 0.40	2.89 ± 0.36
Segmented neutrophils ($10^3/\mu L$)	0.43 ± 0.09	0.61 ± 0.13	0.43 ± 0.07	0.52 ± 0.09
Lymphocytes ($10^3/\mu L$)	2.66 ± 0.34	2.87 ± 0.32	2.38 ± 0.36	2.34 ± 0.29
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.06 ± 0.02	0.02 ± 0.01	0.03 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.10 ± 0.10	0.10 ± 0.10	0.00 ± 0.00
n	10	10	10	10
Clinical chemistry				
Urea nitrogen (mg/dL)	21.8 ± 0.7	21.5 ± 1.6	19.2 ± 0.9*	18.0 ± 0.5**
Creatinine (mg/dL)	0.62 ± 0.04	0.61 ± 0.06	1.04 ± 0.44	0.68 ± 0.13
Sodium (mEq/L)	153 ± 1	154 ± 1	156 ± 0	156 ± 1
Potassium (mEq/L)	7.6 ± 0.7	6.6 ± 0.3	6.7 ± 0.5	6.1 ± 0.4*
Chloride (mEq/L)	120 ± 1	120 ± 1	122 ± 1	121 ± 1
Calcium (mg/dL)	4.65 ± 0.10	4.60 ± 0.09	4.55 ± 0.07	4.47 ± 0.05
Phosphorus (mg/dL)	15.3 ± 1.9	12.5 ± 1.3	14.7 ± 1.5	13.0 ± 1.6
Bicarbonate (mEq/L)	8.45 ± 0.93	10.21 ± 1.35	8.47 ± 1.05	9.80 ± 1.04
Total bilirubin (mg/dL)	0.4 ± 0.0	0.3 ± 0.0	0.4 ± 0.1	0.3 ± 0.0
pH	6.98 ± 0.04	7.06 ± 0.05	7.04 ± 0.04	7.06 ± 0.04
n	10	10	10	10
Urinalysis				
Urine volume (mL/16 hr)	1 ± 0	1 ± 0	1 ± 0	1 ± 0
Specific gravity	1.042 ± 0.004	1.059 ± 0.012	1.041 ± 0.004	1.058 ± 0.003*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[c] n=10

TABLE G6
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene: First Study[a]

Analysis	0 ppm	100 ppm	200 ppm
Male			
n	10	10	9
Hematology			
Hematocrit (%)	58.1 ± 0.5	56.2 ± 0.7	53.4 ± 0.8**
Hemoglobin (g/dL)	16.9 ± 0.2	16.5 ± 0.2	15.8 ± 0.3**
Erythrocytes ($10^6/\mu L$)	11.90 ± 0.12	11.78 ± 0.15	11.21 ± 0.21*
Mean cell volume (fL)	48.7 ± 0.4	47.7 ± 0.3*	47.9 ± 0.5
Mean cell hemoglobin (pg)	14.2 ± 0.1	14.0 ± 0.1	14.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	29.2 ± 0.3	29.3 ± 0.2	29.4 ± 0.3
Platelets ($10^3/\mu L$)	1,471 ± 23	1,479 ± 36	1,415 ± 25
Reticulocytes ($10^6/\mu L$)	1.33 ± 0.12	1.11 ± 0.13	1.24 ± 0.37
Leukocytes ($10^3/\mu L$)	3.28 ± 0.35	2.78 ± 0.20	2.76 ± 0.26
Segmented neutrophils ($10^3/\mu L$)	1.10 ± 0.12	0.71 ± 0.07*	0.86 ± 0.08
Lymphocytes ($10^3/\mu L$)	2.13 ± 0.28	2.04 ± 0.19	1.86 ± 0.24
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.06 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
n	10	10	10
Clinical chemistry			
Urea nitrogen (mg/dL)	32.0 ± 1.3	28.0 ± 0.8*	26.5 ± 1.1**
Creatinine (mg/dL)	0.18 ± 0.02[b]	0.22 ± 0.03	0.17 ± 0.02
Sodium (mEq/L)	155 ± 1	157 ± 1	156 ± 1
Potassium (mEq/L)	4.4 ± 0.1	4.1 ± 0.1	4.1 ± 0.3*
Chloride (mEq/L)	122 ± 1	120 ± 1	121 ± 1
Calcium (mg/dL)	3.96 ± 0.05	3.97 ± 0.05	3.92 ± 0.09
Phosphorus (mg/dL)	7.9 ± 0.4	7.4 ± 0.4	7.9 ± 0.5
Bicarbonate (mEq/L)	13.95 ± 0.77	15.00 ± 0.74	15.73 ± 0.58
Total bilirubin (mg/dL)	0.2 ± 0.1	0.4 ± 0.1	0.3 ± 0.1
pH	7.18 ± 0.01	7.16 ± 0.02	7.18 ± 0.02
n	10	10	10
Urinalysis			
Urine volume (mL/16 hr)	1 ± 0	2 ± 0	1 ± 0
Specific gravity	1.031 ± 0.002	1.030 ± 0.003	1.039 ± 0.004*

TABLE G6
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene: First Study (continued)

Analysis	0 ppm	100 ppm	200 ppm
Female			
n	10	10	10
Hematology			
Hematocrit (%)	57.4 ± 0.8	57.1 ± 0.8	57.9 ± 0.8
Hemoglobin (g/dL)	16.4 ± 0.2	16.5 ± 0.1	16.6 ± 0.2
Erythrocytes ($10^6/\mu L$)	11.62 ± 0.09	11.85 ± 0.10	11.78 ± 0.17
Mean cell volume (fL)	49.4 ± 0.4	48.1 ± 0.5	49.0 ± 0.4
Mean cell hemoglobin (pg)	14.1 ± 0.1	13.9 ± 0.1	14.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.7 ± 0.2	28.9 ± 0.2	28.7 ± 0.2
Platelets ($10^3/\mu L$)	1,149 ± 40	1,186 ± 18	1,168 ± 46
Reticulocytes ($10^6/\mu L$)	1.41 ± 0.18	1.04 ± 0.13	1.40 ± 0.16
Leukocytes ($10^3/\mu L$)	2.48 ± 0.12	2.44 ± 0.20	2.58 ± 0.19
Segmented neutrophils ($10^3/\mu L$)	0.75 ± 0.10	0.89 ± 0.15	0.88 ± 0.14
Lymphocytes ($10^3/\mu L$)	1.68 ± 0.15	1.60 ± 0.14	1.67 ± 0.16
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
n	10	10	10
Clinical chemistry			
Urea nitrogen (mg/dL)	27.2 ± 1.6	23.6 ± 1.3	22.7 ± 1.4
Creatinine (mg/dL)	0.17 ± 0.03	0.18 ± 0.02	0.17 ± 0.03
Sodium (mEq/L)	152 ± 1	155 ± 1	154 ± 1
Potassium (mEq/L)	4.8 ± 0.4	4.5 ± 0.3	4.2 ± 0.4*
Chloride (mEq/L)	116 ± 1	115 ± 1	118 ± 2
Calcium (mg/dL)	3.96 ± 0.08	4.11 ± 0.09	4.20 ± 0.22
Phosphorus (mg/dL)	8.84 ± 0.83	7.68 ± 0.56	7.93 ± 0.58
Bicarbonate (mEq/L)	16.29 ± 0.73	16.54 ± 0.30	16.24 ± 1.10
Total bilirubin (mg/dL)	0.2 ± 0.0[b]	0.2 ± 0.0[c]	0.4 ± 0.2*
pH	7.16 ± 0.02	7.20 ± 0.02	7.20 ± 0.02
n	10	10	10
Urinalysis			
Urine volume (mL/16 hr)	1 ± 0	1 ± 0	1 ± 0
Specific gravity	1.025 ± 0.002	1.029 ± 0.004	1.028 ± 0.003

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[c] n=8

TABLE G7
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene: Second Study[a]

Analysis	0 ppm	400 ppm
Male		
n	10	10
Hematology		
Hematocrit (%)	50.9 ± 0.7	49.7 ± 1.1
Hemoglobin (g/dL)	14.3 ± 0.1	13.7 ± 0.4
Erythrocytes ($10^6/\mu L$)	9.37 ± 0.12	9.08 ± 0.24
Mean cell volume (fL)	54.3 ± 0.2	54.9 ± 0.5
Mean cell hemoglobin (pg)	15.3 ± 0.1	15.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.1 ± 0.2	27.6 ± 0.3
Platelets ($10^3/\mu L$)	1,132.0 ± 25.0	1,090.0 ± 36.0
Reticulocytes ($10^6/\mu L$)	1.57 ± 0.09	1.67 ± 0.16
Leukocytes ($10^3/\mu L$)	4.44 ± 0.40	3.66 ± 0.38
Segmented neutrophils ($10^3/\mu L$)	1.03 ± 0.12	0.85 ± 0.16
Lymphocytes ($10^3/\mu L$)	3.27 ± 0.32	2.65 ± 0.26
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.13 ± 0.03	0.14 ± 0.03
Nucleated erythrocytes (/100 leukocytes)	0.00 ± 0.00	0.00 ± 0.00
n	10	10
Clinical chemistry		
Urea nitrogen (mg/dL)	37.5 ± 1.8	37.1 ± 2.1
Creatinine (IU/L)	0.34 ± 0.03	0.29 ± 0.04
Sodium (mEq/L)	160 ± 1	159 ± 1
Potassium (mEq/L)	5.0 ± 0.2	4.6 ± 0.2
Chloride (mEq/L)	113 ± 1	114 ± 1
Calcium (mg/dL)	4.98 ± 0.15	4.97 ± 0.11
Phosphorus (mg/dL)	7.6 ± 0.3	7.9 ± 0.4
Bicarbonate (mEq/L)	16.80 ± 1.26	17.30 ± 1.01
Total bilirubin (mg/dL)	0.5 ± 0.1	0.4 ± 0.0
pH	7.15 ± 0.03	7.14 ± 0.04
n	10	9
Urinalysis		
Urine volume (mL/16 hr)	1 ± 0	1 ± 0
Specific gravity	1.039 ± 0.003	1.037 ± 0.003

TABLE G7
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Triamterene: Second Study (continued)

Analysis	0 ppm	400 ppm
Female		
n	10	9
Hematology		
Hematocrit (%)	52.4 ± 0.4	52.6 ± 0.4
Hemoglobin (g/dL)	14.6 ± 0.1	14.6 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.44 ± 0.11	9.62 ± 0.09
Mean cell volume (fL)	55.5 ± 0.3	54.7 ± 0.5
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	27.9 ± 0.1	27.7 ± 0.1
Platelets ($10^3/\mu L$)	878.6 ± 41.8	925.6 ± 31.9
Reticulocytes ($10^6/\mu L$)	1.75 ± 0.13	1.58 ± 0.16
Leukocytes ($10^3/\mu L$)	2.76 ± 0.31	3.04 ± 0.29
Segmented neutrophils ($10^3/\mu L$)	0.73 ± 0.07	0.82 ± 0.08
Lymphocytes ($10^3/\mu L$)	1.93 ± 0.25	2.12 ± 0.24
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.09 ± 0.02	0.10 ± 0.03
Nucleated erythrocytes (/100 leukocytes)	0.20 ± 0.13	0.00 ± 0.00
n	10	9
Clinical chemistry		
Urea nitrogen (mg/dL)	31.5 ± 0.7	33.0 ± 1.3
Creatinine (IU/L)	0.28 ± 0.03	0.19 ± 0.03*
Sodium (mEq/L)	157 ± 1	155 ± 1
Potassium (mEq/L)	4.9 ± 0.3	4.8 ± 0.3
Chloride (mEq/L)	114 ± 1	113 ± 1
Calcium (mg/dL)	4.91 ± 0.13	4.94 ± 0.09
Phosphorus (mg/dL)	7.1 ± 0.3	7.0 ± 0.4
Bicarbonate (mEq/L)	15.36 ± 0.78	14.87 ± 0.69
Total bilirubin (mg/dL)	0.4 ± 0.0[b]	0.4 ± 0.1
pH	7.15 ± 0.03	7.24 ± 0.03*
n	10	9
Urinalysis		
Urine volume (mL/16 hr)	1 ± 0	2 ± 0**[c]
Specific gravity	1.032 ± 0.003	1.022 ± 0.003*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[c] n=8

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF TRIAMTERENE

Triamterene, manufactured by Secifarma (Milan, Italy), was obtained from Gyma Laboratories of America (Garden City, NJ) in one lot (84/1). Lot 84/1 was used during the 15-day, 13-week, and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO). MRI reports on analyses performed in support of the triamterene studies are on file at the National Institutes of Environmental Health Sciences.

The study chemical, a yellow microcrystalline solid, was identified as triamterene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra (Figures H1 and H2) were consistent with those expected for the structure and with the literature description for the spectra of triamterene (*Sadtler Standard Spectra*).

Initially, lot 84/1 was broken into two subbatches. The relative purity of the two subbatches of lot 84/1 was determined by high-performance liquid chromatography (HPLC) using a Waters μBondapak C_{18} column with an isocratic solvent system of: A) 0.005 M sodium hepanesulfonate in water containing 1% glacial acetic acid and B) 0.005 M sodium hepanesulfonate in methanol containing 1% glacial acetic acid at a ratio of 40:60 A:B, and a flow rate of 1 mL/minute. Acetanilide was added as an internal standard. Ultraviolet detection was at 254 nm. The two subbatches of the bulk chemical were identical within the limits of experimental error.

The purity was determined by elemental analyses, Karl Fischer water analysis, potentiometric titration, thin-layer chromatography (TLC), and HPLC. Titration was performed by dissolving triamterene in a mixture of formic acid:acetic anhydride:glacial acetic acid (1:1:2). After cooling, the mixture was titrated with 0.1 N perchloric acid in glacial acetic acid using a combination pH/mV electrode. TLC was performed on Silica Gel 60F-254 plates with two solvent systems: A) chloroform:methanol:concentrated ammonium hydroxide (66:33:1) and B) 2-butoxyethanol:diethanolamine (99:1). Visualization of the dried plates was by visible light, ultraviolet light at 254 nm and 366 nm, and by spraying with a solution of hexachloroplatinic acid in aqueous potassium iodide. HPLC was performed using the system described, for the relative purity analyses, but with a 50:50 ratio of the solvent system.

Elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for triamterene. Karl Fischer water analysis indicated 0.087 ± 0.008% water. Potentiometric titration of the functional amine group with perchloric acid indicated the purity to be 101.1 ± 0.9%. TLC with either solvent system A or B indicated a major spot, a strong trace, a trace, and a slight trace impurity. Two-dimensional development using solvent system B indicated that the impurities were due in part to decomposition of the solvent system. HPLC indicated no impurities with a peak area greater than or equal to 0.1% of the major peak area. The overall purity was determined to be at least 99%.

The United States Pharmacopeia (USP XX) requirement for purity of triamterene is 98% to 102%. Comparison of the major peaks of lot 84/1 and the USP XX standard using the HPLC system described for relative purity analyses indicated a purity of 101.1 ± 2.2% of lot 84/1 relative to the standard. Thus, lot 84/1 met the USP requirement for purity.

Stability studies were performed by the analytical chemistry laboratory using HPLC with the 2:3 isocratic solvent system described above. Lot 84/1 was found to be stable in bulk form when stored for 2 weeks protected from light at temperatures up to 60° C. The stability of the bulk chemical was monitored

periodically at the study laboratory using titration and HPLC; no degradation of the study chemical was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing appropriate amounts of triamterene and feed in a Patterson-Kelley twin-shell blender with an intensifier bar (Table H1). Homogeneity and stability studies were conducted by the analytical chemistry laboratory on the dosed feed preparations. Feed samples for the homogeneity studies, collected from the bottom, top right, and top left areas of the blender, were analyzed by ultraviolet spectroscopy using a dimethylsulfoxide extract of the feed sample in methanol for comparison of ultraviolet absorbance at 370 nm to a standard curve for dose formulations of 1,000 ppm or greater. For dose formulations of 100 to 500 ppm, dosed feed extracts were analyzed by HPLC using a solvent system of: A) 0.06M aqueous sodium bromide and B) 0.06M sodium bromide in methanol 60:40 (A:B) with ultraviolet detection at 370 nm. Stability studies were performed using the same HPLC system described for the homogeneity analyses. Dose formulations in feed were stable for up to 2 weeks when stored protected from light at 5° C.

The dose formulations were analyzed at the beginning of the 15-day studies by the study laboratory and were within 10% of the target concentrations (Table H2). During the 13-week studies, the dose formulations were analyzed twice; all dose formulations for rats and 15 of 17 dose formulations for mice were within 10% of the target concentrations (Table H3). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks (Table H4). All dose formulations were within 10% of the target concentrations, except for dose formulations prepared 12 June 1985 for rats receiving 600 ppm and for mice receiving 400 ppm. Rats in the 600 ppm group received 0 ppm; this dosing period was approximately 1% of the 103-week dosing duration and was considered to have no effect on the results. Mice in the 400 ppm group received approximately 1,600 ppm, which caused 16 deaths. Survivors of the dosing accident were returned to the appropriate dose formulation (first study), but the 2-year study was restarted for the 0 and 400 ppm groups (second study). During the second mouse study, the 400 ppm dose formulations were all within 10% of the target concentration.

Periodic analyses of the dose formulations of triamterene were performed by the study laboratory and the analytical chemistry laboratory with either an HPLC or ultraviolet spectroscopic method. Results of the analyses performed by the analytical chemistry laboratory indicated good agreement with the results of the study laboratory (Table H5).

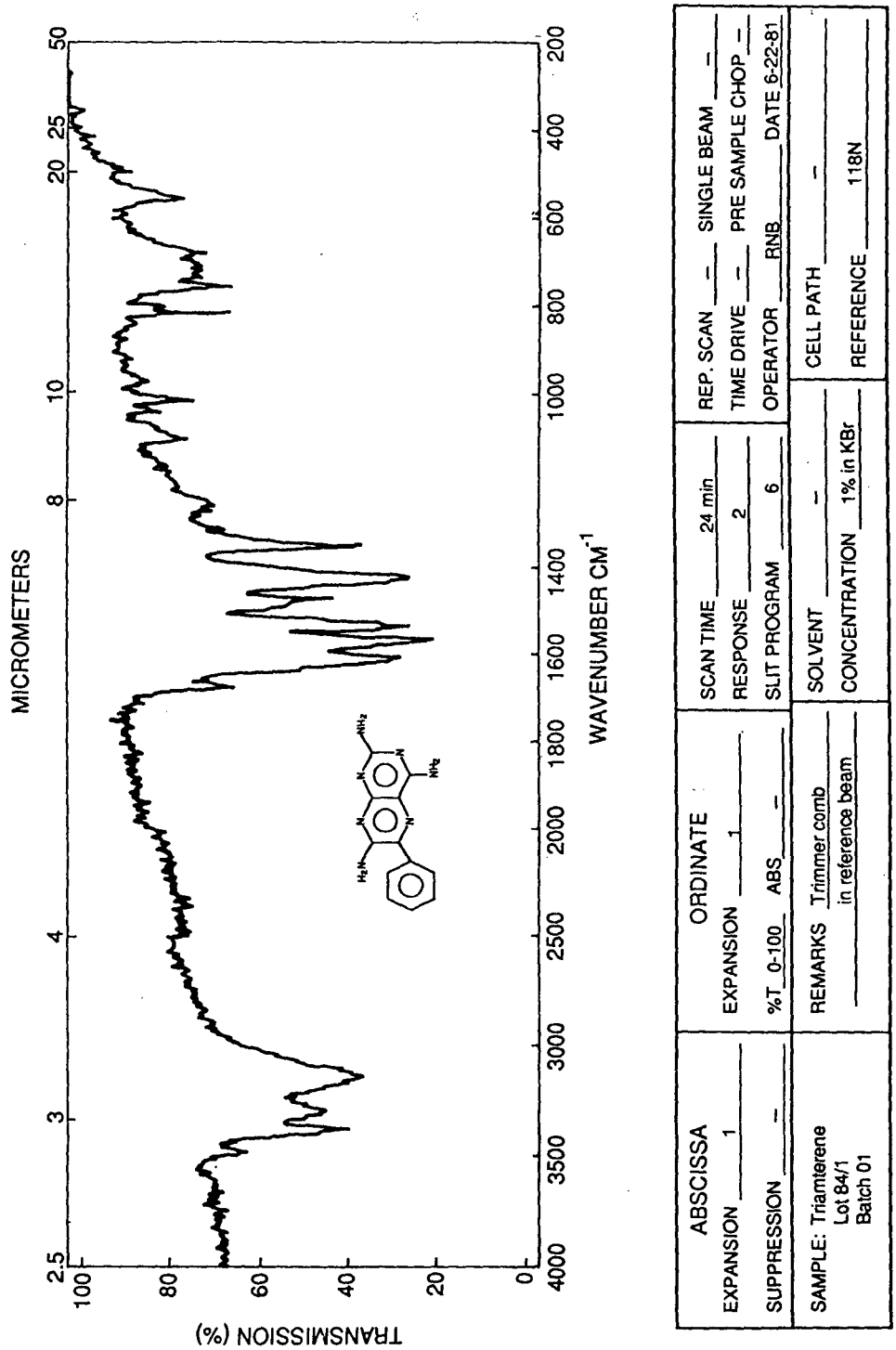

FIGURE H1
Infrared Absorption Spectrum of Triamterene

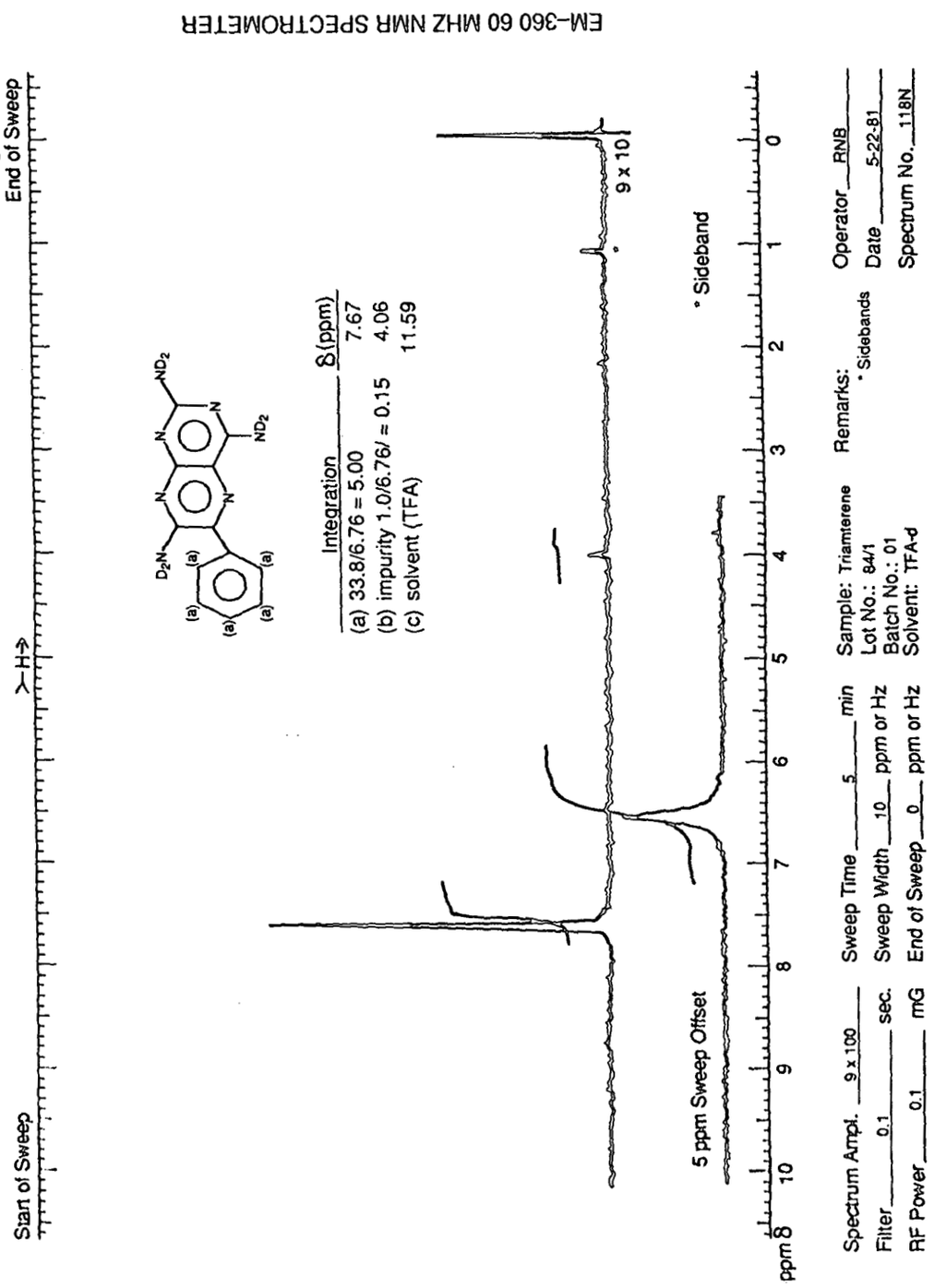

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Triamterene

TABLE H1
Preparation and Storage of Dose Formulations in the Feed Studies of Triamterene

15-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Dose formulations were prepared by mixing triamterene with a small amount of the feed to form a premix. The premix and additional feed were layered into a Patterson-Kelley twin shell blender and mixed for 10 minutes with the intensifier bar on. Dose formulations were prepared weekly.	Same as the 15-day studies, but prepared every 2 weeks	Same as the 15-day studies, but the formulations were mixed for 15 minutes with the intensifier bar on for the first 5 minutes. Dose formulations were prepared weekly.
Chemical Lot Number		
84/1	84/1	84/1
Maximum Storage Time		
2 weeks	2 weeks	2 weeks
Storage Conditions		
In the dark, refrigerated	In the dark, below 5° C	In the dark, at or below 5° C
Study Laboratory		
International Research and Development Corporation, Mattawan, MI	International Research and Development Corporation, Mattawan, MI	Battelle, Columbus Division, Columbus, OH
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Midwest Research Institute, Kansas City, MO	Midwest Research Institute, Kansas City, MO

TABLE H2
Results of Analysis of Dose Formulations for Rats and Mice in the 15-Day Feed Studies of Triamterene

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
29 April 1982	6 May 1982	10,000	9,990	0
		30,000	29,800	−1
	10 May 1982	1,000	1,000	0
		3,000	2,970	−1
	11 May 1982	60,000	60,900	+2
Mice				
29 April 1982	6 May 1982	10,000	10,100	+1
		30,000	31,600	+5
	10 May 1982	1,000	1,040	+4
		3,000	2,930	−2
	12 May 1982	300	296	−1

[a] Results of duplicate analyses

TABLE H3
Results of Analysis of Dose Formulations for Rats and Mice in the 13-Week Feed Studies of Triamterene

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
5 September 1982[b]	10 September 1982	2,400[c]	2,400	0
		2,400[d]	2,340	-2
		2,400[e]	2,420	+1
	16 December 1982[f]	150[c]	147	-2
		150[d]	155	+3
		150[e]	155	+3
13 September 1982	16 September 1982	300	281	-6
		600	576	-4
		1,200	1,210	+1
		2,400[c]	2,470	+3
		2,400[d]	2,460	+3
		2,400[e]	2,420	+1
	10 December 1982[f]	150	144	-4
		150	148	-1
		150	148	-1
15 September 1982	10 December 1982[f]	200	198	-1
25 October 1982	28 October 1982	300	274	-9
		600	593	-1
		1,200	1,250	+4
	10 December 1982[f]	150	148	-1

TABLE H3
Results of Analysis of Dose Formulations for Rats and Mice in the 13-Week Feed Studies of Triamterene (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Mice				
5 September 1982	10 September 1982	1,600[c]	1,470	−8
		1,600[d]	1,410	−12
		1,600[e]	1,430	−11
	16 December 1982[f]	100[c]	108	+8
		100[d]	104	+4
		100[e]	103	+3
15 September 1982	17 September 1982	400	385	−4
		800	813	+2
		1,600	1,620	+1
	10 December 1982[f]	100[c]	105	+5
		100[d]	96	−4
		100[e]	98	−2
		200	198	−1
27 October 1982	28 October 1982	400	378	−5
		800	782	−2
	10 December 1982[f]	100	101	+1
		200	202	+1

[a] Results of duplicate analyses
[b] Prestart dose formulations used for homogeneity evaluation but not for dosing
[c] Sample selection from top of twin-shell blender
[d] Sample selection from middle of twin-shell blender
[e] Sample selection from bottom of twin-shell blender
[f] Analyzed late due to difficulty in developing analysis procedures

TABLE H4
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Feed Studies of Triamterene

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
4 September 1984	5 September 1984	150	149.4	0
		300	296.9	-1
		600	586.6	-2
13 November 1984	15 November 1984	300	277.4	-8
		600	588.6	-2
	16 November 1984	150	148.7	-1
2 January 1985	2 January 1985	150	137.0	-9
		300	276.0	-8
		600	562.6	-6
25 February 1985	28 February 1985	150	145.0	-3
		300	299.5	0
		600	595.5	-1
26 April 1985	2 May 1985	150	145.4	-3
		300	294.4	-2
		600	601.0	0
12 June 1985	3, 5 July 1985	150	163.4	+9
		300	317.9	+6
		600	0.0	
20 June 1985	26 June 1985	150	146.5	-2
		300	292.3	-3
		600	595.9	-1
15 August 1985	16 August 1985	150	138.9	-7
		300	291.6	-3
		600	589.8	-2
10 October 1985	15 October 1985	150	155.3	+4
		300	307.1	+2
		600	595.9	-1
5 December 1985	10 December 1985	150	150.8	+1
		300	301.9	+1
		600	590.3	-2
6 February 1986	10 February 1986	150	147.2	-2
		300	304.5	+2
		600	595.5	-1
27 March 1986	28 March 1986	150	163.5	+9
		300	310.3	+3
		600	594.2	-1

TABLE H4
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Feed Studies of Triamterene (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
22 May 1986	23 May 1986	150	156.0	+4
		300	298.8	0
		600	605.6	+1
17 July 1986	21 July 1986	150	143.6	-4
		300	284.7	-5
		600	579.4	-3
Mice: First Study				
10 September 1984	12 September 1984	100	99.1	-1
		200	209.1	+5
		400	404.6	+1
13 November 1984	15 November 1984	200	185.4	-7
		400	372.7	-7
	16 November 1984	100	99.6	0
2 January 1985	2 January 1985	100	91.7	-8
		200	184.8	-8
		400	366.6	-8
25 February 1985	28 February 1985	100	100.5	+1
		200	197.0	-1
		400	391.5	-2
26 April 1985	2 May 1985	100	98.2	-2
		200	195.8	-2
		400	401.1	0
12 June 1985	3, 5 July 1985	100	107.9	+8
		200	205.1	+3
		400	1,616.0	+404[b]
	5 July 1985[c]	400	1,589.8	+397
20 June 1985	26 June 1985	100	97.8	-2
		200	200.3	0
		400	399.2	0

TABLE H4
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Feed Studies of Triamterene
(continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice: First and Second Study				
15 August 1985	16 August 1985	100	101.1	+1
		200	197.9	-1
		400	412.3	+3
10 October 1985	15 October 1985	100	98.9	-1
		200	205.3	+3
		400	410.4	+3
5 December 1985	10 December 1985	100	101.5	+2
		200	197.6	-1
		400	397.0	-1
6 February 1986	10 February 1986	100	100.4	0
		200	203.2	+2
		400	403.2	+1
27 March 1986	28 March 1986	100	99.5	0
		200	205.7	+3
		400	362.9	-9
22 May 1986	23 May 1986	100	98	-2
		200	192	-4
		400	398	0
17 July 1986	21 July 1986	100	95	-5
		200	194	-3
		400	390	-3
Mice: Second Study				
11 September 1986	11 September 1986	400	400	0
7 November 1986	7 November 1986	400	392	-2
9 January 1987	12 January 1987	400	403	+1
6 March 1987	6 March 1987	400	403	+1
1 May 1987	4 May 1987	400	385	-4
26 June 1987	27 June 1987	400	398	0
14 August 1987	17 August 1987	400	396	-1

[a] Results of duplicate analyses
[b] Analyzed dose preparation room samples after the formulation had been used for dosing of animals
[c] Analyzed dose formulations taken from the animal room

TABLE H5
Results of Referee Analysis of Dose Formulations for Rats and Mice in the 13-Week and 2-Year Feed Studies of Triamterene

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
Mice			
15 September 1982	200	198	194 ± 8
2-Year Studies			
Rats			
4 September 1984	150	149	151 ± 3
15 August 1985	600	590	596 ± 6
27 March 1986	300	310	301 ± 6
Mice			
25 February 1985	100	101	99 ± 0.7
12 June 1985	400	1,616	1,590 ± 10
11 September 1986	400	400	409 ± 7
6 March 1987	400	403	404 ± 4
14 August 1987	400	396	403 ± 3

[a] Results of duplicate analyses
[b] Results of triplicate analyses; mean ± standard error

APPENDIX I
FEED AND COMPOUND CONSUMPTION

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TABLE I1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Triamterene

Week	0 ppm		150 ppm			300 ppm			600 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
4	16.6	241	15.9	237	10.0	17.3	234	22.2	15.8	231	41.0
5	17.4	263	17.4	263	9.9	18.0	254	21.2	17.4	255	40.8
9	14.6	316	15.4	317	7.3	14.4	308	14.0	14.1	305	27.7
12	15.8	350	15.6	349	6.7	17.0	347	14.7	15.8	347	27.3
13	17.9	356	18.0	358	7.5	17.9	355	15.1	17.9	355	30.2
17	16.1	379	15.4	384	6.0	15.4	378	12.3	15.9	374	25.6
21	16.9	396	17.3	399	6.5	18.0	391	13.8	17.7	390	27.2
25	15.8	414	15.8	415	5.7	16.1	409	11.8	16.0	408	23.5
29	15.8	425	16.9	426	5.9	15.8	417	11.3	16.4	418	23.5
33	16.7	444	17.5	445	5.9	16.7	441	11.4	16.5	434	22.9
37	16.8	451	16.4	457	5.4	17.0	448	11.4	16.0	439	21.8
42	17.1	455	16.7	458	5.5	16.5	453	10.9	16.2	447	21.8
45	17.4	465	18.0	467	5.8	17.4	460	11.4	16.5	449	22.0
49	17.2	479	17.1	483	5.3	17.6	470	11.2	17.2	458	22.5
53	17.3	482	16.1	481	5.0	16.9	472	10.7	16.8	459	21.9
57	8.3	481	16.2	488	5.0	16.8	478	10.5	17.4	466	22.5
61	15.4	485	15.8	488	4.9	15.7	476	9.9	16.4	467	21.0
65	14.8	484	15.1	491	4.6	14.9	477	9.4	14.3	466	18.4
73	17.3	490	16.4	489	5.0	16.7	480	10.4	15.6	463	20.1
77	15.9	488	15.3	486	4.7	15.7	473	9.9	15.7	466	20.2
81	16.5	487	16.7	489	5.1	16.8	477	10.5	16.2	466	20.9
85	15.8	482	15.1	482	4.7	15.8	473	10.0	14.8	459	19.3
89	15.3	471	15.2	467	4.9	15.8	462	10.3	14.8	455	19.5
93	14.6	454	13.7	449	4.6	14.9	447	10.0	15.4	446	20.8
97	14.8	435	13.9	439	4.8	13.7	421	9.7	14.7	426	20.6
101	14.7	420	14.7	415	5.3	14.7	405	10.9	15.6	401	23.4
104	10.8	382	14.5	418	5.2	11.4	391	8.8	14.0	393	21.4
Mean for weeks											
1-13	16.4	305	16.4	305	8.3	16.9	300	17.4	16.2	299	33.4
14-52	16.6	434	16.8	437	5.8	16.7	430	11.7	16.5	424	23.4
53-104	14.7	465	15.3	468	4.9	15.4	456	10.1	15.5	449	20.8

[a] Grams of feed consumed per animal per day
[b] Milligrams of triamterene consumed per day per kilogram body weight

TABLE I2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Triamterene

Week	0 ppm Feed (g/day)[a]	0 ppm Body Weight (g)	150 ppm Feed (g/day)	150 ppm Body Weight (g)	150 ppm Dose/ Day (mg/kg/day)[b]	300 ppm Feed (g/day)	300 ppm Body Weight (g)	300 ppm Dose/ Day (mg/kg/day)	600 ppm Feed (g/day)	600 ppm Body Weight (g)	600 ppm Dose/ Day (mg/kg/day)
5	11.5	164	11.2	162	10.4	11.3	160	21.2	11.1	159	41.8
9	10.9	188	10.6	186	8.6	10.9	183	17.8	10.7	184	35.0
13	10.3	200	10.2	199	7.7	10.5	199	15.8	9.7	192	30.3
17	10.7	206	10.1	204	7.4	10.7	207	15.5	10.8	203	31.7
21	10.9	211	11.3	210	8.0	11.0	211	15.7	10.9	208	31.5
25	9.9	214	9.4	212	6.6	9.7	214	13.6	9.7	212	27.6
29	10.4	221	11.0	219	7.6	11.0	221	14.9	10.6	217	29.3
33	11.0	229	10.9	227	7.2	11.0	230	14.3	10.8	224	29.0
37	11.4	241	11.3	237	7.1	11.5	240	14.4	11.5	235	29.4
41	11.5	246	11.5	244	7.1	11.2	241	14.0	11.2	241	28.0
45	11.8	252	11.7	248	7.1	12.1	250	14.5	11.4	245	27.9
49	12.5	262	12.5	258	7.3	12.5	262	14.3	12.1	252	28.9
53	12.7	276	12.6	273	6.9	12.8	272	14.1	12.4	264	28.0
57	11.5	284	11.9	283	6.3	11.7	286	12.3	12.2	274	26.8
61	11.1	290	11.2	287	5.9	11.5	290	11.9	11.6	279	24.9
65	11.2	298	11.5	295	5.8	11.4	297	11.5	11.3	284	23.9
69	11.6	304	11.7	301	5.8	11.8	303	11.7	11.5	290	23.8
73	12.5	314	11.8	310	5.7	12.2	313	11.7	11.7	297	23.7
77	12.7	319	12.6	316	6.0	12.5	315	11.9	12.7	301	25.4
81	12.6	327	12.8	324	5.9	12.9	321	12.1	12.7	307	24.9
85	12.7	335	12.0	327	5.5	12.6	326	11.6	11.8	309	22.9
89	13.0	344	12.8	333	5.8	12.4	323	11.5	11.9	305	23.5
93	13.3	343	12.5	331	5.7	12.9	331	11.7	12.3	312	23.6
97	11.9	339	12.1	332	5.5	11.7	324	10.8	11.8	309	23.0
101	11.4	337	12.1	336	5.4	13.3	332	12.1	12.7	318	23.9
104	10.4	333	11.8	337	5.2	12.2	332	11.0	10.2	317	19.3
Mean for weeks											
1-13	10.9	184	10.7	182	8.9	10.9	181	18.3	10.5	178	35.7
14-52	11.1	231	11.1	229	7.3	11.2	231	14.6	11.0	226	29.3
53-104	12.0	317	12.1	313	5.8	12.3	312	11.8	11.9	298	24.1

[a] Grams of feed consumed per animal per day
[b] Milligrams of triamterene consumed per day per kilogram body weight

TABLE I3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Triamterene: First Study

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
7	4.8	26.6	5.4	26.9	20	4.9	26.8	36	5.0	26.7	75
9	5.3	28.7	5.9	28.8	20	4.9	28.2	35	4.9	28.3	69
13	4.5	31.5	4.6	31.3	15	4.6	31.4	29	4.8	30.7	63
18	4.5	34.0	4.6	33.9	14	4.6	33.7	27	4.7	33.6	57
21	4.8	34.4	4.5	34.8	13	4.8	34.3	28	4.7	34.0	55
25	4.9	34.5	4.8	35.2	14	5.2	34.6	30	5.1	34.7	59
29	4.6	36.0	4.5	36.7	12	4.8	35.9	27	4.8	35.6	54
33	4.7	37.9	4.9	38.4	13	5.1	37.6	27	4.9	37.3	52
37	4.8	38.3	5.3	39.0	14	5.6	38.6	29	5.3	38.5	55
41	5.5	39.4	5.6	40.5	14	5.7	39.4	29	3.8	32.9	47
45	4.6	40.7	5.1	41.0	12	5.2	40.5	25	5.5	38.0	58
49	4.8	41.6	4.9	41.9	12	5.0	41.1	24	5.4	39.3	55
53	5.2	42.3	5.4	43.3	12	5.6	42.3	27	5.7	40.9	55
57	5.0	43.1	5.4	43.8	12	5.4	42.8	25	5.5	41.9	52
61	5.0	43.8	5.2	44.1	12	5.3	42.9	25	5.6	42.5	52
65	5.0	44.8	5.0	44.9	11	5.3	43.6	25	5.1	43.1	48
69	4.6	44.8	4.4	45.8	10	4.3	44.4	19	4.3	44.2	39
73	5.0	45.2	5.2	46.2	11	5.4	45.2	24	5.6	44.8	50
77	5.0	45.5	5.1	46.6	11	5.0	45.7	22	5.3	45.5	47
81	5.0	45.5	5.0	46.1	11	5.2	45.2	23	5.1	44.5	46
85	5.0	45.7	4.6	46.2	10	5.0	45.2	22	5.1	44.7	46
89	5.2	44.9	5.1	46.0	11	5.4	44.6	24	5.7	44.3	52
93	4.9	47.1	5.0	46.9	11	5.1	45.5	22	5.1	44.9	45
97	5.1	46.6	5.1	48.3	11	5.5	45.8	24	5.5	45.3	49
101	4.8	46.0	4.8	46.6	10	5.1	45.2	23	5.2	45.0	46
104	4.7	44.4	4.6	45.1	10	4.6	43.8	21	4.7	43.0	44
Mean for weeks											
1-13	4.9	28.9	5.3	29.0	18	4.8	28.8	34	4.9	28.6	69
14-52	4.8	37.4	4.9	37.9	13	5.1	37.3	27	4.9	36.0	54
53-104	5.0	45.0	5.0	45.7	11	5.2	44.4	23	5.3	43.9	48

[a] Grams of feed consumed per animal per day
[b] Milligrams of triamterene consumed per day per kilogram body weight

TABLE I4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Triamterene: First Study

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
7	4.9	22.9	5.0	22.9	22	5.1	22.9	45	4.8	22.7	85
9	5.3	25.0	5.1	24.8	20	5.3	24.6	43	5.3	24.8	85
13	5.2	26.8	6.0	26.7	22	6.3	26.8	47	6.1	26.3	93
18	5.2	30.3	6.3	30.1	21	6.2	30.0	41	6.1	29.7	82
21	6.0	31.6	6.0	31.0	19	6.9	31.1	44	6.7	30.4	89
25	6.2	33.5	6.3	33.2	19	6.5	33.4	39	6.4	32.9	78
29	6.1	36.2	4.5	35.6	13	6.3	35.4	35	5.9	35.2	68
33	6.1	37.5	6.3	36.9	17	6.3	37.1	34	6.5	36.4	72
37	7.0	39.7	6.9	39.1	18	7.2	38.5	38	7.0	37.6	75
41	6.6	40.6	6.3	40.3	16	6.6	39.6	33	3.9	30.3	51
45	5.5	42.3	5.8	41.9	14	6.2	41.2	30	6.3	38.2	66
49	5.3	43.9	5.4	43.6	12	5.7	42.7	27	5.9	40.9	58
53	5.9	45.5	6.1	45.3	13	6.2	44.4	28	6.2	42.1	59
57	5.4	46.2	5.7	46.4	12	5.4	45.3	24	5.6	43.3	51
61	5.5	46.8	5.5	47.0	12	5.4	46.1	23	5.7	44.1	52
65	5.2	48.0	5.2	48.7	11	5.3	47.5	23	5.3	45.8	46
69	6.1	48.7	4.9	49.8	10	5.2	48.3	21	5.1	46.8	44
73	5.1	49.8	5.4	51.3	11	5.2	49.6	21	5.6	48.0	47
77	5.0	50.2	5.1	52.6	10	5.0	51.0	19	5.2	49.2	42
81	5.3	50.6	5.1	52.1	10	5.0	50.7	20	5.0	48.7	41
85	5.1	50.9	4.9	52.6	9	4.9	50.7	20	5.1	49.0	42
89	4.9	50.3	5.1	52.1	10	5.2	50.6	20	5.4	48.1	45
93	5.5	51.2	5.7	53.8	11	5.4	51.2	21	5.9	49.5	48
97	5.3	51.6	5.2	54.2	10	5.0	50.2	20	5.1	49.1	42
101	4.9	49.4	4.8	52.8	9	4.9	49.3	20	4.9	46.6	42
104	4.9	47.0	5.1	49.9	10	5.0	47.4	21	5.0	44.4	45
Mean for weeks											
1-13	5.1	24.9	5.4	24.8	22	5.6	24.8	45	5.4	24.6	88
14-52	6.0	37.3	6.0	36.9	17	6.4	36.6	36	6.1	34.6	71
53-104	5.3	49.0	5.3	50.6	10	5.2	48.7	22	5.4	46.8	46

[a] Grams of feed consumed per animal per day
[b] Milligrams of triamterene consumed per day per kilogram body weight

TABLE I5
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Triamterene: Second Study

Week	0 ppm		400 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]
4	4.3	23.8	4.8	24.0	79
8	4.3	27.6	4.4	27.9	63
12	4.9	31.5	4.9	31.4	62
17	4.5	34.4	4.4	34.3	51
21	3.8	36.9	3.8	36.9	41
25	4.6	38.9	4.6	39.3	46
29	4.1	40.8	4.1	40.9	40
33	4.1	42.1	4.2	42.8	39
37	4.0	43.2	2.6	43.6	24
41	4.0	44.0	4.1	44.3	37
45	4.0	44.6	4.1	45.0	36
49	4.2	45.8	4.3	46.1	37
53	4.2	45.8	4.1	46.0	36
57	4.2	45.2	4.3	45.8	38
61	4.1	46.4	4.3	46.9	37
65	4.0	46.2	4.4	46.1	38
69	4.3	46.7	4.3	47.0	36
73	4.6	47.2	4.4	48.1	37
77	5.0	46.7	4.7	47.7	39
81	4.5	46.5	4.4	46.9	38
85	4.6	47.4	4.5	47.5	38
89	4.5	45.9	4.4	46.0	38
93	4.4	45.6	4.2	44.4	38
97	4.3	45.4	4.1	42.9	38
101	4.7	43.4	4.8	41.4	46
Mean for weeks					
1-13	4.5	27.6	4.7	27.8	68
14-52	4.1	41.2	4.0	41.5	39
53-101	4.4	46.0	4.4	45.9	38

[a] Grams of feed consumed per animal per day
[b] Milligrams of triamterene consumed per day per kilogram body weight

TABLE I6
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Triamterene: Second Study

Week	0 ppm		400 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)[b]
4	4.8	20.1	5.2	20.0	105
8	5.7	23.4	5.6	23.7	94
12	6.6	26.6	6.6	26.4	100
17	6.2	30.4	6.0	30.2	79
21	6.0	32.9	5.9	32.5	72
25	6.3	35.5	6.8	35.0	78
29	5.5	37.5	5.8	37.2	63
33	5.4	39.5	5.9	39.2	60
37	5.5	40.0	5.5	39.8	55
41	5.3	42.1	5.7	41.4	55
45	6.0	43.3	6.5	42.9	60
49	6.1	45.0	6.1	44.5	55
53	5.5	45.6	5.7	44.8	51
57	5.4	45.8	5.8	45.1	52
61	4.9	47.7	5.2	46.9	45
65	5.9	47.7	5.5	47.0	47
69	5.8	48.6	5.5	47.7	46
73	5.6	49.3	5.6	48.8	45
77	6.1	49.5	5.9	48.7	49
81	5.7	49.2	5.3	48.8	43
85	5.7	49.9	5.6	48.8	46
89	5.5	49.5	5.6	47.8	47
93	5.5	49.6	5.9	47.7	50
97	5.2	48.7	5.2	44.2	47
101	6.0	45.9	6.2	43.3	57
Mean for weeks					
1-13	5.7	23.4	5.8	23.4	99
14-52	5.8	38.5	6.0	38.1	64
53-101	5.6	48.2	5.6	46.9	48

[a] Grams of feed consumed per animal per day
[b] Milligrams of triamterene consumed per day per kilogram body weight

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

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TABLE J1
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 were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE J2
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 J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.21 ± 0.55	21.0–23.2	27
Crude fat (% by weight)	5.59 ± 0.41	4.6–6.3	27
Crude fiber (% by weight)	3.50 ± 0.37	2.8–4.7	27
Ash (% by weight)	6.65 ± 0.43	6.0–7.9	27
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210–1.390	8
Cystine	0.306 ± 0.084	0.181–0.400	8
Glycine	1.150 ± 0.047	1.060–1.210	8
Histidine	0.576 ± 0.024	0.531–0.607	8
Isoleucine	0.917 ± 0.029	0.881–0.944	8
Leucine	1.946 ± 0.055	1.850–2.040	8
Lysine	1.270 ± 0.058	1.200–1.370	8
Methionine	0.448 ± 0.128	0.306–0.699	8
Phenylalanine	0.987 ± 0.140	0.665–1.110	8
Threonine	0.877 ± 0.042	0.824–0.940	8
Tryptophan	0.236 ± 0.176	0.107–0.671	8
Tyrosine	0.676 ± 0.105	0.564–0.794	8
Valine	1.103 ± 0.040	1.050–1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830–2.570	7
Linolenic	0.280 ± 0.040	0.210–0.320	7
Vitamins			
Vitamin A (IU/kg)	8,694 ± 3,836	4,500–19,000	27
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α-Tocopherol (ppm)	37.95 ± 9.406	22.50–48.90	8
Thiamine (ppm)	21.67 ± 3.52	18.0–37.0	27
Riboflavin (ppm)	7.92 ± 0.87	6.10–9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0–150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0–34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60–14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80–3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19–0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6–65.0	8
Choline (ppm)	3,089 ± 328.69	2,400–3,430	8
Minerals			
Calcium (%)	1.13 ± 0.12	0.90–1.40	26
Phosphorus (%)	0.92 ± 0.06	0.81–1.10	27
Potassium (%)	0.883 ± 0.078	0.772–0.971	6
Chloride (%)	0.526 ± 0.092	0.380–0.635	8
Sodium (%)	0.313 ± 0.390	0.258–0.371	8
Magnesium (%)	0.168 ± 0.010	0.151–0.181	8
Sulfur (%)	0.280 ± 0.064	0.208–0.420	8
Iron (ppm)	360.54 ± 100	255.0–523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70–99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10–64.50	8
Copper (ppm)	11.06 ± 2.50	8.090–15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52–4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04–2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.64 ± 0.23	0.17–0.98	27
Cadmium (ppm)[b]	0.10 ± 0.02	<0.10–0.20	27
Lead (ppm)	0.42 ± 0.20	0.05–0.87	27
Mercury (ppm)[c]	0.05 ± 0.01	<0.05–0.08	27
Selenium (ppm)	0.36 ± 0.07	0.25–0.48	27
Aflatoxins (ppb)	<5.0	–	27
Nitrate nitrogen (ppm)	18.25 ± 8.38	2.9–34.0	27
Nitrite nitrogen (ppm)	0.16 ± 0.18	<0.10–1.00	27
BHA (ppm)[d]	2.30 ± 0.78	<2.00–5.00	27
BHT (ppm)[d]	1.67 ± 1.04	<1.00–4.00	27
Aerobic plate count (CFU/g)[e]	140,329 ± 151,668	39,000–570,000	27
Coliform (MPN/g)[f]	266 ± 491	<3.00–2,400	27
E. coli (MPN/g)[g]	4.92 ± 7.86	<3.00–43.0	26
E. coli (MPN/g)[h]	10.30 ± 28.96	<3.00–150	27
Total nitrosoamines (ppb)[i]	7.02 ± 2.67	3.30–13.30	27
N-Nitrosodimethylamine (ppb)[i]	6.16 ± 2.47	3.00–13.00	27
N-Nitrosopyrrolidine (ppb)[i]	0.87 ± 0.94	0.30–4.30	27
Pesticides			
α-BHC[j]	<0.01		27
ß-BHC	<0.02		27
γ-BHC	<0.01		27
δ-BHC	<0.01		27
Heptachlor	<0.01		27
Aldrin	<0.01		27
Heptachlor epoxide	<0.01		27
DDE	<0.01		27
DDD	<0.01		27
DDT	<0.01		27
HCB	<0.01		27
Mirex	<0.01		27
Methoxychlor	<0.05		27
Dieldrin	<0.01		27
Endrin	<0.01		27
Telodrin	<0.01		27
Chlordane	<0.05		27
Toxaphene	<0.1		27
Estimated PCBs	<0.2		27
Ronnel	<0.01		27
Ethion	<0.02		27
Trithion	<0.05		27
Diazinon	<0.1		27
Methyl parathion	<0.02		27
Ethyl parathion	<0.02		27
Malathion[k]	0.15 ± 0.19	0.05–0.85	27
Endosulfan I	<0.01		27
Endosulfan II	<0.01		27
Endosulfan sulfate	<0.03		27

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Mean, standard deviation, and range include one value of 0.20 ppm obtained from the lot milled 8 October 1985; all other values are less than or equal to the detecton limit.
[c] Mean, standard deviation, and range include one value of 0.08 ppm obtained from the lot milled 3 September 1986; all other values were less than or equal to the detection limit.
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony forming unit.
[f] MPN = most probable number.
[g] Mean, standard deviation, and range exclude 1 large value of 150 MPN/g obtained in lot 17 October 1984.
[h] Mean, standard deviation, and range include value given in [g].
[i] All values were corrected for percent recovery.
[j] BHC = hexachlorocyclohexane or benzene hexachloride
[k] Fourteen lots contained more than 0.05 ppm.

APPENDIX K
SENTINEL ANIMAL PROGRAM

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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 serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and are subject to identical environmental conditions as the study animals. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Rats

At the end of the 13-week study, samples for viral screening were collected from five sentinel rats of each sex. In the 2-year study, five rats of each sex were sampled during quarantine and at the beginning of the 2-year study. During the 2-year study, five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Five rats of each sex assigned to the 600 ppm group in the 2-year studies were killed at 24 months. One female rat in the sentinel animal group was sampled at moribund sacrifice on 13 February 1986. Blood from each animal sampled was collected and allowed to clot. Serum for the viral screening was separated, cooled on ice, and shipped to Microbiological Associates, Incorporated (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

13 Weeks

Method of Analysis	Time of Analysis
Complement Fixation	
RCV (rat coronavirus)	End of study
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	End of study
KRV (Kilham rat virus)	End of study
PVM (pneumonia virus of mice)	End of study
Sendai	End of study
ELISA	
RCV/SDA (rat coronavirus/sialodacryoadenitis)	End of study

2 Years

Method of Analysis	Time of Analysis
ELISA	
CARB (cilia associated-respiratory *bacillus*)	24 months
Mycoplasma arthritidis	6, 12, 18, and 24 months
Mycoplasma pulmonis	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
RCV/SDA	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
H-1	6, 12, 18, and 24 months
KRV	6, 12, 18, and 24 months

Mice

At the end of the 13-week study, samples for viral screening were collected from five sentinel mice of each sex. In the 2-year study, five mice of each sex were sampled in quarantine. During the initial 2-year study (first study) and the restarted 2-year study (second study), five mice of each sex from the sentinel animal group were sampled at the beginning of the studies and at approximately 6, 12, and 18 months. At the end of the 2-year studies, samples were also collected from five mice of each sex in the 400 ppm groups of the first study and from five mice of each sex from 0 and 400 ppm groups of the second study. On 22 May 1985, five mice of each sex from the first study sentinel animals were sampled for MHV screening. Seven male mice in the first study, which were sacrificed moribund, were sampled. Blood from each animal sampled was collected and allowed to clot. Serum for the viral screenings was separated, cooled on ice, and shipped to Microbiological Associates, Incorporated (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

13 Weeks

Method of Analysis	Time of Analysis
Complement Fixation	
MHV	End of study
RCV	End of study
Hemagglutination Inhibition	
Ectromelia virus	End of study
GDVII (mouse encephalomyelitis virus)	End of study
MVM (minute virus of mice)	End of study
PVM	End of study
Polyoma virus	End of study
Reovirus 3	End of study
Sendai	End of study

2 Years

First Study

Method of Analysis	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	6, 12, 18, and 24 months
ELISA	
CARB	24 months
Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
M. arthritidis	6, 12, 18, and 24 months
M. pulmonis	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Reo 3	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
K (papovavirus)	6, 12, 18, and 24 months
MVM	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	6, 12, 18, and 24 months

Second Study Method of Analysis	Time of Analysis
Complement Fixation	
LCM	6 and 12 months
ELISA	
CARB	12 and 24 months
Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
MHV	6, 12, 18, and 24 months
M. arthritidis	6, 12, and 24 months (males only)
M. pulmonis	6, 12, and 24 months (males only)
PVM	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
K	6, 12, 18, and 24 months
MVM	6, 12, and 18 months
Polyoma virus	6, 12, 18, and 24 months
Immunofluorescence Assay	
EDIM	6, 12, 18, and 24 months

The serology results for sentinel animals are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of Triamterene

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies			
Rats	13 weeks	0/10	None positive
2-Year Studies			
Rats	6 months	1/10	*M. arthritidis*[a]
	12 months	1/10	*M. arthritidis*
	18 months	1/9	*M. arthritidis*
	24 months	2/10	CARB
First Study			
Mice	6 months	0/10	None positive
	12 months	0/10	None positive
	18 months	0/10	None positive
	24 months	1/10	*M. arthritidis*
Second Study			
Mice	6 months	0/10	None positive
	12 months	1/10	*M. arthritidis*
	18 months	0/10	None positive
	24 months	1/10	*M. arthritidis*

[a] Possible *Mycoplasma arthritidis*

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
404	5,5-Diphenylhydantoin
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Hellow 4
421	Talc
422	Coumarin
423	Dihydrocoumarin
427	Turmeric Oleoresin
431	Benzyl Acetate
434	1,3-Butadiene
443	Oxazepam

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