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TOXICOLOGY AND CARCINOGENESIS STUDIES OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE (CAS NO. 81-49-2) 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. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

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(CAS NO. 81-49-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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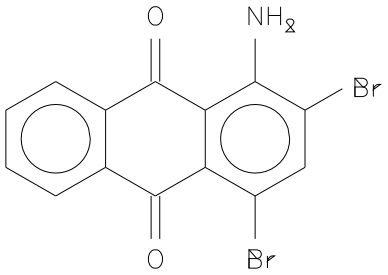
CONTENTS

ABSTRACT



1-AMINO-2,4-DIBROMOANTHRAQUINONE

CAS No. 81-49-2

Chemical Formula: $C_{14}H_7Br_2NO_2$ Molecular Weight: 381.04

Synonym: ADBAQ

1-Amino-2,4-dibromoanthraquinone is an anthraquinone-derived vat dye, a member of a class of insoluble dyes that are impregnated into textile fibers. Five anthraquinone-derived dyes with representative and diverse structures, as well as the parent chemical, anthraquinone, were selected for toxicology and carcinogenesis evaluation. Similar to the benzidine dye initiative, the rationale for selecting these vat dyes was to generate sufficient toxicologic data to permit more reliable predictions of carcinogenicity to be made on other chemicals in this class, thereby eliminating or reducing the need to study every anthraquinone dye. 1-Amino-2,4-dibromoanthraquinone is the last anthraquinone-derived dye in this group to be studied.

Groups of male and female F344/N rats and B6C3F$_1$ mice were exposed to 1-amino-2,4-dibromoanthraquinone (87% to 97% pure) for 13 weeks or for 9, 15, or 24 months. Because 1-amino-2,4-dibromoanthraquinone was predicted to be carcinogenic, these studies were designed to evaluate the potential for tumor progression and regression. Absorption and excretion studies were carried out in male F344/N rats. Genetic toxicity was determined *in vitro* using *Salmonella typhimurium* and cultured Chinese hamster ovary cells. Extensive chemical analyses were performed to identify and characterize impurities of the 1-amino-2,4-dibromoanthraquinone used in these studies.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were given 0, 2,500, 5,000, 10,000, 25,000, or 50,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 13 weeks. These levels correspond to approximately 150 to 3,200 mg 1-amino-2,4-dibromoanthraquinone/kg body weight per day for males and to approximately 170 to 3,200 mg/kg for females. Chemical-related mortality was limited to one male and one female in the 50,000 ppm groups. Final mean body weights and body weight gains of all exposed groups of rats were significantly lower than those of the controls. Feed consumption by all exposed groups was less than that by the controls throughout the study and generally decreased with increasing exposure concentration. Pink-red staining of the fur and tail was observed in all exposed groups. Absolute and relative liver weights of all exposed groups were generally significantly greater than those of the controls.

Chemical-related lesions were present in the liver, kidney, and spleen of male and female rats. Nonneoplastic lesions in the liver included foci of hepatocellular alteration, diffuse hepatocellular hypertrophy (cytomegaly), hepatocellular cytoplasmic vacuolation, bile duct hyperplasia, inflammation, and pigmentation. These differences were observed primarily in the 25,000 and 50,000 ppm groups of males and females; the spectrum of proliferative lesions of the bile ducts (hyperplasia, fibrosis, and necrotizing cholangitis) in the 25,000 and 50,000 ppm groups was morphologically consistent with the lesion described as cholangiofibrosis. Pigmentation was present in the renal tubule epithelium of all groups of exposed rats; nuclear enlargement (karyomegaly) was also present in the renal tubule epithelium in some of the exposed rats. Accumulation of hyaline droplets in the cytoplasm of the renal tubule epithelium and tubule lumina was present in 2,500, 5,000, 10,000, and 25,000 ppm males. Incidences of hematopoiesis of the spleen in exposed groups of males and females were increased compared to those in the controls.

13-Week Study in Mice

Groups of 10 male and 10 female mice were given 0, 2,500, 5,000, 10,000, 25,000, or 50,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 13 weeks. These levels correspond to approximately 500 to 10,600 mg 1-amino-2,4-dibromoanthraquinone/kg body weight per day for males and approximately 660 to 11,700 mg/kg per day for females. There was no chemical-related mortality. Feed consumption and final mean body weights of exposed groups were similar to those of the controls. Red staining of the fur was observed in all exposed groups. Absolute and relative liver weights of the exposed groups were greater than those of the controls except for the absolute liver weight of 2,500 ppm males. Absolute and relative kidney weights of 25,000 and 50,000 ppm males were lower than those of the controls.

Chemical-related lesions were limited to the livers of males and consisted of pigmentation of hepatocytes at all exposure concentrations and centrilobular hepatocellular hypertrophy at 10,000, 25,000, and 50,000 ppm. Minimal pigment was present in the liver of one female in the 25,000 ppm group and in one female in the 50,000 ppm group.

2-Year Study in Rats

Groups of 70 male and 70 female rats were given 0, 5,000, or 10,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 103 weeks. In addition, groups of 50 male and 50 female rats were given 2,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 104 weeks. These exposure concentrations were approximately equal to 90, 240, or 490 mg 1-amino-2,4-dibromoanthraquinone/kg body weight for males and 110, 285, or 600 mg/kg for females. Ten animals from each group were evaluated for histopathology at 9 months. Additional groups of 10 animals from the 0 and 10,000 ppm groups were evaluated for histopathology at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

In the 2-year study, survival of the 10,000 ppm males and females was significantly lower than that of the controls. Survival of the 2,000 and 5,000 ppm groups was similar to that of the controls. During the last year of the study, the mean body weights of exposed males were 80% to 91% those of controls, and the mean body weights of exposed females were 67% to 84% those of controls. Feed consumption among exposed groups was generally similar, but was less than that by controls. The fur and urine of all exposed male and female groups were discolored.

Pathology Findings

In the 2-year study, 1-amino-2,4-dibromoanthraquinone was associated with significant chemical-related increases in the incidences of benign and malignant neoplasms in the liver, large intestine, kidney, and urinary bladder of males and females. Chemical-related nonneoplastic proliferative and degenerative lesions occurred in the liver, kidney, urinary bladder, and forestomach of males and females.

The incidences of foci of hepatocellular alteration and pigmentation in the liver of males and females were increased at the 9-month interim evaluation, and a hepatocellular adenoma was present in one 5,000 ppm male. At the 15-month interim evaluation, hepatocellular adenoma or carcinoma (combined) occurred in all males and nine females in the 10,000 ppm groups. By the end of the 2-year study, hepatocellular adenoma, carcinoma, cholangioma, or cholangiocarcinoma were observed in males and

females in the 5,000 and 10,000 ppm groups. In the 2,000 ppm groups, similar liver neoplasms were present in 63% of the males and in 83% of the females. Of the hepatocellular carcinomas in the 5,000 and 10,000 ppm groups of males and females, 31% to 49% were metastatic to the lungs or other sites. Increases in the incidences of foci of hepatocellular alteration (basophilic, eosinophilic, and clear cell) and pigmentation of the liver were also observed in exposed groups of males and females.

Adenomatous polyps (adenoma) of the large intestine were present in six 10,000 ppm males at the 15-month interim evaluation. Incidences of adenomatous polyp (adenoma) and carcinoma of the large intestine were significantly increased in exposed groups of males and females after 2 years; multiple benign and malignant intestinal neoplasms were observed in many of these rats.

In the kidney, incidences of renal tubule adenoma and carcinoma were significantly increased in exposed groups of males and females after 2 years. Renal tubule adenomas were present in two 10,000 ppm males at 15 months. There were also chemical-related increases in the incidences and severities of renal tubule epithelial hyperplasia, pigmentation, and transitional cell hyperplasia in the kidney of males and females. Hyaline droplet accumulation was present in all exposed male rats at 9 months.

Incidences of transitional cell papilloma and carcinoma of the urinary bladder were increased at 2 years in males and females in the 10,000 ppm groups. Transitional cell hyperplasia was observed in exposed males and females at the 15-month interim evaluation. Other nonneoplastic lesions observed in the urinary bladder at 2 years included metaplasia of the transitional epithelium and submucosal stromal tissue.

In the forestomach, the incidences and severities of inflammation, ulceration, hyperkeratosis, and hyperplasia of the squamous mucosa were increased in all exposed groups of males and females at 2 years, but not at the 9- or 15-month interim evaluations.

In exposed males and females, the incidences of mononuclear cell leukemia were significantly decreased. The incidences of atrophy of the seminal vesicle were increased in exposed male rats in the 2-year study.

Stop-Exposure Evaluation in Rats

Groups of 40 male and 40 female rats were given 20,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 9 or 15 months. At 9 months, 10 males and 10 females were evaluated for histopathology (9-month interim evaluation groups). After 9 months of exposure, an additional 10 males and 10 females were fed control diet until the end of the 15-month evaluation (9-month stop-exposure groups), and 20 males and 20 females continued to receive 20,000 ppm 1-amino-2,4-dibromoanthraquinone until the end of the evaluation (15-month exposure groups). The approximate daily consumption of 1-amino-2,4-dibromoanthraquinone was 1,335 mg/kg for males and 1,790 mg/kg for females in the 9-month stop-exposure groups and 1,115 mg/kg for males and 1,435 mg/kg for females in the 15-month exposure groups.

Survival was similar among groups except for the females in the 15-month exposure group; the survival of this group was lower than that of the controls. Lower mean body weights were related to increased exposure duration. The mean body weights of exposed males were 76% to 82% that of controls, and the mean body weights of exposed females were 73% to 84% that of controls.

For the stop-exposure evaluation, similar chemical-related neoplasms and nonneoplastic lesions were observed in the same sites as in the 2-year study: liver, large intestine, kidney, urinary bladder, and forestomach.

After 9 months of dietary exposure to a concentration of 20,000 ppm 1-amino-2,4-dibromoanthraquinone, hepatocellular adenoma and carcinoma occurred in males and females. Nonneoplastic chemical-related lesions in the liver of exposed rats included pigmentation, focal hepatocellular alteration, and bile duct hyperplasia. Neoplasms at other sites in males included one adenomatous polyp (adenoma) in the large intestine and one transitional cell papilloma in the urinary bladder. Hyaline droplet accumulation was present in the kidney of exposed males at 9 months.

In the stop-exposure groups examined at 15 months, hepatocellular adenoma and carcinoma were present in most males and females. Adenomatous polyp (adenoma) of the colon, renal tubule cell adenoma, and urinary bladder transitional cell papilloma and

carcinoma also occurred in males and females. Nonneoplastic chemical-related lesions included foci of hepatocellular alteration in the liver and hyperplasia of the renal tubule epithelium and urinary bladder transitional epithelium. Hyperplasia, hyperkeratosis, inflammation, and ulceration were observed in the forestomachs of some male and female rats continuously exposed for 15 months.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female mice were given 0, 10,000, or 20,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 104 weeks. The daily compound consumption was approximately 1,690 or 3,470 mg 1-amino-2,4-dibromoanthraquinone/kg body weight for males and 1,950 or 4,350 mg/kg for females. Ten animals from each group were evaluated for histopathology at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

In the 2-year study, survival of exposed males was significantly lower than that of the controls. Survival of exposed females was similar to that of the controls. The final mean body weights of exposed males were 83% to 85% that of controls, and the final mean body weights of exposed females were 81% to 86% that of controls. Feed consumption by exposed groups was generally similar to that by controls. Discoloration of the fur, urine, and feces was observed in all exposed groups.

Pathology Findings

In the 2-year study, 1-amino-2,4-dibromoanthraquinone was associated with significant chemical-related increases in the incidences of benign and malignant neoplasms in the liver, forestomach, and lung of males and females.

Incidences of hepatocellular adenoma and carcinoma were increased in exposed groups at the 15-month interim evaluation and at 2 years. At 2 years, there were significant increases in the incidences of multiple hepatocellular adenoma and carcinoma in males and females and in the incidences of hepatoblastoma in males. Centrilobular hypertrophy of hepatocytes in males and foci of hepatocellular alteration and pigmentation in the liver of males and females were also chemical-related changes.

Squamous cell papilloma of the forestomach mucosa occurred in 10,000 ppm females and 20,000 ppm males and females at the 15-month interim evaluation, and the incidences of squamous cell papilloma and carcinoma were significantly increased in exposed groups of males and females at 2 years. Chemical-related hyperplasia of forestomach epithelium was also present at 15 months and at 2 years.

Alveolar/bronchiolar adenomas were present only in the exposed groups of males and females at 15 months, and the incidences of alveolar/bronchiolar adenoma were significantly increased in exposed males and females at 2 years. The incidences of multiple alveolar/bronchiolar adenoma were also increased in exposed males.

In the kidney, pigmentation was present in the renal tubules of most mice after 2 years of exposure.

DISPOSITION AND METABOLISM STUDIES

Adult male F344/N rats were given [^{14}C]-labeled 1-amino-2,4-dibromoanthraquinone as a single intravenous dose of 0.4 mg/kg body weight or as a single oral dose of 2, 23, 118, 814, or 1,473 mg/kg. A 6-hour bile cannulation study was also performed. From day 0 through day 3 after intravenous administration, about 50% of the ^{14}C was excreted in the feces, 15% in the urine, and 6% in expired air. Unmetabolized 1-amino-2,4-dibromoanthraquinone accounted for less than 3% of the excreted ^{14}C after intravenous administration. For oral doses administered, the amount of the dose that was absorbed fit the equation: $absorbed\ dose = 6.6 \log(dose)$. After intravenous administration, the metabolites of 1-amino-2,4-dibromoanthraquinone in blood were primarily in the plasma fraction (blood:plasma ratio of approximately 0.5:1). The highest concentrations of ^{14}C in tissues 15 minutes after intravenous dosing were in excretory organs, lung, kidney, small intestine, liver, adipose tissue, and adrenal gland.

GENETIC TOXICOLOGY

1-Amino-2,4-dibromoanthraquinone was mutagenic in *Salmonella typhimurium* strains TA98 and TA1537 in the absence of S9; with S9, an equivocal response was observed in TA1537. 1-Amino-2,4-dibromoanthraquinone resulted in an equivocal response in

strain TA100 with and without S9, and no mutagenic activity was detected with strain TA1535. In cultured Chinese hamster ovary cells, 1-amino-2,4-dibromoanthraquinone induced sister chromatid exchanges with and without S9; chromosomal aberrations were induced only in the absence of S9.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** of 1-amino-2,4-dibromoanthraquinone in male and female F344/N rats based on increased incidences of neoplasms in the liver, large intestine, kidney, and urinary bladder. There was *clear evidence of carcinogenic activity* of 1-amino-2,4-dibromoanthraquinone in male and female $B6C3F_1$ mice based on increased incidences of neoplasms in the liver, forestomach, and lung.

Exposure of male and female rats to 1-amino-2,4-dibromoanthraquinone for 2 years was associated with basophilic focus (males only), clear cell focus, eosinophilic focus, and pigmentation in the liver; renal tubule hyperplasia, renal tubule pigmentation, and transitional cell hyperplasia in the kidney; transitional cell hyperplasia, squamous metaplasia, and stromal metaplasia (females only) in the urinary bladder; squamous hyperplasia, hyperkeratosis, ulceration, and inflammation of the forestomach mucosa; and seminal vesicle atrophy. Exposure of male and female mice to 1-amino-2,4-dibromoanthraquinone for 2 years was associated with centrilobular hepatocellular hypertrophy (males only), basophilic focus, clear cell focus (females only), eosinophilic focus, and pigmentation in the liver; pigmentation in the kidney; and hyperplasia, basal cell hyperplasia, hyperkeratosis, and inflammation of the forestomach mucosa.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

Font Size:11pt**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 1-Amino-2,4-dibromoanthraquinone**

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 2,000, 5,000, or 10,000 ppm [approximately 90, 240, or 490 mg/kg/day]	0, 2,000, 5,000, or 10,000 ppm [approximately 110, 285, or 600 mg/kg/day]	0, 10,000, or 20,000 ppm [approximately 1,690 or 3,470 mg/kg/day]	0, 10,000, or 20,000 ppm [approximately 1,950 or 4,350 mg/kg/day]
Body weights	Exposed groups lower than controls	Exposed groups lower than controls	Exposed groups lower than controls	Exposed groups lower than controls
2-Year survival rates	26/50, 24/40, 21/60, 10/50	38/50, 32/40, 38/60, 12/49	40/50, 22/51, 23/50	39/50, 34/50, 33/50
Nonneoplastic effects	Liver: basophilic focus (9/50, 12/40, 24/59, 22/50); clear cell focus (3/50, 26/40, 39/59, 27/50); eosinophilic focus (1/50, 13/40, 14/59, 6/50); pigmentation (3/50, 19/40, 48/59, 39/50) Kidney: renal tubule hyperplasia (9/50, 30/40, 25/59, 19/50); renal tubule pigmentation (5/50, 40/40, 58/59, 49/50); transitional cell hyperplasia (30/50, 40/40, 51/59, 35/50) Urinary bladder: transitional cell hyperplasia (1/50, 5/38, 17/58, 30/50); squamous metaplasia (0/50, 0/38, 0/58, 3/50)	Liver: clear cell focus (3/50, 28/40, 39/60, 17/48); eosinophilic focus (7/50, 23/40, 12/60, 1/48); pigmentation (1/50, 19/40, 51/60, 45/48) Kidney: renal tubule hyperplasia (1/50, 12/40, 23/60, 27/48); renal tubule pigmentation (0/50, 40/40, 60/60, 48/48); transitional cell hyperplasia (10/50, 16/40, 44/60, 21/48) Urinary bladder: transitional cell hyperplasia (1/50, 2/40, 41/60, 41/46); squamous metaplasia (0/50, 1/40, 4/60, 8/46); stromal metaplasia (0/50, 0/40, 4/60, 2/46)	Liver: centrilobular hepatocyte hypertrophy (0/50, 17/51, 13/50); basophilic focus (0/50, 4/51, 3/50); eosinophilic focus (0/50, 6/51, 1/50); pigmentation (1/50, 50/51, 47/50) Kidney: renal tubule pigmentation (0/50, 42/51, 43/50) Forestomach: hyperplasia (1/50, 9/50, 4/50); basal cell hyperplasia (0/50, 0/50, 2/50); hyperkeratosis (1/50, 7/50, 6/50); inflammation (2/50, 6/50, 13/50)	Liver: basophilic focus (0/50, 4/50, 5/50); clear cell focus (0/50, 10/50, 9/50); eosinophilic focus (0/50, 4/50, 2/50); pigmentation (0/50, 44/50, 49/50) Kidney: renal tubule pigmentation (0/50, 43/50, 43/50) Forestomach: hyperplasia (9/48, 15/50, 19/50); basal cell hyperplasia (0/48, 7/50, 3/50); hyperkeratosis (10/48, 14/50, 17/50); inflammation (7/48, 10/50, 21/50)

(continued)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 1-Amino-2,4-dibromoanthraquinone (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Nonneoplastic effects (continued)	Forestomach: squamous hyperplasia (3/49, 19/39, 25/59, 26/49); hyperkeratosis (5/49, 18/39, 21/59, 20/49); ulcer (3/49, 10/39, 15/59, 16/49); inflammation (3/49, 12/39, 11/59, 11/49); Seminal vesicle: atrophy (1/49, 30/40, 35/59, 23/50)	Forestomach: squamous hyperplasia (2/49, 7/40, 26/60, 33/47); hyperkeratosis (2/49, 7/40, 23/60, 28/47); ulcer (1/49, 2/40, 7/60, 17/47); inflammation (0/49, 1/40, 13/60, 10/47)		
Neoplastic effects	Liver: hepatocellular adenoma (1/50, 20/40, 40/59, 34/50); hepatocellular carcinoma (1/50, 12/40, 55/59, 46/50); hepatocholangio-carcinoma (0/50, 0/40, 6/59, 2/50) Large intestine (all sites): adenomatous polyp (adenoma) (0/50, 13/40, 51/59, 40/50); carcinoma (0/50, 1/40, 11/59, 17/50) Kidney (renal tubule): adenoma (2/50, 10/40, 11/59, 14/50); carcinoma (0/50, 0/40, 2/59, 1/50) Urinary bladder: transitional cell papilloma (0/50, 1/38, 2/58, 8/50); transitional cell carcinoma (0/50, 0/38, 1/58, 4/50)	Liver: hepatocellular adenoma (0/50, 28/40, 47/60, 29/48); hepatocellular carcinoma (0/50, 12/40, 57/60, 45/48); hepatocholangio-carcinoma (0/50, 0/40, 11/60, 13/48) Large intestine (all sites): adenomatous polyp (adenoma) (0/50, 28/40, 53/60, 43/49); carcinoma (0/50, 2/40, 21/60, 8/49) Kidney (renal tubule): adenoma (0/50, 3/40, 16/60, 16/48); carcinoma (0/50, 0/40, 0/60, 2/48) Urinary bladder: transitional cell papilloma (0/50, 2/40, 7/60, 9/46); transitional cell carcinoma (0/50, 0/40, 8/60, 16/46)	Liver: hepatocellular adenoma (10/50, 38/51, 39/50); hepatocellular carcinoma (9/50, 18/51, 21/50); hepatoblastoma (0/50, 3/51, 5/50) Forestomach: squamous cell papilloma (0/50, 13/51, 16/50); squamous cell carcinoma (0/50, 12/51, 13/50) Lung: alveolar/ bronchiolar adenoma (7/50, 26/51, 24/50)	Liver: hepatocellular adenoma (6/50, 45/50, 49/50); hepatocellular carcinoma (0/50, 23/50, 27/50) Forestomach: squamous cell papilloma (2/50, 16/50, 27/50); squamous cell carcinoma (0/50, 12/50, 11/50) Lung: alveolar/ bronchiolar adenoma (4/50, 17/50, 13/49)

(continued)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 1-Amino-2,4-dibromoanthraquinone (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Level of evidence of carcinogenic activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Equivocal in strain TA100 with and without S9; negative in strain TA1535 with and without S9; positive in strain TA1537 without S9, equivocal with S9; positive in strain TA98 without S9, negative with S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Positive with and without S9 (combined results from testing in two laboratories)			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Weakly positive without S9, negative with S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-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 chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-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 1-amino-2,4-dibromoanthraquinone on June 21, 1994, 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 June 21, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of 1-amino--2,4-dibromoanthraquinone received public review by the National Toxicology Program's 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.E. Huff, NIEHS, introduced the toxicology and carcinogenesis studies of 1-amino-2,4-dibromoanthraquinone by discussing the uses and rationale for study, including it being a part of a class study of anthraquinone derivatives. He described the experimental design, reported on survival and body weight effects, and commented on chemical-related neoplasms and nonneoplastic lesions in male and female rats and mice. The proposed conclusions for the studies were *clear evidence of carcinogenic activity* in male and female F344/N rats and in male and female B6C3F_1 mice.

Dr. Huff reviewed the carcinogenic responses in other anthraquinone derivatives that had been studied, noting that the liver seemed to be a major site and that 1-amino-2,4-dibromoanthraquinone was the most active as far as the number of sites. Interpretive conclusions that could be drawn from the cumulative National Toxicology Program studies on this class of insoluble dyes were that anthraquinones are typically mutagenic and clastogenic, they are carcinogenic to male and female rats and mice, and they are predicted to represent likely carcinogenic hazards to humans exposed to these agents, especially occupationally. Dr. J.R. Bucher, NIEHS, reported that the toxicology and carcinogenesis studies on anthraquinone were in progress.

Dr. van Zwieten, a principal reviewer, agreed with the proposed conclusions. He thought there should be more discussion of the findings from the stop-exposure groups of rats. (Stop-exposure groups were evaluated at 9 and 15 months as part of an attempt to gain insight into the progression or regression of chemical-induced lesions.) Dr. van Zwieten noted the high impurity levels in the first lot of the chemical used for the 13-week studies and for the first 2 months of the 2-year studies and said that a statement indicating that this did not affect the integrity of the studies might be helpful. Dr. Huff responded that the impurities had been characterized (page 20; Arneson *et al.*, 1996).

Dr. Ward, the second principal reviewer, agreed with the proposed conclusions. He commented that no hyaline droplets were reported in the kidney of rats after 9 months, and since 1-amino-2,4-dibromoanthraquinone might cause accumulation of $\alpha_{2\mu}$-globulin, the report should indicate that droplets were searched for but not found or found but not reported (page 83). Dr. Ward objected to characterizing cholangiofibrosis found in the liver of rats in a 13-week study as "premalignant." He stated that this lesion is usually induced by liver carcinogens but does not typically progress to bile duct neoplasms. Dr. M.R. Elwell, NIEHS, said this interpretation was from the literature and the wording on neoplastic potential would be revised to also reflect Dr. Ward's experience.

Dr. Reddy, the third principal reviewer, also agreed with the proposed conclusions. He said it would have been useful to characterize the chemical nature of the pigment that accumulated in the liver, kidney, and other organs, as well as in the fur and tail. Dr. Huff responded that, logically, the pigment was either the chemical or one of its metabolites, but the feasibility of going back and defining it better would have to be determined.

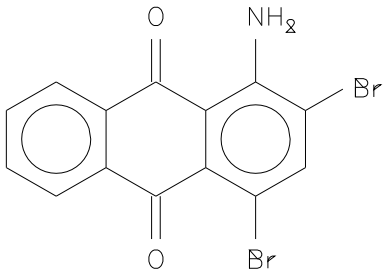
Dr. Russo had observed evidence of chronic inflammation in one of the plates and wondered whether the liver lesions were associated with hepatitis. Dr. Karol asked if there was inflammation of the eosinophilic foci, which would suggest a hypersensitivity-type reaction. Dr. Elwell said there was some inflammation with the cholangiofibrosis, but this was really limited to the focal lesions where there was fibrosis and to cystic bile ducts, and there was not an eosinophilic inflammation; the term "eosinophilic foci" referred to a focal cellular alteration of hepatocytes.

Dr. Bailey cited a statement from the use, production, and human exposure sections that "no individualized information was located regarding amounts produced

or specific uses of 1-amino-2,4-dibromoanthraquinone," leading him to wonder if this chemical is currently used. Dr. Huff said this was a valid question for 1-amino-2,4-dibromoanthraquinone and the other anthraquinone derivatives. He said proprietary information was difficult to obtain, although he was hopeful that a request to the American Pharmaceutical Association concerning anthraquinone dyes in over-the-counter or prescription items might yield some data on human exposure. There was some discussion that primary exposure to these dyes would be from topical application or exposure.

Dr. van Zwieten moved that the Technical Report on 1-amino-2,4-dibromoanthraquinone be accepted with the revisions discussed and the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity.* Dr. Reddy seconded the motion, which was accepted unanimously with eleven votes.

INTRODUCTION



1-AMINO-2,4-DIBROMOANTHRAQUINONE

CAS No. 81-49-2

Chemical Formula: $C_{14}H_7Br_2NO_2$ Molecular Weight: 381.04

Synonym: ADBAQ

CHEMICAL AND PHYSICAL PROPERTIES

1-Amino-2,4-dibromoanthraquinone, a reddish brown to orange powder, is an anthraquinone-derived vat dye. Anthraquinone (9,10-anthraquinone: CAS No. 84-65-1), which does not occur naturally, was first synthesized by Laurent in 1835 as an oxidation product of anthracene and nitric acid (Chung, 1978). "Anthra" comes from the Greek word for coal, from which anthracene was originally obtained.

USE, PRODUCTION, AND HUMAN EXPOSURE

Anthraquinone is an important and widely used starting material for the manufacture of vat dyes (*Merck Index*, 1989). Class homologues of anthraquinone comprise a greater number of dyes having outstanding "fastness" properties than any other group of commercial dyes (Chung, 1978; Chung and Farris, 1979). No information was located regarding amounts produced or specific uses of 1-amino-2,4-dibromoanthraquinone. The 2-alkyl derivatives of anthraquinone with alkyl chains ranging from one to five carbons are most often used in the dye industry (Chung, 1978).

Vat dyes are a class of water-insoluble dyes that can be easily reduced (i.e., vatted) to a water-soluble and usually colorless leuco form in which they can readily impregnate fibers and textiles. Subsequent oxidation then produces the insoluble colored form that is remarkably "fast" to washing, light, and chemicals. The reducing agents are usually alkaline solutions of sodium hydrosulfite; oxidation takes place in the presence of air, perborate, dichromate, and other agents (Hawley, 1981). Vat dyes are used typically for cotton, wool, and cellulose acetate. Production of vat dyes in the United States totaled 14,000,000 kg (30.8 million pounds) in 1991 (USITC, 1993); these figures do not account for the "large" amounts extracted from botanical species containing naturally occurring anthraquinones used therapeutically and for other purposes.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

No information on the absorption, distribution, metabolism, and excretion of 1-amino-2,4-dibromoanthraquinone in experimental animals or in humans was found in a search of the available literature.

TOXICITY

No information on the toxicity of 1-amino-2,4-dibromoanthraquinone in experimental animals or in humans was found in a search of the available literature.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No information on the reproductive and developmental toxicity of 1-amino-2,4-dibromoanthraquinone in experimental animals or in humans was found in a search of the available literature.

CARCINOGENICITY

Experimental Animals

Chemicals belonging to the anthraquinone class of dyes are carcinogenic to rodents (IARC, 1987; Sendelbach, 1989) and consistently induce neoplasms of the liver (Huff *et al.*, 1991). However, each anthraquinone derivative appears to induce cancer in other organs or tissue sites as well (Huff *et al.*, 1991).

For the five anthraquinones evaluated and reported by NCI/NTP, the 2-year exposure concentrations in the feed varied from a low of 300 ppm (0.03%) for 2-methyl-1-nitroanthraquinone to a high of 20,000 ppm (2%) for 1-amino-2,4-dibromoanthraquinone (Table 1).

Humans

No information on the potential carcinogenicity of 1-amino-2,4-dibromoanthraquinone in humans was found in a search of the available literature.

GENETIC TOXICITY

All five anthraquinones evaluated and reported by NCI/NTP induced mutations in *Salmonella typhimurium* (Brown and Brown, 1976; Haworth *et al.*, 1983; Dunkel *et al.*, 1985; Zeiger *et al.*, 1988). Each also caused sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells (Anderson *et al.*, 1990; Loveday *et al.*, 1990; NTP, unpublished). S9 activation was not required for 1-amino-2,4-dibromoanthraquinone to produce these effects. The parent compound, anthraquinone, is also mutagenic in *S. typhimurium*; significant increases in mutant colonies were observed with strains TA98 and TA100 with and without S9 (Zeiger *et al.*, 1988). In addition, anthraquinone and 1-aminoanthraquinone (250 mg/kg) were reported to induce DNA strand breaks in liver and kidney tissue of male Swiss (CD-1®) mice following intraperitoneal injection (Cesarone *et al.*, 1982).

STUDY RATIONALE

The NCI selected and evaluated several of the anthraquinone-derived dyes for a class study to determine whether these dyes have any inherent potential for carcinogenicity in laboratory rodents and, if so, in humans as well. The first three studies were conducted with 2-aminoanthraquinone (NCI, 1978a), 1-amino-2-methylanthraquinone (NCI, 1978b), and 2-methyl-1-nitroanthraquinone (NCI, 1978c). A fourth substance, 1,4,5,8-tetraaminoanthraquinone (C.I. Disperse Blue 1) was selected and evaluated for carcinogenicity by the NTP (NTP, 1986a). This Technical Report addresses the fifth chemical in this class, 1-amino-2,4-dibromoanthraquinone. In addition, the parent chemical, anthraquinone, has been selected for study to complete the overall effort on these dyes.

Anthraquinone and the five substituted anthraquinones (Figure 1), representative of a large group of amino-, alkyl-, and nitro-, or halogen-containing anthraquinones, were chosen for toxicologic characterization and to establish some predictive structure-activity relationships that could be used on other dyes in this category rather than testing each and every one. Other chemical classes that have been likewise evaluated by the NCI/NTP to reduce the need for "one-by-one" testing include benzidine-based dyes (Morgan *et al.,* 1994), phthalates (Kluwe *et al.*, 1982; Huff and Kluwe, 1984; Kluwe *et al.*, 1985), benzene and metabolites (Huff, 1992), dioxins (Huff, 1992), anilines (Weisburger *et al.*, 1984; Lamb *et al.*, 1986), naturally occurring "gums" (Melnick *et al.*, 1983), chlorinated paraffins (Bucher *et al.*, 1987), 1,3-butadiene and derivatives (Melnick and Huff, 1992), pesticides (Yang *et al.*, 1989; Huff and Haseman, 1991), and penicillins and tetracyclines (Dunnick *et al.*, 1989; Dietz *et al.*, 1991).

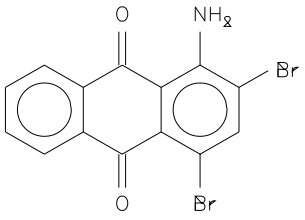
The bases for selection of anthraquinones (and other chemical classes as well) centered mainly on four criteria: 1) lack of available or adequate data on carcinogenicity, 2) magnitude of production and use

TABLE 1
Exposure Concentrations in the NCI/NTP 2-Year Feed Studies of Anthraquinone Derivatives[a]

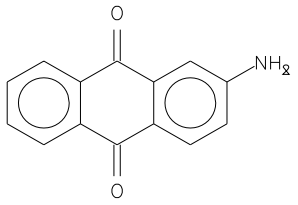
Anthraquinone Derivative	Low Dose (ppm)	High Dose (ppm)	Carcinogenic Response
Rats			
Male			
2-Aminoanthraquinone[b]	3,500	6,900	liver
1-Amino-2,4-dibromoanthraquinone	2,000	10,000	liver, large intestine, kidney, urinary bladder
1-Amino-2-methylanthraquinone[b]	1,000	2,000	liver, kidney
2-Methyl-1-nitroanthraquinone	600	1,200	liver, skin
1,4,5,8-Tetraaminoanthraquinone	1,250	5,000	urinary bladder, pancreas
Female			
2-Aminoanthraquinone[c]	2,000		
1-Amino-2,4-dibromoanthraquinone	2,000	10,000	liver, large intestine, kidney, urinary bladder
1-Amino-2-methylanthraquinone	1,000	2,000	liver
2-Methyl-1-nitroanthraquinone	600	1,200	skin
1,4,5,8-Tetraaminoanthraquinone	1,250	5,000	urinary bladder
Mice			
Male			
2-Aminoanthraquinone	5,000	10,000	liver
1-Amino-2,4-dibromoanthraquinone	10,000	20,000	liver, forestomach, lung
1-Amino-2-methylanthraquinone	600	–[d]	
2-Methyl-1-nitroanthraquinone	300	600	hemangiosarcoma
1,4,5,8-Tetraaminoanthraquinone	600	2,500	liver, lung[e]
Female			
2-Aminoanthraquinone	5,000	10,000	liver, lymphoma
1-Amino-2,4-dibromoanthraquinone	10,000	20,000	liver, forestomach, lung
1-Amino-2-methylanthraquinone	600	–[d]	liver
2-Methyl-1-nitroanthraquinone	300	600	hemangiosarcoma
1,4,5,8-Tetraaminoanthraquinone	600	2,500	

[a] Data from NCI, 1978a, 1978b, 1978c; NTP, 1986a
[b] Exposure concentrations in this study were time-weighted averages.
[c] Inadequate study
[d] Two dosage regimens were used, but the time-weighted average concentrations were the same.
[e] "Equivocal evidence" for both organs

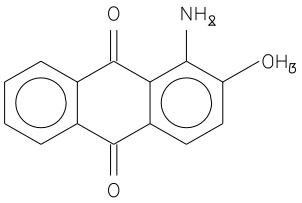
patterns, 3) awareness of potential and actual human exposure, and 4) representation of as broad a spec-trum of structural diversity within this class as possible. 1-Amino-2,4-dibromoanthraquinone was selected from a group of 36 environmentally significant aryl bromides. Because every other anthraquinone derivative tested so far for carcinogenic activity had been shown to be carcinogenic in rodents, 1-amino-2,4--dibromoanthraquinone was also expected to be carcinogenic in laboratory animals. Thus, the experimental design, while being consistent with a "core protocol" (Huff *et al.*, 1988), contains several modifications such as "stop-exposure" groups to better characterize this chemical. Additionally, chemical disposition studies were accomplished prior to the 2-year exposures to permit optimal selection of exposure concentrations for this water-insoluble dye. Because these chemicals may and often do contain considerable quantities of the parent chemical and other anthraquinone derivatives, an extensive chemical analysis was undertaken on these five chemicals to quantitate their purity and to identify the major impurities of 1-amino-2,4-dibromoanthraquinone (Arneson *et al.*, 1996).



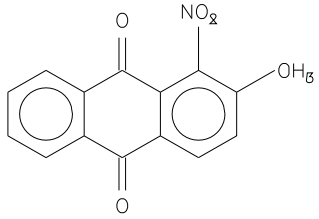
1-Amino-2,4-dibromoanthraquinone



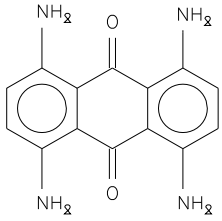
2-Aminoanthraquinone



1-Amino-2-methylanthraquinone



2-Methyl-1-nitroanthraquinone



1,4,5,8-Tetraaminoanthraquinone

FIGURE 1
Five Anthraquinone Derivatives Evaluated by the NCI/NTP

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

1-Amino-2,4-dibromoanthraquinone was obtained from American Color and Chemical Corporation (Charlotte, NC; lot 1076-C) and Mobay Corporation (Pittsburgh, PA). The second lot was procured from Mobay Corporation since American Color and Chemical Corporation had stopped production. Lot 1076-C was used in the 13-week studies and for 2 months of the 2-year studies. The lot from Mobay Corporation was assigned lot number M061583 and was used throughout the remainder of the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix I). Reports on analyses performed in support of the 1-amino-2,4-dibromoanthraquinone studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The two lots of the chemical, a reddish brown to orange powder, were identified as 1-amino-2,4-dibromoanthraquinone by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of each lot was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography, and high-performance liquid chromatography.

For lot 1076-C, elemental analyses for carbon, hydrogen, nitrogen, and bromine were in general agreement with theoretical values for 1-amino-2,4-dibromoanthraquinone. Karl Fischer water analysis indicated approximately 0.21% water. Thin-layer and high-performance liquid chromatography indicated a major peak and eight impurities. Five of the impurities had peak areas of less than 0.3%. The three major impurities were identified as anthraquinone, 1-amino-2-bromoanthraquinone, and 2-amino-1,3-dibromoanthraquinone. By high-performance liquid chromatography, anthraquinone was found to be present at a concentration of approximately 5.0%. 1-Amino-2-bromoanthraquinone and 2-amino-1,3-dibromoanthraquinone were found to be present at concentrations of approximately 4.3% and 2.2%, respectively. The overall purity of lot 1076-C was determined to be approximately 87%.

For lot M061583, elemental analyses for carbon, hydrogen, nitrogen, and bromine were in general agreement with theoretical values for 1-amino-2,4-dibromoanthraquinone. Karl Fischer water analysis indicated approximately 0.32% water. Thin-layer and high-performance liquid chromatography indicated a major peak and six impurities with the same retention times as found for lot 1076-C. A total impurity area of 3% of the total chromatographic peak area was found. The overall purity of lot M061583 was determined to be approximately 97%.

Stability studies performed using high-performance liquid chromatography indicated that 1-amino-2,4-dibromoanthraquinone, when stored protected from light, was stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the dark at 4° ± 3° C throughout the studies. During the 2-year studies, the stability of the bulk chemical was monitored periodically by the study laboratory using high-performance liquid chromatography; no degradation of 1-amino-2,4-dibromoanthraquinone was observed throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared weekly by mixing 1-amino-2,4-dibromoanthraquinone with feed (Table I1). Homogeneity and at least 2-week stability at 25° C were confirmed by the analytical chemistry laboratory using spectrophotometry and high-performance liquid chromatography, respectively. During the 13-week and 2-year feed studies, the dose formulations were stored in the dark for no longer than 2 weeks.

The study laboratory conducted periodic analyses of the 1-amino-2,4-dibromoanthraquinone dose formulations using a spectrophotometric method. For the 13-week feed studies, dose formulations were

analyzed at the beginning, midpoint, and end of the studies (Table I2). During the 2-year feed studies, the dose formulations were analyzed every 6 to 10 weeks (Table I3). All dose formulations for rats and mice were within 10% of the target concentrations during the 13-week and 2-year studies. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table I4).

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 1-amino-2,4-dibromoanthraquinone and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, MI). Upon receipt, the animals were 5 weeks old. The rats and mice were quarantined for 15 days before the studies began.

Groups of 10 male and 10 female rats and 10 male and 10 female mice received 0, 2,500, 5,000, 10,000, 25,000, or 50,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 13 weeks. Males and females were housed five per cage; water and feed were available *ad libitum*, and feed consumption was measured weekly. Clinical findings were recorded twice daily. Animals were weighed at study initiation, weekly, and at the end of the studies. Further details of study design and animal maintenance are summarized in Table 2.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus of all animals were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all animals that died prior to the end of the studies, control animals, and animals administered 50,000 ppm. Table 2 lists the tissues and organs examined.

2-YEAR STUDIES

Study Design

Groups of 70 male and 70 female rats received 0, 5,000, or 10,000 ppm 1-amino-2,4-dibromoanthraquinone in feed, and a group of 50 male and 50 female rats received 2,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 104 weeks. Ten male and 10 female rats from the 0, 2,000, 5,000, and 10,000 ppm groups were designated for an interim evaluation after 9 months. Ten male and 10 female rats from the 0 and 10,000 ppm groups were designated for an interim evaluation after 15 months. Groups of 60 male and 60 female mice received 0, 10,000, or 20,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 104 weeks. Ten male and 10 female mice per group were evaluated after 15 months.

Stop-Exposure Evaluation

Groups of 40 male and 40 female rats received 20,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 9 months, when 10 males and 10 females were evaluated. At 9 months, the dosed feed was replaced with a control diet for 10 male and 10 female rats, which were then necropsied and evaluated at 15 months. Twenty male and 20 female rats continued to receive 20,000 ppm 1-amino-2,4-dibromoanthraquinone in feed and were also evaluated at 15 months.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). Rats were quarantined 12 to 14 days (males) or 9 days (females) and mice were quarantined 12 days (males) or 15 days (females) before the beginning of the studies. Five male and five female rats and mice were selected and evaluated for evidence of parasites and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 6 weeks old at the beginning of the 2-year studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Males and females were housed five per cage. Feed and water were available *ad libitum*. Feed consumption was measured monthly (Appendix J). Cages and

racks were rotated every 2 weeks during the studies. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded weekly for 14 weeks then monthly until the end of the studies. Animals were weighed at study initiation, weekly for 14 weeks, and monthly thereafter.

Animals were killed with CO_2, and a complete necropsy was performed on all animals. The right kidney and liver of rats and mice were weighed at the interim evaluations (Appendix H). At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all tissues with grossly visible lesions. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscope 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 pathology quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated by the quality assessment laboratory. The quality assessment pathologist microscopically reviewed selected neoplasms or nonneoplastic lesions.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected slides and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chair to the PWG for review. Tissues examined included the adrenal cortex (female rats), ear (rats), kidney (rats), large intestine (rats), liver, lung (mice), skin (rats), forestomach, thyroid gland (rats), and urinary bladder (rats). The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of exposure groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis 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 found dead of other than natural causes or missexed animals were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, D5, E1, E3, F1, and F3 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, D3, E2a, E2b, F2a, and F2b) and of all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation or when neoplasms

had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, D3, E2a, E2b, F2a, and F2b also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

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 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 the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When 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, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of lesion-bearing animals.

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test, a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related 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-related trend (Dunnett's test). Prior to analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of lesion incidence in certain instances. 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.

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these

studies 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 a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of 1-amino-2,4-dibromoanthraquinone was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* cells and sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix G.

The genetic toxicity studies of 1-amino-2,4-dibromoanthraquinone are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other in vitro genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.,* 1987; Zeiger et al., 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive in vitro test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of 1-Amino-2,4-dibromoanthraquinone

13-Week Studies	2-Year Studies	Stop-Exposure Evaluation
Study Laboratory		
EG&G Mason Research Institute (Worcester, MA)	Same as 13-week studies	Same as 13-week studies
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Frederick Cancer Research Facility (Frederick, MD)	Same as 2-year studies
Time Held Before Studies		
15 days	Rats: 12-14 days (males) or 9 days (females) Mice: 12 days (males) or 15 days (females)	12-14 days (males) or 9 days (females)
Average Age When Studies Began		
7 weeks	6 weeks	6 weeks
Date of First Dose		
Rats: 22 April (males) or 29 April (females) 1982 Mice: 6 May (males) or 13 May (females) 1982	Rats: 13 July (males) or 4 August (females) 1983 Mice: 20 June (males) or 30 June (females) 1983	13 July (males) or 4 August (females) 1983
Duration of Dosing		
13 weeks	104 weeks	9-Month stop-exposure group: 39 weeks (males) or 40 weeks (females) followed by control feed for remainder of study 15-Month exposure group: 66 weeks
Date of Last Dose		
Rats: 21-23 July (males) or 28-30 July (females) 1982 Mice: 4-6 August (males) or 11-13 August (females) 1982	Rats: 3 July (males) or 25 July (females) 1985 Mice: 10 June (males) or 20 June (females) 1985	9-Month stop-exposure group: 10-13 April (males) or 8-10 May (females) 1984 15-Month exposure group: 10-12 October (males) or 7-9 November (females) 1984

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of 1-Amino-2,4-dibromoanthraquinone (continued)

13-Week Studies	2-Year Studies	Stop-Exposure Evaluation
Necropsy Dates		
Rats: 21-23 July (males) or 28-30 July (females) 1982 Mice: 4-6 August (males) or 11-13 August (females) 1982	Rats: 9-Month interim evaluation: 10-13 April (males) or 8-10 May (females) 1984 15-Month interim evaluation: 10-12 October (males) or 7-9 November (females) 1984 Terminal: 10-16 July (males) or 1-8 August (females) 1985 Mice: 15-Month interim evaluation: 19-21 September (males) or 26-28 September (females) 1984 Terminal: 17-20 June (males) or 27 June - 2 July (females) 1985	9-Month interim evaluation: 10-13 April (males) or 8-10 May (females) 1984 15-Month terminal: 10-12 October (males) or 7-9 November (females) 1984
Average Age at Necropsy		
20 weeks	9-Month interim evaluation: 45-46 weeks 15-Month interim evaluation: 72 weeks Terminal: 110-112 weeks	9-Month interim evaluation: 45-46 weeks 15-Month terminal: 72 weeks
Size of Study Groups		
10 males and 10 females	Rats: 70 males and 70 females in the 0, 5,000, and 10,000 ppm groups; 50 males and 50 females in the 2,000 ppm group Mice: 60 males and 60 females	40 males and 40 females
Method of Animal Distribution		
Animals were caged by 1-gram weight classes and then distributed into treatment groups such that within a given sex, all cage weights were approximately equal (± 2 g).	Animals were distributed randomly into groups of approximately equal initial mean body weight.	Same as 2-year studies
Animals per Cage		
5	5	5
Method of Animal Identification		
Ear punch	Ear punch	Ear punch

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of 1-Amino-2,4-dibromoanthraquinone (continued)

13-Week Studies	2-Year Studies	Stop-Exposure Evaluation
Diet		
NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), Available *ad libitum*, changed weekly	Same as 13-week studies	Same as 13-week studies
Water		
Tap water (City of Worcester) available *ad libitum* via automatic watering system (Edstrom Industries, Inc., Waterford, WI)	Same as 13-week studies	Same as 13-week studies
Cages		
Polycarbonate cage (Lab Products, Inc., Rochelle Park, NJ), changed twice weekly	Same as 13-week studies	Same as 13-week studies
Bedding		
Aspen Bed® heat-treated hardwood chips (American Excelsior, Baltimore, MD), changed twice weekly	Same as 13-week studies; BetaChips® hardwood chips (Northeastern Products, Warrensburg, NY) were used if necessary.	Same as 2-year studies
Cage Filters		
Nonwoven fiber filters (Lab Products, Rochelle Park, NJ; or Snow Filtration, Cincinnati, OH); changed every 2 weeks	Nonwoven fiber filters (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks	Same as 2-year studies
Racks		
Stainless steel racks (Lab Products, Inc., Maywood, NY), changed every 2 weeks	Same as 13-week studies	Same as 13-week studies
Animal Room Environment		
Average temperature: 22° to 26° C Relative humidity: 24% to 66% (rats), 28% to 66% (mice) Fluorescent light: 12 hours/day Room air: 12 to 15 changes/hour	Average temperature: 19° to 26° C Relative humidity: 16% to 76% Fluorescent light: 12 hours/day Room air: 12 to 15 changes/hour	Same as 2-year studies

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of 1-Amino-2,4-dibromoanthraquinone (continued)

13-Week Studies	2-Year Studies	Stop-Exposure Evaluation
Doses 0, 2,500, 5,000, 10,000, 25,000, or 50,000 ppm in feed, available *ad libitum*	Rats: 0, 2,000, 5,000, or 10,000 ppm in feed, available *ad libitum* Mice: 0, 10,000, or 20,000 ppm in feed, available *ad libitum*	20,000 ppm in feed, available *ad libitum*
Type and Frequency of Observation Observed twice daily; animals weighed initially, weekly, and at end of studies; clinical observations recorded twice daily; feed consumption measured weekly	Observed twice daily; animals weighed initially, weekly for 14 weeks, and monthly thereafter; clinical observations recorded weekly for 14 weeks, then monthly until end of the studies; feed consumption measured monthly	Same as 2-year studies
Method of Sacrifice CO_2 asphyxiation	CO_2 asphyxiation	CO_2 asphyxiation
Necropsy Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lungs, right testis, and thymus.	Necropsy was performed on all animals. Organs weighed at the 9- and 15-month interim evaluations were right kidney and liver.	Necropsy was performed on all animals. Organs weighed at 9 months and 15 months were right kidney and liver.
Histopathology Complete histopathologic examinations were performed on all animals that died during the study, control animals, and 50,000 ppm animals. In addition to tissue masses, gross lesions, and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidney, liver, spleen (rats), thymus (rats), and uterus (rats) of all other exposed animals were examined.	Complete histopathologic examinations were performed on all animals. In addition to tissue masses, gross lesions, and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathologic examinations were performed on all animals. In addition to tissue masses, gross lesions, and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

13-WEEK STUDY

One male (week 13) and one female (week 8) in the 50,000 ppm groups died during the study (Table 3). The deaths of one 5,000 ppm male (week 4) and two additional 50,000 ppm males (week 13) were not chemical related. The final mean body weights and body weight gains of all exposed rat groups were significantly lower than those of the controls. Feed consumption by all exposed groups was less than that by the controls throughout the study and generally decreased with increasing exposure concentration (Table 3). The greatest differences in feed consumption from that by the controls occurred in the 25,000 and 50,000 ppm males and females. Feed consumption by these groups ranged from 45% to 79% that by the controls at week 1 and from 64% to 82% that by the controls at week 13. Dietary levels of 2,500, 5,000, 10,000, 25,000, and 50,000 ppm delivered daily doses of approximately 150, 300, 620, 1,600, and 3,200 mg 1-amino-2,4-dibromoanthraquinone/kg body

TABLE 3
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone

Dose (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	180 ± 3	358 ± 3	179 ± 3		14.9	18.1
2,500	10/10	180 ± 3	325 ± 3**	145 ± 3**	91	14.3	16.7
5,000	9/10[d]	180 ± 3	328 ± 3**	148 ± 6**	92	13.9	17.1
10,000	10/10	181 ± 3	310 ± 3**	129 ± 3**	86	13.5	17.0
25,000	10/10	181 ± 3	232 ± 3**	52 ± 4**	65	11.7	14.9
50,000	7/10[e]	180 ± 3	164 ± 6**	-17 ± 6**	46	10.3	11.6
Female							
0	10/10	140 ± 2	211 ± 3	71 ± 2		13.0	15.7
2,500	10/10	140 ± 2	197 ± 3**	57 ± 3**	93	10.5	12.7
5,000	10/10	140 ± 2	188 ± 3**	47 ± 3**	89	10.2	12.1
10,000	10/10	140 ± 2	185 ± 2**	45 ± 2**	88	9.6	11.9
25,000	10/10	140 ± 2	159 ± 2**	19 ± 2**	75	7.0	10.6
50,000	9/10[f]	140 ± 2	130 ± 4**	-10 ± 4**	61	5.9	11.5

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 weeks/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.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Week of death: 4
[e] Week of death: 13, 13, 13 (2 were accidental deaths)
[f] Week of death: 8

weight to males and 170, 340, 660, 1,500, and 3,200 mg/kg to females. Pink-red staining of the fur and tail was observed in all exposed groups of rats. The bedding of all exposed groups except the 2,500 ppm groups was stained pink-red from day 2 of the study. Lethargy and emaciation were noted in all 50,000 ppm males. Female rats in the 25,000 and 50,000 ppm groups were lethargic and staggered, and 50,000 ppm females exhibited hunched posture.

The relative liver weights of exposed groups of males and the absolute and relative liver weights of exposed groups of females were significantly greater than those of the controls (Table H1). The absolute and relative thymus weights of exposed males and females were significantly lower than those of controls. The lower absolute brain, heart, kidney, lung, and testis weights of exposed male and female rats were probably related to the lower final mean body weights of these groups.

Observations at necropsy included red or pink staining of the gastrointestinal tract contents and/or mucosa, kidneys, and urine. In addition, regional lymph nodes and livers were dark in color, and capsular surfaces of the livers were granular in appearance. These findings were most common in the 25,000 and 50,000 ppm groups.

Chemical-related lesions were present in the liver, kidney, and spleen of male and female rats. In the liver, a spectrum of nonneoplastic degenerative and proliferative lesions occurred in males and females in the 25,000 and 50,000 ppm groups (Table 4). Hepatocellular cytomegaly (hypertrophy) was present in all rats in the 25,000 and 50,000 ppm groups and in most females in the 10,000 ppm group. This lesion consisted of enlarged hepatocytes with eosinophilic cytoplasm and marked variation in nuclear size. In the centrilobular areas of a few rats from exposed groups, there was a minimal to mild cytoplasmic vacuolation (vacuolar degeneration). The incidence of vacuolar degeneration was not dose-related, but at the higher exposure concentrations, minimal hepatocellular necrosis was sometimes associated with vacuolar change. Focal hepatocellular alterations including basophilic, eosinophilic, or clear cell foci were also present in the 25,000 and 50,000 ppm groups. In the periportal region of the hepatic lobules, there was an increased number of inflammatory cells around the bile ducts. Bile duct hyperplasia consisted of proliferation of oval cells in the periportal area as well as proliferation of larger bile ducts lined by hyperchromatic, pleomorphic biliary epithelium. Focal necrosis of biliary epithelium and acute inflammation (necrotizing cholangitis) in some hyperplastic bile ducts were associated with periportal fibrosis. The spectrum of proliferative bile duct lesions (hyperplasia, necrotizing cholangitis, and fibrosis) was morphologically consistent with the lesion described as cholangiofibrosis. A brown pigment was present in the cytoplasm of hepatocytes. The pigment was negative for iron, PAS, bile, and acid-fast staining; did not polarize light or fluoresce; and was considered to representl-amino-2,4-dibromoanthraquinone and/or its metabolites.

In the kidney of exposed groups of males and females, there were chemical-related increases in the incidences of a brown, granular pigment in the tubule epithelium (Table 4). This brown pigment had the same staining features as the pigment that was present in the liver. In both males and females, there were renal tubule cells with enlarged nuclei. In males, there was a hyaline droplet nephropathy characterized by an increase in eosinophilic protein droplets (hyaline droplet accumulation) in the cytoplasm of the renal tubule epithelium as well as in the lumen of the tubules. There was no evidence of increased severity of tubule regeneration in males or females.

Chemical-related effects in the spleen of all exposed groups of males and females consisted of a slight increase in the amount of hematopoiesis relative to that normally present in controls.

Other nonspecific changes included lymphoid depletion in the thymus and decreased uterus size. These findings were attributed to the markedly lower body weight gain in rats from the higher exposure groups.

Dose Selection Rationale: Based on chemical disposition studies, mean body weights, and chemical-related lesions of the liver, kidney, and spleen present mainly in the 25,000 and 50,000 ppm groups, exposure concentrations selected for the 2-year feed study of 1-amino-2,4-dibromoanthraquinone in rats were 0, 2,000, 5,000, and 10,000 ppm. Much of the differences in mean body weights recorded for the 13-week studies were more likely due to decreased feed palatability than to any overt toxicity. Nonetheless, if

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
Liver[a]	10	10	10	10	10	10
Basophilic Focus[b]	0	0	0	0	4* (1.5)[d]	9** (2.3)
Clear Cell Focus	0	0	0	0	6** (1.0)	0
Eosinophilic Focus	0	0	0	0	4* (1.5)	0
Cytomegaly	0	0	0	0	10** (3.2)	10** (4.0)
Bile Duct Hyperplasia	0	0	0	0	8** (2.3)	10** (3.1)
Inflammation	0	0	0	0	10** (2.1)	10** (3.0)
Fibrosis[c]	0	0	0	0	10** (1.9)	10** (3.1)
Necrotizing Cholangitis[c]	0	0	0	0	7** (1.3)	10** (2.8)
Vacuolar Degeneration[c]	0	0	4* (1.5)	5* (1.8)	3 (1.3)	4* (1.5)
Pigmentation	0	0	0	0	10** (1.5)	9** (1.0)
Kidney	10	10	10	10	10	10
Renal Tubule Pigmentation	0	10** (1.0)	9** (1.0)	10** (1.1)	10** (2.2)	10** (1.8)
Hyaline Droplet Accumulation	0	10** (1.7)	9** (1.7)	10** (2.0)	2 (1.0)	0
Female						
Liver	10	10	10	10	10	10
Basophilic Focus	0	0	0	0	1 (1.0)	9** (2.6)
Eosinophilic Focus	0	0	0	0	1 (1.0)	0
Cytomegaly	0	0	0	8** (1.0)	10** (2.2)	10** (4.0)
Bile Duct Hyperplasia	0	0	0	4* (1.0)	9** (1.6)	10** (2.4)
Inflammation	0	0	0	0	10** (1.6)	9** (2.3)
Fibrosis[c]	0	0	0	0	2 (2.0)	9** (2.7)
Necrotizing Cholangitis[c]	0	0	0	0	0	9** (2.6)
Vacuolar Degeneration[c]	0	0	0	1 (1.0)	2 (2.0)	8** (1.4)
Pigmentation	0	0	1 (1.0)	7** (1.0)	9** (1.2)	10** (1.5)
Kidney	10	10	10	10	10	10
Renal Tubule Pigmentation	0	10** (1.0)	9** (1.0)	10** (1.2)	10** (1.7)	10** (1.9)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Data from Fleischman *et al.*, 1986
[d] Average severity of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

exposure selection were based on mean body weights alone for male rats, the 10,000 ppm exposure concentration could have been considered slightly high. Moreover, considering the lack of liver toxicity at exposures of 10,000 ppm and below, this exposure concentration was predicted not to adversely affect the health or survival of these animals. Higher exposure concentrations (20,000 ppm) were chosen for the start-stop, progression/regression experiments (stop-exposure evaluation).

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves in Figure 2. Survival of male and female rats in the 10,000 ppm groups was significantly lower than that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of exposed male and female rats were lower than those of the controls after week 2 (Tables 6 and 7, Figure 3). Final mean body weights of exposed males were 14% to 30% lower than that of the controls; final mean body weights of exposed females were 20% to 46% lower than that of the controls. Feed consumption by exposed males and females was similar among exposed groups and was slightly lower than that by the controls (Tables J3 and J4). Dietary levels of 2,000, 5,000, and 10,000 ppm delivered average daily doses of approximately 90, 240, and 490 mg 1-amino-2,4-dibromoanthraquinone/kg body weight to males and 110, 285, and 600 mg/kg to females. Discoloration of the fur and urine was evident in all exposed groups as early as day 8 and was observed throughout the study. Emaciation occurred in a dose-related manner in male and female rats and occurred in over 50% of the rats exposed to 10,000 ppm.

TABLE 5
Survival of Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male				
Animals initially in study	70	50	70	70
9-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	0	0	10
Moribund	19	15	34	33
Natural deaths	5	1	5	7
Animals surviving to study termination	26[e]	24	21	10
Percent probability of survival at end of study[b]	53	60	35	20
Mean survival (days)[c]	586	618	615	547
Survival analyses[d]	P<0.001	P=0.467N	P=0.141	P<0.001
Female				
Animals initially in study	70	50	70	70
9-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	0	0	10
Missexed[a]	0	0	0	1
Moribund	8	5	15	29
Natural deaths	4	3	7	8
Animals surviving to study termination	38[f]	32	38	12
Percent probability of survival at end of study	76	80	63	25
Mean survival (days)	610	626	643	569
Survival analyses	P<0.001	P=0.857N	P=0.216	P<0.001

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and 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 lower mortality in an exposure group is indicated by N.
[e] Includes three males that died during the last week of the study.
[f] Includes one female that died during the last week of the study.

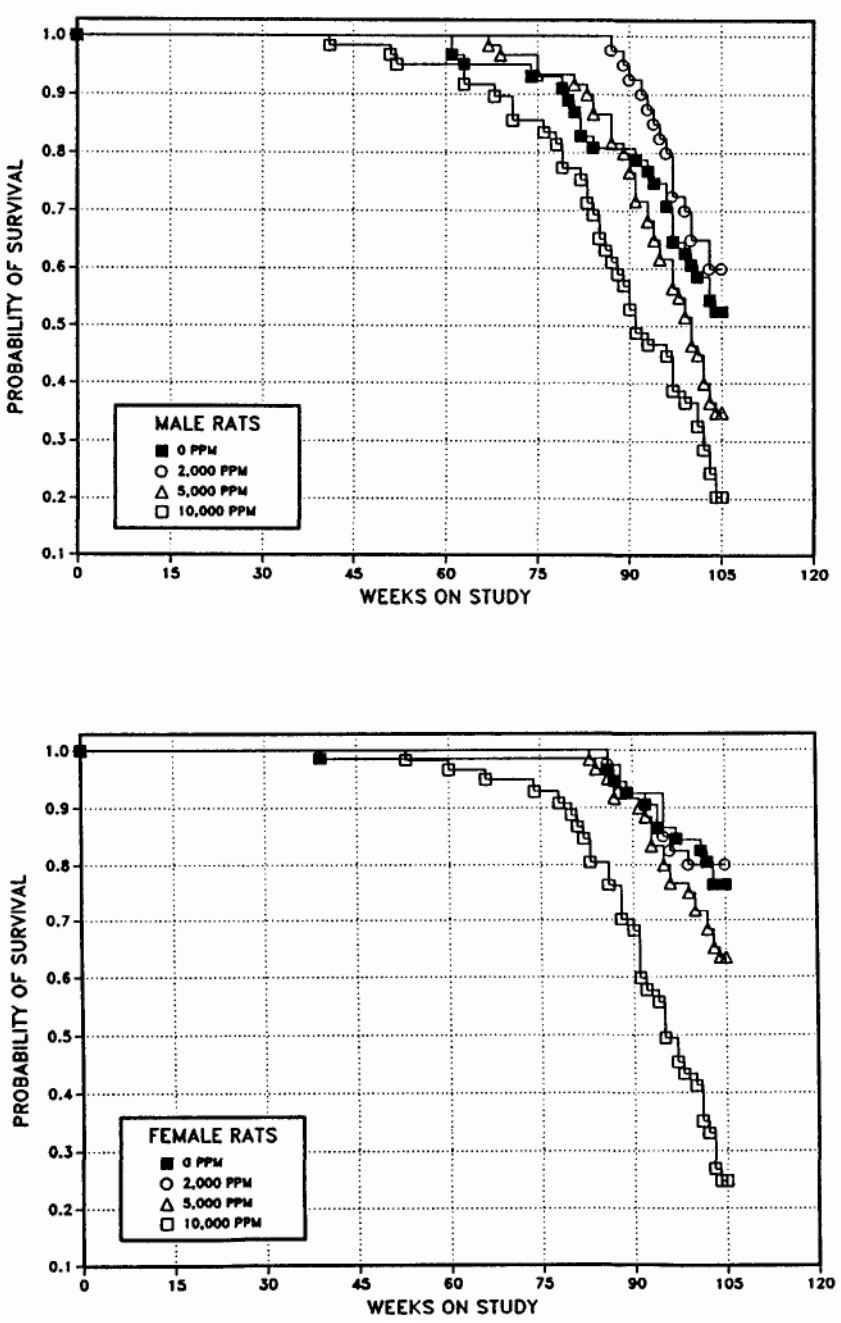


FIGURE 2
Kaplan-Meier Survival Curves for Rats Administered l-Amino-2,4-dibromoanthraquinone in Feed for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Weeks on Study	0 ppm		2,000 ppm			5,000 ppm			10,000 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	139	70	136	98	50	136	98	70	134	97	70
2	161	70	165	103	50	164	102	70	155	97	70
3	206	70	203	99	50	198	96	70	184	89	70
4	235	70	225	96	50	222	95	70	204	87	70
5	240	70	233	97	50	230	96	70	215	90	70
6	269	70	258	96	50	257	96	70	237	88	70
7	287	70	271	94	50	269	94	70	248	86	70
8	302	70	285	94	50	280	93	70	260	86	70
9	312	70	295	95	50	287	92	70	268	86	70
10	325	70	308	95	50	303	93	70	281	86	70
11	333	70	316	95	50	313	94	70	293	88	70
12	338	70	323	96	50	318	94	70	300	89	70
13	332	70	321	97	50	309	93	70	298	90	70
14	356	70	339	95	50	330	93	70	314	88	70
17	387	70	363	94	50	350	91	70	335	87	70
21	406	70	382	94	50	368	91	70	356	88	70
25	423	70	398	94	50	383	90	70	369	87	70
29	435	70	403	93	50	384	88	70	376	86	70
33	445	70	413	93	50	398	89	70	383	86	70
37	453	70	420	93	50	401	89	70	388	86	70
41[a]	468	60	433	92	40	415	89	60	397	85	59
45	473	60	440	93	40	424	90	60	403	85	59
49	479	60	452	94	40	428	89	60	409	84	57
53	489	60	457	93	40	439	90	60	415	85	57
57	486	60	453	93	40	430	88	60	409	84	57
61	484	59	445	92	40	430	89	60	405	84	57
65	484	57	448	93	40	426	88	60	408	84	55
69[a]	479	47	442	92	40	417	87	59	398	83	44
72	472	46	429	91	40	407	86	58	389	82	42
77	460	46	412	90	40	392	85	56	381	83	41
80	462	44	418	91	40	390	84	56	373	81	38
85	467	40	419	90	40	388	83	52	365	78	34
89	455	40	405	89	39	378	83	49	357	79	29
93	445	39	396	89	36	363	82	43	347	78	24
97	432	35	380	88	32	355	82	37	332	77	22
101	422	30	380	90	26	343	81	28	301	71	18
103	406	29	349	86	24	341	84	22	283	70	13
Mean for weeks											
1-13	268		257	96		253	94		237	89	
14-52		433		404	93		388	90		373	86
53-103	460		417	91		393	85		369	80	

[a] Interim evaluations occurred during week 39 for all groups and week 66 for the 0 and 10,000 ppm groups.

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Weeks on Study	0 ppm		2,000 ppm			5,000 ppm			10,000 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	93	70	93	100	50	94	101	70	94	101	70
2	114	70	110	96	50	107	94	70	102	90	70
3	133	70	128	96	50	121	91	70	116	87	70
4	147	70	141	96	50	136	93	70	128	87	70
5	157	70	151	96	50	146	93	70	137	87	70
6	166	70	159	96	50	152	91	70	145	87	70
7	173	70	169	97	50	161	93	70	150	87	69
8	180	70	174	97	50	167	93	70	158	88	69
9	186	70	178	96	50	173	93	70	167	90	69
10	191	70	185	97	50	179	94	70	173	90	69
11	196	70	189	96	50	184	94	70	177	90	69
12	203	70	194	95	50	188	93	70	181	89	69
13	208	70	195	94	50	192	93	70	185	89	69
14	212	70	201	95	50	196	93	70	189	89	69
17	222	70	209	94	50	205	92	70	200	90	69
21	228	70	216	95	50	213	93	70	205	90	69
25	237	70	219	93	50	216	91	70	208	88	69
29	246	70	223	91	50	219	89	70	212	86	69
33	251	70	227	90	50	222	88	70	213	85	69
37	258	70	233	90	50	230	89	70	218	85	69
41[a]	265	59	233	88	40	227	86	60	217	82	59
45	272	59	239	88	40	231	85	60	221	81	59
49	284	59	246	87	40	237	84	60	227	80	59
53	299	59	257	86	40	245	82	60	232	78	59
57	311	59	264	85	40	249	80	60	238	77	58
61	315	59	267	85	40	251	80	60	238	76	57
65	328	59	275	84	40	257	78	60	242	74	57
68[a]	333	49	277	83	40	257	77	60	241	72	47
73	343	49	286	83	40	263	77	60	245	71	46
77	347	49	289	83	40	269	78	60	243	70	45
81	351	49	296	84	40	270	77	60	239	68	43
85	354	49	295	83	40	268	76	58	234	66	39
89	354	47	298	84	37	262	74	55	229	65	34
93	356	45	299	84	37	251	71	53	224	63	28
97	358	43	298	83	33	250	70	46	213	60	23
100	361	42	293	81	32	243	67	43	202	56	20
103	362	38	290	80	32	234	65	39	194	54	13
Mean for weeks											
1-13	165		159	96		154	93		147	89	
14-52	248		225	91		220	89		211	85	
53-103	341		285	84		255	75		230	67	

[a] Interim evaluations occurred during week 40 for all groups and week 66 for the 0 and 10,000 ppm groups.

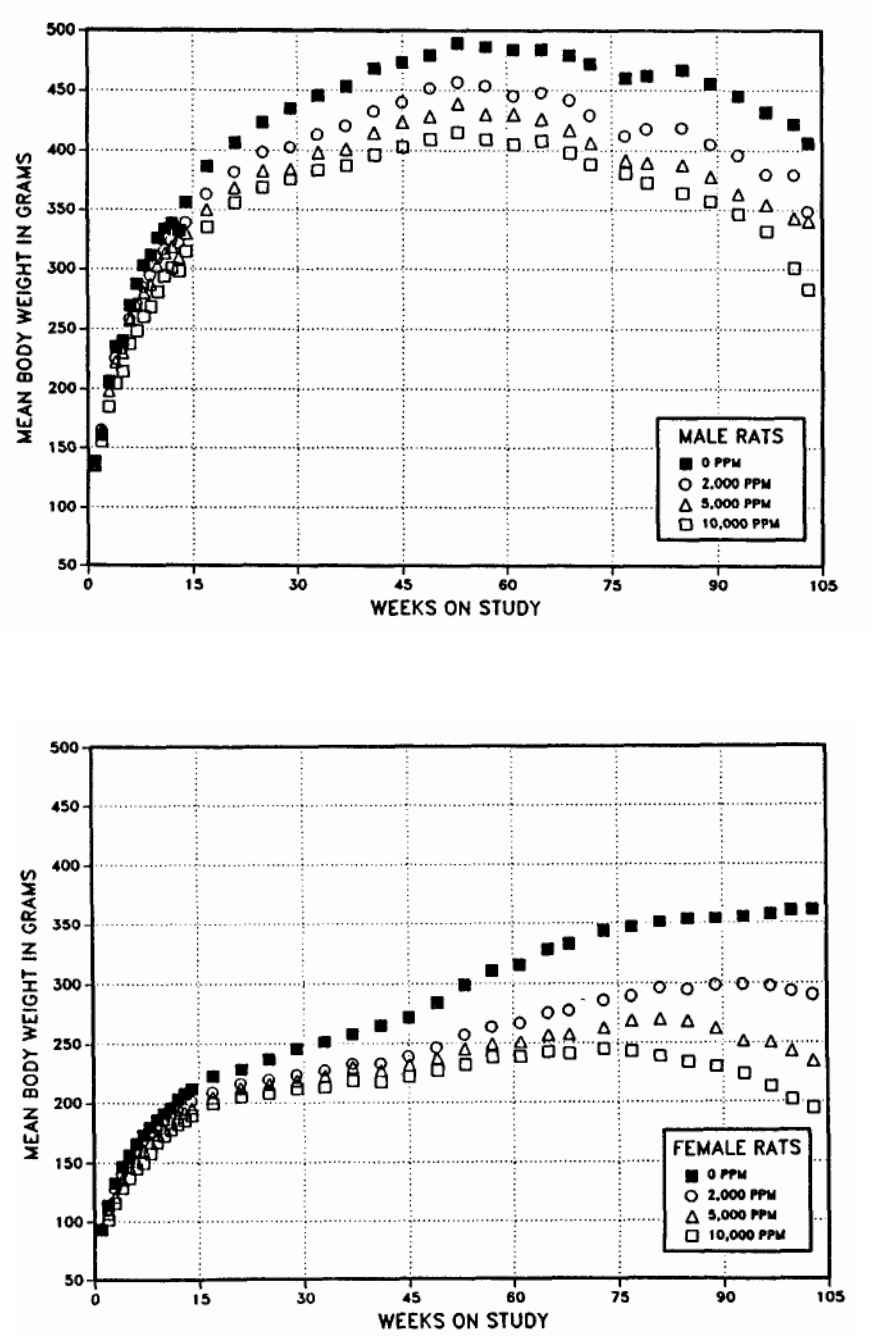


FIGURE 3
Growth Curves for Rats Administered 1-Amino-2,4-dibromoanthraquinone in Feed for 2 Years

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia; neoplasms of the liver, large intestine, kidney, urinary bladder, and other organs; and nonneoplastic lesions of the liver, kidney, urinary bladder, forestomach, and seminal vesicles of rats. 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 exposure group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Liver: At the 9-month interim evaluation, the absolute and relative liver weights of exposed groups of males and females were significantly greater than those of the controls (Table H2). One hepatocellular adenoma was observed in a 5,000 ppm male at 9 months (Tables 8 and A1). Incidences of foci of hepatocellular alteration were increased in males in the 10,000 ppm group, and a minimal accumulation of pigment in hepatocytes was present in males and females from the 10,000 ppm groups and in females from the 5,000 ppm group (Tables 8, A5, and B5). At the 15-month interim evaluation, the absolute and relative liver weights of exposed groups of females were significantly greater than those of the controls (Table H3). Incidences of single and multiple hepatocellular adenomas and carcinomas were increased at 15 months in 10,000 ppm males and females (Tables 8, A1, and B1). Incidences of foci of hepatocellular alteration and accumulation of pigment in hepatocytes were also increased in exposed groups of males and females (Tables 8, A5, and B5).

At the end of the 2-year study, the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) were significantly increased in all exposed groups of males and females (Tables 8, A3, and B3).

The incidences of multiple hepatocellular adenomas and multiple hepatocellular carcinomas in exposed male and female groups were greater than those of the controls (Tables 8, A1, and B1). Incidences of hepatocellular adenoma or carcinoma (combined) in all exposed groups of males and females exceeded the NTP historical ranges (males: 0%-10%; females: 0%-6%) for feed study controls (Tables 8, A4a, and B4a). The majority of the benign and malignant liver neoplasms consisted of well-differentiated neoplastic hepatocytes with cellular atypia and increased numbers of mitoses. Carcinomas had trabecular, glandular, or solid growth patterns (Plate 1) with areas of necrosis, cavitation, and fibrosis. Metastases were common in the lungs (Plates 2 and 3), but metastatic foci were also present in the stomach, pancreas, adrenal gland, lymph node, and spleen.

The incidences of single and multiple hepatocholangiocarcinoma were significantly increased in 5,000 ppm males and females and in 10,000 ppm females (Tables 8, A3, and B3). These neoplasms consisted of a mixture of malignant hepatocytes and well-differentiated cuboidal epithelium forming distinct ductular structures (Plate 4). Both hepatocellular and biliary components of this neoplasm were present in metastatic foci. In addition, several other benign (cholangioma and hepatocholangioma) and malignant (cholangiocarcinoma) liver neoplasms occurred only in exposed groups of males and females (Tables 8, A1, and B1).

During the 2-year study, the incidences of pigmentation and foci of hepatocellular alteration (clear cell, basophilic, and eosinophilic) were increased in exposed groups of males and females (Tables 8, A5, and B5). Cells in some foci had intensely eosinophilic cytoplasm and hepatocellular atypia similar to the appearance of cells in the hepatocellular neoplasms. The pigment was considered to be 1-amino-2,4-dibromoanthraquinone or a metabolite based on the results of the histochemical procedures performed during the 13-week study and the 15-month interim evaluation.

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male				
9-Month Interim Evaluation				
Number Examined	10	10	10	10
Basophilic Focus[a]	0	0	1 (1.0)[b]	1 (1.0)
Clear Cell Focus	0	0	0	4* (1.0)
Eosinophilic Focus	0	0	0	1 (1.0)
Pigmentation	0	1 (1.0)	0	6** (1.0)
Hepatocellular Adenoma	0	0	1	0
15-Month Interim Evaluation				
Number Examined	10	-[c]	-	10
Basophilic Focus	1 (1.0)			5 (1.0)
Clear Cell Focus	0			7** (1.0)
Eosinophilic Focus	1 (1.0)			0
Pigmentation	0			10** (1.0)
Hepatocellular Adenoma (Multiple)	0			2
Hepatocellular Adenoma (Single or Multiple)	0			4*
Hepatocellular Carcinoma (Multiple)	0			3
Hepatocellular Carcinoma (Single or Multiple)	0			7**
Hepatocellular Adenoma or Carcinoma	0			10**
2-Year Study				
Number Examined	50	40	59	50
Basophilic Focus	9 (1.1)	12 (1.7)	24** (1.8)	22** (1.5)
Clear Cell Focus	3 (1.0)	26** (1.8)	39** (1.8)	27** (1.8)
Eosinophilic Focus	1 (1.0)	13** (2.9)	14** (2.1)	6 (2.6)
Pigmentation	3 (1.0)	19** (1.1)	48** (1.1)	39** (1.1)
Hepatocellular Adenoma (Multiple)	0	10**	23**	24**
Hepatocellular Adenoma (Single or Multiple)				
Overall rate[d]	1/50 (2%)	20/40 (50%)	40/59 (68%)	34/50 (68%)
Terminal rate[e]	1/26 (4%)	16/24 (67%)	18/21 (86%)	9/10 (90%)
Adjusted rate[f]	3.8%	71.3%	92.3%	97.0%
First incidence (days)	729 (T)	675	521	435
Logistic regression test[g]	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma (Multiple)	0	1	43**	37**
Hepatocellular Carcinoma (Single or Multiple)				
Overall rate	1/50 (2%)	12/40 (30%)	55/59 (93%)	46/50 (92%)
Terminal rate	0/26 (0%)	9/24 (38%)	21/21 (100%)	10/10 (100%)
Adjusted rate	2.7%	43.5%	100.0%	100.0%
First incidence (days)	666	650	465	436
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001

(continued)

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male (continued)				
2-Year Study (continued)				
Hepatocellular Adenoma or Carcinoma[h]				
Overall rate	2/50 (4%)	25/40 (63%)	57/59 (97%)	47/50 (94%)
Terminal rate	1/26 (4%)	19/24 (79%)	21/21 (100%)	10/10 (100%)
Adjusted rate	6.4%	83.1%	100.0%	100.0%
First incidence (days)	666	650	465	435
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Number Examined	50	40	59	50
Hepatocholangioma	0	0	1	1
Hepatocholangiocarcinoma	0	0	6*	2
Cholangioma	0	0	2	0
Cholangiocarcinoma	0	0	0	1
Female				
9-Month Interim Evaluation				
Number Examined	10	10	10	10
Basophilic Focus	1 (1.0)	0	0	1 (1.0)
Clear Cell Focus	0	0	0	1 (1.0)
Pigmentation	0	2 (1.0)	6** (1.0)	6** (1.0)
15-Month Interim Evaluation				
Number Examined	10	-	-	10
Basophilic Focus	8 (1.0)			9 (1.4)
Clear Cell Focus	0			5* (1.6)
Pigmentation	1 (1.0)			10** (1.1)
Hepatocellular Adenoma (Multiple)	0			5*
Hepatocellular Adenoma (Single or Multiple)	0			8**
Hepatocellular Carcinoma (Multiple)	0			3
Hepatocellular Carcinoma (Single or Multiple)	0			6**
Hepatocellular Adenoma or Carcinoma	0			9**
2-Year Study				
Number Examined	50	40	60	48
Basophilic Focus	39 (1.3)	15** (1.6)	22** (1.7)	16** (1.4)
Clear Cell Focus	3 (1.3)	28** (1.6)	39** (2.0)	17** (1.6)
Eosinophilic Focus	7 (1.4)	23** (2.0)	12 (2.5)	1 (4.0)
Pigmentation	1 (1.0)	19** (1.1)	51** (1.4)	45** (1.1)

(continued)

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Female (continued)				
2-Year Study (continued)				
Number Examined	50	40	60	48
Hepatocellular Adenoma (Multiple)	0	18**	39**	22**
Hepatocellular Adenoma (Single or Multiple)				
Overall rate	0/50 (0%)	28/40 (70%)	47/60 (78%)	29/48 (60%)
Terminal rate	0/38 (0%)	23/32 (72%)	29/38 (76%)	8/12 (67%)
Adjusted rate	0.0%	75.5%	83.7%	83.6%
First incidence (days)_	-[i]	600	575	418
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma (Multiple)	0	7**	51**	41**
Hepatocellular Carcinoma (Single or Multiple)				
Overall rate	0/50 (0%)	12/40 (30%)	57/60 (95%)	45/48 (94%)
Terminal rate	0/38 (0%)	12/32 (38%)	37/38 (97%)	12/12 (100%)
Adjusted rate	0.0%	37.5%	98.3%	100.0%
First incidence (days)	-	729 (T)	575	460
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma or Carcinoma[j]				
Overall rate	0/50 (0%)	33/40 (83%)	59/60 (98%)	47/48 (98%)
Terminal rate	0/38 (0%)	28/32 (88%)	38/38 (100%)	12/12 (100%)
Adjusted rate	0.0%	89.1%	100.0%	100.0%
First incidence (days)	-	600	575	418
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocholangioma	0	0	2	0
Hepatocholangiocarcinoma	0	0	11**	13**
Cholangioma	0	0	0	1

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (9-month and 15-month interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Liver not microscopically examined in this group
[d] Number of animals with neoplasm per number of animals with liver examined microscopically
[e] Observed incidence in animals surviving until the end of the study
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[h] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 45/1,350 (3.3% ± 3.6%); range, 0%-10%
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 9/1,351 (0.7% ± 1.5%); range, 0%-6%

Large Intestine: Adenomatous polyps (adenomas) were observed in the large intestine of 10,000 ppm males and females at the 15-month interim evaluation (Tables 9, A1, and B1).

At 2 years, the incidences of adenomatous polyps (adenomas) in the rectum were significantly increased in all exposed groups of males and females (Tables 9, A3, and B3). The incidence of carcinoma of the

TABLE 9
Incidences of Neoplasms of the Large Intestine in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male				
15-Month Interim Evaluation				
Rectum[a]	9	-[c]	-	10
Adenomatous Polyp (Adenoma)[b]	0			6**
2-Year Study				
Colon				
Adenomatous Polyp (Adenoma)				
Overall rate[d]	0/50 (0%)	1/40 (3%)	1/59 (2%)	3/50 (6%)
Terminal rate[e]	0/26 (0%)	1/24 (4%)	0/21 (0%)	1/10 (10%)
Adjusted rate[f]	0.0%	4.2%	4.3%	19.9%
First incidence (days)	-[h]	729 (T)	720	590
Logistic regression test[g]	P=0.027	P=0.484	P=0.494	P=0.081
Carcinoma[i]				
Overall rate	0/50 (0%)	0/40 (0%)	1/59 (2%)	4/50 (8%)
Terminal rate	0/26 (0%)	0/24 (0%)	1/21 (5%)	0/10 (0%)
Adjusted rate	0.0%	0.0%	4.8%	20.4%
First incidence (days)	-	-	729 (T)	590
Logistic regression test P=0.003	-	P=0.457	P=0.046	
Rectum				
Adenomatous Polyp (Adenoma)				
Overall rate	0/50 (0%)	13/40 (33%)	51/59 (86%)	40/50 (80%)
Terminal rate	0/26 (0%)	9/24 (38%)	21/21 (100%)	10/10 (100%)
Adjusted rate	0.0%	45.8%	100.0%	100.0%
First incidence (days)	-	659	478	352
Logistic regression test P<0.001	P<0.001	P<0.001	P<0.001	
Carcinoma[i]				
Overall rate	0/50 (0%)	1/40 (3%)	10/59 (17%)	15/50 (30%)
Terminal rate	0/26 (0%)	0/24 (0%)	5/21 (24%)	4/10 (40%)
Adjusted rate	0.0%	3.8%	32.4%	63.0%
First incidence (days)	-	718	608	493
Logistic regression test P<0.001	P=0.480	P=0.003	P<0.001	
Large Intestine (All Sites)	50	40	59	50
Adenomatous Polyp (Adenoma) (Multiple)	0	1	34**	32**
Adenomatous Polyp (Adenoma) (Single or Multiple)	0	13**	51**	40**
Carcinoma (Multiple)	0	0	0	3
Carcinoma (Single or Multiple)	0	1	11**	17**

(continued)

TABLE 9
Incidences of Neoplasms of the Large Intestine in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Female				
15-Month Interim Evaluation				
Rectum	10			10
Adenomatous Polyp (Adenoma)	0	-	-	2
2-Year Study				
Colon	50	40	60	49
Adenomatous Polyp (Adenoma)	0	1	2	2
Carcinoma[j]	0	1	2	1
Rectum				
Adenomatous Polyp (Adenoma)				
Overall rate	0/50 (0%)	27/40 (68%)	53/60 (88%)	43/49 (88%)
Terminal rate	0/38 (0%)	23/32 (72%)	38/38 (100%)	12/12 (100%)
Adjusted rate	0.0%	75.0%	100.0%	100.0%
First incidence (days)	-	616	582	512
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Carcinoma[j]				
Overall rate	0/50 (0%)	1/40 (3%)	19/60 (32%)	7/49 (14%)
Terminal rate	0/38 (0%)	1/32 (3%)	13/38 (34%)	4/12 (33%)
Adjusted rate	0.0%	3.1%	41.7%	41.9%
First incidence (days)	-	729 (T)	606	625
Logistic regression test	P<0.001	P=0.466	P<0.001	P=0.001
Large Intestine (All Sites)	50	40	60	49
Adenomatous Polyp (Adenoma) (Multiple)	0	18**	46**	32**
Adenomatous Polyp (Adenoma) (Single or Multiple)	0	28**	53**	43**
Carcinoma (Multiple)	0	1	1	1
Carcinoma (Single or Multiple)	0	2	21**	8**

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
(T)Terminal sacrifice
[a] Number of animals with large intestine examined microscopically
[b] Number of animals with lesion
[c] Large intestine not microscopically examined in this group
[d] Number of animals with neoplasm per number of animals necropsied
[e] Observed incidence in animals surviving until the end of the study
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 1/1,353 (0.1% ± 0.4%); range, 0%-2% (includes all carcinomas of the large intestine)
[j] Historical incidence: 0/1,351 (includes all carcinomas of the large intestine)

colon was significantly increased in 10,000 ppm males, and the incidences of rectal carcinoma were significantly increased in 5,000 and 10,000 ppm males and females (Tables 9, A3, and B3). The intestinal neoplasms that occurred in the distal colon and rectum of rats were morphologically similar.

Adenomatous polyps (adenomas) consisted of pedunculated, exophytic masses (Plate 5) of well-differentiated, columnar epithelium with prominent, hyperchromatic nuclei. Carcinoma (adenocarcinoma) was generally similar to adenoma, except that invasion of the stromal stalk of the neoplasm and extension into the submucosa, and occasionally into the muscular wall, were evident microscopically. In the malignant neoplasms, irregular glandular structures or cords of atypical epithelial cells were present in the submucosa (Plate 6) and were frequently associated with a scirrhous response. In males, metastatic colon carcinoma was observed in the lung and mesenteric lymph nodes, and metastatic rectal carcinoma was observed in the lumbar lymph nodes and pancreas (Table A1). Incidences of carcinoma (colon and rectum combined) in exposed groups of males and females exceeded the NTP historical ranges (males: 0%-2%; females: 0%) for feed study controls (Tables 9, A4b, and B4b).

Kidney: At the 9-month interim evaluation, the relative kidney weights of exposed groups of males and females were significantly greater than those of the controls (Table H2). Pigmentation and hyaline droplet accumulation were present in the kidneys of all exposed males (Tables 10 and A5). The sizes of some renal tubule nuclei were minimally increased in males and females from all exposure groups, and the severity of the nephropathy (tubule epithelial regeneration, mononuclear inflammation, and renal tubule dilation with protein casts) was slightly more severe than that observed in the controls (Table 10). At the 15-month interim evaluation, the relative kidney weights of 10,000 ppm males and females were significantly greater than those of the controls (Table H3). The severity of nephropathy was increased in 10,000 ppm males and females compared to controls (Table 10). This was characterized by an increase in the foci of tubule epithelial regeneration; nuclear enlargement in some tubule epithelium, similar to that in the 13-week studies and at the 9-month interim evaluation, was also present. At 15 months in the 10,000 ppm groups, pigmentation of renal tubule epithelium was present in all rats; renal tubule epithelial hyperplasia was observed in two males and three females; and adenomas were observed in two males (Tables 10, A1, A5, and B5).

At 2 years, there was a significant dose-related increase in the incidences of renal tubule adenoma in exposed groups of males and females (Tables 10, A3, and B3). Multiple adenomas were observed in all exposed groups of males and in the 5,000 and 10,000 ppm females. Adenomas were expansile lesions involving one or more adjacent tubules and were generally five or more times the diameter of the normal renal tubule. The cells within the adenomas were generally similar in morphology to those in the focal hyperplastic lesions. Carcinomas were larger than adenomas and frequently had more cellular atypia, necrosis, and local invasion. One carcinoma in a male rat metastasized to the lung, and one in a female rat metastasized to the adrenal gland. Renal tubule carcinomas occurred in two 5,000 ppm males, one 10,000 ppm male, and two 10,000 ppm females. The combined incidences of renal tubule adenoma or carcinoma were significantly increased in exposed males and females and exceeded the NTP historical ranges (males: 0%-6%; females: 0%-2%) for feed study controls (Tables 10, A4c, and B4c).

Incidences of renal tubule hyperplasia were significantly increased in exposed males and females (Tables 10, A5, and B5). Hyperplasia consisted of a tubule lined by two or more layers of renal tubule epithelium; these were most often located in the cortex or outer stripe of the outer medulla. Foci of hyperplasia were distinguished from the more basophilic foci of tubule epithelial regeneration typically associated with nephropathy. There was no clear dose-related increase in the incidence or severity of nephropathy in rats at 2 years (Table 10). The incidences and severity of transitional cell hyperplasia in the renal pelvis were increased in exposed groups of males and females (Tables 10, A5, and B5); there were no increases in the incidences of transitional cell papilloma or carcinoma of the renal pelvis (Tables 10, A1, and B1). The incidence of a reddish brown pigment within the renal tubule epithelium and lumina of exposed rats was increased at the 9- and 15-month interim evaluations and at 2 years. The pigment was characterized in the 13-week study and at the 15-month interim evaluation as PAS-negative; resistant to digestion by diastase; isotropic; and negative for melanin, hemosiderin, hematoidin, bile, lipofuscin, or ceroid staining methods. The pigment was presumed to be 1-amino-2,4-dibromoanthraquinone or one of its metabolites.

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male				
9-Month Interim Evaluation				
Number Examined	10	10	10	10
Renal Tubule Hyaline Droplet Accumulation[a]	0	10** (2.0)[b]	10** (2.0)	10** (1.9)
Renal Tubule Pigmentation	0	10** (1.1)	10** (1.4)	10** (1.9)
15-Month Interim Evaluation				
Number Examined	10	–[c]	–	10
Nephropathy	10 (2.0)			10 (2.5)
Renal Tubule Hyperplasia	0			2 (1.0)
Renal Tubule Pigmentation	0			10** (2.0)
Transitional Cell Hyperplasia	0			4* (1.3)
Renal Tubule Adenoma	0			2
2-Year Study				
Number Examined	50	40	59	50
Nephropathy	50 (2.9)	40 (3.6)	59 (2.9)	49 (2.7)
Renal Tubule Hyperplasia	9 (2.2)	30** (2.9)	25** (2.4)	19** (2.9)
Renal Tubule Pigmentation	5 (2.0)	40** (1.9)	58** (2.0)	49** (1.9)
Transitional Cell Hyperplasia	30 (1.4)	40** (2.1)	51** (1.9)	35* (1.6)
Transitional Cell Papilloma	0	0	1	0
Renal Tubule Adenoma (Multiple)	0	4*	4	5*
Renal Tubule Adenoma (Single or Multiple)				
Overall rate[d]	2/50 (4%)	10/40 (25%)	11/59 (19%)	14/50 (28%)
Terminal rate[e]	2/26 (8%)	6/24 (25%)	4/21 (19%)	5/10 (50%)
Adjusted rate[f]	7.7%	33.6%	34.6%	68.3%
First incidence (days)	729 (T)	618	636	588
Logistic regression test[g]	P<0.001	P=0.007	P=0.014	P<0.001
Renal Tubule Carcinoma	0	0	2	1
Renal Tubule Adenoma or Carcinoma[h]				
Overall rate	2/50 (4%)	10/40 (25%)	13/59 (22%)	15/50 (30%)
Terminal rate	2/26 (8%)	6/24 (25%)	4/21 (19%)	5/10 (50%)
Adjusted rate	7.7%	33.6%	39.4%	69.1%
First incidence (days)	729 (T)	618	636	497
Logistic regression test	P<0.001	P=0.007	P=0.005	P<0.001

(continued)

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Female				
15-Month Interim Evaluation				
Number Examined	10	-	-	10
Nephropathy	10 (1.7)			10 (2.5)
Renal Tubule Hyperplasia	0			3 (1.0)
Renal Tubule Pigmentation	0			10** (2.0)
Transitional Cell Hyperplasia	3 (1.0)			4 (1.8)
2-Year Study				
Number Examined	50	40	60	48
Nephropathy	50 (1.9)	39 (2.6)	60 (2.7)	46 (2.7)
Renal Tubule Hyperplasia	1 (3.0)	12** (2.5)	23** (2.7)	27** (2.7)
Renal Tubule Pigmentation	0	40** (2.0)	60** (2.0)	48** (2.0)
Transitional Cell Hyperplasia	10 (1.2)	16* (1.8)	44** (1.5)	21** (1.6)
Transitional Cell Papilloma	0	0	0	1
Transitional Cell Carcinoma	0	1	0	0
Renal Tubule Adenoma (Multiple)	0	0	5*	5*
Renal Tubule Adenoma (Single or Multiple)				
Overall rate	0/50 (0%)	3/40 (8%)	16/60 (27%)	16/48 (33%)
Terminal rate	0/38 (0%)	1/32 (3%)	11/38 (29%)	6/12 (50%)
Adjusted rate	0.0%	8.0%	36.0%	69.7%
First incidence (days)	-[i]	600	601	625
Logistic regression test	P<0.001	P=0.049	P<0.001	P<0.001
Renal Tubule Carcinoma	0	0	0	2
Renal Tubule Adenoma or Carcinoma[j]				
Overall rate	0/50 (0%)	3/40 (8%)	16/60 (27%)	16/48 (33%)
Terminal rate	0/38 (0%)	1/32 (3%)	11/38 (29%)	6/12 (50%)
Adjusted rate	0.0%	8.0%	36.0%	69.7%
First incidence (days)	-	600	601	625
Logistic regression test	P<0.001	P=0.049	P<0.001	P<0.001

* Significantly different ($P \leq 0.05$) from the control group by the Fischer exact test (9-month and 15-month interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Kidney not microscopically examined in this group
[d] Number of animals with neoplasm per number of animals with kidney examined microscopically
[e] Observed incidence in animals surviving until the end of the study
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[h] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 15/1,350 (1.1% ± 1.7%); range, 0%-6%
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 1/1,348 (0.1% ± 0.4%); range, 0%-2%

Urinary Bladder: Hyperplasia of the transitional cell epithelium of the urinary bladder was observed in 10,000 ppm females at 9 months and in 10,000 ppm males and females at 15 months (Tables 11, A5, and B5). Transitional cell hyperplasia was present in most 5,000 and 10,000 ppm females at 2 years, and the incidences of this lesion were significantly increased in 5,000 and 10,000 ppm males. Hyperplasia consisted of a diffuse or focal increase in thickness of the transitional epithelium; minimal cellular pleomorphism and increased numbers of mitotic cells were sometimes present. Other nonneoplastic lesions that occurred only in exposed rats included squamous metaplasia of the transitional epithelium and fatty metaplasia (fat proliferation) of the stroma of the bladder wall.

Two transitional cell carcinomas and one papilloma occurred in 10,000 ppm females at the 15-month interim evaluation. At 2 years, incidences of transitional cell papilloma, carcinoma, and papilloma or carcinoma (combined) were significantly increased in 10,000 ppm males and 5,000 and 10,000 ppm females (Tables 11, A3, and B3) and exceeded the NTP historical ranges (males: 0%-2%; females: 0%-2%) for feed study controls (Tables 11, A4d, and B4d). Transitional cell papilloma consisted of a pedunculated or broad-based mass of transitional epithelium with a central fibrovascular stroma; there was squamous metaplasia of the surface epithelium in some papillomas. Transitional cell carcinoma was characterized by an exophytic or endophytic growth pattern and invasion of the lamina propria or muscularis of the bladder wall (Plates 7 and 8). There was cellular atypia and squamous or mucous metaplasia of transitional epithelium in some carcinomas.

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Urinary Bladder in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male				
15-Month Interim Evaluation				
Number Examined	10	–[b]	–	10
Transitional Cell Hyperplasia[a]	0			3 (1.3)[c]
Metaplasia, Squamous	0			1 (2.0)
2-Year Study				
Number Examined	50	38	58	50
Transitional Cell Hyperplasia	1 (2.0)	5 (2.0)	17** (1.9)	30** (2.1)
Metaplasia, Squamous	0	0	0	3 (1.7)
Transitional Cell Papilloma				
Overall rate[d]	0/50 (0%)	1/38 (3%)	2/58 (3%)	8/50 (16%)
Terminal rate[e]	0/26 (0%)	0/22 (0%)	2/21 (10%)	2/10 (20%)
Adjusted rate[f]	0.0%	3.7%	9.5%	40.3%
First incidence (days)	–[h]	700	729 (T)	493
Logistic regression test[g]	P<0.001	P=0.459	P=0.192	P=0.004
Transitional Cell Carcinoma				
Overall rate	0/50 (0%)	0/38 (0%)	1/58 (2%)	4/50 (8%)
Terminal rate	0/26 (0%)	0/22 (0%)	0/21 (0%)	1/10 (10%)
Adjusted rate	0.0%	0.0%	4.3%	24.5%
First incidence (days)	–	–	720	674
Logistic regression test	P=0.001	–	P=0.491	P=0.022
Transitional Cell Papilloma or Carcinoma[i]				
Overall rate	0/50 (0%)	1/38 (3%)	3/58 (5%)	12/50 (24%)
Terminal rate	0/26 (0%)	0/22 (0%)	2/21 (10%)	3/10 (30%)
Adjusted rate	0.0%	3.7%	13.5%	56.2%
First incidence (days)	–	700	720	493
Logistic regression test	P<0.001	P=0.459	P=0.096	P<0.001
Female				
9-Month Interim Evaluation				
Number Examined	10	10	10	10
Transitional Cell Hyperplasia	0	0	0	2 (1.5)
15-Month Interim Evaluation				
Number Examined	10	–	–	10
Transitional Cell Hyperplasia	0			9** (2.6)
Transitional Cell Papilloma	0			1
Transitional Cell Carcinoma	0			2
Squamous Cell Carcinoma	0			2

(continued)

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Urinary Bladder in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Female (continued)				
2-Year Study				
Number Examined	50	40	60	46
Transitional Cell Hyperplasia	1 (1.0)	2 (3.0)	41** (2.0)	41** (2.3)
Metaplasia, Squamous	0	1 (1.0)	4 (2.3)	8** (2.9)
Fat Proliferation	0	0	4 (2.3)	2 (2.5)
Transitional Cell Papilloma				
Overall rate	0/50 (0%)	2/40 (5%)	7/60 (12%)	9/46 (20%)
Terminal rate	0/38 (0%)	2/32 (6%)	6/38 (16%)	1/12 (8%)
Adjusted rate	0.0%	6.3%	17.6%	39.5%
First incidence (days)	–	729 (T)	691	637
Logistic regression test	P<0.001	P=0.201	P=0.012	P=0.003
Transitional Cell Carcinoma				
Overall rate	0/50 (0%)	0/40 (0%)	8/60 (13%)	16/46 (35%)
Terminal rate	0/38 (0%)	0/32 (0%)	6/38 (16%)	4/12 (33%)
Adjusted rate	0.0%	0.0%	19.5%	55.8%
First incidence (days)	–	–	670	367
Logistic regression test	P<0.001	–	P=0.008	P<0.001
Transitional Cell Papilloma or Carcinoma[j]				
Overall rate	0/50 (0%)	2/40 (5%)	17/60 (28%)	26/46 (57%)
Terminal rate	0/38 (0%)	2/32 (6%)	14/38 (37%)	6/12 (50%)
Adjusted rate	0.0%	6.3%	40.9%	78.1%
First incidence (days)	–	729 (T)	670	367
Logistic regression test	P<0.001	P=0.201	P<0.001	P<0.001
Squamous Cell Papilloma (Single or Multiple)	0	0	1	2
Squamous Cell Carcinoma	0	0	1	0

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test (9-month and 15-month interim evaluations) or the logistic regression test (2-year study)
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Urinary bladder not microscopically examined in this group
[c] Average severity grade of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Number of animals with neoplasm per number of animals necropsied or examined microscopically
[e] Observed incidence in animals surviving until the end of the study
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 3/1,329 (0.2% ± 0.6%); range, 0%-2%
[j] Historical incidence: 3/1,334 (0.2% ± 0.6%); range, 0%-2%

Forestomach: Several proliferative and degenerative lesions occurred with increased incidences in the forestomach of exposed males and females (Table 12). These mucosal lesions frequently occurred together and consisted of thickening (hyperplasia) of the squamous epithelium and an increase in the surface keratin layers (hyperkeratosis) (Tables 12, A5, and B5). Focal areas of hyperplasia were sometimes adjacent to ulceration and inflammation of the squamous mucosa. There was no significant increase in incidences of neoplasms of the forestomach (Tables 12, A1, and B1).

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male				
Number Examined	49	39	59	49
Hyperkeratosis[a]	5 (2.4)[b]	18** (1.8)	21** (2.0)	20** (2.0)
Hyperplasia, Squamous	3 (1.7)	19** (3.0)	25** (3.2)	26** (3.0)
Inflammation, Chronic Active	3 (2.0)	12** (2.4)	11 (2.0)	11* (2.2)
Ulcer	3 (2.7)	10** (3.2)	15** (2.7)	16** (2.6)
Squamous Cell Papilloma[c]	0	2	0	1
Squamous Cell Carcinoma	0	0	0	1
Squamous Cell Papilloma or Carcinoma[d]	0	2	0	2
Female				
Number Examined	49	40	60	47
Hyperkeratosis	2 (2.0)	7* (1.4)	23** (2.1)	28** (1.9)
Hyperplasia, Squamous	2 (2.0)	7* (1.9)	26** (2.9)	33** (3.0)
Inflammation, Chronic Active	0	1 (2.0)	13** (2.2)	10** (2.2)
Ulcer	1 (2.0)	2 (2.5)	7 (1.7)	17** (2.9)
Squamous Cell Papilloma	0	0	0	1
Squamous Cell Carcinoma	0	1	1	1
Squamous Cell Papilloma or Carcinoma[e]	0	1	1	2

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Number of animals with neoplasm per number of animals necropsied
[d] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 4/1,353 (0.3% ± 0.7%); range, 0%-2%
[e] Historical incidence: 2/1,351 (0.2% ± 0.5%); range, 0%-2%

Miscellaneous Neoplasms and Nonneoplastic Lesions: In exposed males and females, incidences of mononuclear cell leukemia occurred with significant negative trends (Tables 13, A3, and B3). The incidences of pituitary gland adenoma in males and females (males: 0 ppm, 21/48; 2,000 ppm, 14/40; 5,000 ppm, 10/56; 10,000 ppm, 10/49; females: 32/50, 19/39, 32/60, 13/47; Tables A3 and B3) and the incidence of mammary gland fibroadenoma (21/50, 10/40, 9/60, 5/49; Table B3) in females also occurred with significant negative trends. These decreases may have been related to lower body weights.

TABLE 13
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Male				
15-Month Interim Evaluation				
Mononuclear Cell Leukemia[a]	0/10	–[b]	–	2/10
2-Year Study				
Mononuclear Cell Leukemia				
Overall rate[a]	25/50 (50%)	5/40 (13%)	3/59 (5%)	1/50 (2%)
Terminal rate[c]	9/26 (35%)	4/24 (17%)	2/21 (10%)	0/10 (0%)
Adjusted rate[d]	59.0%	18.8%	11.7%	2.9%
First incidence (days)	514	604	650	590
Life table test[e]	P<0.001N	P<0.001N	P<0.001N	P<0.001N
Logistic regression test	P<0.001N	P<0.001N	P<0.001N	P<0.001N
Female				
2-Year Study				
Mononuclear Cell Leukemia				
Overall rate	9/50 (18%)	1/40 (3%)	5/60 (8%)	1/49 (2%)
Terminal rate	6/38 (16%)	0/32 (0%)	1/38 (3%)	0/12 (0%)
Adjusted rate	21.5%	3.0%	10.0%	3.7%
First incidence (days)	620	689	601	662
Life table test	P=0.112N	P=0.026N	P=0.177N	P=0.162N
Logistic regression test	P=0.011N	P=0.023N	P=0.111N	P=0.024N

[a] Number of animals with neoplasm per number of animals necropsied
[b] Animals not microscopically examined in this group
[c] Observed incidence in animals surviving until the end of the study
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[e] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table analysis 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. A negative trend or a lower incidence in an exposure group is indicated by N.

In males, there was a chemical-related increased incidence of atrophy of the seminal vesicles (1/49, 30/40, 35/59, 23/50; Table A5). This was not evident at the 9- or 15-month interim evaluation, but was present in most males at the end of the 2-year study.

Atrophy of the seminal vesicles of exposed males was characterized by a reduction in the size of the secretory epithelium from a tall columnar shape to a low cuboidal shape and by an increase in the amount of connective tissue stroma in the gland.

STOP-EXPOSURE EVALUATION

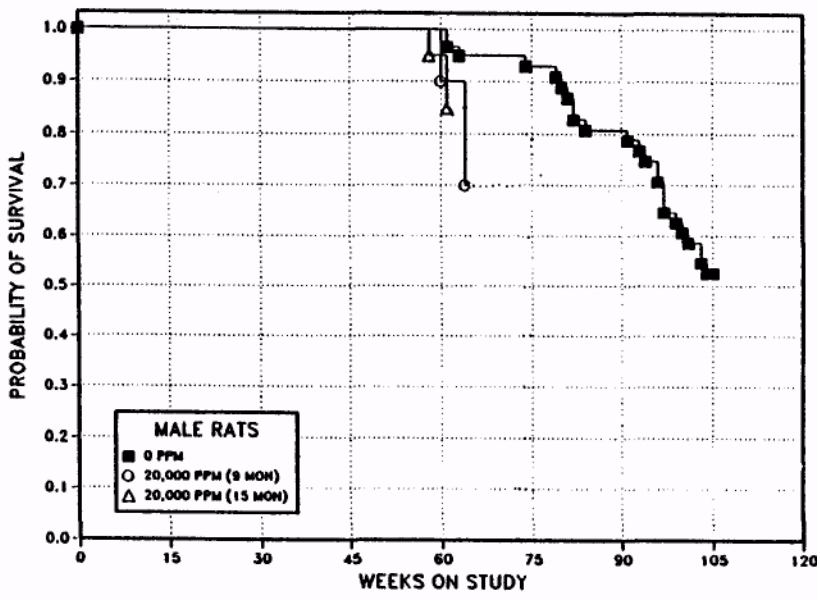
Stop-exposure groups of male and female rats were included in the NTP 2-year study to evaluate the potential for progression or regression of chemical-related liver, large intestine, kidney, urinary bladder, and forestomach lesions during a recovery period. Ten male and 10 female rats were exposed to 20,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 9 months followed by administration of undosed feed until the end of the 15-month period (9-month stop-exposure groups). In addition, 30 males and 30 females were exposed to 20,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 15 months (15-month exposure groups). Ten males and 10 females from the 15-month exposure groups were evaluated at the 9-month interim evaluation (9-month interim evaluation groups).

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in the Kaplan-Meier survival curves in Figure 4. All males survived 9 months; three males from the 9-month stop-exposure group and three males from the 15-month exposure group died before the end of the 15-month evaluation (Table 14). All females in the 9-month stop-exposure group survived until the end of the 15-month evaluation. One female from the 15-month exposure group died during the first 9 months; an additional seven females died between month 9 and the end of the 15-month evaluation (Table 15).

Body Weights and Feed and Compound Consumption

The mean body weights of male and female rats in the 9-month stop-exposure and 15-month exposure groups are compared with the controls from the 2-year core study in Tables 14 and 15, and the growth curves for exposed rats in the 15-month exposure groups are shown in Figure 5. The mean body weights of males and females in the 9-month stop-exposure groups were 20% to 22% lower than those of the controls at the 9-month interim evaluation of the 2-year core study and were 20% to 21% lower than those of the controls at the 15-month interim evaluation of the 2-year core study. The mean body weights of males and females in the 15-month exposure groups were 19% to 21% lower than those of the controls at the 9-month interim evaluation of the 2-year core study and were 25% to 33% lower than those of the controls at the 15-month interim evaluation of the 2-year core study. Feed consumption by 9-month stop-exposure and 15-month exposure males and females was generally lower than that by the controls throughout the study (Tables J1 and J2). The dietary level of 20,000 ppm delivered daily doses of approximately 1,300 mg 1-amino-2,4-dibromoanthraquinone/kg body weight to males and 1,800 mg/kg to females in the 9-month stop-exposure groups and daily doses of approximately 1,100 mg/kg to males and 1,400 mg/kg to females in the 15-month exposure groups.



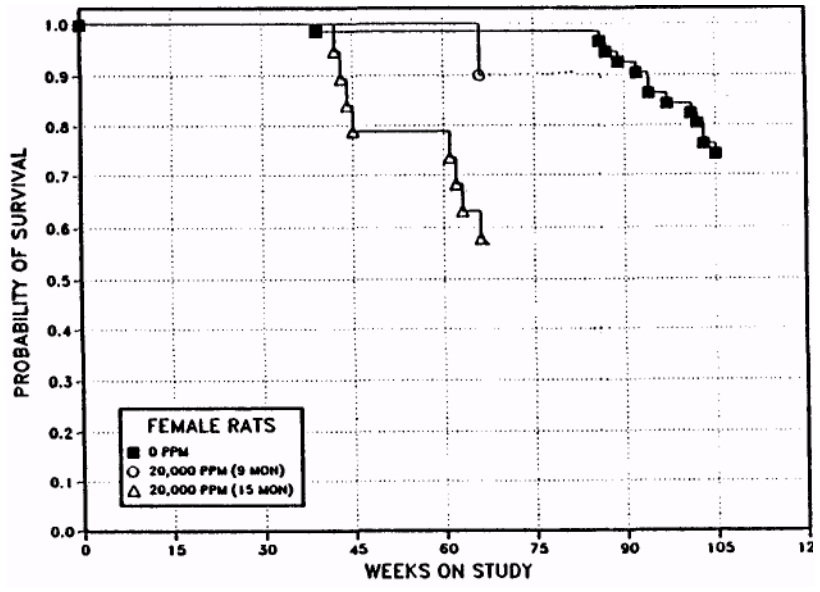
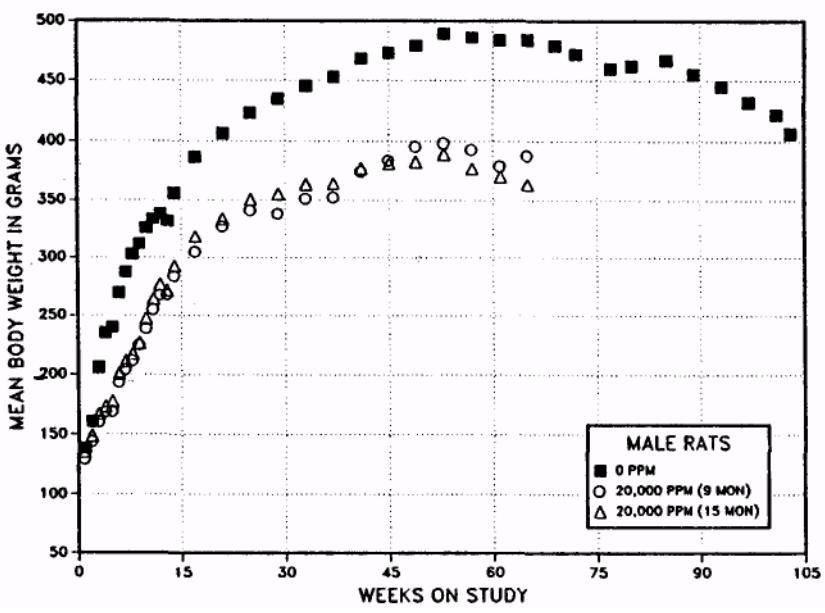


FIGURE 4
Kaplan-Meier Survival Curves for Rats Administered l-Amino-2,4-dibromoanthraqninone in Feed in the 15-Month Stop-Exposure Evaluation



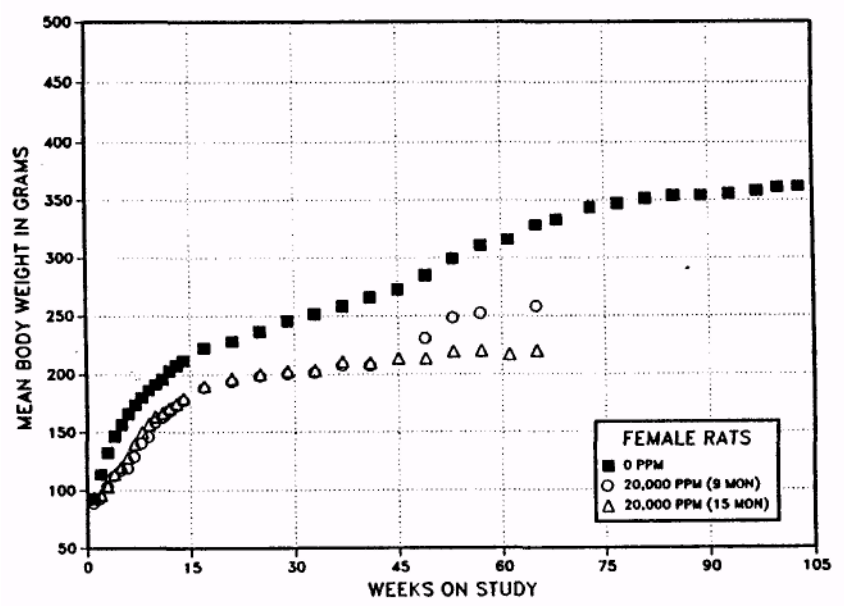


FIGURE 5
Growth Curves for Rats Administered l-Amino-2,4-dibromoanthraquinone in Feed in the 15-Month Stop-Exposure Evaluation

TABLE 14
Mean Body Weights and Survival of Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone

Weeks on Study	0 ppm		20,000 ppm (9-Month Stop-Exposure)			20,000 ppm (15-Month Exposure)		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	139	70	130	94	10	136	98	30
2	161	70	144	90	10	149	93	30
3	206	70	160	78	10	167	81	30
4	235	70	169	72	10	173	74	30
5	240	70	169	71	10	177	74	30
6	269	70	193	72	10	201	75	30
7	287	70	204	71	10	211	74	30
8	302	70	211	70	10	217	72	30
9	312	70	225	72	10	226	73	30
10	325	70	239	73	10	247	76	30
11	333	70	255	76	10	264	79	30
12	338	70	267	79	10	277	82	30
13	332	70	267	81	10	271	82	30
14	356	70	284	80	10	292	82	30
17	387	70	305	79	10	318	82	30
21	406	70	327	81	10	334	82	30
25	423	70	341	81	10	351	83	30
29	435	70	338	78	10	355	82	30
33	445	70	351	79	10	364	82	30
37	453	70	352	78	10	364	80	30
41	468	60[a]	374	80	10[b]	377	81	20[a]
45	473	60	384	81	10	381	81	20
49	479	60	395	83	10	383	80	20
53	489	60	398	81	10	389	80	20
57	486	60	393	81	10	377	78	20
61	484	59	379	78	9	370	77	19
65	484	57	388	80	7	364	75	17
Mean for weeks								
1-13	268		203	76		209	78	
14-37	415		328	79		340	82	
41-65	480		387	81		377	79	

[a] Interim evaluation occurred during week 39.
[b] Animals switched to undosed feed

TABLE 15
Mean Body Weights and Survival of Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone

Weeks on Study	0 ppm		20,000 ppm (9-Month Stop-Exposure)			20,000 ppm (15-Month Exposure)		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	93	70	90	96	10	94	101	30
2	114	70	93	82	10	97	85	30
3	133	70	103	78	10	104	78	30
4	147	70	113	77	10	114	78	30
5	157	70	117	75	10	121	77	30
6	166	70	119	72	10	129	78	30
7	173	70	129	75	10	141	81	30
8	180	70	141	78	10	150	84	30
9	186	70	146	79	10	157	84	30
10	191	70	159	83	10	163	85	30
11	196	70	163	83	10	166	85	29
12	203	70	168	83	10	171	84	29
13	208	70	172	83	10	175	84	29
14	212	70	177	84	10	179	85	29
17	222	70	188	85	10	190	85	29
21	228	70	194	85	10	196	86	29
25	237	70	198	84	10	200	85	29
29	246	70	200	82	10	203	83	29
33	251	70	201	80	10	203	81	29
37	258	70	207	80	10	211	82	29
41	265	59[a]	207	78	10[b]	210	79	19[a]
45	272	59				213	78	16
49	284	59	231	81	10	213	75	15
53	299	59	248	83	10	219	73	15
57	311	59	252	81	10	220	71	15
61	315	59				217	69	15
65	328	59	258	79	10	220	67	12
Mean for weeks								
1-13	165		132	80		137	83	
14-37	236		195	83		197	84	
41-65	296		239	81		216	73	

[a] Interim evaluation occurred during week 40.
[b] Animals switched to undosed feed

Pathology and Statistical Analysis of Results

Summaries of the incidences of neoplasms and nonneoplastic lesions are shown in Tables E1 and E3 for male rats and Tables F1 and F3 for female rats. For statistical analyses, the incidences in the 9-month stop-exposure groups and the 15-month exposure groups at the end of 15 months are compared with the 15-month interim evaluation controls of the 2-year core study for male rats (Table E2a) and female rats (Table F2a). The incidences in the 15-month exposure groups are compared with the 9-month stop-exposure groups after 6 months of recovery for male rats (Table E2b) and female rats (Table F2b).

Progression or Regression of Chemical-Induced Lesions

Liver: Rats in the stop-exposure study exposed to 20,000 ppm 1-amino-2,4-dibromoanthraquinone in the feed for 9 or 15 months had chemical-related effects similar to those observed in rats exposed to concentrations up to 10,000 ppm in the 2-year core study. The absolute and relative liver weights of exposed males and females were significantly greater than those of the controls at both the 9-month interim and 15-month evaluations of the 15-month exposure groups (Tables H2 and H3). With respect to both neoplasms and nonneoplastic lesions in the liver, there was no evidence of regression in the incidence or severity of chemical-related pigmentation, focal hepatocellular alteration, or hepatocellular adenoma or carcinoma when administration of 1-amino--2,4-dibromoanthraquinone was discontinued after 9 months. The incidences and severity of liver lesions after 9 months of exposure were similar with and without a 6-month recovery period. The incidences of liver lesions in the 15-month exposure groups were greater than in the 9-month stop-exposure groups but the severities were comparable (Tables 16, E2a, and F2a).

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 9-Month, 9-Month with 6-Month Recovery, and 15-Month Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone

	9-Month Evaluation[a]		15-Month Evaluation[b]		
	0 ppm	20,000 ppm (9-Month Exposure)	0 ppm	20,000 ppm (9-Month Exposure Plus 6-Month Recovery)	20,000 ppm (15-Month Exposure)
Male					
Number Examined	10	10	10	10	20
Basophilic Focus[c]	0	6** (1.5)[d]	1 (1.0)	4 (1.0)	13** (1.5)
Clear Cell Focus	0	4* (1.0)	0	6** (1.6)	13** (1.2)
Eosinophilic Focus	0	0	1 (1.0)	0	2 (1.5)
Bile Duct Hyperplasia	1 (1.0)	7** (1.3)	10 (1.1)	7 (1.0)	19 (1.3)
Chronic and Chronic Active Periportal Inflammation	(1.0)	10 (1.0)	10 (1.1)	7 (1.7)	18 (1.9)
Pigmentation	0	10**(1.0)	0	8** (1.0)	18** (1.0)
Hepatocellular Adenoma	0	2	0	7**	8*
Hepatocellular Carcinoma	0	2	0	7**	19**
Hepatocellular Adenoma or Carcinoma	0	2	0	9**	20**
Female					
Number Examined	10	10	10	10	18
Basophilic Focus	1 (1.0)	3 (1.3)	8 (1.0)	6 (1.2)	13 (1.5)
Clear Cell Focus	0	1 (1.0)	0	5* (1.0)	13** (1.2)
Eosinophilic Focus	0	0	2 (1.5)	2 (1.0)	3 (1.7)
Bile Duct Hyperplasia	1 (1.0)	9** (1.1)	7 (1.1)	10 (1.5)	18* (1.6)
Chronic and Chronic Active Periportal Inflammation	6 (1.0)	10* (1.7)	10 (1.0)	9 (1.6)	18 (1.7)
Pigmentation	0	10**(1.2)	1 (1.0)	10** (1.0)	17** (1.2)
Hepatocellular Adenoma	0	2	0	6**	10**
Hepatocellular Carcinoma	0	1	0	6**	15**
Hepatocellular Adenoma or Carcinoma	0	2	0	8**	16**

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Controls from the 9-month interim evaluation of the 2-year core study were used for statistical comparison.
[b] Controls from the 15-month interim evaluation of the 2-year core study were used for statistical comparison.
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Large Intestine: The stop-exposure regimen had no effect on the development of adenomatous polyps (adenomas) of the large intestine. An adenomatous polyp was observed in the colon of one exposed male at 9 months. After 15 months, the incidence of adenomatous polyps of the rectum was significantly increased in the 9-month stop-exposure females (Tables 17 and F2a). At the 15-month evaluation, adenomatous polyps were observed in the rectums of three males in the 9-month stop-exposure group, seven males in the 15-month exposure group, five females in the 9-month stop-exposure group, and three females in the 15-month exposure group. No carcinomas of the colon or rectum were observed.

Kidney: At the 9-month and 15-month evaluations, the relative kidney weights of males and females in the 15-month exposure groups were significantly greater than those of the controls (Tables H2 and H3). In the exposed males and females at 9 months, kidney changes included pigmentation and minimal enlargement of some renal tubule cell nuclei (karyomegaly). In exposed males, there was also hyaline droplet accumulation and a slight increase in the severity of nephropathy. At 15 months, renal tubule epithelial pigmentation, karyomegaly, and increased severity of nephropathy and transitional cell hyperplasia of the renal pelvis were observed in exposed groups of males and females. The severities of these lesions were similar or slightly less severe in the stop-exposure groups than in those exposed continuously for 15 months. At the 15-month evaluation, renal tubule adenomas were observed in the 9-month stop-exposure and 15-month exposure groups of males and females (Tables 17, E1, and F1). In the 9-month

TABLE 17
Incidences of Neoplasms and Nonneoplastic Lesions of the Large Intestine and Kidney in Rats in the 9-Month, 9-Month with 6-Month Recovery, and 15-Month Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone

	9-Month Evaluation[a]		15-Month Evaluation[b]		
	0 ppm	20,000 ppm (9-Month Exposure)	0 ppm	20,000 ppm (9-Month Exposure Plus 6-Month Recovery)	20,000 ppm (15-Month Exposure)
Male					
Large Intestine, Colon[c]	10	10	10	10	20
Adenomatous Polyp (Adenoma)[d]	0	1	0	0	0
Large Intestine, Rectum	10	10	9	10	20
Adenomatous Polyp (Adenoma)	0	0	0	3	7*
Kidney	10	10	10	10	20
Nephropathy	10 (1.0)[e]	10 (1.8)	10 (2.0)	10 (2.0)	20 (2.5)
Transitional Cell Hyperplasia	0	0	0	1 (1.0)	11** (1.3)
Hyaline Droplet Accumulation	0	10** (2.1)	0	0	0
Pigmentation	0	10** (2.0)	0	9** (1.2)	20** (2.0)
Renal Tubule Hyperplasia	0	0	0	1 (1.0)	1 (1.0)
Renal Tubule Adenoma	0	0	0	3	2
Female					
Large Intestine, Rectum	10	10	10	10	17
Adenomatous Polyp (Adenoma)	0	0	0	5*	3
Kidney	10	10	10	10	18
Nephropathy	4 (1.0)	7 (1.0)	10 (1.7)	10 (2.2)	18 (2.1)
Transitional Cell Hyperplasia	0	0	3 (1.0)	1 (1.0)	5 (1.6)
Pigmentation	0	10** (2.0)	0	10** (1.9)	18** (2.0)
Renal Tubule Hyperplasia	0	0	0	2 (2.0)	2 (1.5)
Renal Tubule Adenoma	0	0	0	3	2

* Significantly different ($P \le 0.05$) from the control group by the Fisher exact test
** $P \le 0.01$
[a] Controls from the 9-month interim evaluation of the 2-year core study were used for statistical comparison.
[b] Controls from the 15-month interim evaluation of the 2-year core study were used for statistical comparison.
[c] Number of animals with organ examined microscopically
[d] Number of animals with lesion
[e] Average severity grade of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

stop-exposure and 15-month exposure groups, renal tubule hyperplasia and adenomas were observed in males and females. At 15 months, renal tubule adenomas were observed in three males and three females in the 9-month stop-exposure groups and in two males and two females in the 15-month exposure groups. No renal tubule carcinomas were found.

Urinary Bladder: A transitional cell papilloma was present in the urinary bladder of one exposed male at 9 months (Tables 18 and E1). When exposure was discontinued at 9 months, no chemical-related nonneoplastic lesions or neoplasms were present at 15 months. With continuous treatment, transitional cell hyperplasia and neoplasms of the urinary bladder developed by 15 months. In females, a minimal to mild transitional cell hyperplasia was observed at 9 months and did not completely regress with the cessation of exposure; a squamous cell papilloma was observed in one female at 15 months (Tables 18 and F1). In contrast, continuous exposure for 15 months resulted in an increased incidence and severity of transitional cell hyperplasia, as well as squamous metaplasia of the transitional epithelium and a fatty metaplasia (fat proliferation) of the stroma of the bladder wall.

Forestomach: Chemical-related lesions of the forestomach were not present in males or females at the 9-month interim evaluation. Hyperplasia, hyperkeratosis, inflammation, and ulceration were present in approximately 20% of exposed males, but not in the controls at 15 months (Table 18). A squamous cell papilloma was present in one male from the 15-month exposure group (Table E1). In female rats, forestomach lesions were not present in the control or 9-month stop-exposure groups. Hyperplasia, hyperkeratosis, and/or ulceration were observed in a few females in the 15-month exposure group; no neoplasms were present in the forestomach.

TABLE 18
Incidences of Neoplasms and Nonneoplastic Lesions of the Urinary Bladder and Forestomach in Rats in the 9-Month, 9-Month with 6-Month Recovery, and 15-Month Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone

	9-Month Evaluation[a]		15-Month Evaluation[b]		
	0 ppm	20,000 ppm (9-Month Exposure)	0 ppm	20,000 ppm (9-Month Exposure Plus 6-Month Recovery)	20,000 ppm (15-Month Exposure)
Male					
Urinary Bladder[c]	10	9	10	10	19
Fat Proliferation[d]	0	0	0	0	1 (3.0)[e]
Transitional Epithelial Hyperplasia	0	0	0	0	9** (1.9)
Squamous Cell Carcinoma	0	0	0	0	1
Transitional Epithelial Papilloma	0	1	0	0	3
Transitional Epithelial Carcinoma	0	0	0	0	1
Forestomach	10	10	10	10	20
Hyperkeratosis	0	0	0	2 (2.5)	1 (1.0)
Hyperplasia	0	0	0	2 (2.0)	3 (1.3)
Inflammation	0	0	0	1 (3.0)	1 (3.0)
Ulceration	0	0	0	2 (2.5)	0
Female					
Urinary Bladder	10	10	10	10	18
Fat Proliferation	0	0	0	0	2 (3.0)
Transitional Epithelial Hyperplasia	0	4* (1.5)	0	4* (1.8)	17** (2.6)
Transitional Epithelial Squamous Metaplasia	0	0	0	0	3 (2.7)
Squamous Cell Papilloma	0	0	0	0	1
Squamous Cell Carcinoma	0	0	0	1	4
Transitional Epithelial Papilloma	0	0	0	0	1
Transitional Epithelial Carcinoma	0	0	0	0	1
Forestomach	10	10	10	10	18
Hyperkeratosis	0	0	0	0	1 (1.0)
Hyperplasia	0	0	0	0	6* (1.0)
Ulceration	0	0	0	0	1 (3.0)

* Significantly different ($P \le 0.05$) from the control group by the Fisher exact test
** $P \le 0.01$
[a] Controls from the 9-month interim evaluation of the 2-year core study were used for statistical comparison.
[b] Controls from the 15-month interim evaluation of the 2-year core study were used for statistical comparison.
[c] Number of animals with organ examined microscopically
[d] Number of animals with lesion
[e] Average severity grade of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

MICE

13-WEEK STUDY

One 25,000 ppm male (week 11) and one 5,000 ppm male (week 13) died during the study (Table 19). Neither death was chemical related. One 10,000 ppm female was accidently killed. Final mean body weights of exposed groups of male and female mice were similar to those of the controls. Mean body weight gains of exposed groups of males and females were generally greater than those of the controls. Feed consumption by exposed mice was similar to that by the controls. Dietary levels of 2,500, 5,000, 10,000, 25,000, and 50,000 ppm delivered average daily doses of approximately 500, 1,080, 1,850, 6,200, and 10,600 mg 1-amino-2,4-dibromoanthraquinone/kg body weight to males and approximately 660, 1,150, 2,600, 5,900, and 11,700 mg/kg to females. Reddened fur was observed in 10,000, 25,000, and 50,000 ppm mice as early as day 4 in males and day 5 in females and was observed throughout the study. No other clinical observations were attributed to 1-amino-2,4-dibromoanthraquinone.

TABLE 19
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone

Dose (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	23.7 ± 0.4	30.5 ± 0.6	6.9 ± 0.7		5.8	6.0
2,500	10/10	23.5 ± 0.3	30.6 ± 0.6	7.1 ± 0.6	100	5.3	5.6
5,000	9/10[d]	23.5 ± 0.4	30.7 ± 0.7	7.3 ± 0.5	101	6.1	5.6
10,000	10/10	23.7 ± 0.5	32.1 ± 0.4	8.4 ± 0.4	105	5.5	4.8
25,000	9/10[e]	23.4 ± 0.3	30.9 ± 0.6	7.5 ± 0.5	101	6.3	7.1
50,000	10/10	23.4 ± 0.3	31.5 ± 0.4	8.1 ± 0.4	103	6.1	5.5
Female							
0	10/10	18.2 ± 0.3	24.0 ± 0.2	5.8 ± 0.2		4.8	6.2
2,500	10/10	18.1 ± 0.3	24.7 ± 0.6	6.6 ± 0.4	103	5.0	6.4
5,000	10/10	18.4 ± 0.3	25.0 ± 0.6	6.5 ± 0.4	104	4.3	5.7
10,000	9/10[f]	18.3 ± 0.3	25.0 ± 0.4	6.5 ± 0.3	104	4.5	6.7
25,000	10/10	18.2 ± 0.2	23.6 ± 0.3	5.4 ± 0.3	98	3.8	6.1
50,000	10/10	18.4 ± 0.3	24.7 ± 0.4	6.3 ± 0.2	103	4.0	6.1

[a] Number of animals surviving at 13 weeks/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.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Week of death: 13
[e] Week of death: 11
[f] Week of death: 2 (accidental)

Absolute and relative liver weights of 5,000, 10,000, 25,000, and 50,000 ppm male and female mice were significantly greater than those of the controls (Table H4). Absolute and relative kidney weights of 25,000 and 50,000 ppm males were significantly lower than those of the controls. Observations at necropsy included red staining of the gastrointestinal tract and its contents in all exposed male mice except those in the 2,500 ppm group and red staining in the kidney and urine. These findings were observed less frequently in females than in males.

Chemical-related lesions were present in the liver (Table 20). There were increased incidences of centrilobular hypertrophy in the 10,000, 25,000, and 50,000 ppm males with a dose-related increased severity. Minimal gold to brown pigment granules were present in the cytoplasm of hepatocytes of all exposed groups of males. Pigment was generally located in the centrilobular portion of the hepatic lobule. Pigment similar to that in male mice was present in just a few hepatocytes in the liver of one female in the 25,000-ppm group and one 50,000 ppm female.

TABLE 20
Incidences of Nonneoplastic Lesions of the Liver in Mice in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
Number Examined	10	10	10	10	10	10
Centrilobular Hypertrophy[a]	0	0	0	8** (1.8)[b]	8** (2.0)	10** (2.8)
Pigmentation	0	5* (1.0)	8** (1.0)	8** (1.0)	8** (1.0)	10** (1.1)
Female						
Number Examined	10	10	10	10	10	10
Pigmentation	0	0	0	0	1 (1.0)	1 (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected mice: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Dose Selection Rationale: As no 1-amino-2,4-dibromoanthraquinone-related adverse effects were observed in feed consumption, mean body weights, or survival, exposure concentrations chosen for the 2-year study were based mainly on the frequency and especially the severity of centrilobular hypertrophy of the liver in male mice. Because only lesions of mild severity were observed in the 10,000 and 25,000 ppm groups, and lesions of moderate severity were observed in the 50,000 ppm group, and these were not life-jeopardizing lesions, exposure concentrations selected for the 2-year study of 1-amino-2,4-dibromoanthraquinone in mice were 0, 10,000, and 20,000 ppm. Other considerations include consistency among males and females (since females could have been given higher exposure concentrations) and correspondence to the exposure concentrations selected for the start-stop, progression/regression experiments (stop-exposure evaluation) in rats.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 21 and in the Kaplan-Meier survival curves in Figure 6. Survival of exposed male mice was significantly lower than that of the controls; survival of exposed female mice was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of exposed groups of male mice were lower than that of the controls after week 9; mean body weights of exposed groups of females were lower than that of the controls after week 17 (Figure 7, Tables 22 and 23). Final mean body weights of exposed groups of males were 15% to 17% lower than that of the controls; final mean body weights of exposed females were 14% to 19% lower than that of the controls. Feed consumption by exposed males and females was generally similar to that by the controls (Tables J5 and J6). Dietary levels of 10,000 and 20,000 ppm were estimated to deliver daily doses of approximately 1,700 and 3,500 mg 1-amino-2,4-dibromoanthraquinone/kg body weight to males and 2,000 and 4,400 mg/kg to females. Discoloration of the fur, urine, and feces was evident in all exposed groups as early as day 8.

TABLE 21
Survival of Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	10,000 ppm	20,000 ppm
Male			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	10	9	10
Accidental death[a]	0	1	0
Moribund	7	23	21
Natural deaths	3	5	6
Animals surviving to study termination	40	22	23
Percent probability of survival at end of study[b]	81	45	47
Mean survival (days)[c]	656	620	609
Survival analyses[d]	P=0.001	P<0.001	P<0.001
Female			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	10	10	10
Moribund	5	11	11
Natural deaths	6	5	6
Animals surviving to study termination	39[e]	34[e]	33
Percent probability of survival at end of study	78	69	66
Mean survival (days)	659	649	657
Survival analyses	P=0.234	P=0.381	P=0.259

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and 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.
[e] Includes one female that died during the last week of the study.

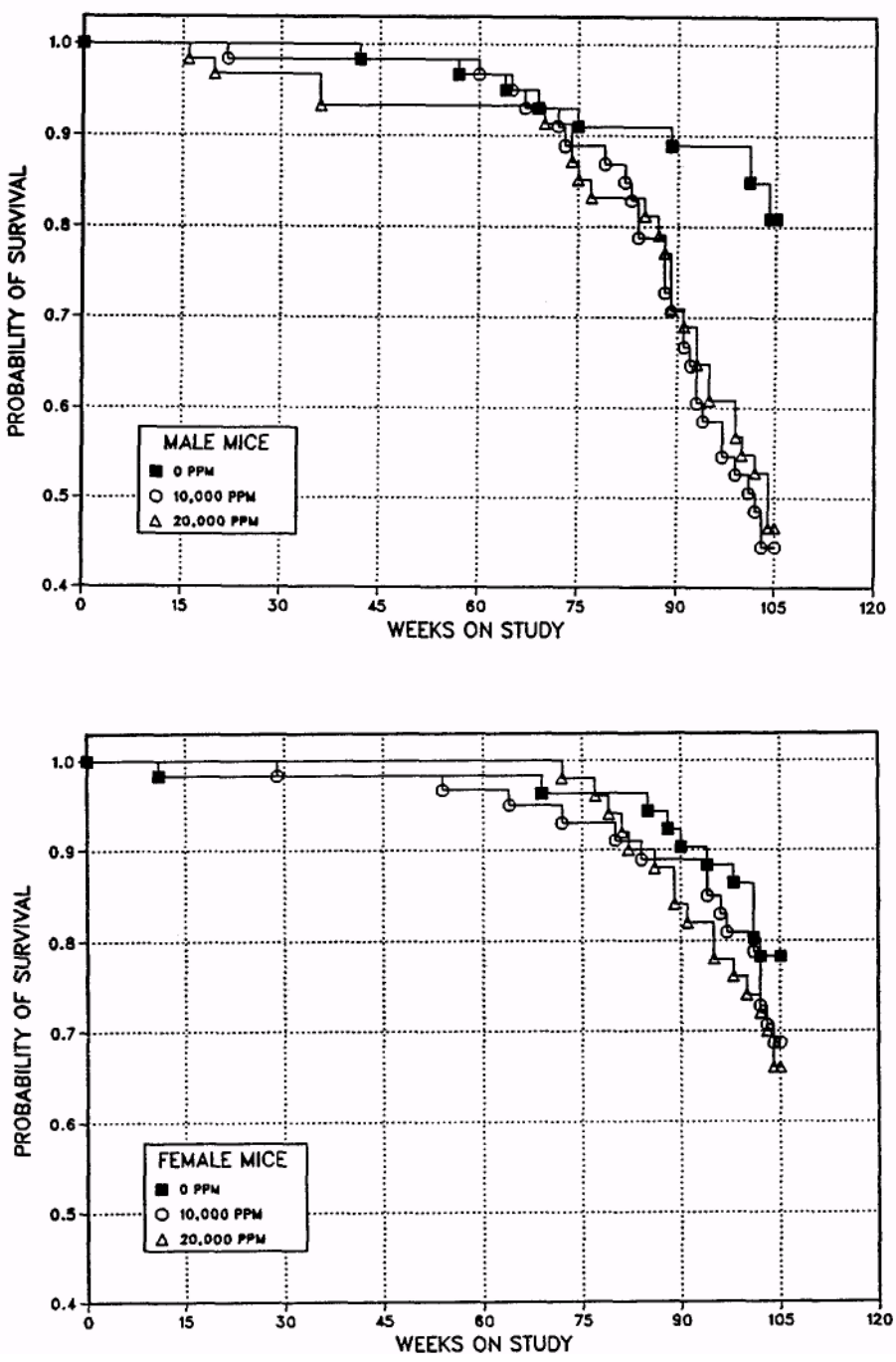


FIGURE 6
Kaplan-Meier Survival Curves for Mice Administered l-Amino-2,4-dibromoanthraquinone in Feed for 2 Years

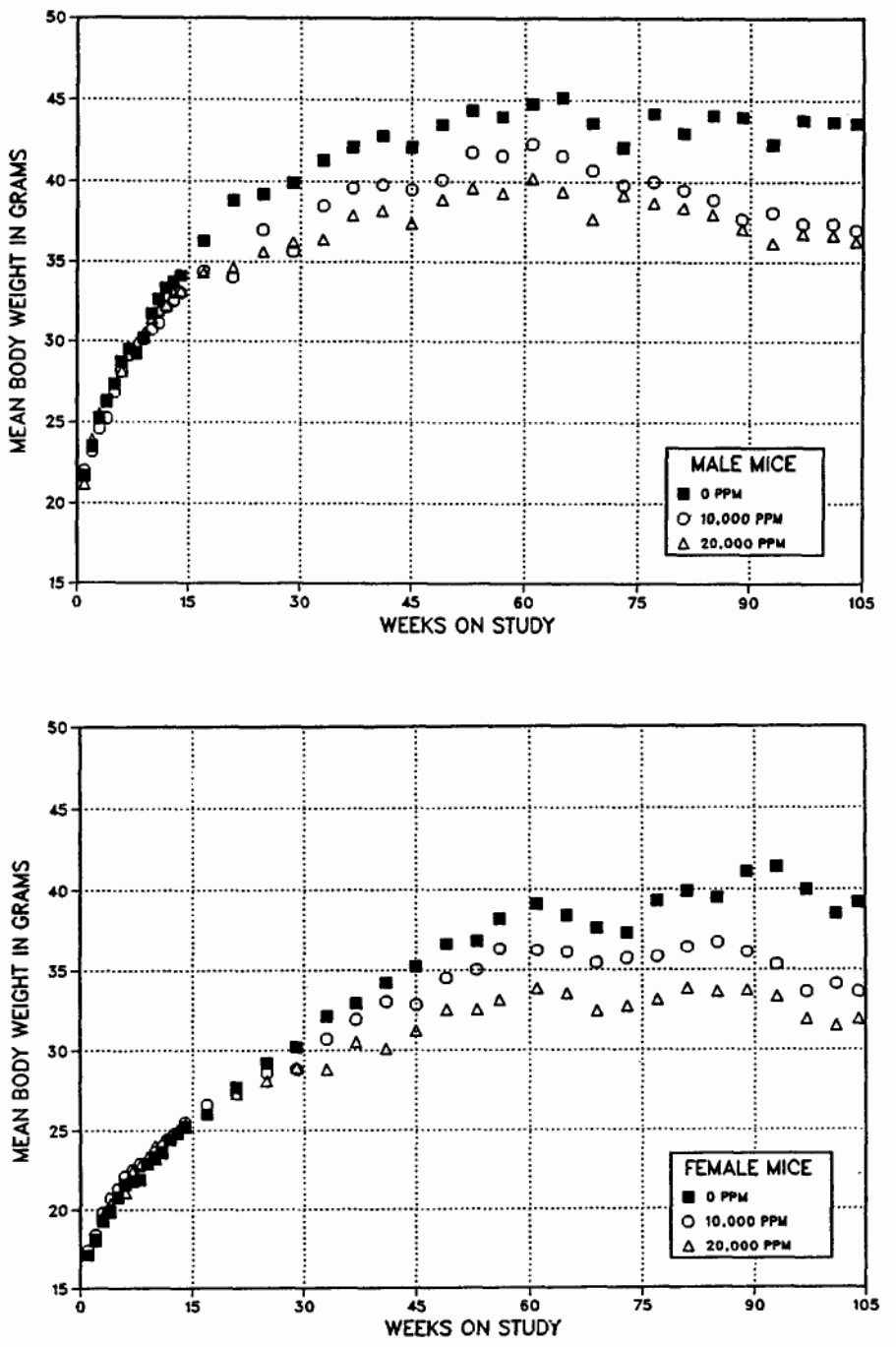


FIGURE 7
Growth Curves for Mice Administered l-Amino-2,4-dibromoanthraquinone in Feed for 2 Years

TABLE 22
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Weeks on Study	0 ppm		10,000 ppm			20,000 ppm		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	21.7	60	22.0	101	60	21.2	98	60
2	23.5	60	23.2	99	60	23.9	102	60
3	25.2	60	24.6	98	60	25.5	101	60
4	26.3	60	25.2	96	60	26.2	100	60
5	27.3	60	26.9	99	60	27.3	100	60
6	28.7	60	28.1	98	60	28.1	98	60
7	29.5	60	29.2	99	60	29.6	100	60
8	29.2	60	29.3	100	60	29.9	102	60
9	30.2	60	30.1	100	60	30.5	101	60
10	31.7	60	30.7	97	60	31.4	99	60
11	32.6	60	31.1	95	60	31.9	98	60
12	33.3	60	32.1	96	60	32.2	97	60
13	33.7	60	32.5	96	60	33.0	98	60
14	34.1	60	33.0	97	60	33.1	97	60
17	36.3	60	34.4	95	60	34.3	95	59
21	38.8	60	34.0	88	60	34.6	89	58
25	39.2	60	37.0	94	59	35.6	91	58
29	39.9	60	35.6	89	59	36.2	91	58
33	41.3	60	38.5	93	59	36.4	88	58
37	42.1	60	39.6	94	59	37.9	90	56
41	42.8	60	39.8	93	59	38.2	89	56
45	42.1	59	39.5	94	59	37.4	89	56
49	43.5	59	40.1	92	59	38.9	89	56
53	44.4	59	41.8	94	59	39.6	89	56
57	44.0	59	41.6	95	59	39.3	89	56
61	44.8	58	42.3	94	58	40.2	90	56
65	45.2	57	41.6	92	58	39.4	87	56
69[a]	43.6	47	40.7	93	46	37.7	87	46
73	42.1	46	39.8	95	45	39.2	93	45
77	44.2	45	40.0	91	44	38.7	88	42
81	43.0	45	39.5	92	43	38.4	89	41
85	44.1	45	38.9	88	39	38.0	86	41
89	44.0	45	37.7	86	36	37.1	84	38
93	42.3	44	38.1	90	32	36.2	86	34
97	43.8	44	37.4	85	29	36.8	84	30
101	43.7	44	37.4	86	26	36.7	84	27
104	43.6	42	37.0	85	22	36.3	83	26
Mean for weeks								
1-13	28.7		28.1	98		28.5	99	
14-52	40.0		37.2	93		36.3	91	
53-104	43.8		39.6	90		38.1	87	

[a] Interim evaluation occurred during week 66.

TABLE 23
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Weeks on Study	0 ppm		10,000 ppm			20,000 ppm		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	17.1	60	17.4	102	60	17.1	100	60
2	18.1	60	18.4	102	60	18.0	99	60
3	19.3	60	19.8	103	60	19.6	102	60
4	19.9	60	20.7	104	60	20.4	103	60
5	20.8	60	21.3	102	60	20.8	100	60
6	21.6	60	22.1	102	60	21.1	98	60
7	21.8	60	22.5	103	60	22.4	103	60
8	21.9	60	22.9	105	60	22.8	104	60
9	22.9	60	22.9	100	60	23.3	102	60
10	23.2	60	23.6	102	60	24.0	103	60
11	23.6	60	24.0	102	60	24.3	103	60
12	24.4	59	24.4	100	60	24.7	101	60
13	24.8	59	24.8	100	60	25.0	101	60
14	25.2	59	25.5	101	60	25.4	101	60
17	26.0	59	26.6	102	60	26.0	100	60
21	27.7	59	27.3	99	60	27.3	99	60
25	29.2	59	28.6	98	60	28.1	96	60
29	30.2	59	28.8	95	60	28.9	96	60
33	32.1	59	30.7	96	59	28.8	90	60
37	32.9	59	31.9	97	59	30.5	93	60
41	34.2	59	33.0	97	59	30.1	88	60
45	35.2	59	32.8	93	59	31.2	89	60
49	36.6	59	34.5	94	59	32.5	89	60
53	36.8	59	35.0	95	59	32.5	88	60
56	38.2	59	36.3	95	58	33.1	87	60
61	39.1	59	36.2	93	58	33.8	86	60
65	38.4	59	36.1	94	57	33.5	87	60
69[a]	37.6	49	35.4	94	47	32.4	86	50
73	37.3	48	35.7	96	46	32.7	88	49
77	39.3	48	35.8	91	46	33.1	84	49
81	39.9	48	36.4	91	45	33.8	85	47
85	39.5	48	36.7	93	44	33.6	85	45
89	41.1	46	36.1	88	44	33.7	82	44
93	41.4	45	35.3	85	44	33.3	80	41
97	40.0	44	33.6	84	41	31.9	80	39
101	38.5	43	34.1	89	40	31.5	82	37
104	39.2	39	33.6	86	35	31.9	81	35
Mean for weeks								
1-13	21.5		21.9	102		21.8	101	
14-52	30.9		30.0	97		28.8	93	
53-104	39.0		35.5	91		32.9	84	

[a] Interim evaluation occurred during week 65.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver, forestomach, lung, kidney, uterus, and pituitary gland of mice. 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 exposure group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: At the 15-month interim evaluation, absolute and relative liver weights of exposed groups of females were significantly greater than those of the controls (Table H5). Hepatocellular adenomas and carcinomas were observed in exposed groups of males and females; none were present in the controls (Tables 24, C1, and D1). At the end of the 2-year study, the incidences of hepatocellular adenoma and hepatocellular carcinoma in exposed groups of males and females were significantly increased (Tables 24, C3, and D3). The incidences of multiple hepatocellular adenomas or multiple hepatocellular carcinomas in exposed groups of males and females were also increased (Tables 24, C1, and D1). Incidences of hepatocellular adenomas or carcinomas (combined) in exposed groups of males and females exceeded the NTP historical ranges for feed study controls (Tables 24, C4a, and D4a). In addition to hepatocellular adenomas and carcinomas, a small number of hepatoblastomas occurred in exposed groups of males and females (Tables 24, C1, and D1). These malignant hepatocellular neoplasms contained areas resembling hepatocellular carcinoma; in addition, there were prominent lobules or nodular foci separated by vascular channels and composed of undifferentiated cells (Plates 9 and 10). The neoplastic cells were elongated with a scant amount of darkly staining cytoplasm and oval hyperchromatic nuclei. Cellular pleomorphism and mitotic figures were commonly present.

At the 15-month interim evaluation and at the end of the 2-year study, the incidences of centrilobular hypertrophy of hepatocytes in exposed groups of males were significantly increased, and the incidences of hepatocellular pigmentation were significantly increased in exposed groups of males and females (Tables 24, C5, and D5). This brown, granular pig-ment resembled that found in the 13-week studies of 1-amino-2,4-dibromoanthraquinone; histochemical procedures were not repeated during this 2-year study. The incidences of clear cell focus in exposed groups of female mice were significantly increased at the end of the 2-year study.

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	10,000 ppm	20,000 ppm
Male			
15-Month Interim Evaluation			
Number Examined	10	9	10
Centrilobular Hepatocyte Hypertrophy[a]	0	9** (2.9)[b]	8** (2.9)
Pigmentation	0	9** (1.1)	10** (1.2)
Hepatocellular Adenoma	0	2	4*
Hepatocellular Adenoma or Carcinoma	0	3	4*
2-Year Study			
Number Examined	50	51	50
Basophilic Focus	0	4 (1.0)	3 (1.0)
Centrilobular Hepatocyte Hypertrophy	0	17** (2.0)	13** (2.0)
Clear Cell Focus	4 (1.3)	4 (1.0)	2 (1.0)
Eosinophilic Focus	0	6** (1.5)	1 (1.0)
Pigmentation	1 (3.0)	50** (1.1)	47** (1.4)
Hepatocellular Adenoma (Multiple)	6	29**	31**
Hepatocellular Adenoma (Single or Multiple)			
Overall rate[c]	10/50 (20%)	38/51 (75%)	39/50 (78%)
Terminal rate[d]	9/40 (23%)	20/22 (91%)	21/23 (91%)
Adjusted rate[e]	24.3%	94.7%	95.0%
First incidence (days)	723	451	484
Logistic regression test[f]	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma (Multiple)	1	3	9**
Hepatocellular Carcinoma (Single or Multiple)			
Overall rate	9/50 (18%)	18/51 (35%)	21/50 (42%)
Terminal rate	7/40 (18%)	10/22 (45%)	9/23 (39%)
Adjusted rate	21.1%	58.1%	58.4%
First incidence (days)	445	505	535
Logistic regression test	P=0.002	P=0.017	P=0.003
Hepatocellular Adenoma or Carcinoma[g]			
Overall rate	18/50 (36%)	43/51 (84%)	42/50 (84%)
Terminal rate	15/40 (38%)	21/22 (95%)	22/23 (96%)
Adjusted rate	41.7%	97.7%	97.7%
First incidence (days)	445	451	484
Logistic regression test	P<0.001	P<0.001	P<0.001
Hepatoblastoma	0	3	5*

(continued)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected mice: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Number of animals with neoplasm per number of animals with liver examined microscopically

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Female			
15-Month Interim Evaluation			
Number Examined	10	10	10
Pigmentation	0	10** (1.0)	9** (1.0)
Hepatocellular Adenoma (Multiple)	0	1	4*
Hepatocellular Adenoma (Single or Multiple)	0	2	7**
Hepatocellular Adenoma or Carcinoma	0	2	8**
2-Year Study			
Number Examined	50	50	50
Basophilic Focus	0	4 (1.3)	5* (1.2)
Clear Cell Focus	0	10** (1.2)	9** (1.6)
Eosinophilic Focus	0	4* (1.5)	2 (2.5)
Pigmentation	0	44** (1.1)	49** (1.6)
Hepatocellular Adenoma (Multiple)	0	40**	45**
Hepatocellular Adenoma (Single or Multiple)			
Overall rate	6/50 (12%)	45/50 (90%)	49/50 (98%)
Terminal rate	6/39 (15%)	32/34 (94%)	33/33 (100%)
Adjusted rate	15.4%	95.7%	100.0%
First incidence (days)	729 (T)	442	501
Logistic regression test	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma (Multiple)	0	13**	13**
Hepatocellular Carcinoma (Single or Multiple)			
Overall rate	0/50 (0%)	23/50 (46%)	27/50 (54%)
Terminal rate	0/39 (0%)	17/34 (50%)	16/33 (48%)
Adjusted rate	0.0%	57.2%	60.8%
First incidence (days)	–[h]	503	538
Logistic regression test	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma or Carcinoma[i]			
Overall rate	6/50 (12%)	46/50 (92%)	50/50 (100%)
Terminal rate	6/39 (15%)	33/34 (97%)	33/33 (100%)
Adjusted rate	15.4%	97.9%	100.0%
First incidence (days)	729 (T)	442	501
Logistic regression test	P<0.001	P<0.001	P<0.001
Hepatoblastoma	0	0	2

[d] Observed incidence in animals surviving until the end of the study
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[f] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[g] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 531/1,466 (36.2% ± 14.1%); range, 10%-68%
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 247/1,462 (16.9% ± 10.7%); range, 3%-42%

Forestomach: Squamous cell papillomas were observed in 20,000 ppm males and in 10,000 and 20,000 ppm females at the 15-month interim evaluation (Tables 25, C1, and D1). At the end of the 2-year study, the incidences of squamous cell papilloma and squamous cell carcinoma in exposed groups of males and females were significantly increased (Tables 25, C3, and D3). The incidences of multiple squamous cell papilloma in 20,000 ppm males and females were also significantly increased in the 2-year study (Tables 25, C1, and D1). Incidences of squamous cell papilloma or carcinoma (combined) in exposed groups of males and females were significantly greater than those in the controls and exceeded the NTP historical ranges for feed study controls (Tables 25, C4b, and D4b). Compared to the exophytic masses with well-differentiated squamous epithelium typical of the squamous cell papillomas, the squamous cell carcinomas were locally invasive neoplasms that sometimes resulted in perforation of the forestomach (Plate 11). Frequently, a squamous cell carcinoma appeared to arise at the base of a squamous cell papilloma. Metastatic neoplasms arising from squamous cell carcinomas of the forestomach were observed in the coagulating glands, colon, duodenum, epididymis, gallbladder, glandular stomach, jejunum, kidney, liver, lung, ovary, pancreas, prostate gland, spleen, testis, and thymus of exposed mice (Tables C1 and D1).

Nonneoplastic lesions of the forestomach included acanthosis, hyperkeratosis, and basal cell hyperplasia (Tables 25, C5, and D5). At the 15-month interim evaluation, there were exposure-related increases in the incidences and severities of acanthosis and hyperkeratosis in exposed groups of males and females. At the end of the 2-year study, the incidences and severities of these lesions in exposed groups of males and females were generally greater than those in the controls.

TABLE 25
Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach in Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	10,000 ppm	20,000 ppm
Male			
15-Month Interim Evaluation			
Number Examined	9	9	10
Acanthosis (Hyperplasia)[a]	0	2 (1.0)[b]	3 (2.0)
Basal Cell Hyperplasia	0	1 (1.0)	1 (1.0)
Hyperkeratosis	1 (2.0)	2 (1.0)	3 (2.0)
Inflammation	0	0	3 (1.2)
Squamous Cell Papilloma	0	0	5*
2-Year Study			
Number Examined	50	50	50
Acanthosis	1 (1.0)	9** (1.1)	4 (2.0)
Basal Cell Hyperplasia	0	0	2 (1.5)
Hyperkeratosis	1 (1.0)	7* (1.0)	6 (1.8)
Inflammation	2 (1.5)	6 (1.2)	13** (1.5)
Squamous Cell Papilloma (Multiple)	0	2	5*
Squamous Cell Papilloma (Single or Multiple)			
Overall rate[c]	0/50 (0%)	13/51 (25%)	16/50 (32%)
Terminal rate[d]	0/40 (0%)	10/22 (45%)	11/23 (48%)
Adjusted rate[e]	0.0%	51.0%	55.6%
First incidence (days)	–[g]	613	606
Logistic regression test[f]	P<0.001	P<0.001	P<0.001
Squamous Cell Carcinoma			
Overall rate	0/50 (0%)	12/51 (24%)	13/50 (26%)
Terminal rate	0/40 (0%)	4/22 (18%)	4/23 (17%)
Adjusted rate	0.0%	36.5%	37.7%
First incidence (days)	–	505	523
Logistic regression test	P<0.001	P<0.001	P<0.001
Squamous Cell Papilloma or Carcinoma[h]			
Overall rate	0/50 (0%)	19/51 (37%)	27/50 (54%)
Terminal rate	0/40 (0%)	11/22 (50%)	14/23 (61%)
Adjusted rate	0.0%	61.2%	73.9%
First incidence (days)	–	505	523
Logistic regression test	P<0.001	P<0.001	P<0.001

(continued)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
(T)Terminal sacrifice

TABLE 25
Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach in Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Female			
15-Month Interim Evaluation			
Number Examined	10	10	10
Acanthosis (Hyperplasia)	0	1 (1.0)	8** (2.0)
Basal Cell Hyperplasia	0	0	2 (1.5)
Hyperkeratosis	0	2 (1.0)	7** (2.0)
Inflammation	0	1 (1.0)	5* (1.6)
Squamous Cell Papilloma	0	4*	2
2-Year Study			
Number Examined	48	50	50
Acanthosis (Hyperplasia)	9 (1.7)	15 (1.7)	19* (1.6)
Basal Cell Hyperplasia	0	7* (1.4)	3 (1.7)
Hyperkeratosis	10 (1.4)	14 (1.4)	17 (1.5)
Inflammation	7 (1.4)	10 (1.4)	21** (1.7)
Squamous Cell Papilloma (Multiple)	0	4	14**
Squamous Cell Papilloma (Single or Multiple)			
Overall rate	2/50 (4%)	16/50 (32%)	27/50 (54%)
Terminal rate	2/39 (5%)	12/34 (35%)	23/33 (70%)
Adjusted rate	5.1%	41.7%	72.4%
First incidence (days)	729 (T)	671	538
Logistic regression test	P<0.001	P<0.001	P<0.001
Squamous Cell Carcinoma			
Overall rate	0/50 (0%)	12/50 (24%)	11/50 (22%)
Terminal rate	0/39 (0%)	8/34 (24%)	5/33 (15%)
Adjusted rate	0.0%	30.9%	27.3%
First incidence (days)	–	587	501
Logistic regression test	P=0.002	P<0.001	P<0.001
Squamous Cell Papilloma or Carcinoma[i]			
Overall rate	2/50 (4%)	25/50 (50%)	34/50 (68%)
Terminal rate	2/39 (5%)	18/34 (53%)	25/33 (76%)
Adjusted rate	5.1%	60.7%	80.5%
First incidence (days)	729	587	501
Logistic regression test	P<0.001	P<0.001	P<0.001

[a] Number of animals with lesion
[b] Average severity grade of lesions in affected mice: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Number of animals with neoplasm per number of animals necropsied
[d] Observed incidence in animals surviving until the end of the study
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[f] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[g] Not applicable; no neoplasms in animal group
[h] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 22/1,474 (1.5% ± 2.0%); range, 0%-6%
[i] Historical incidence: 33/1,470 (2.2% ± 3.1%); range, 0%-14%

Lung: Alveolar/bronchiolar adenomas were observed in exposed groups of males and females at the 15-month interim evaluation (Tables 26, C1, and D1). During the 2-year study, the incidences of alveolar/bronchiolar adenomas in exposed groups of males and females were significantly increased (Tables 26, C3, and D3). In male mice, the incidences of multiple alveolar/bronchiolar adenomas in exposed groups were significantly greater than that in the controls (Tables 26, C1, and D1). The incidences of alveolar/bronchiolar adenoma in exposed groups of males and females exceeded the NTP historical ranges for feed study controls (Tables 26, C4c, and D4c). The alveolar/bronchiolar adenomas were generally well-circumscribed, expansile masses that slightly compressed the surrounding normal pulmonary alveolar tissue (Plate 12). Well-differentiated cuboidal to columnar epithelial cells formed papillary structures or solid foci that filled alveolar spaces.

TABLE 26
Incidences of Neoplasms of the Lung in Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	10,000 ppm	20,000 ppm
Male			
15-Month Interim Evaluation			
Number Examined	10	9	10
Alveolar/bronchiolar Adenoma[a]	0	3	5*
2-Year Study			
Number Examined	50	51	50
Alveolar/bronchiolar Hyperplasia	1 (1.0)[b]	0	4 (1.3)
Alveolar/bronchiolar Adenoma (Multiple)	0	6**	9**
Alveolar/bronchiolar Adenoma (Single or Multiple)			
Overall rate[c]	7/50 (14%)	26/51 (51%)	24/50 (48%)
Terminal rate[d]	6/40 (15%)	12/22 (55%)	12/23 (52%)
Adjusted rate[e]	16.8%	71.0%	66.5%
First incidence (days)	445	578	248
Logistic regression test[f]	P<0.001	P<0.001	P<0.001
Alveolar/bronchiolar Carcinoma			
Overall rate	3/50 (6%)	4/51 (8%)	1/50 (2%)
Terminal rate	2/40 (5%)	2/22 (9%)	0/23 (0%)
Adjusted rate	6.9%	15.9%	3.0%
First incidence (days)	393	673	648
Logistic regression test	P=0.259N	P=0.512	P=0.251N
Alveolar/bronchiolar Adenoma or Carcinoma[g]			
Overall rate	10/50 (20%)	28/51 (55%)	25/50 (50%)
Terminal rate	8/40 (20%)	13/22 (59%)	12/23 (52%)
Adjusted rate	23.3%	75.0%	67.5%
First incidence (days)	393	578	248
Logistic regression test	P<0.001	P<0.001	P=0.002

(continued)

TABLE 26
Incidences of Neoplasms of the Lung in Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Female			
15-Month Interim Evaluation			
Number Examined	10	10	10
Alveolar/bronchiolar Adenoma	0	3	2
2-Year Study			
Number Examined	50	50	49
Alveolar/bronchiolar Hyperplasia	0	0	1 (1.0)
Alveolar/bronchiolar Adenoma (Multiple)	0	2	1
Alveolar/bronchiolar Adenoma (Single or Multiple)			
Overall rate	4/50 (8%)	17/50 (34%)	13/49 (27%)
Terminal rate	3/39 (8%)	14/34 (41%)	9/33 (27%)
Adjusted rate	9.8%	45.6%	33.5%
First incidence (days)	685	587	538
Logistic regression test	P=0.017	P=0.001	P=0.015
Alveolar/bronchiolar Carcinoma	0	0	2
Alveolar/bronchiolar Adenoma or Carcinoma[h]			
Overall rate	4/50 (8%)	17/50 (34%)	15/49 (31%)
Terminal rate	3/39 (8%)	14/34 (41%)	10/33 (30%)
Adjusted rate	9.8%	45.6%	37.9%
First incidence (days)	685	587	538
Logistic regression test	P=0.006	P=0.001	P=0.005

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected mice: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Number of animals with neoplasm per number of animals with lung examined microscopically
[d] Observed incidence in animals surviving until the end of the study
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[f] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[g] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 265/1,469 (18.0% ± 7.6%); range, 4%-32%
[h] Historical incidence: 110/1,469 (7.5% ± 5.0%); range, 2%-26%

Kidney: Pigmentation was present in the kidneys of most mice after 2 years of exposure to 1-amino-2,4-dibromoanthraquinone (males: 0 ppm, 0/50; 10,000 ppm, 42/51; 20,000 ppm, 43/50; females: 0/50, 43/50, 43/50; Tables C5 and D5). This brown, granular pigment in the renal tubule epithelium and tubule lumina resembled the pigment described in the liver. There were no other chemical-related lesions in the kidney.

Uterus: There was a significant, but not exposure-related, increase in the incidence of uterine polyps or sarcomas (combined) (0/50, 5/50, 0/50; Table D1) in the 10,000 ppm females. Although this incidence (10%) was above the average for historical controls (3.5%), the combined incidence was within the historical control range (0%-16%; Table D4d). This marginal increase was not considered to be chemical related. There were no chemical-related nonneoplastic lesions in the reproductive tract (Table D5).

Pituitary Gland: A significant, but not exposure-related, increase in the incidence of adenoma of the pituitary gland (pars distalis) was observed in the 10,000 ppm females (1/43, 9/45, 4/43; Table D1). The incidence of adenoma (20%) in the 10,000 ppm females is slightly above the average for historical controls (15.2%), but is within the historical range (2%-36%; Table D4e). This marginal increase was not considered to be chemical related. The incidence of hyperplasia of the pars distalis of the pituitary gland was also increased in the 10,000-ppm females (7/43, 22/45, 7/43; Table D5).

DISPOSITION AND METABOLISM STUDIES

Adult male F344/N rats received [^{14}C]-labeled 1-amino-2,4-dibromoanthraquinone as a single intravenous dose of 0.4 mg 1-amino-2,4-dibromoanthraquinone/kg body weight or as a single oral dose of 2, 23, 118, 814, or 1,473 mg/kg. After excreta were collected for 72 hours, the animals were killed, and tissues were removed for analysis. Additional animals that received intravenous doses of 1-amino-2,4-dibromoanthraquinone were killed 0.25, 0.75, 2, 6, or 24 hours after chemical administration, and their tissues were analyzed. A 6-hour bile cannulation study was also performed.

From day 0 through day 3 after intravenous administration of [^{14}C]-1-amino-2,4-dibromoanthraquinone, about 50% of the ^{14}C was excreted in the feces, 15% in the urine, and 6% in expired air. Unmetabolized 1-amino-2,4-dibromoanthraquinone accounted for less than 3% of the excreted ^{14}C after intravenous administration. The amount of an oral dose that was absorbed was calculated from the percent of the dose that was excreted in expired air or urine after oral administration versus the percent of the dose excreted after intravenous administration. Excretion of ^{14}C in expired air yielded the most consistent results. For oral doses greater than or equal to 2 mg/kg, the amount of the dose that was absorbed fitted the equation: $absorbed\ dose = 6.6 \log(dose)$, with both doses expressed in mg/kg. While 90% of the 2 mg/kg dose was absorbed, only 2% of the 814 mg/kg dose was absorbed.

Two hours after intravenous administration, less than 3% of the circulating ^{14}C was attributed to the parent compound. The metabolites of 1-amino-2,4-dibromoanthraquinone in blood were primarily in the plasma fraction (blood:plasma ratio of approximately 0.5:1). The highest concentrations of ^{14}C in tissues 15 minutes after intravenous dosing were in excretory organs, lung, kidney, small intestine, liver, adipose tissue, and adrenal gland. Tissue:blood ratios (TBR) for these tissues were greater than or equal to 3:1. Only the liver and kidney had TBRs significantly greater than 1:1 at 72 hours. The terminal half-life of ^{14}C was approximately 40 hours in the liver and approximately 90 hours in the kidney. Adipose tissue contained primarily unmetabolized 1-amino-2,4-dibromoanthraquinone at 24 hours; liver, muscle, and skin contained mostly metabolites of 1-amino-2,4-dibromoanthraquinone. The elimination half-life of 1-amino-2,4-dibromoanthraquinone in adipose tissue was approximately 11 hours.

GENETIC TOXICOLOGY

1-Amino-2,4-dibromoanthraquinone (100 to 10,000 µg/plate) was tested for induction of gene mutations in four strains of *Salmonella typhimurium* in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table G1; Haworth *et al.*, 1983). 1-Amino-2,4-dibromoanthraquinone was

positive in the absence of S9 in the frameshift strains TA98 and TA1537; with S9, an equivocal response was obtained in TA1537, and TA98 was negative. In TA100, 1-amino-2,4-dibromoanthraquinone gave equivocal responses with and without S9, and all trials were negative with TA1535. The equivocal calls were the results of positive or weakly positive responses that were not duplicated in a second trial. Precipitation of 1-amino-2,4-dibromoanthraquinone occurred at concentrations of 100 µg/plate and above, and this may have been a factor in the nonreproducibility of the results.

1-Amino-2,4-dibromoanthraquinone was tested in two laboratories for induction of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9. In the sister chromatid exchange test, one laboratory observed a significant increase in sister chromatid exchanges only in the absence of S9, while the second laboratory recorded positive responses with and without S9 (Table G2; Loveday *et al.*, 1990). This discrepancy cannot be explained by a difference in dose levels employed at the two laboratories because the positive responses with S9 were observed at 3, 10, 15, and 30 µg/mL at the second laboratory, whereas negative trials resulted from testing doses up to 100 µg/mL at the first laboratory. In the chromosomal aberrations test, one laboratory observed a weakly positive response only in the absence of S9 (Table G3). Another laboratory obtained a positive response in the first trial without S9 but did not duplicate the positive response in the second trial, and the overall call without S9 was concluded to be equivocal (Loveday *et al.*, 1990). Neither laboratory observed an increase in chromosomal aberrations with 1-amino-2,4-dibromoanthraquinone in the presence of S9.

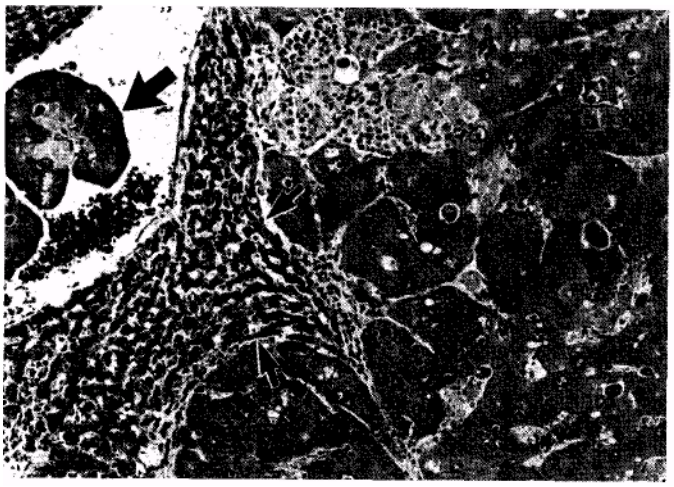


PLATE 1

An hepatocellular carcinoma in a female F344/N rat exposed to 10,000 ppm 1-amino-2,4-dibromoanthraquinone in feed for 2 years. Note compression of normal liver (small arrows) by neoplastic hepatocytes. Carcinoma embolus (large arrow) is in an hepatic vein. H&E; 90x

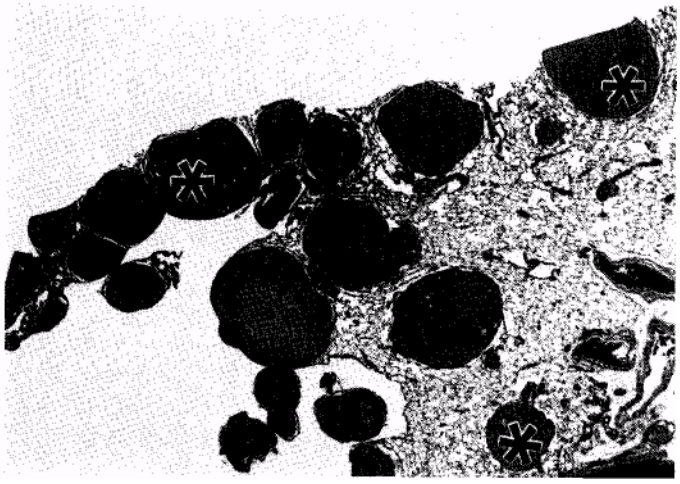


PLATE 2

Multiple metastatic foci (*) of an hepatocellular carcinoma in the lung of a female F344/N rat exposed to 5,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years. H&E; 15x

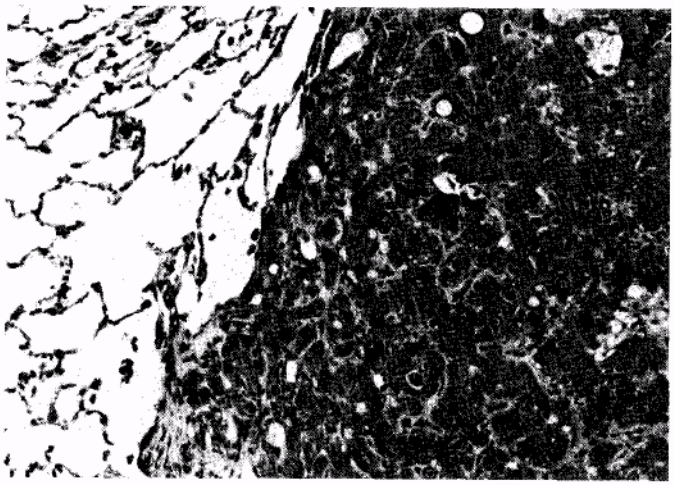


PLATE 3

Detail of a metastatic focus of the hepatocellular carcinoma shown in Plate 2 shows the solid and acinar growth patterns of the well-differentiated neoplastic hepatocytes. H&E; 90x

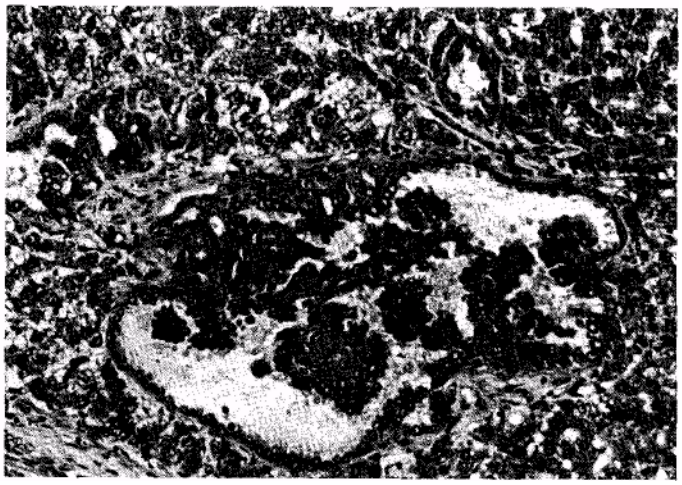


PLATE 4

An hepatocholangiocarcinoma in a female F344/N rat exposed to 10,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years. Note the well-differentiated hepatocyte (solid areas) and biliary components within the neoplasm. H&E; 140x

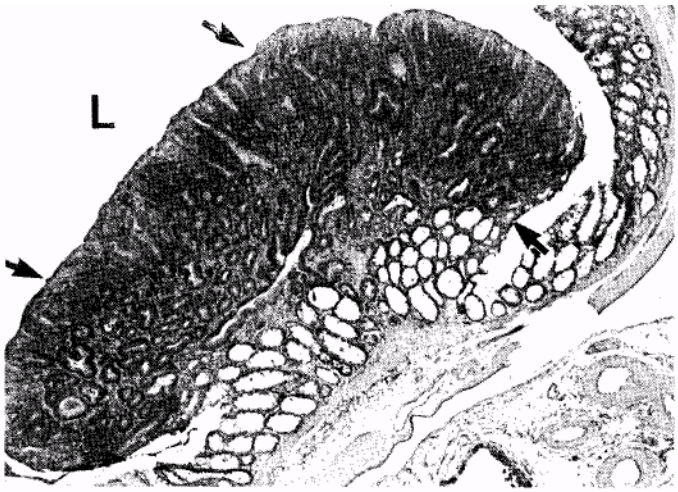


PLATE 5
An adenoma (adenomatous polyp) in the colon of a female F344/N rat exposed to 10,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years forms an exophytic mass (arrows) that partially occludes the intestinal lumen (L). H&E; 25*

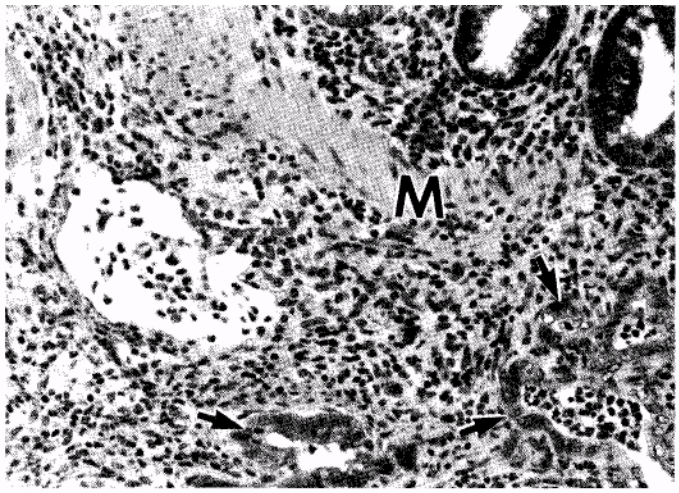


PLATE 6
Detail of a carcinoma in the colon of a female F344/N rat exposed to 10,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years. Note the disruption of the muscularis mucosa (M) layer at right with formation of irregular-shaped neoplastic glands (arrows), inflammation, and fibrosis in the submucosa. H&E; 160x

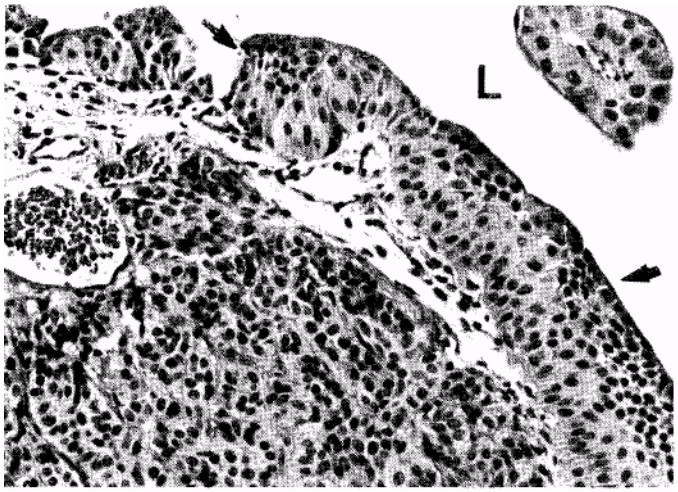


PLATE 7
A transitional cell carcinoma in the urinary bladder of a female F344/N rat exposed to 10,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years. Note the thickened neoplastic mucosal surface and a papillary projection of the neoplasm extending into the bladder lumen (L). The mucosal surface consists of a thickened layer of neoplastic transitional cells (arrows); a large nodule of transitional epithelium invades the wall of the urinary bladder. H&E; 160x

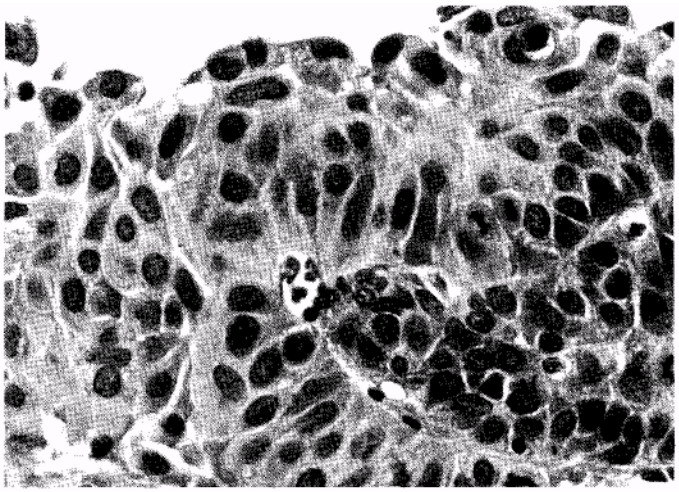


PLATE 8
Detail of the transitional cell carcinoma shown in Plate 7 shows cellular atypia and an increased number of mitotic cells. H&E; 320x

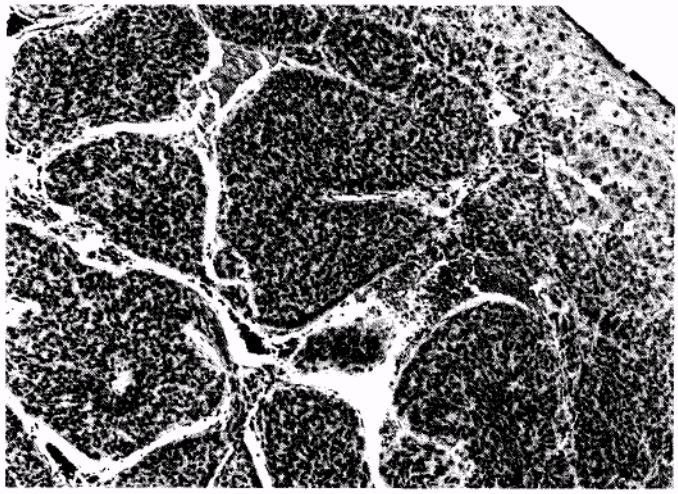


PLATE 9
An hepatoblastoma in the liver of a female B6C3F$_1$ mouse exposed to 20,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years consists of prominent neoplasm lobules separated by vascular channels. H&E; 80x

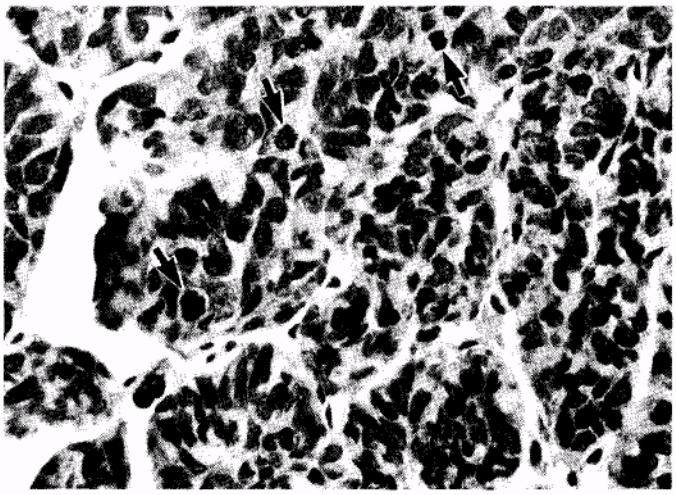


PLATE 10
Detail of the hepatoblastoma shown in Plate 9 shows closely packed undifferentiated neoplastic cells with scant cytoplasm, oval nuclei, and numerous mitotic cells (arrows). H&E; 320x

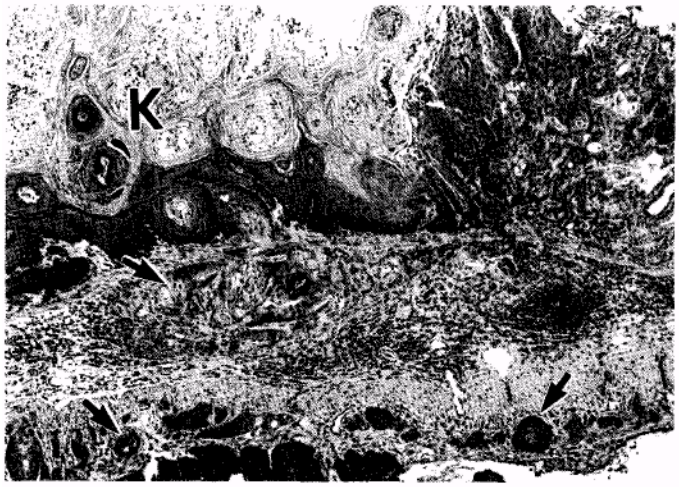


PLATE **11**
A squamous cell carcinoma of the forestomach in a male B6C3F$_1$ mouse exposed to 20,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years. Note the thickened keratin (K) layer on the mucosal surface and invasion of the wall by nodules (arrows) of neoplastic squamous cells that have extended through the peritoneal surface of the stomach. H&E; 40x

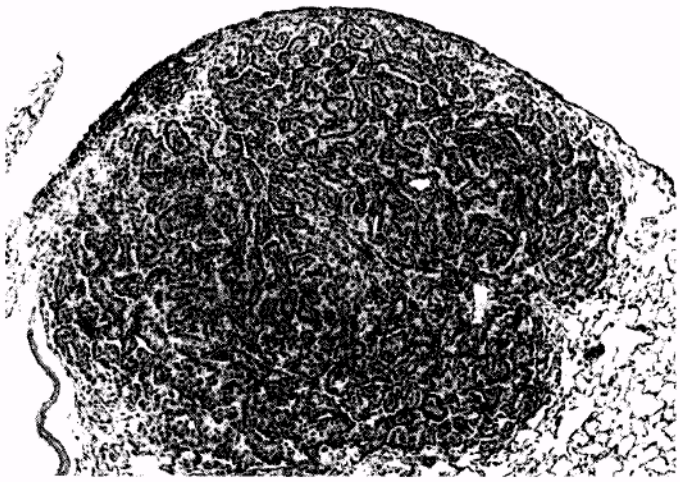


PLATE 12
An alveolar/bronchiolar adenoma of the lung in a male B6C3F$_1$ mouse exposed to 20,000 ppm l-amino-2,4-dibromoanthraquinone in feed for 2 years forms a non-encapsulated subpleural nodule. H&E; 60*

DISCUSSION AND CONCLUSIONS

Anthraquinones represent the largest group of naturally occurring quinones. Both natural and synthetic anthraquinones have been and continue to be widely used as colorants in food, drugs, cosmetics, hair dyes, and textiles. Dantron (1,8-dihydroxyanthraquinone) and emodin (1,3,8-trihydroxy-6-methylanthraquinone) are also used therapeutically as cathartics and purgatives. Chrysophanol (1,8-dihydroxy-3-methylanthraquinone) occurs in cascara sagrada, senna, and various species of *Rumex* and *Rheum* (rhubarb).

Anthraquinone and five substituted anthraquinones were selected for toxicologic characterization from a large group of amino-, alkyl-, nitro-, or halogen-containing anthraquinones. The basis for selection centered mainly on four criteria: 1) lack of available data on carcinogenicity, 2) magnitude of production and use patterns, 3) awareness of potential and actual human exposure, 4) and representation of as broad a spectrum of structural diversity within this class as possible. 1-Amino-2,4-dibromoanthraquinone was selected from a group of 36 environmentally significant aryl bromides. Since all other substituted anthraquinone chemicals already evaluated for long-term effects induced carcinogenic responses in laboratory animals (NCI, 1978a, 1978b, 1978c; IARC, 1982, 1987; NTP, 1986a), 1-amino-2,4-dibromoanthraquinone was predicted to be carcinogenic in laboratory animals as well (Fung *et al.,* 1993).

1-Amino-2,4-dibromoanthraquinone was studied for long-term toxicity and carcinogenesis using a "start-stop" experimental design. One of the first chemicals to be studied by the National Toxicology Program (NTP) with a start-stop protocol, 1-amino-2,4-dibromoanthraquinone was predicted to be carcinogenic, so the experimental design was selected in an attempt to gain some insight into the progression and/or regression of chemical-induced lesions as well as to perhaps gain knowledge about potential mechanisms of action.

Because 1-amino-2,4-dibromoanthraquinone caused significant carcinogenic responses in male and female rats and mice and in several organs and tissues, the discussion of lesions that follows has been grouped by organ.

Liver: 1-Amino-2,4-dibromoanthraquinone differs from other chemicals studied by the NTP because it induced greater than 90% incidences of multiple benign and malignant hepatocellular neoplasms in rats with frequent metastases (almost 50%) of the malignant liver neoplasms. Although other chemicals including 3,3′-dimethylbenzidine dihydrochloride (NTP, 1991) and furan (NTP, 1993a) have caused significant increases in benign and malignant liver neoplasms that approach a 100% incidence, metastases occurred in only one or two instances in a group of 50 rats. Only in the 18-month study of methyl carbamate (NTP, 1988) has a similarly high incidence of malignant, metastatic liver neoplasms occurred in male rats.

The liver lesions present after 13 weeks in the 25,000 and 50,000 ppm groups of rats included proliferative bile duct lesions (cholangiofibrosis) and foci of hepatocellular alteration. Based on morphological features of this proliferative bile duct lesion and results of transplantation and stop-exposure studies, cholangiofibrosis has been considered a "premalignant" lesion which is autonomous and progressive and not qualitatively different from cholangiocarcinoma (Maronpot *et al.,* 1991). While there is some disagreement on the biological behavior of cholangiofibrosis, this has generally been considered to be a preneoplastic lesion (Bannasch and Massner, 1976; Ohshima *et al*., 1984). Cholangiofibrosis has been described in toxicity studies of methapyrilene (Ohshima *et al.*, 1984), aflatoxin (Wilson *et al.,* 1985), and furan (NTP, 1993a) in rats.

Exposure concentrations of 1-amino-2,4-dibromoanthraquinone administered in the 2-year study were below those which produced cholangiofibrosis at 13 weeks; however, many of the benign and malignant liver neoplasms in the 2-year study in rats were composed of a mixed growth pattern of both hepatocytes and bile duct formation. The incidences of foci

of hepatocellular alteration were increased with 1-amino-2,4-dibromoanthraquinone exposure at 13 weeks and all scheduled intervals examined during the 2-year study. A detailed analysis of foci of hepatocellular alteration in the liver of rats from this study has been reported by Harada *et al.* (1989). In addition to overall exposure-related increased incidences of eosinophilic and clear cell foci of alteration, there were increases in size, number, and volume fraction of atypical eosinophilic, basophilic, and clear cell foci in rats that correlated with concentration and duration of 1-amino-2,4-dibromoanthraquinone exposure.

Although foci of hepatocellular alteration in rats are believed to be precursors of liver neoplasms, their biological nature and potential for progression to neoplasms is uncertain (Popp and Goldsworthy, 1989; Squire, 1989). Some of this uncertainty results from a considerable variation in phenotypes of hepatocellular foci and the different biomarkers used in their classification. In many studies, the conversion rate of foci to neoplasms has been considered to be extremely low, and, in some instances, increases in the incidences of basophilic foci have not been associated with liver neoplasms (MacDonald *et al.,* 1988; Harada *et al.,* 1989; Squire, 1989). Clear and acidophilic cell foci have been suggested to be important in the development of some chemical-induced liver neoplasms (Bannasch *et al.*, 1989; Bannasch and Zerban, 1992). The atypical eosinophilic foci that occurred in rats administered 1-amino-2,4-dibromoanthraquinone were rarely observed in controls or in groups of rats receiving other hepatocarcinogens (Harada *et al.*, 1989). Adenomas in the livers of rats treated with 1-amino-2,4-dibromoanthraquinone often contained cells morphologically identical to those in the atypical eosinophilic foci, suggesting that some of these foci may have been precursors for the hepatic neoplasms.

Liver effects in male mice administered 1-amino-2,4-dibromoanthraquinone for 13 weeks consisted of pigmentation and hypertrophy that persisted throughout the 2-year study. Although hypertrophy did not occur in female mice during this early period, pigmentation in the liver was present by 15 months. Foci of hepatocellular alteration were not present in the 13-week study, and after 2 years, the incidences were only slightly increased in mice. After 2 years, there were increased incidences of liver neoplasms in all groups of mice exposed to 1-amino-2,4-dibromoanthraquinone in feed. This response was more prominent in females that also had a greater number of hepatocellular carcinomas and more multiple liver neoplasms than male mice. Unlike the highly metastatic liver neoplasms observed in rats, only a few neoplasms in mice had detectable metastatic foci. The incidences of hepatoblastomas were also increased in the exposed groups of male and female mice. These distinctive liver neoplasms rarely occur in control animals but have been induced in mice administered acetylaminofluorene (Nonoyama *et al.*, 1988) or *N*-nitrosodiethylamine (Ward *et al.*, 1983).

Large Intestine: Adenomatous polyps (adenomas) and carcinomas of the large intestine (distal colon and rectum) in rats were generally observed after 15 months of exposure to 1-amino-2,4-dibromoanthraquinone, although one adenomatous polyp (adenoma) was observed as early as 9 months in the 20,000 ppm group of male rats in the "stop-exposure" study. Further, these lesions were often grossly visible. Even when exposure was stopped after 9 months, the percentage of chemical-induced rectal neoplasms was equal to or greater than that observed with continuous exposure for 15 months. In many rats, these neoplasms were multiple and malignant, based upon local invasion and/or metastases. Neoplasms of the large intestine have not been observed for other previously tested anthraquinones. One other chemical studied by the NTP, bromodichloromethane (NTP, 1987a), resulted in similarly high incidences of benign and malignant neoplasms of the large intestine.

Kidney: Accumulation of pigment in the kidney was observed in both male and female rats by 13 weeks and throughout the 2-year study. 1-Amino-2,4-dibromoanthraquinone (or metabolite) pigment in the kidney of mice was not evident until after the 15-month evaluation; there were no increased incidences of other nonneoplastic lesions or neoplasms of the kidney in mice. In the kidney of rats, several changes in addition to pigment were present at 13 weeks. In male rats, increased accumulation of hyaline droplets was observed in the cytoplasm of the renal tubule epithelium, yet no chemical-related exacerbation of renal tubule epithelial regeneration was observed at 13 weeks. There was a slight enlargement (karyomegaly) of some nuclei in the renal tubule epithelium of male and female rats. At

the 15-month evaluation, this slight nuclear enlargement was still evident, and the severity of nephropathy (tubule epithelial regeneration; transitional cell hyperplasia of the renal pelvis) was increased in exposed male and female rats. Accumulation of hyaline droplets was not present in exposed male rats after the 9-month evaluation. The morphological appearance of hyaline droplets and their presence only in males is suggestive of accumulation of $\alpha_{2\mu}$-globulin in the renal tubule epithelium, although the identity of the protein droplets was not determined. Their absence in the kidney tubule cells of exposed male rats after the 9-month evaluation is consistent with the normally decreased production of $\alpha_{2\mu}$-globulin by the liver beginning at 5 months of age (Baetcke *et al*., 1991). Chemicals that cause a hyaline droplet nephropathy syndrome are often empirically associated with increases in the incidences of benign and malignant renal tubule neoplasms, linear foci of mineralization of the renal medulla, and enhanced nephropathy in male rats after 2 years (Baetcke *et al.*, 1991); however, other alternative mechanistic explanations exist that do not show a dominant role for $\alpha_{2\mu}$-globulin. The key to this view centers on several chemicals that incite the "hyaline droplet syndrome," yet do not induce tubule cell neoplasms of the kidney (Barrett and Huff, 1991; Huff, 1992, 1993; Melnick, 1992). Another strong neoplastic response in the kidney of female rats shows that mechanisms other than those associated with hyaline droplet nephropathy were involved in the renal tubule neoplasm response in rats administered 1-amino-2,4-dibromoanthraquinone. Increased incidences of benign and malignant neoplasms of the kidney occurred in male and female rats in the NTP study of bromodichloromethane (NTP, 1987a).

Urinary Bladder: Chemical-related increased incidences of proliferative lesions (hyperplasia and neoplasia) of the transitional cell epithelium of the urinary bladder occurred in male and female rats with a greater number of neoplasms observed in female rats (45/146, 31%) than in male rats (16/146, 11%). In the stop-exposure groups, transitional cell hyperplasia was present in four female rats at 9 months, and, with the absence of continued chemical exposure, hyperplasia did not develop in male rats at the 15-month evaluation. A transitional cell carcinoma occurred in one female rat from the 15-month exposure group. With continuous exposure to 1-amino-2,4-dibromoanthraquinone, benign and malignant neoplasms of the urinary bladder developed by 15 months in female rats and in both male and female rats after 2 years of exposure. In rats following chronic administration of 1,4,5,8-tetraaminoanthraquinone, a spectrum of nonneoplastic lesions and neoplasms of the urinary bladder was observed with similar morphologic features including squamous metaplasia, squamous cell carcinoma, and proliferation of fat (fatty metaplasia) in the wall of the urinary bladder (NTP, 1986a). In that study, calculi were present in the urinary bladder of most rats, yet there was a significant increase in the incidence of smooth muscle neoplasms of the wall of the urinary bladder. The hypothesis of cell proliferation and development of urinary bladder neoplasms has been described (Greenfield *et al.*, 1984; Cohen *et al.*, 1991). The mechanism for formation of neoplasms of the urinary bladder is uncertain. Increased cell proliferation evidenced by transitional cell hyperplasia in the urinary bladder did not occur before 9 months in rats. Potential local irritant effects and associated neoplasm formation in the urinary bladder attributed to calculus formation (Okumara *et al.*, 1992) were not identified in this study. Most mice in that study had calculi of the urinary bladder, yet did not have any evidence of carcinogenic activity. No scientific consensus exists that endorses the notion that calculi or stones cause cancer; there may be some co-carcinogenic or promotion activity, yet even this does not occur consistently (Huff, 1992, 1993).

Forestomach: In both rats and mice, there were several nonneoplastic proliferative and inflammatory lesions in the forestomach at the end of the 2-year studies. These forestomach lesions were not observed in either species in the 13-week studies or in rats at the 9- and 15-month evaluations. In the stop-exposure evaluation, rats exposed to 20,000 ppm developed nonneoplastic lesions of the forestomach by 15 months. However, in the 9-month stop-exposure group, forestomach lesions were observed in a few males by the 15-month evaluation, but the incidences were higher than those observed in male rats with the continuous 15-month exposure. In female rats, forestomach lesions were present at 15 months with continuous exposure but were not observed at 9 months or after 6 months of nonexposure. Chemical-related lesions consisted of hyperplasia, hyperkeratosis and associated inflammation, and focal erosion or ulceration of the squamous mucosa. The inflammatory and ulcerative lesions were generally more severe and more common in

rats, but significant increases in the incidences of benign and malignant forestomach neoplasms were limited to mice. These data provide further evidence that inflammation or ulceration does not always result in neoplasia (Berenblum, 1944; Huff, 1992, 1993; Melnick *et al*., 1993a, 1993b). The absence of forestomach neoplasms in rats may have been related to lower exposure concentrations. Many of the malignant forestomach neoplasms of mice metastasized or invaded adjacent organs.

Increases in the incidences of forestomach neoplasms have not been observed in mice or rats following long-term administration of four other structurally related anthraquinones. However, administration of 1-amino-2-methylanthraquinone (NCI, 1978b) to rats for 62 weeks followed by a 6-month nonexposure period was associated with an increased incidence in hyperplasia of the forestomach. Administration of 2-methyl-1-nitroanthraquinone (NCI, 1978c) to rats for 78 weeks followed by a 6-month nonexposure period was also associated with an increased incidence of proliferative lesions of the forestomach. Marked increases in the incidences of forestomach neoplasms have been reported for some chemicals that caused a sustained proliferative response in the squamous mucosa that was evident within the first 2 to 13 weeks of chemical administration (NTP, 1987b). However, a number of other chemicals causing forestomach neoplasms in rodents have not been associated with an early, sustained increase in the incidence of hyperplasia (NTP, 1990a, 1990b, 1990c).

Lung: The incidences of alveolar/bronchiolar adenoma and multiple alveolar/bronchiolar adenoma (males only) of the lung were significantly increased in mice in the 10,000 and 20,000 ppm groups. Although there was no evidence for an increase in the incidence of hyperplasia or for a progression of the lung neoplasms to malignancy, the incidence of adenoma in all four exposure groups exceeded the NTP historical control ranges. Administration of a structurally related anthraquinone, C.I. Disperse Blue 1 (1,4,5,8-tetraaminoanthraquinone) (NTP, 1986a), resulted in a marginal increase in the incidence of alveolar/bronchiolar adenoma in male mice with no associated increase in the incidence of alveolar/bronchiolar hyperplasia. Other chemicals tested by the NTP have also caused increased incidences of lung neoplasms without increased incidences of alveolar/bronchiolar hyperplasia (NTP, 1994), but more commonly an increase in the incidence of alveolar/bronchiolar hyperplasia or inflammation is also present with increased incidences of lung neoplasms (NTP, 1986b, 1989, 1990a, 1992). Although the incidence of alveolar/bronchiolar carcinoma was not increased in the lungs of mice administered 1-amino-2,4-dibromoanthraquinone, a number of chemicals have induced both alveolar/bronchiolar adenomas and carcinomas (NTP, 1990b, 1990c, 1993b; Huff, 1994).

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** of 1-amino-2,4-dibromoanthraquinone in male and female F344/N rats based on increased incidences of neoplasms in the liver, large intestine, kidney, and urinary bladder. There was *clear evidence of carcinogenic activity* of 1-amino-2,4-dibromoanthraquinone in male and female B6C3F$_1$ mice based on increased incidences of neoplasms in the liver, forestomach, and lung.

Exposure of male and female rats to 1-amino-2,4-dibromoanthraquinone for 2 years was associated with basophilic focus (males only), clear cell focus, eosinophilic focus, and pigmentation in the liver; renal tubule hyperplasia, renal tubule pigmentation, and transitional cell hyperplasia in the kidney; transitional cell hyperplasia, squamous metaplasia, and stromal metaplasia (females only) in the urinary bladder; squamous hyperplasia, hyperkeratosis, ulceration, and inflammation of the forestomach mucosa; and seminal vesicle atrophy. Exposure of male and female mice to 1-amino-2,4-dibromoanthraquinone for 2 years was associated with centrilobular hepatocellular hypertrophy (males only), basophilic focus, clear cell focus (females only), eosinophilic focus, and pigmentation in the liver; pigmentation in the kidney; and hyperplasia, basal cell hyperplasia, hyperkeratosis, and inflammation of the forestomach mucosa.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS
IN THE 2-YEAR FEED STUDY
OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Disposition Summary				
Animals initially in study	70	50	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10			10
Early deaths				
Moribund	19	15	34	33
Natural deaths	5	1	5	7
Survivors				
Died last week of study	3			
Terminal sacrifice	23	24	21	10
Animals examined microscopically	70	50	69[b]	70
9-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma			1 (10%)	
Endocrine System				
Adrenal medulla	(10)	(10)	(10)	(10)
Ganglioneuroma			1 (10%)	
Thyroid gland	(10)	(10)	(10)	(10)
Nervous System				
Brain	(10)	(10)	(10)	(10)
Cerebrum, meningioma benign	1 (10%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
15-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(9)			(10)
Polyp adenomatous				6 (60%)
Liver	(10)			(10)
Hepatocellular carcinoma				4 (40%)
Hepatocellular carcinoma, multiple				3 (30%)
Hepatocellular adenoma				2 (20%)
Hepatocellular adenoma, multiple				2 (20%)
Pancreas	(10)			
Adenoma	1 (10%)			
Stomach, forestomach	(10)			(10)
Endocrine System				
Pituitary gland	(8)			
Pars distalis, adenoma	1 (13%)			
Thyroid gland	(10)			(1)
Adenoma	1 (10%)			
C-cell, adenoma	1 (10%)			
Genital System				
Preputial gland	(9)			
Testes	(10)			(8)
Adenoma	1 (10%)			
Interstitial cell, adenoma	2 (20%)			5 (63%)
Respiratory System				
Lung	(10)			(3)
Alveolar/bronchiolar adenoma	1 (10%)			1 (33%)
Urinary System				
Kidney	(10)			(10)
Renal tubule, adenoma				2 (20%)
Urinary bladder	(10)			(10)
Systemic Lesions				
Multiple organs[c]	(10)			(10)
Leukemia mononuclear				2 (20%)
Mesothelioma malignant				1 (10%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(47)	(40)	(59)	(49)
Adenocarcinoma			1 (2%)	4 (8%)
Polyp adenomatous		1 (3%)		
Polyp adenomatous, multiple			1 (2%)	3 (6%)
Intestine large, rectum	(46)	(40)	(58)	(49)
Adenocarcinoma		1 (3%)	10 (17%)	12 (24%)
Adenocarcinoma, multiple				3 (6%)
Polyp adenomatous		12 (30%)	17 (29%)	10 (20%)
Polyp adenomatous, multiple		1 (3%)	34 (59%)	30 (61%)
Intestine large, cecum	(48)	(40)	(59)	(50)
Intestine small, duodenum	(48)	(40)	(59)	(50)
Intestine small, jejunum	(48)	(38)	(57)	(48)
Intestine small, ileum	(48)	(40)	(57)	(49)
Liver	(50)	(40)	(59)	(50)
Cholangiocarcinoma				1 (2%)
Cholangioma			2 (3%)	
Hepatocellular carcinoma	1 (2%)	11 (28%)	12 (20%)	9 (18%)
Hepatocellular carcinoma, multiple		1 (3%)	43 (73%)	37 (74%)
Hepatocellular adenoma	1 (2%)	10 (25%)	17 (29%)	10 (20%)
Hepatocellular adenoma, multiple		10 (25%)	23 (39%)	24 (48%)
Hepatocholangiocarcinoma			5 (8%)	2 (4%)
Hepatocholangiocarcinoma, multiple			1 (2%)	
Hepatocholangioma			1 (2%)	1 (2%)
Myxoma			1 (2%)	
Mesentery	(3)	(2)	(4)	(4)
Pancreas	(50)	(40)	(59)	(50)
Adenocarcinoma, metastatic, intestine large, rectum				1 (2%)
Adenoma	2 (4%)			
Salivary glands	(50)	(40)	(58)	(49)
Stomach, forestomach	(49)	(39)	(59)	(49)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma		2 (5%)		1 (2%)
Stomach, glandular	(50)	(40)	(59)	(50)
Cardiovascular System				
Heart	(50)	(40)	(59)	(49)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(40)	(58)	(50)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Adrenal medulla	(50)	(40)	(58)	(50)
Pheochromocytoma malignant	1 (2%)	2 (5%)	1 (2%)	
Pheochromocytoma benign	11 (22%)	12 (30%)	11 (19%)	5 (10%)
Bilateral, pheochromocytoma benign	1 (2%)	3 (8%)	2 (3%)	2 (4%)
Islets, pancreatic	(50)	(40)	(58)	(50)
Adenoma	2 (4%)	2 (5%)		1 (2%)
Parathyroid gland	(43)	(35)	(55)	(44)
Adenoma			1 (2%)	
Pituitary gland	(48)	(40)	(56)	(49)
Pars distalis, adenoma	20 (42%)	12 (30%)	9 (16%)	10 (20%)
Pars distalis, adenoma, multiple	1 (2%)	2 (5%)	1 (2%)	
Pars distalis, carcinoma		1 (3%)		
Pars intermedia, adenoma		1 (3%)		
Thyroid gland	(49)	(40)	(59)	(50)
Adenoma			1 (2%)	
C-cell, adenoma	9 (18%)	5 (13%)	3 (5%)	3 (6%)
Follicular cell, adenoma			2 (3%)	1 (2%)
Follicular cell, carcinoma	2 (4%)	3 (8%)	1 (2%)	3 (6%)
General Body System				
None				
Genital System				
Coagulating gland	(2)	(2)		
Epididymis	(50)	(40)	(59)	(50)
Preputial gland	(49)	(39)	(58)	(47)
Adenocarcinoma	1 (2%)		1 (2%)	
Adenoma	3 (6%)	2 (5%)	1 (2%)	1 (2%)
Prostate	(50)	(40)	(59)	(49)
Seminal vesicle	(49)	(40)	(59)	(50)
Testes	(50)	(40)	(59)	(50)
Bilateral, interstitial cell, adenoma	40 (80%)	34 (85%)	49 (83%)	38 (76%)
Interstitial cell, adenoma	3 (6%)	3 (8%)	6 (10%)	5 (10%)
Hematopoietic System				
Bone marrow	(50)	(40)	(59)	(50)
Lymph node	(17)	(5)	(12)	(20)
Lumbar, adenocarcinoma, metastatic, intestine large, rectum			1 (8%)	
Lymph node, mandibular	(50)	(40)	(54)	(48)
Lymph node, mesenteric	(48)	(40)	(57)	(49)
Adenocarcinoma, metastatic, intestine large, colon			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(40)	(58)	(50)
Fibroma			1 (2%)	
Sarcoma		1 (3%)		
Thymus	(37)	(32)	(41)	(34)
Thymoma benign			1 (2%)	
Integumentary System				
Mammary gland	(27)	(22)	(29)	(24)
Adenocarcinoma			1 (3%)	
Fibroadenoma		1 (5%)		
Fibroadenoma, multiple	1 (4%)			
Skin	(50)	(38)	(58)	(50)
Basal cell adenoma			1 (2%)	1 (2%)
Basal cell carcinoma	2 (4%)			
Keratoacanthoma	1 (2%)	1 (3%)		1 (2%)
Squamous cell papilloma	1 (2%)		3 (5%)	1 (2%)
Trichoepithelioma	1 (2%)			
Pinna, squamous cell papilloma		2 (5%)	2 (3%)	1 (2%)
Subcutaneous tissue, fibroma	2 (4%)		3 (5%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)	
Subcutaneous tissue, lipoma	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)	3 (8%)	1 (2%)	
Musculoskeletal System				
Skeletal muscle	(2)	(1)	(1)	
Nervous System				
Brain	(50)	(40)	(59)	(50)
Carcinoma, metastatic, pituitary gland		1 (3%)		
Oligodendroglioma benign	1 (2%)			
Meninges, granular cell tumor benign			1 (2%)	
Peripheral nerve			(2)	
Squamous cell carcinoma, metastatic, uncertain primary site			1 (50%)	
Spinal cord	(5)	(1)	(1)	(4)
Respiratory System				
Lung	(50)	(40)	(59)	(49)
Adenocarcinoma, metastatic, kidney			1 (2%)	
Adenocarcinoma, metastatic, intestine large, colon			1 (2%)	
Alveolar/bronchiolar adenoma		2 (5%)	2 (3%)	3 (6%)
Alveolar/bronchiolar carcinoma		1 (3%)	2 (3%)	
Hepatocellular carcinoma, metastatic, liver		1 (3%)	18 (31%)	19 (39%)
Sarcoma, metastatic, kidney				1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Mediastinum, alveolar/bronchiolar carcinoma				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(48)	(40)	(59)	(50)
Trachea	(50)	(40)	(59)	(50)
Special Senses System				
Ear	(3)	(7)	(2)	(1)
Fibrosarcoma	1 (33%)			
Eye	(6)	(3)	(1)	(6)
Zymbal's gland	(1)	(1)	(1)	(2)
Carcinoma	1 (100%)	1 (100%)		1 (50%)
Squamous cell carcinoma			1 (100%)	1 (50%)
Urinary System				
Kidney	(50)	(40)	(59)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (3%)		
Pelvis, transitional epithelium, papilloma			1 (2%)	
Renal tubule, adenoma	2 (4%)	6 (15%)	7 (12%)	9 (18%)
Renal tubule, adenoma, multiple		4 (10%)	4 (7%)	5 (10%)
Renal tubule, carcinoma			2 (3%)	1 (2%)
Urinary bladder	(50)	(38)	(58)	(50)
Transitional epithelium, carcinoma			1 (2%)	4 (8%)
Transitional epithelium, papilloma		1 (3%)	2 (3%)	8 (16%)
Systemic Lesions				
Multiple organs	(50)	(40)	(59)	(50)
Leukemia mononuclear	25 (50%)	5 (13%)	3 (5%)	1 (2%)
Mesothelioma malignant	1 (2%)	1 (3%)	1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
9-Month interim evaluation	1		2	
15-Month interim evaluation	7			10
2-Year study	49	40	59	48
Total primary neoplasms				
9-Month interim evaluation	1		2	
15-Month interim evaluation	8			28
2-Year study	140	160	297	258
Total animals with benign neoplasms				
9-Month interim evaluation	1		2	
15-Month interim evaluation	7			10
2-Year study	49	40	58	47
Total benign neoplasms				
9-Month interim evaluation	1		2	
15-Month interim evaluation	8			18
2-Year study	103	129	209	176

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Neoplasm Summary (continued)				
Total animals with malignant neoplasms				
15-Month interim evaluation				8
2-Year study	29	24	57	47
Total malignant neoplasms				
15-Month interim evaluation				10
2-Year study	37	31	88	82
Total animals with metastatic neoplasms				
2-Year study	2	3	20	22
Total metastatic neoplasms				
2-Year study	2	3	23	22
Total animals with malignant neoplasms of uncertain primary site				
2-Year study		1		

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] One animal not examined microscopically
[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 1-Amino-2,4-dibromoanthraquinone: 0 ppm

Number of Days on Study	421	427	435	514	549	556	562	573	574	587	631	646	654	666	671	674	674	679	692	696	707	721	721	727	731
Carcass ID Number	11115	11222	07075	08085	11414	03033	14525	13434	12424	01515	08484	03032	05404	03031	06065	01414	01055	08833	01202	09303	02303	07404	11313	01553	13131
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X											
Hepatocellular adenoma																									
Mesentery															+			+					+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																			X						
Pheochromocytoma benign									X			X			X			X		X					
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	M
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X				X		X			X	X	X		X		X			X	
Pars distalis, adenoma, multiple																		X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X		X											X	X								X	
Follicular cell, carcinoma																									X
General Body System																									
None																									
Genital System																									
Coagulating gland																	+								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																				X					
Adenoma																				X					

+: 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 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 3 2	1 4 2	1 4 3	0 2 1	0 2 2	0 4 2	0 5 1	0 5 2	0 6 1	0 6 3	0 7 2	0 8 1	0 9 1	1 0 1	1 0 3	1 0 4	1 1 2	1 2 1	1 2 3	1 4 1	0 1 1	0 6 4	0 7 3	0 8 2	1 4 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma																				X						1
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																	X	2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X	X		X			X									X									X	11
Bilateral, pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X														X			2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	48
Pars distalis, adenoma	X				X			X	X	X		X						X			X	X	X			20
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																	X				X	X			X	9
Follicular cell, carcinoma																					X					2
General Body System																										
None																										
Genital System																										
Coagulating gland	+																									2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Adenoma								X									X									3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	421	427	435	514	549	556	562	573	574	587	631	646	654	666	671	674	744	779	892	896	907	921	921	927	931
Carcass ID Number	11 15	12 22	07 75	08 55	11 44	03 33	14 55	13 34	12 44	01 55	08 44	03 22	05 44	03 11	06 55	01 44	10 55	08 33	01 22	09 33	02 33	07 44	11 33	05 33	13 31
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Interstitial cell, adenoma																	X	X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+		+	+		+	+	+	+		+	+			+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	M	M	+	+	M	+	+
Integumentary System																									
Mammary gland	M	+	M	+	+	+	M	M	+	M	+	+	M	+	+	M	M	+	+	+	M	+	M	M	M
Fibroadenoma, multiple																			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																			X						
Squamous cell papilloma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma												X													
Subcutaneous tissue, fibrosarcoma											X														
Subcutaneous tissue, lipoma																					X				
Subcutaneous tissue, sarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							+		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign		X																							
Spinal cord								+		+						+						+		+	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																			X						
Sarcoma, metastatic, skin							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	731	731	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	
Carcass ID Number	13 2	14 2	14 3	02 1	02 2	04 2	05 1	05 2	06 1	06 3	07 2	08 1	09 1	10 1	10 3	10 4	11 2	12 1	12 3	14 1	11 1	06 4	07 3	08 2	14 4	Total Tissues/ Tumors
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	X	40
Interstitial cell, adenoma																		X								3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+				+								+			+		+							17
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	M	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	37
Integumentary System																										
Mammary gland	M	M	+	+	+	M	M	+	+	+	+	M	M	M	M	+	M	+	+	M	M	+	+	+	+	27
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma					X																				X	2
Keratoacanthoma																										1
Squamous cell papilloma			X																							1
Trichoepithelioma																							X			1
Subcutaneous tissue, fibroma									X																	2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																+										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma benign																										1
Spinal cord																										5
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	421	427	435	514	549	556	562	573	574	587	631	646	654	666	671	674	674	679	692	696	707	721	721	727	731
Carcass ID Number	11 15	12 2	07 5	08 5	11 4	03 3	14 5	13 4	12 4	01 5	08 4	03 2	05 4	03 1	06 5	01 4	10 5	08 3	01 2	09 3	02 3	07 4	11 3	05 3	13 1
Special Senses System																									
Ear														+				+		+					
Fibrosarcoma																				X					
Eye				+	+			+		+												+			
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X				X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	731	731	733	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	
Carcass ID Number	13 2	14 2	14 3	02 1	02 2	04 2	05 1	05 2	06 1	06 3	07 2	08 1	09 1	10 1	10 3	10 4	11 2	12 1	12 3	14 1	01 1	06 4	07 3	08 2	14 4	Total Tissues/ Tumors
Special Senses System																										
Ear																										3
Fibrosarcoma																										1
Eye									I										+							6
Zymbal's gland													+													1
Carcinoma													X													1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																		X						X		2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X	X								X	X				X						X	25
Mesothelioma malignant																X										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm

Number of Days on Study	604	618	629	640	650	653	659	668	673	674	675	693	694	700	718	720	730	730	730	731	731	731	731	731	731
Carcass ID Number	15454	16655	18844	22242	22021	16164	20404	24343	15353	20303	21414	17755	24402	20202	16313	17474	23323	23434	23535	15151	15252	18181	18282	18383	19191
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X										
Polyp adenomatous							X				X			X		X		X	X	X					
Polyp adenomatous, multiple																									
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X					X						X	X		X	X				X	
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma											X					X	X			X				X	
Hepatocellular adenoma, multiple													X	X				X			X		X		X
Mesentery										+															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma														X							X				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant						X																		X	
Pheochromocytoma benign			X	X				X			X	X		X						X			X		
Bilateral, pheochromocytoma benign							X						X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X									X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X	X	X			X	X	X	X										X				
Pars distalis, adenoma, multiple																									X
Pars distalis, carcinoma		X																							
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X		X	X		
Follicular cell, carcinoma																			X		X			X	
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	734	734	734	734	734	734	734	734	734	
Carcass ID Number	19 2	19 3	19 4	20 1	23 1	23 2	16 1	16 2	17 1	17 2	17 3	21 1	21 2	21 3	24 1	Total Tissues/ Tumors
Alimentary System																
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Polyp adenomatous					X											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenocarcinoma																1
Polyp adenomatous	X			X	X	X		X								12
Polyp adenomatous, multiple		X														1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hepatocellular carcinoma	X	X										X			X	11
Hepatocellular carcinoma, multiple							X									1
Hepatocellular adenoma		X	X		X		X	X								10
Hepatocellular adenoma, multiple	X			X						X	X					10
Mesentery													+			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Squamous cell papilloma																2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Cardiovascular System																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Endocrine System																
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Pheochromocytoma malignant																2
Pheochromocytoma benign			X	X					X		X					12
Bilateral, pheochromocytoma benign							X									3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenoma																2
Parathyroid gland	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Pars distalis, adenoma			X			X		X								12
Pars distalis, adenoma, multiple													X			2
Pars distalis, carcinoma																1
Pars intermedia, adenoma	X															1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
C-cell, adenoma			X											X		5
Follicular cell, carcinoma																3
General Body System																
None																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	604	618	629	640	650	653	659	668	673	674	675	693	694	700	718	720	730	730	730	731	731	731	731	731	731
Carcass ID Number	15 54	16 55	18 84	22 22	22 21	16 64	20 44	24 33	15 53	20 33	21 41	17 75	24 42	20 22	16 63	17 41	23 33	23 34	23 35	15 11	15 12	18 81	18 82	18 83	19 01
Genital System																									
Coagulating gland									+									+							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma							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	
Interstitial cell, adenoma															X						X				X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+		+																+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Thymus	M	M	M	M	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	M	+	M	+	M	+	M	M	+	+	+	M	M	+	M	M	M	+	M	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Keratoacanthoma			X																						
Pinna, squamous cell papilloma														X											
Subcutaneous tissue, sarcoma											X					X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland		X																							
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	734	734	734	734	734	734	734	734	734	
Carcass ID Number	19 2	19 3	19 4	20 1	23 1	23 2	16 1	16 2	17 1	17 2	17 3	21 1	21 2	21 3	24 1	Total Tissues/ Tumors
Genital System																
Coagulating gland																2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Adenoma																2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	34
Interstitial cell, adenoma																3
Hematopoietic System																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node																5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Sarcoma				X												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Integumentary System																
Mammary gland	+	M	+	+	+	+	M	+	M	+	M	M	M	M	+	22
Fibroadenoma								X								1
Skin	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	38
Keratoacanthoma																1
Pinna, squamous cell papilloma														X		2
Subcutaneous tissue, sarcoma									X							3
Musculoskeletal System																
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Skeletal muscle																1
Nervous System																
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Carcinoma, metastatic, pituitary gland																1
Spinal cord																1
Respiratory System																
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Alveolar/bronchiolar adenoma				X											X	2
Alveolar/bronchiolar carcinoma																1
Hepatocellular carcinoma, metastatic, liver		X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	604	618	629	640	650	653	659	668	673	674	675	693	694	700	718	720	730	730	730	731	731	731	731	731	731
Carcass ID Number	154	165	184	222	221	164	204	243	153	203	214	175	242	202	163	174	233	234	235	151	152	181	182	183	191
Special Senses System																									
Ear		+	+			+	+								+	+							+		
Eye						I											+								
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver					X																				
Renal tubule, adenoma		X					X				X														
Renal tubule, adenoma, multiple									X									X		X				X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Transitional epithelium, papilloma														X											
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X																			X					X
Mesothelioma malignant																							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	19 2	19 3	19 4	20 1	23 1	23 2	16 1	16 2	17 1	17 2	17 3	21 1	21 2	21 3	24 1		Total Tissues/ Tumors
Special Senses System																	
Ear																	7
Eye						+							+				3
Zymbal's gland																	1
Carcinoma																	1
Urinary System																	
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Hepatocellular carcinoma, metastatic, liver																	1
Renal tubule, adenoma			X		X			X									6
Renal tubule, adenoma, multiple																	4
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		38
Transitional epithelium, papilloma																	1
Systemic Lesions																	
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Leukemia mononuclear	X													X			5
Mesothelioma malignant																	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm

Number of Days on Study	465	478	521	521	563	576	582	584	605	608	609	623	629	629	636	636	637	650	650	652	653	659	661	674	674	674	685	687	693	700
Carcass ID Number	355	323	263	354	304	275	334	322	385	375	294	293	314	353	342	343	333	285	321	384	255	341	254	274	313	332	352	383	273	303
Alimentary System																														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																														
Polyp adenomatous, multiple																														
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma										X			X							X	X	X								
Polyp adenomatous		X		X			X	X			X				X			X				X		X		X	X		
Polyp adenomatous, multiple													X	X		X	X		X	X	X		X					X	X	X
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangioma																		X												
Hepatocellular carcinoma	X					X				X					X								X	X					
Hepatocellular carcinoma, multiple		X		X	X		X		X		X	X		X		X	X	X	X	X	X	X			X	X	X	X	X	X
Hepatocellular adenoma			X	X		X					X							X		X	X				X			X		
Hepatocellular adenoma, multiple							X						X	X			X							X		X			X	X
Hepatocholangiocarcinoma					X																									
Hepatocholangiocarcinoma, multiple													X																	
Hepatocholangioma														X																
Myxoma																														
Mesentery				+																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+											+													
Cardiovascular System																														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																													X	
Pheochromocytoma benign			X				X											X			X							X		X
Bilateral, pheochromocytoma benign																														
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																														
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma																				X									X	
Pars distalis, adenoma, multiple										X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																														
Follicular cell, adenoma															X															
Follicular cell, carcinoma												X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	700	702	709	712	714	715	720	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	
Carcass ID Number	373	312	365	262	284	364	253	363	251	252	261	271	272	281	282	283	291	292	301	302	311	331	351	361	362	371	372	381	382	Total Tissues/ Tumors
Alimentary System																														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma																										X				1
Polyp adenomatous, multiple							X																							1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma											X								X	X			X						X	10
Polyp adenomatous											X			X				X			X					X		X		17
Polyp adenomatous, multiple	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X		X	X		X	X	X	X		X		X	34
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	57
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Cholangioma																					X									2
Hepatocellular carcinoma				X				X				X		X	X								X							12
Hepatocellular carcinoma, multiple	X	X			X	X	X		X	X	X		X			X	X	X	X	X	X	X		X	X	X	X	X	X	43
Hepatocellular adenoma	X			X			X		X					X									X				X		X	17
Hepatocellular adenoma, multiple		X				X				X			X		X	X	X	X	X	X	X	X		X	X			X		23
Hepatocholangiocarcinoma	X		X							X			X																	5
Hepatocholangiocarcinoma, multiple																														1
Hepatocholangioma																														1
Myxoma										X																				1
Mesentery		+								+					+															4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Tooth																														2
Cardiovascular System																														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	58
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	58
Pheochromocytoma malignant																														1
Pheochromocytoma benign		X	X	X											X					X										11
Bilateral, pheochromocytoma benign																			X							X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	55
Adenoma														X																1
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Pars distalis, adenoma	X		X	X											X			X								X			X	9
Pars distalis, adenoma, multiple																														1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
C-cell, adenoma		X	X						X																					3
Follicular cell, adenoma																										X				2
Follicular cell, carcinoma																														1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	465	478	521	521	563	576	582	584	605	608	609	623	629	629	636	636	637	650	650	652	653	659	661	674	674	674	685	687	693	700
Carcass ID Number	355	323	263	354	304	275	334	322	385	375	294	293	314	353	342	443	333	285	321	384	255	341	254	274	313	332	352	383	273	303
General Body System																														
None																														
Genital System																														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																														X
Adenoma																		X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X
Interstitial cell, adenoma																						X		X						
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+					+	+			+		+															
Lumbar, adenocarcinoma, metastatic, intestine large, rectum										X																				
Lymph node, mandibular	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenocarcinoma, metastatic, intestine large, colon																														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																														
Thymus	+	M	+	+	M	+	M	M	M	M	+	+	+	+	+	+	+	+	M	M	M	+	+	M	+	+	M	+	+	+
Thymoma benign																														
Integumentary System																														
Mammary gland	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	M	M	M	M	+	+	+	+	M	M	M	+	+
Adenocarcinoma																								X						
Skin	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																														
Squamous cell papilloma																													X	
Pinna, squamous cell papilloma																														
Subcutaneous tissue, fibroma																														
Subcutaneous tissue, fibrosarcoma	X																													
Subcutaneous tissue, sarcoma																											X			
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																													+	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	700	702	709	712	714	715	720	728	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	373	312	365	262	284	364	253	363	251	252	261	271	272	281	282	283	291	292	301	302	311	331	351	361	362	371	372	381	382	Total Tissues/ Tumors
General Body System																														
None																														
Genital System																														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma																														1
Adenoma																														1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Bilateral, interstitial cell, adenoma		X		X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	49
Interstitial cell, adenoma	X										X							X						X						6
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Lymph node					+								+		+				+		+				+			+		12
Lumbar, adenocarcinoma, metastatic, intestine large, rectum																														1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	54
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Adenocarcinoma, metastatic, intestine large, colon																										X				1
Spleen	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Fibroma													X																	1
Thymus	M	+	M	M	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	41
Thymoma benign																								X						1
Integumentary System																														
Mammary gland	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	M	M	M	+	M	+	+	+	+	+	M	+	+	+	29
Adenocarcinoma																														1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Basal cell adenoma							X																							1
Squamous cell papilloma			X																X											3
Pinna, squamous cell papilloma				X																				X						2
Subcutaneous tissue, fibroma						X		X																	X					3
Subcutaneous tissue, fibrosarcoma																														1
Subcutaneous tissue, sarcoma																														1
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Skeletal muscle																														1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	465	478	521	521	563	576	582	584	605	608	609	623	629	629	636	636	637	650	650	652	653	659	661	674	674	674	685	687	693	700
Carcass ID Number	35 5	32 3	26 3	35 4	30 4	27 5	33 4	32 2	38 5	37 5	29 4	29 3	31 4	35 3	34 2	34 3	33 3	28 5	32 1	38 4	25 5	34 1	25 4	27 4	31 3	33 2	35 2	38 3	27 3	30 3
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, granular cell tumor benign																														
Peripheral nerve																									+					
Squamous cell carcinoma, metastatic, uncertain primary site																														
Spinal cord																									+					
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney																										X				
Adenocarcinoma, metastatic, intestine large, colon																														
Alveolar/bronchiolar adenoma																					X									
Alveolar/bronchiolar carcinoma																														
Hepatocellular carcinoma, metastatic, liver		X		X	X				X			X		X		X				X		X	X			X	X		X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																														
Ear													+																	
Eye													+																	
Zymbal's gland						+																								
Squamous cell carcinoma						X																								
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, papilloma													X																	
Renal tubule, adenoma															X										X			X		
Renal tubule, adenoma, multiple																			X										X	
Renal tubule, carcinoma																										X				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Transitional epithelium, carcinoma																														
Transitional epithelium, papilloma																														
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X												
Mesothelioma malignant																														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	700	702	709	712	714	715	720	728	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	
Carcass ID Number	373	312	365	262	284	364	253	363	251	252	261	271	272	281	282	283	291	292	301	302	311	331	351	361	362	371	372	381	382	Total Tissues/ Tumors
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Meninges, granular cell tumor benign							X																							1
Peripheral nerve							+																							2
Squamous cell carcinoma, metastatic, uncertain primary site							X																							1
Spinal cord																														1
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma, metastatic, kidney																														1
Adenocarcinoma, metastatic, intestine large, colon																										X				1
Alveolar/bronchiolar adenoma										X																				2
Alveolar/bronchiolar carcinoma																					X				X					2
Hepatocellular carcinoma, metastatic, liver							X					X								X			X				X			18
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Special Senses System																														
Ear																							+							2
Eye																														1
Zymbal's gland																														1
Squamous cell carcinoma																														1
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Pelvis, transitional epithelium, papilloma																														1
Renal tubule, adenoma											X			X						X						X				7
Renal tubule, adenoma, multiple		X	X																											4
Renal tubule, carcinoma								X																						2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Transitional epithelium, carcinoma							X																							1
Transitional epithelium, papilloma																	X	X												2
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear																					X	X								3
Mesothelioma malignant		X																												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm

Number of Days on Study	281	352	364	435	436	476	493	497	527	542	552	553	573	577	581	588	590	591	596	605	610	622	624	625	631
Carcass ID Number	44545	49595	50404	44444	49494	43434	39395	47575	45555	48383	50202	39494	48282	45454	42323	46262	43303	45353	39292	51515	42202	44343	44144	49393	43131
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																	X							X	
Polyp adenomatous, multiple																	X								
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X							X				X						X	
Adenocarcinoma, multiple															X				X						
Polyp adenomatous		X							X		X		X	X		X	X			X					
Polyp adenomatous, multiple															X			X			X	X	X	X	X
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hepatocellular carcinoma					X	X			X	X			X					X			X				X
Hepatocellular carcinoma, multiple							X	X			X	X		X	X	X	X		X	X		X	X	X	
Hepatocellular adenoma				X									X						X		X				
Hepatocellular adenoma, multiple											X			X		X				X		X	X		X
Hepatocholangiocarcinoma									X																
Hepatocholangioma																						X			
Mesentery										+		+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large, rectum							X																		
Pharynx																				+					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																	X								
Bilateral, pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	631	646	671	674	674	679	689	702	703	709	714	715	721	724	724	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	524	501	523	514	522	404	474	513	492	391	452	473	421	471	481	401	412	413	441	442	461	491	511	512	521	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Adenocarcinoma												X			X											4
Polyp adenomatous, multiple															X		X									3
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma			X		X				X			X							X		X		X	X		12
Adenocarcinoma, multiple													X													3
Polyp adenomatous					X												X									10
Polyp adenomatous, multiple	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	30
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma							X																			1
Hepatocellular carcinoma						X																				9
Hepatocellular carcinoma, multiple	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	37
Hepatocellular adenoma		X			X		X		X							X							X			10
Hepatocellular adenoma, multiple	X		X	X		X				X	X	X	X	X	X		X	X	X		X	X		X	X	24
Hepatocholangiocarcinoma																			X							2
Hepatocholangioma																										1
Mesentery																		+					+			4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, intestine large, rectum																										1
Pharynx																										1
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																				X						1
Squamous cell papilloma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue		+																								1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver										X																1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X		X			X												X	5
Bilateral, pheochromocytoma benign																X										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	281	352	364	435	436	476	493	497	527	542	552	553	573	577	581	588	590	591	596	605	610	622	624	625	631
Carcass ID Number	44545	49595	50404	44444	49444	43434	39535	47755	45555	48383	50252	39434	48282	45454	42323	46262	43303	45353	39232	51515	42202	44343	41414	49393	43331
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X			X	X	X	X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
C-cell, adenoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma														X											
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X		X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node														+			+	+				+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	M	+	+	+	M	+	+	+	+	M	+	+	M	+	M	+	+	+	M	+	M	+
Integumentary System																									
Mammary gland	M	+	M	M	M	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma									X																
Squamous cell papilloma																									
Pinna, squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+			+														+							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	631	646	671	674	674	679	689	702	703	709	714	715	721	724	724	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	524	501	523	514	522	404	447	513	492	391	452	473	421	471	481	401	412	413	441	442	461	491	511	512	521	Total Tissues/ Tumors
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma						X										X	X			X			X			10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
C-cell, adenoma			X															X				X				3
Follicular cell, adenoma																									X	1
Follicular cell, carcinoma												X				X										3
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	38
Interstitial cell, adenoma					X			X		X				X									X			5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+		+			+		+	+	+	+	+			+			+		+	+	+		20
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	M	+	+	M	+	M	+	M	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	34
Integumentary System																										
Mammary gland	M	+	M	+	M	M	M	+	+	M	M	M	+	M	M	M	M	M	M	M	M	+	+	+	M	24
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma						X																				1
Keratoacanthoma																										1
Squamous cell papilloma										X																1
Pinna, squamous cell papilloma					X																					1
Subcutaneous tissue, fibroma	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																						+				4

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	281	352	364	435	436	476	493	497	527	542	552	553	573	577	581	588	590	591	596	605	610	622	624	625	631
Carcass ID Number	445	495	504	444	494	434	395	475	455	483	502	394	482	454	423	462	433	453	392	515	422	443	414	493	431
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Hepatocellular carcinoma, metastatic, liver					X				X		X				X				X	X		X		X	X
Sarcoma, metastatic, kidney								X																	
Mediastinum, alveolar/bronchiolar carcinoma				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																			M						
Zymbal's gland				+																					
Carcinoma				X																					
Squamous cell carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																X									
Renal tubule, adenoma, multiple																						X			
Renal tubule, carcinoma								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																									
Transitional epithelium, papilloma							X	X							X										
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Mesothelioma malignant					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	631	646	671	674	674	679	689	702	703	709	714	715	721	724	724	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	524	501	523	514	522	404	474	513	492	391	452	473	421	471	481	401	412	413	441	442	461	491	511	512	521	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X																				X					3
Hepatocellular carcinoma, metastatic, liver	X		X		X			X			X	X	X				X		X				X			19
Sarcoma, metastatic, kidney																										1
Mediastinum, alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear						+																				1
Eye					+				+						+	+						+	+			6
Zymbal's gland						+																				2
Carcinoma																										1
Squamous cell carcinoma						X																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma	X	X			X	X		X			X										X	X				9
Renal tubule, adenoma, multiple														X		X			X	X						5
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma				X					X		X								X							4
Transitional epithelium, papilloma								X				X		X							X		X			8
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesothelioma malignant																										1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	12/50 (24%)	15/40 (38%)	13/58 (22%)	7/50 (14%)
Adjusted rate[b]	36.6%	45.3%	38.7%	39.0%
Terminal rate[c]	7/26 (27%)	7/24 (29%)	4/20 (20%)	2/10 (20%)
First incidence (days)	574	629	521	590
Life table test[d]	P=0.496	P=0.257	P=0.407	P=0.475
Logistic regression test[d]	P=0.130N	P=0.160	P=0.536N	P=0.357N
Cochran-Armitage test[d]	P=0.041N			
Fisher exact test[d]		P=0.124	P=0.512N	P=0.154N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/50 (2%)	2/40 (5%)	1/58 (2%)	0/50 (0%)
Adjusted rate	3.1%	6.9%	3.2%	0.0%
Terminal rate	0/26 (0%)	1/24 (4%)	0/20 (0%)	0/10 (0%)
First incidence (days)	692	653	693	–[e]
Life table test	P=0.359N	P=0.470	P=0.757	P=0.615N
Logistic regression test	P=0.250N	P=0.429	P=0.738N	P=0.557N
Cochran-Armitage test	P=0.207N			
Fisher exact test		P=0.416	P=0.714N	P=0.500N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	13/50 (26%)	17/40 (43%)	14/58 (24%)	7/50 (14%)
Adjusted rate	38.6%	50.0%	40.7%	39.0%
Terminal rate	7/26 (27%)	8/24 (33%)	4/20 (20%)	2/10 (20%)
First incidence (days)	574	629	521	590
Life table test	P=0.504N	P=0.200	P=0.409	P=0.547
Logistic regression test	P=0.075N	P=0.231	P=0.525N	P=0.277N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.077	P=0.499N	P=0.105N
Kidney (Renal Tubule): Adenoma				
Overall rate	2/50 (4%)	10/40 (25%)	11/59 (19%)	14/50 (28%)
Adjusted rate	7.7%	33.6%	34.6%	68.3%
Terminal rate	2/26 (8%)	6/24 (25%)	4/21 (19%)	5/10 (50%)
First incidence (days)	729 (T)	618	636	588
Life table test	P<0.001	P=0.012	P=0.007	P<0.001
Logistic regression test	P<0.001	P=0.007	P=0.014	P<0.001
Cochran-Armitage test	P=0.008			
Fisher exact test		P=0.004	P=0.017	P<0.001
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	10/40 (25%)	13/59 (22%)	15/50 (30%)
Adjusted rate	7.7%	33.6%	39.4%	69.1%
Terminal rate	2/26 (8%)	6/24 (25%)	4/21 (19%)	5/10 (50%)
First incidence (days)	729 (T)	618	636	497
Life table test	P<0.001	P=0.012	P=0.002	P<0.001
Logistic regression test	P<0.001	P=0.007	P=0.005	P<0.001
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.004	P=0.006	P<0.001

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Large Intestine (Colon): Adenomatous Polyp				
Overall rate	0/50 (0%)	1/40 (3%)	1/59 (2%)	3/50 (6%)
Adjusted rate	0.0%	4.2%	4.3%	19.9%
Terminal rate	0/26 (0%)	1/24 (4%)	0/21 (0%)	1/10 (10%)
First incidence (days)	–	729 (T)	720	590
Life table test	P=0.009	P=0.484	P=0.454	P=0.037
Logistic regression test	P=0.027	P=0.484	P=0.494	P=0.081
Cochran-Armitage test	P=0.065			
Fisher exact test		P=0.444	P=0.541	P=0.121
Large Intestine (Colon): Carcinoma				
Overall rate	0/50 (0%)	0/40 (0%)	1/59 (2%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	4.8%	20.4%
Terminal rate	0/26 (0%)	0/24 (0%)	1/21 (5%)	0/10 (0%)
First incidence (days)	–	–	729 (T)	590
Life table test	P<0.001	–	P=0.457	P=0.018
Logistic regression test	P=0.003	–	P=0.457	P=0.046
Cochran-Armitage test	P=0.007			
Fisher exact test		–	P=0.541	P=0.059
Large Intestine (Rectum): Adenomatous Polyp				
Overall rate	0/50 (0%)	13/40 (33%)	51/59 (86%)	40/50 (80%)
Adjusted rate	0.0%	45.8%	100.0%	100.0%
Terminal rate	0/26 (0%)	9/24 (38%)	21/21 (100%)	10/10 (100%)
First incidence (days)	–	659	478	352
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Large Intestine (Rectum): Carcinoma				
Overall rate	0/50 (0%)	1/40 (3%)	10/59 (17%)	15/50 (30%)
Adjusted rate	0.0%	3.8%	32.4%	63.0%
Terminal rate	0/26 (0%)	0/24 (0%)	5/21 (24%)	4/10 (40%)
First incidence (days)	–	718	608	493
Life table test	P<0.001	P=0.478	P=0.001	P<0.001
Logistic regression test	P<0.001	P=0.480	P=0.003	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.444	P=0.001	P<0.001
Large Intestine (All Sites): Adenomatous Polyp				
Overall rate	0/50 (0%)	13/40 (33%)	51/59 (86%)	40/50 (80%)
Adjusted rate	0.0%	45.8%	100.0%	100.0%
Terminal rate	0/26 (0%)	9/24 (38%)	21/21 (100%)	10/10 (100%)
First incidence (days)	–	659	478	352
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Large Intestine (All Sites): Carcinoma				
Overall rate	0/50 (0%)	1/40 (3%)	11/59 (19%)	17/50 (34%)
Adjusted rate	0.0%	3.8%	36.6%	67.1%
Terminal rate	0/26 (0%)	0/24 (0%)	6/21 (29%)	4/10 (40%)
First incidence (days)	–	718	608	493
Life table test	P<0.001	P=0.478	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.480	P=0.002	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.444	P<0.001	P<0.001
Liver: Hepatocellular Adenoma				
Overall rate	1/50 (2%)	20/40 (50%)	40/59 (68%)	34/50 (68%)
Adjusted rate	3.8%	71.3%	92.3%	97.0%
Terminal rate	1/26 (4%)	16/24 (67%)	18/21 (86%)	9/10 (90%)
First incidence (days)	729 (T)	675	521	435
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	1/50 (2%)	12/40 (30%)	55/59 (93%)	46/50 (92%)
Adjusted rate	2.7%	43.5%	100.0%	100.0%
Terminal rate	0/26 (0%)	9/24 (38%)	21/21 (100%)	10/10 (100%)
First incidence (days)	666	650	465	436
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	2/50 (4%)	25/40 (63%)	57/59 (97%)	47/50 (94%)
Adjusted rate	6.4%	83.1%	100.0%	100.0%
Terminal rate	1/26 (4%)	19/24 (79%)	21/21 (100%)	10/10 (100%)
First incidence (days)	666	650	465	435
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocholangiocarcinoma				
Overall rate	0/50 (0%)	0/40 (0%)	6/59 (10%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	19.1%	12.1%
Terminal rate	0/26 (0%)	0/24 (0%)	2/21 (10%)	1/10 (10%)
First incidence (days)	–	–	563	527
Life table test	P=0.025	–	P=0.019	P=0.133
Logistic regression test	P=0.110	–	P=0.029	P=0.250
Cochran-Armitage test	P=0.117			
Fisher exact test		–	P=0.022	P=0.247

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	2/40 (5%)	2/59 (3%)	3/49 (6%)
Adjusted rate	0.0%	8.3%	7.2%	15.5%
Terminal rate	0/26 (0%)	2/24 (8%)	1/21 (5%)	1/10 (10%)
First incidence (days)	–	729 (T)	653	527
Life table test	P=0.024	P=0.220	P=0.219	P=0.052
Logistic regression test	P=0.103	P=0.220	P=0.269	P=0.124
Cochran-Armitage test	P=0.130			
Fisher exact test		P=0.195	P=0.291	P=0.117
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/40 (8%)	4/59 (7%)	4/49 (8%)
Adjusted rate	0.0%	12.0%	16.5%	17.3%
Terminal rate	0/26 (0%)	2/24 (8%)	3/21 (14%)	1/10 (10%)
First incidence (days)	–	720	653	435
Life table test	P=0.010	P=0.105	P=0.046	P=0.028
Logistic regression test	P=0.089	P=0.099	P=0.068	P=0.094
Cochran-Armitage test	P=0.100			
Fisher exact test		P=0.084	P=0.082	P=0.056
Pancreatic Islets: Adenoma				
Overall rate	2/50 (4%)	2/40 (5%)	0/58 (0%)	1/50 (2%)
Adjusted rate	7.7%	7.4%	0.0%	10.0%
Terminal rate	2/26 (8%)	1/24 (4%)	0/21 (0%)	1/10 (10%)
First incidence (days)	729 (T)	675	–	729 (T)
Life table test	P=0.519N	P=0.664	P=0.286N	P=0.671
Logistic regression test	P=0.415N	P=0.660	P=0.286N	P=0.671
Cochran-Armitage test	P=0.255N			
Fisher exact test		P=0.603	P=0.212N	P=0.500N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	21/48 (44%)	14/40 (35%)	10/56 (18%)	10/49 (20%)
Adjusted rate	56.3%	40.8%	33.0%	51.1%
Terminal rate	10/25 (40%)	6/24 (25%)	4/21 (19%)	4/10 (40%)
First incidence (days)	549	604	608	577
Life table test	P=0.298N	P=0.190N	P=0.041N	P=0.430N
Logistic regression test	P=0.006N	P=0.155N	P=0.005N	P=0.035N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.269N	P=0.004N	P=0.012N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	21/48 (44%)	15/40 (38%)	10/56 (18%)	10/49 (20%)
Adjusted rate	56.3%	42.3%	33.0%	51.1%
Terminal rate	10/25 (40%)	6/24 (25%)	4/21 (19%)	4/10 (40%)
First incidence (days)	549	604	608	577
Life table test	P=0.273N	P=0.248N	P=0.041N	P=0.430N
Logistic regression test	P=0.004N	P=0.222N	P=0.005N	P=0.035N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.354N	P=0.004N	P=0.012N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Preputial Gland: Adenoma				
Overall rate	3/49 (6%)	2/39 (5%)	1/58 (2%)	1/47 (2%)
Adjusted rate	11.0%	7.2%	2.4%	2.5%
Terminal rate	2/25 (8%)	1/23 (4%)	0/21 (0%)	0/9 (0%)
First incidence (days)	696	659	650	552
Life table test	P=0.368N	P=0.543N	P=0.332N	P=0.557N
Logistic regression test	P=0.198N	P=0.554N	P=0.264N	P=0.384N
Cochran-Armitage test	P=0.179N			
Fisher exact test		P=0.608N	P=0.248N	P=0.324N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/49 (6%)	2/39 (5%)	2/58 (3%)	1/47 (2%)
Adjusted rate	11.0%	7.2%	5.6%	2.5%
Terminal rate	2/25 (8%)	1/23 (4%)	0/21 (0%)	0/9 (0%)
First incidence (days)	696	659	650	552
Life table test	P=0.432N	P=0.543N	P=0.525N	P=0.557N
Logistic regression test	P=0.247N	P=0.554N	P=0.448N	P=0.384N
Cochran-Armitage test	P=0.212N			
Fisher exact test		P=0.608N	P=0.420N	P=0.324N
Skin: Squamous Cell Papilloma				
Overall rate	1/50 (2%)	2/40 (5%)	5/59 (8%)	2/50 (4%)
Adjusted rate	3.8%	7.7%	18.9%	10.5%
Terminal rate	1/26 (4%)	1/24 (4%)	2/21 (10%)	0/10 (0%)
First incidence (days)	729 (T)	700	693	674
Life table test	P=0.117	P=0.469	P=0.079	P=0.278
Logistic regression test	P=0.351	P=0.466	P=0.100	P=0.366
Cochran-Armitage test	P=0.413			
Fisher exact test		P=0.416	P=0.146	P=0.500
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	3/50 (6%)	0/40 (0%)	1/59 (2%)	1/50 (2%)
Adjusted rate	11.5%	0.0%	4.3%	5.0%
Terminal rate	3/26 (12%)	0/24 (0%)	0/21 (0%)	0/10 (0%)
First incidence (days)	729 (T)	–	720	679
Life table test	P=0.564N	P=0.134N	P=0.386N	P=0.627N
Logistic regression test	P=0.462N	P=0.134N	P=0.351N	P=0.501N
Cochran-Armitage test	P=0.294N			
Fisher exact test		P=0.167N	P=0.249N	P=0.309N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	5/50 (10%)	3/40 (8%)	6/59 (10%)	4/50 (8%)
Adjusted rate	18.0%	10.1%	22.5%	17.0%
Terminal rate	4/26 (15%)	1/24 (4%)	2/21 (10%)	0/10 (0%)
First incidence (days)	692	629	693	527
Life table test	P=0.205	P=0.403N	P=0.394	P=0.377
Logistic regression test	P=0.448	P=0.421N	P=0.494	P=0.629
Cochran-Armitage test	P=0.483N			
Fisher exact test		P=0.488N	P=0.616	P=0.500N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	0/40 (0%)	3/59 (5%)	1/50 (2%)
Adjusted rate	6.3%	0.0%	12.9%	3.8%
Terminal rate	1/26 (4%)	0/24 (0%)	1/21 (5%)	0/10 (0%)
First incidence (days)	646	–	715	631
Life table test	P=0.389	P=0.258N	P=0.437	P=0.707N
Logistic regression test	P=0.568	P=0.283N	P=0.529	P=0.543N
Cochran-Armitage test	P=0.549N			
Fisher exact test		P=0.306N	P=0.579	P=0.500N
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	1/50 (2%)	3/40 (8%)	1/59 (2%)	0/50 (0%)
Adjusted rate	2.3%	11.1%	3.0%	0.0%
Terminal rate	0/26 (0%)	1/24 (4%)	0/21 (0%)	0/10 (0%)
First incidence (days)	562	675	685	–
Life table test	P=0.283N	P=0.272	P=0.732N	P=0.529N
Logistic regression test	P=0.156N	P=0.187	P=0.741N	P=0.416N
Cochran-Armitage test	P=0.152N			
Fisher exact test		P=0.229	P=0.709N	P=0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	2/50 (4%)	3/40 (8%)	2/59 (3%)	0/50 (0%)
Adjusted rate	4.7%	11.1%	4.7%	0.0%
Terminal rate	0/26 (0%)	1/24 (4%)	0/21 (0%)	0/10 (0%)
First incidence (days)	562	675	465	–
Life table test	P=0.207N	P=0.456	P=0.638N	P=0.304N
Logistic regression test	P=0.062N	P=0.321	P=0.703	P=0.175N
Cochran-Armitage test	P=0.103N			
Fisher exact test		P=0.394	P=0.626N	P=0.247N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	4/50 (8%)	3/40 (8%)	5/59 (8%)	1/50 (2%)
Adjusted rate	10.7%	11.1%	17.0%	3.8%
Terminal rate	1/26 (4%)	1/24 (4%)	1/21 (5%)	0/10 (0%)
First incidence (days)	562	675	465	631
Life table test	P=0.412N	P=0.550N	P=0.493	P=0.351N
Logistic regression test	P=0.136N	P=0.637	P=0.601	P=0.160N
Cochran-Armitage test	P=0.148N			
Fisher exact test		P=0.624N	P=0.605	P=0.181N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	2/40 (5%)	0/59 (0%)	1/50 (2%)
Adjusted rate	0.0%	7.7%	0.0%	5.6%
Terminal rate	0/26 (0%)	1/24 (4%)	0/21 (0%)	0/10 (0%)
First incidence (days)	–	700	–	702
Life table test	P=0.427	P=0.220	–	P=0.398
Logistic regression test	P=0.487	P=0.215	–	P=0.426
Cochran-Armitage test	P=0.604			
Fisher exact test		P=0.195	–	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	2/40 (5%)	0/59 (0%)	2/50 (4%)
Adjusted rate	0.0%	7.7%	0.0%	15.0%
Terminal rate	0/26 (0%)	1/24 (4%)	0/21 (0%)	1/10 (10%)
First incidence (days)	–	700	–	702
Life table test	P=0.117	P=0.220	–	P=0.099
Logistic regression test	P=0.157	P=0.215	–	P=0.130
Cochran-Armitage test	P=0.299			
Fisher exact test		P=0.195	–	P=0.247
Testes: Adenoma				
Overall rate	43/50 (86%)	37/40 (93%)	55/59 (93%)	42/50 (84%)
Adjusted rate	97.7%	100.0%	100.0%	100.0%
Terminal rate	25/26 (96%)	24/24 (100%)	21/21 (100%)	10/10 (100%)
First incidence (days)	421	604	521	476
Life table test	P<0.001	P=0.404N	P=0.022	P<0.001
Logistic regression test	P=0.068	P=0.471N	P=0.235	P=0.150
Cochran-Armitage test	P=0.341N			
Fisher exact test		P=0.265	P=0.177	P=0.500N
Thyroid Gland (C-cell): Adenoma				
Overall rate	9/49 (18%)	5/40 (13%)	3/59 (5%)	3/50 (6%)
Adjusted rate	26.8%	20.8%	11.6%	23.5%
Terminal rate	4/25 (16%)	5/24 (21%)	1/21 (5%)	2/10 (20%)
First incidence (days)	427	729 (T)	702	671
Life table test	P=0.231N	P=0.243N	P=0.088N	P=0.348N
Logistic regression test	P=0.052N	P=0.332N	P=0.030N	P=0.085N
Cochran-Armitage test	P=0.026N			
Fisher exact test		P=0.324N	P=0.030N	P=0.056N
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	2/49 (4%)	3/40 (8%)	1/59 (2%)	3/50 (6%)
Adjusted rate	8.0%	12.5%	2.1%	18.7%
Terminal rate	2/25 (8%)	3/24 (13%)	0/21 (0%)	1/10 (10%)
First incidence (days)	729 (T)	729 (T)	623	577
Life table test	P=0.201	P=0.481	P=0.519N	P=0.205
Logistic regression test	P=0.396	P=0.481	P=0.445N	P=0.369
Cochran-Armitage test	P=0.546			
Fisher exact test		P=0.404	P=0.430N	P=0.510
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/49 (4%)	3/40 (8%)	3/59 (5%)	4/50 (8%)
Adjusted rate	8.0%	12.5%	8.8%	27.7%
Terminal rate	2/25 (8%)	3/24 (13%)	1/21 (5%)	2/10 (20%)
First incidence (days)	729 (T)	729 (T)	623	577
Life table test	P=0.051	P=0.481	P=0.482	P=0.079
Logistic regression test	P=0.178	P=0.481	P=0.576	P=0.192
Cochran-Armitage test	P=0.332			
Fisher exact test		P=0.404	P=0.588	P=0.349

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Urinary Bladder: Papilloma				
Overall rate	0/50 (0%)	1/38 (3%)	2/58 (3%)	8/50 (16%)
Adjusted rate	0.0%	3.7%	9.5%	40.3%
Terminal rate	0/26 (0%)	0/22 (0%)	2/21 (10%)	2/10 (20%)
First incidence (days)	–	700	729 (T)	493
Life table test	P<0.001	P=0.479	P=0.192	P<0.001
Logistic regression test	P<0.001	P=0.459	P=0.192	P=0.004
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.432	P=0.286	P=0.003
Urinary Bladder: Carcinoma				
Overall rate	0/50 (0%)	0/38 (0%)	1/58 (2%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	4.3%	24.5%
Terminal rate	0/26 (0%)	0/22 (0%)	0/21 (0%)	1/10 (10%)
First incidence (days)	–	–	720	674
Life table test	P<0.001	–	P=0.454	P=0.012
Logistic regression test	P=0.001	–	P=0.491	P=0.022
Cochran-Armitage test	P=0.007			
Fisher exact test		–	P=0.537	P=0.059
Urinary Bladder: Papilloma or Carcinoma				
Overall rate	0/50 (0%)	1/38 (3%)	3/58 (5%)	12/50 (24%)
Adjusted rate	0.0%	3.7%	13.5%	56.2%
Terminal rate	0/26 (0%)	0/22 (0%)	2/21 (10%)	3/10 (30%)
First incidence (days)	–	700	720	493
Life table test	P<0.001	P=0.479	P=0.087	P<0.001
Logistic regression test	P<0.001	P=0.459	P=0.096	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.432	P=0.151	P<0.001
All Organs: Mononuclear Cell Leukemia				
Overall rate	25/50 (50%)	5/40 (13%)	3/59 (5%)	1/50 (2%)
Adjusted rate	59.0%	18.8%	11.7%	2.9%
Terminal rate	9/26 (35%)	4/24 (17%)	2/21 (10%)	0/10 (0%)
First incidence (days)	514	604	650	590
Life table test	P<0.001N	P<0.001N	P<0.001N	P<0.001N
Logistic regression test	P<0.001N	P<0.001N	P<0.001N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P<0.001N	P<0.001N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	40/40 (100%)	58/59 (98%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	26/26 (100%)	24/24 (100%)	21/21 (100%)	10/10 (100%)
First incidence (days)	421	604	478	352
Life table test	P<0.001	P=0.263N	P=0.074	P<0.001
Logistic regression test	P=0.543	–[f]	P=0.486N	P=0.727
Cochran-Armitage test	P=0.102N			
Fisher exact test		P=0.556	P=0.709	P=0.309N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
All Organs: Malignant Neoplasms				
Overall rate	29/50 (58%)	24/40 (60%)	57/59 (97%)	47/50 (94%)
Adjusted rate	67.0%	71.7%	100.0%	100.0%
Terminal rate	12/26 (46%)	15/24 (63%)	21/21 (100%)	10/10 (100%)
First incidence (days)	514	604	465	435
Life table test	P<0.001	P=0.398N	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.583	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.510	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	40/40 (100%)	59/59 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	26/26 (100%)	24/24 (100%)	21/21 (100%)	10/10 (100%)
First incidence (days)	421	604	465	352
Life table test	P<0.001	P=0.263N	P=0.061	P<0.001
Logistic regression test	P=0.296	–	P=0.943	P=0.501
Cochran-Armitage test	P=0.252N			
Fisher exact test		P=0.556	P=0.459	P=0.500N

(T)Terminal sacrifice
[a] Number of lesion-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, pancreatic islets, pituitary gland, preputial gland, stomach, 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 exposed group. The life table analysis 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
[f] Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	1/50	1/50	2/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	1/50	0/50	1/50
Methylphenidate Hydrochloride	0/50	0/50	0/50
Pentaerythritol Tetranitrate	2/49	1/49	3/49
Quercetin	3/50	0/50	3/50
Turmeric Oleoresin	0/50	1/50	1/50
Overall Historical Incidence			
Total	35/1,350 (2.6%)	14/1,350 (1.0%)	45/1,350 (3.3%)
Standard deviation	3.2%	1.8%	3.6%
Range	0%-10%	0%-6%	0%-10%

[a] Data as of 31 March 1993

TABLE A4b
Historical Incidence of Large Intestine Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenomatous Polyp (Adenoma)	Carcinoma	Adenomatous Polyp (Adenoma) or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	0/50	0/50	0/50
Methylphenidate Hydrochloride	0/50	0/50	0/50
Pentaerythritol Tetranitrate	0/50	0/50	0/50
Quercetin	0/50	0/50	0/50
Turmeric Oleoresin	0/50	1/50	1/50
Overall Historical Incidence			
Total	0/1,353 (0.0%)	1/1,353 (0.1%)	1/1,353 (0.1%)
Standard deviation		0.4%	0.4%
Range		0%-2%	0%-2%

[a] Data as of 31 March 1993; the data include incidences for the colon and rectum.

TABLE A4c
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	2/50	0/50	2/50
Acetaminophen	3/50	0/50	3/50
HC Yellow 4	1/50	0/50	1/50
Methylphenidate Hydrochloride	0/49	0/49	0/49
Pentaerythritol Tetranitrate	0/49	0/49	0/49
Quercetin	0/50	0/50	0/50
Turmeric Oleoresin	0/50	0/50	0/50
Overall Historical Incidence			
Total	9/1,350 (0.7%)	6/1,350 (0.4%)	15/1,350 (1.1%)
Standard deviation	1.5%	1.0%	1.7%
Range	0%-6%	0%-4%	0%-6%

[a] Data as of 31 March 1993

TABLE A4d
Historical Incidence of Urinary Bladder Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/49	0/49	0/49
HC Yellow 4	0/48	0/48	0/48
Methylphenidate Hydrochloride	0/43	0/43	0/43
Pentaerythritol Tetranitrate	0/46	0/46	0/46
Quercetin	0/50	0/50	0/50
Turmeric Oleoresin	0/49	0/49	0/49
Overall Historical Incidence			
Total	3/1,329 (0.2%)	0/1,329 (0.0%)	3/1,329 (0.2%)
Standard deviation	0.6%		0.6%
Range	0%-2%		0%-2%

[a] Data as of 31 March 1993

TABLE A4e
Historical Incidence of Forestomach Squamous Cell Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	0/50	1/50	1/50
Methylphenidate Hydrochloride	0/50	0/50	0/50
Pentaerythritol Tetranitrate	0/50	0/50	0/50
Quercetin	0/50	0/50	0/50
Tumeric Oleoresin	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/1,353 (0.1%)	3/1,353 (0.2%)	4/1,353 (0.3%)
Standard deviation	0.4%	0.6%	0.7%
Range	0%-2%	0%-2%	0%-2%

[a] Data as of 31 March 1993

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Disposition Summary				
Animals initially in study	70	50	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10			10
Early deaths				
Moribund	19	15	34	33
Natural deaths	5	1	5	7
Survivors				
Died last week of study	3			
Terminal sacrifice	23	24	21	10
Animals examined microscopically	70	50	69[b]	70
9-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)	3 (30%)	3 (30%)	2 (20%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan		2 (20%)		
Intestine large, cecum	(10)	(10)	(10)	(10)
Parasite metazoan			1 (10%)	
Lymphoid tissue, hemorrhage			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus			1 (10%)	1 (10%)
Clear cell focus				4 (40%)
Developmental malformation				1 (10%)
Eosinophilic focus				1 (10%)
Fatty change	3 (30%)	7 (70%)	6 (60%)	
Inflammation, chronic				1 (10%)
Inflammation, chronic active	1 (10%)			1 (10%)
Necrosis, coagulative	1 (10%)	2 (20%)		2 (20%)
Pigmentation		1 (10%)		6 (60%)
Bile duct, hyperplasia	1 (10%)	1 (10%)		5 (50%)
Periportal, inflammation				1 (10%)
Periportal, inflammation, chronic active	9 (90%)	10 (100%)	10 (100%)	8 (80%)
Mesentery		(1)		(1)
Hemorrhage				1 (100%)
Inflammation, chronic, granulomatous		1 (100%)		
Inflammation, chronic active				1 (100%)
Necrosis				1 (100%)
Necrosis, coagulative		1 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Atrophy	2 (20%)	1 (10%)		1 (10%)
Infiltration cellular, mononuclear cell	3 (30%)	5 (50%)	2 (20%)	3 (30%)
Infiltration cellular, mixed cell		1 (10%)		
Inflammation, chronic	1 (10%)			
Inflammation, chronic active	1 (10%)			

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] One animal not examined microscopically

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
9-Month Interim Evaluation (continued)								
Alimentary System (continued)								
Pancreas (continued)	(10)		(10)		(10)		(10)	
Necrosis, coagulative	2	(20%)						
Pigmentation 1	(10%)							
Acinus, atrophy	1	(10%)						
Cardiovascular System								
Heart	(10)		(10)		(10)		(10)	
Cardiomyopathy	9	(90%)	8	(80%)	8	(80%)	6	(60%)
Infiltration cellular, mononuclear cell							1	(10%)
Endocrine System								
Adrenal cortex	(10)		(10)		(10)		(10)	
Adrenal medulla	(10)		(10)		(10)		(10)	
Hyperplasia	1	(10%)						
Pituitary gland	(9)		(10)		(9)		(9)	
Cyst							1	(11%)
Pars distalis, cyst	1	(11%)			1	(11%)	2	(22%)
Pars distalis, hyperplasia	3	(33%)	4	(40%)	1	(11%)	5	(56%)
Pars nervosa, cyst							1	(11%)
Thyroid gland		(10)		(10)		(10)		(10)
Infiltration cellular, mononuclear cell			1	(10%)				
Ultimobranchial cyst			1	(10%)	1	(10%)	1	(10%)
Genital System								
Preputial gland	(9)		(9)		(8)		(9)	
Inflammation, acute					1	(13%)		
Inflammation, chronic	2	(22%)			1	(13%)	2	(22%)
Inflammation, chronic active	7	(78%)	6	(67%)	2	(25%)	2	(22%)
Prostate	(10)		(10)		(9)		(10)	
Inflammation, acute	1	(10%)	2	(20%)				
Inflammation, chronic active			4	(40%)	1	(11%)	1	(10%)
Testes	(10)		(10)		(10)		(10)	
Abscess, chronic							1	(10%)
Atrophy					1	(10%)	1	(10%)
Infarct					1	(10%)	1	(10%)
Infarct, chronic							1	(10%)
Mineralization		1	(10%)					
Interstitial cell, hyperplasia	1	(10%)	9	(90%)	5	(50%)	5	(50%)
Hematopoietic System								
Lymph node	(2)		(1)		(6)		(2)	
Lumbar, pigmentation					1	(17%)		
Mediastinal, hemorrhage	1	(50%)			4	(67%)	2	(100%)
Mediastinal, pigmentation	1	(50%)					2	(100%)
Pancreatic, hemorrhage					1	(17%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
9-Month Interim Evaluation (continued)								
Hematopoietic System (continued)								
Lymph node (continued)	(2)		(1)		(6)		(2)	
Pancreatic, infiltration cellular, histiocyte					1	(17%)	1	(50%)
Pancreatic, inflammation, chronic active					1	(17%)		
Pancreatic, pigmentation							1	(50%)
Renal, hemorrhage	1	(50%)	1	(100%)				
Renal, pigmentation	1	(50%)	1	(100%)				
Lymph node, mandibular	(10)		(10)		(10)		(10)	
Hemorrhage	9	(90%)	5	(50%)	7	(70%)	7	(70%)
Infiltration cellular, histiocyte					1	(10%)		
Lymph node, mesenteric	(10)		(10)		(10)		(10)	
Hemorrhage			1	(10%)				
Infiltration cellular, histiocyte	10	(100%)	10	(100%)	10	(100%)	10	(100%)
Pigmentation					1	(10%)	6	(60%)
Spleen	(10)		(10)		(10)		(10)	
Depletion lymphoid			1	(10%)				
Pigmentation							2	(20%)
Thymus	(9)		(9)		(10)		(10)	
Depletion lymphoid	3	(33%)	4	(44%)	5	(50%)	7	(70%)
Hemorrhage			1	(11%)	1	(10%)	5	(50%)
Integumentary System								
Mammary gland	(8)		(7)		(5)		(5)	
Hyperplasia	7	(88%)	7	(100%)	5	(100%)	5	(100%)
Respiratory System								
Lung	(10)		(10)		(10)		(10)	
Hemorrhage							1	(10%)
Infiltration cellular, histiocyte	1	(10%)	1	(10%)	2	(20%)	1	(10%)
Alveolar epithelium, hyperplasia			1	(10%)				
Artery, mineralization	6	(60%)	3	(30%)	5	(50%)	4	(40%)
Nose	(10)		(10)		(10)		(10)	
Special Senses System								
Ear	(1)							
Inflammation, chronic active	1	(100%)						
Ulcer	1	(100%)						
Urinary System								
Kidney	(10)		(10)		(10)		(10)	
Granuloma	1	(10%)						
Infiltration cellular, mononuclear cell			9	(90%)	9	(90%)	9	(90%)
Inflammation, chronic	4	(40%)						
Renal tubule, degeneration, hyaline			10	(100%)	10	(100%)	10	(100%)
Renal tubule, pigmentation			10	(100%)	10	(100%)	10	(100%)
Renal tubule, regeneration	10	(100%)	10	(100%)	10	(100%)	9	(90%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
9-Month Interim Evaluation (continued)				
Urinary System (continued)				
Urinary bladder	(10)	(10)	(9)	(10)
Calculus, microscopic observation only	2 (20%)		1 (11%)	
Serosa, mineralization	1 (10%)			
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)			(2)
Parasite metazoan	4 (40%)			2 (100%)
Intestine large, rectum	(9)			(10)
Parasite metazoan	1 (11%)			
Intestine large, cecum	(10)			
Parasite metazoan	3 (30%)			
Intestine small, ileum	(10)			
Liver	(10)			(10)
Basophilic focus	1 (10%)			5 (50%)
Clear cell focus				7 (70%)
Cytomegaly				1 (10%)
Degeneration	2 (20%)			1 (10%)
Eosinophilic focus	1 (10%)			
Fatty change	6 (60%)			9 (90%)
Hematopoietic cell proliferation	2 (20%)			
Inflammation, chronic, granulomatous	2 (20%)			1 (10%)
Inflammation, chronic active	6 (60%)			
Mixed cell focus				1 (10%)
Necrosis, coagulative	6 (60%)			2 (20%)
Pigmentation				10 (100%)
Bile duct, hyperplasia	10 (100%)			10 (100%)
Periportal, inflammation, chronic	10 (100%)			10 (100%)
Pancreas	(10)			
Atrophy	4 (40%)			
Inflammation, chronic	8 (80%)			
Salivary glands	(10)			
Stomach, forestomach	(10)			(10)
Arteriole, mineralization				1 (10%)
Muscularis, mineralization	1 (10%)			1 (10%)
Stomach, glandular	(10)			(10)
Inflammation, chronic	1 (10%)			
Muscularis, mineralization	1 (10%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
15-Month Interim Evaluation (continued)								
Cardiovascular System								
Heart	(10)							
Cardiomyopathy	10	(100%)						
Endocrine System								
Adrenal cortex	(10)							
Hyperplasia	1	(10%)						
Bilateral, vacuolization cytoplasmic	1	(10%)						
Adrenal medulla	(9)							
Bilateral, hyperplasia	1	(11%)						
Islets, pancreatic	(4)							
Hemorrhage	1	(25%)						
Pituitary gland	(8)							
Pars distalis, hyperplasia	8	(100%)						
Thyroid gland		(10)						(1)
C-cell, hyperplasia	1	(10%)					1	(100%)
Genital System								
Epididymis	(10)							
Preputial gland	(9)							
Inflammation, chronic	5	(56%)						
Inflammation, chronic active	4	(44%)						
Prostate	(10)							
Inflammation, acute	1	(10%)						
Inflammation, chronic active	6	(60%)						
Testes	(10)						(8)	
Interstitial cell, hyperplasia	10	(100%)					8	(100%)
Seminiferous tubule, atrophy	2	(20%)					3	(38%)
Hematopoietic System								
Lymph node							(3)	
Mediastinal, pigmentation							1	(33%)
Pancreatic, infiltration cellular, histiocyte							3	(100%)
Pancreatic, pigmentation							3	(100%)
Lymph node, mandibular	(10)						(1)	
Hemorrhage	3	(30%)					1	(100%)
Lymph node, mesenteric	(10)						(1)	
Depletion lymphoid	1	(10%)						
Hemorrhage	1	(10%)						
Infiltration cellular, histiocyte	10	(100%)					1	(100%)
Pigmentation	9	(90%)					1	(100%)
Thymus	(10)						(9)	
Cyst	1	(10%)						
Depletion lymphoid							3	(33%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
15-Month Interim Evaluation (continued)				
Integumentary System				
Mammary gland	(4)			
Hyperplasia	2 (50%)			
Skin	(10)			
Respiratory System				
Lung	(10)			(3)
Hemorrhage				1 (33%)
Infiltration cellular, histiocyte	2 (20%)			2 (67%)
Alveolar epithelium, hyperplasia	3 (30%)			
Alveolus, mineralization	1 (10%)			
Artery, mineralization	8 (80%)			2 (67%)
Nose	(10)			
Glands, inflammation, acute	3 (30%)			
Glands, inflammation, chronic active	1 (10%)			
Nasolacrimal duct, inflammation, chronic active	1 (10%)			
Urinary System				
Kidney	(10)			(10)
Nephropathy	10 (100%)			10 (100%)
Renal tubule, hyperplasia				2 (20%)
Renal tubule, pigmentation				10 (100%)
Transitional epithelium, hyperplasia				4 (40%)
Urinary bladder	(10)			(10)
Metaplasia, squamous				1 (10%)
Transitional epithelium, hyperplasia				3 (30%)
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(47)	(40)	(59)	(49)
Autolysis	1 (2%)	1 (3%)	4 (7%)	5 (10%)
Hyperplasia, lymphoid			1 (2%)	
Parasite metazoan	13 (28%)	14 (35%)	9 (15%)	3 (6%)
Polyarteritis		1 (3%)	1 (2%)	
Ulcer			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
2-Year Study (continued)								
Alimentary System (continued)								
Intestine large, rectum	(46)		(40)		(58)		(49)	
Atypia cellular					2	(3%)		
Autolysis	1	(2%)					5	(10%)
Inflammation, chronic active					1	(2%)		
Parasite metazoan	6	(13%)	6	(15%)	9	(16%)	2	(4%)
Artery, neovascularization					2	(3%)		
Artery, thrombosis					1	(2%)		
Epithelium, hyperplasia					1	(2%)	1	(2%)
Intestine large, cecum	(48)		(40)		(59)		(50)	
Atypia cellular					1	(2%)		
Autolysis	2	(4%)	1	(3%)	3	(5%)	5	(10%)
Hyperplasia, lymphoid					1	(2%)		
Inflammation, chronic active			1	(3%)			1	(2%)
Parasite metazoan	4	(8%)	8	(20%)	10	(17%)	3	(6%)
Ulcer, acute			1	(3%)				
Intestine small, duodenum	(48)		(40)		(59)		(50)	
Autolysis	2	(4%)	1	(3%)	3	(5%)	5	(10%)
Ectopic tissue					1	(2%)		
Inflammation, chronic active					1	(2%)		
Intestine small, jejunum	(48)		(38)		(57)		(48)	
Autolysis	2	(4%)	1	(3%)	5	(9%)	6	(13%)
Intestine small, ileum	(48)		(40)		(57)		(49)	
Autolysis	3	(6%)	1	(3%)	4	(7%)	9	(18%)
Hyperplasia, lymphoid	1	(2%)					2	(4%)
Liver	(50)		(40)		(59)		(50)	
Angiectasis	3	(6%)	3	(8%)				
Autolysis	2	(4%)					2	(4%)
Basophilic focus	9	(18%)	12	(30%)	24	(41%)	22	(44%)
Clear cell focus	3	(6%)	26	(65%)	39	(66%)	27	(54%)
Cyst					1	(2%)	2	(4%)
Degeneration	10	(20%)	3	(8%)	12	(20%)	3	(6%)
Eosinophilic focus	1	(2%)	13	(33%)	14	(24%)	6	(12%)
Fatty change	7	(14%)	4	(10%)	7	(12%)	2	(4%)
Fibrosis	1	(2%)						
Hematopoietic cell proliferation					4	(7%)		
Hemorrhage					1	(2%)	1	(2%)
Hepatodiaphragmatic nodule	3	(6%)	2	(5%)				
Hyperplasia							1	(2%)
Infarct			1	(3%)	1	(2%)		
Inflammation, chronic active	3	(6%)	1	(3%)	4	(7%)	6	(12%)
Mixed cell focus	2	(4%)	17	(43%)	8	(14%)	1	(2%)
Necrosis, coagulative	3	(6%)	6	(15%)	8	(14%)	6	(12%)
Pigmentation	3	(6%)	19	(48%)	48	(81%)	39	(78%)
Regeneration	4	(8%)						
Bile duct, cyst			1	(3%)				
Bile duct, hyperplasia	45	(90%)	9	(23%)	54	(92%)	45	(90%)
Periportal, inflammation, chronic active	2	(4%)	2	(5%)	51	(86%)	36	(72%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
2-Year Study (continued)								
Alimentary System (continued)								
Mesentery	(3)		(2)		(4)		(4)	
Fibrosis			2	(100%)	2	(50%)	2	(50%)
Hemorrhage					1	(25%)	1	(25%)
Inflammation, chronic active	1	(33%)	2	(100%)	3	(75%)	3	(75%)
Necrosis, coagulative			1	(50%)	2	(50%)	1	(25%)
Polyarteritis			1	(50%)				
Pancreas		(50)		(40)		(59)		(50)
Atrophy	11	(22%)	26	(65%)	29	(49%)	20	(40%)
Autolysis					2	(3%)	2	(4%)
Cytoplasmic alteration							1	(2%)
Ectopic tissue	1	(2%)						
Inflammation, chronic active	10	(20%)	28	(70%)	45	(76%)	26	(52%)
Vacuolization cytoplasmic	17	(34%)	2	(5%)	6	(10%)	15	(30%)
Acinus, hyperplasia					1	(2%)	1	(2%)
Artery, fibrosis					1	(2%)	1	(2%)
Artery, polyarteritis	4	(8%)	8	(20%)	4	(7%)	3	(6%)
Duct, hyperplasia	1	(2%)					1	(2%)
Pharynx						(1)		
Palate, hyperkeratosis							1	(100%)
Salivary glands	(50)		(40)		(58)		(49)	
Duct, submandibular gland, inflammation, acute							1	(2%)
Parotid gland, inflammation, chronic					1	(2%)		
Submandibular gland, inflammation, chronic					2	(3%)		
Submandibular gland, metaplasia, squamous					1	(2%)		
Stomach, forestomach	(49)		(39)		(59)		(49)	
Erosion					1	(2%)	1	(2%)
Fibrosis					1	(2%)	1	(2%)
Hyperkeratosis	5	(10%)	18	(46%)	21	(36%)	20	(41%)
Hyperplasia, basal cell	11	(22%)	18	(46%)	23	(39%)	23	(47%)
Hyperplasia, squamous	3	(6%)	19	(49%)	25	(42%)	26	(53%)
Infarct					1	(2%)		
Inflammation, chronic active	3	(6%)	12	(31%)	11	(19%)	11	(22%)
Ulcer	3	(6%)	10	(26%)	15	(25%)	16	(33%)
Stomach, glandular	(50)		(40)		(59)		(50)	
Autolysis					2	(3%)	2	(4%)
Inflammation, chronic active	3	(6%)	2	(5%)	2	(3%)	3	(6%)
Mucosa, hyperplasia							1	(2%)
Mucosa, necrosis, coagulative	1	(2%)						
Cardiovascular System								
Heart	(50)		(40)		(59)		(49)	
Autolysis			1	(3%)				
Cardiomyopathy	47	(94%)	38	(95%)	57	(97%)	48	(98%)
Metaplasia, osseous					1	(2%)		
Polyarteritis			1	(3%)				
Thrombosis	2	(4%)			1	(2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
2-Year Study (continued)								
Endocrine System								
Adrenal cortex	(50)		(40)		(58)		(50)	
Angiectasis	2	(4%)	5	(13%)	13	(22%)	15	(30%)
Autolysis							2	(4%)
Hematopoietic cell proliferation	2	(4%)					1	(2%)
Hyperplasia	4	(8%)	1	(3%)	2	(3%)	1	(2%)
Necrosis, coagulative	1	(2%)						
Vacuolization cytoplasmic	23	(46%)	18	(45%)	19	(33%)	11	(22%)
Adrenal medulla	(50)		(40)		(58)		(50)	
Autolysis							2	(4%)
Fibrosis	1	(2%)						
Hematopoietic cell proliferation	1	(2%)						
Hyperplasia	17	(34%)	25	(63%)	24	(41%)	21	(42%)
Necrosis, coagulative	2	(4%)						
Islets, pancreatic	(50)		(40)		(58)		(50)	
Autolysis					1	(2%)	1	(2%)
Hyperplasia	1	(2%)					2	(4%)
Parathyroid gland		(43)		(35)		(55)		(44)
Hyperplasia	4	(9%)	12	(34%)			1	(2%)
Pituitary gland	(48)		(40)		(56)		(49)	
Autolysis							1	(2%)
Pars distalis, cyst	6	(13%)	4	(10%)	7	(13%)	7	(14%)
Pars distalis, hyperplasia	12	(25%)	11	(28%)	23	(41%)	27	(55%)
Pars intermedia, cyst	2	(4%)	1	(3%)			2	(4%)
Thyroid gland		(49)		(40)		(59)		(50)
Autolysis					2	(3%)	2	(4%)
Inflammation, chronic active	2	(4%)	1	(3%)	1	(2%)		
Ultimobranchial cyst			2	(5%)	3	(5%)	1	(2%)
C-cell, hyperplasia	10	(20%)	8	(20%)	5	(8%)	3	(6%)
Follicle, cyst	2	(4%)	1	(3%)	7	(12%)	3	(6%)
Follicular cell, hyperplasia	3	(6%)	1	(3%)	2	(3%)		
General Body System								
None								
Genital System								
Coagulating gland	(2)		(2)					
Inflammation, chronic active	1	(50%)	2	(100%)				
Epididymis	(50)		(40)		(59)		(50)	
Aspermia	1	(2%)						
Autolysis					2	(3%)		
Inflammation, chronic active	3	(6%)	2	(5%)	10	(17%)	3	(6%)
Vacuolization cytoplasmic	1	(2%)					1	(2%)
Preputial gland	(49)		(39)		(58)		(47)	
Abscess	6	(12%)	1	(3%)	1	(2%)		
Cyst	2	(4%)			1	(2%)	1	(2%)
Hyperplasia					2	(3%)		
Inflammation, chronic active	46	(94%)	38	(97%)	57	(98%)	43	(91%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
2-Year Study (continued)								
Genital System (continued)								
Prostate	(50)		(40)		(59)		(49)	
Abscess			3	(8%)	1	(2%)	1	(2%)
Fibrosis							1	(2%)
Inflammation, chronic active	11	(22%)	18	(45%)	24	(41%)	23	(47%)
Metaplasia, squamous	1	(2%)	11	(28%)	6	(10%)	1	(2%)
Polyarteritis			1	(3%)				
Epithelium, hyperplasia	8	(16%)	4	(10%)	2	(3%)	1	(2%)
Seminal vesicle	(49)		(40)		(59)		(50)	
Atrophy	1	(2%)	30	(75%)	35	(59%)	23	(46%)
Autolysis					1	(2%)		
Inflammation, chronic active			3	(8%)	2	(3%)	1	(2%)
Metaplasia, squamous			1	(3%)				
Testes		(50)		(40)		(59)		(50)
Infarct			1	(3%)				
Inflammation, chronic					1	(2%)		
Polyarteritis	1	(2%)						
Interstitial cell, hyperplasia	16	(32%)	3	(8%)	27	(46%)	19	(38%)
Seminiferous tubule, atrophy	41	(82%)	37	(93%)	55	(93%)	36	(72%)
Seminiferous tubule, mineralization	8	(16%)			2	(3%)	6	(12%)
Hematopoietic System								
Bone marrow	(50)		(40)		(59)		(50)	
Sternal, autolysis					1	(2%)		
Sternal, hypoplasia							1	(2%)
Sternal, myelofibrosis	1	(2%)						
Lymph node	(17)		(5)		(12)		(20)	
Deep cervical, hyperplasia							1	(5%)
Lumbar, hyperplasia			1	(20%)			1	(5%)
Mediastinal, hemorrhage	1	(6%)						
Mediastinal, infiltration cellular, histiocyte			1	(20%)			2	(10%)
Mediastinal, sinus, ectasia	1	(6%)						
Pancreatic, hyperplasia			1	(20%)	1	(8%)	2	(10%)
Pancreatic, infiltration cellular, histiocyte			2	(40%)	9	(75%)	19	(95%)
Renal, infiltration cellular, histiocyte	1	(6%)			1	(8%)		
Lymph node, mandibular	(50)		(40)		(54)		(48)	
Hyperplasia	11	(22%)	7	(18%)	7	(13%)	4	(8%)
Infiltration cellular, histiocyte	2	(4%)			1	(2%)	8	(17%)
Inflammation, chronic active	1	(2%)						
Lymph node, mesenteric	(48)		(40)		(57)		(49)	
Autolysis					1	(2%)		
Hyperplasia					1	(2%)	2	(4%)
Infiltration cellular, histiocyte	44	(92%)	40	(100%)	56	(98%)	49	(100%)
Pigmentation	1	(2%)						

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(40)	(58)	(50)
Autolysis			1 (2%)	2 (4%)
Depletion lymphoid	12 (24%)	2 (5%)		2 (4%)
Fibrosis	6 (12%)	3 (8%)	2 (3%)	5 (10%)
Hyperplasia, RE cell			1 (2%)	
Infiltration cellular, histiocyte				1 (2%)
Necrosis, coagulative	2 (4%)			
Thymus	(37)	(32)	(41)	(34)
Cyst	2 (5%)			
Integumentary System				
Mammary gland	(27)	(22)	(29)	(24)
Galactocele	3 (11%)	1 (5%)	1 (3%)	
Hyperplasia	16 (59%)	18 (82%)	17 (59%)	12 (50%)
Skin	(50)	(38)	(58)	(50)
Abscess		2 (5%)	1 (2%)	
Cyst epithelial inclusion	1 (2%)		3 (5%)	
Fibrosis	1 (2%)			
Inflammation, chronic active	1 (2%)		2 (3%)	2 (4%)
Musculoskeletal System				
Bone	(50)	(40)	(59)	(50)
Cranium, abscess				1 (2%)
Joint, tarsal, hyperostosis			1 (2%)	
Joint, tarsal, inflammation, chronic active			1 (2%)	
Rib, hyperostosis		1 (3%)		
Skeletal muscle	(2)	(1)	(1)	
Fibrosis			1 (100%)	
Polyarteritis		1 (100%)		
Nervous System				
Brain	(50)	(40)	(59)	(50)
Infarct	3 (6%)			
Spinal cord	(5)	(1)	(1)	(4)
Infarct	1 (20%)	1 (100%)		
Respiratory System				
Lung	(50)	(40)	(59)	(49)
Crystals	1 (2%)			
Fibrosis			3 (5%)	
Foreign body			1 (2%)	
Infiltration cellular, histiocyte	21 (42%)	22 (55%)	32 (54%)	23 (47%)
Inflammation, chronic active		1 (3%)	5 (8%)	3 (6%)
Metaplasia, osseous				1 (2%)
Respiratory epithelium, hyperplasia	2 (4%)		1 (2%)	2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
2-Year Study (continued)								
Respiratory System (continued)								
Lung (continued)	(50)		(40)		(59)		(49)	
Necrosis, coagulative	1	(2%)						
Alveolar epithelium, hyperplasia	4	(8%)	1	(3%)	7	(12%)	1	(2%)
Artery, mineralization	22	(44%)	14	(35%)	36	(61%)	28	(57%)
Artery, thrombosis	1	(2%)						
Bronchiole, epithelium, hyperplasia					1	(2%)		
Mediastinum, polyarteritis			2	(5%)				
Nose	(48)		(40)		(59)		(50)	
Autolysis	1	(2%)						
Foreign body			2	(5%)	7	(12%)	1	(2%)
Hemorrhage					3	(6%)		
Inflammation, chronic active	26	(54%)	25	(63%)	27	(46%)	18	(36%)
Metaplasia, squamous	10	(21%)	7	(18%)	7	(12%)	6	(12%)
Ulcer	2	(4%)						
Glands, hyperplasia	9	(19%)					3	(6%)
Respiratory epithelium, hyperplasia	2	(4%)			1	(2%)	2	(4%)
Trachea	(50)		(40)		(59)		(50)	
Autolysis					1	(2%)		
Inflammation, chronic active			1	(3%)	3	(5%)	2	(4%)
Special Senses System								
Ear	(3)		(7)		(2)		(1)	
Acanthosis			1	(33%)	1	(14%)	1	(50%)
Hyperkeratosis	1	(33%)						
Hyperplasia, basal cell	1	(33%)	1	(14%)	1	(50%)		
Inflammation, chronic active	1	(33%)						
Submucosa, abscess							1	(100%)
Eye	(6)		(3)		(1)		(6)	
Cataract					1	(100%)		
Synechia							1	(17%)
Anterior, synechia	1	(17%)						
Cornea, inflammation, chronic active	1	(17%)						
Lens, cataract							3	(50%)
Retina, degeneration	1	(17%)			1	(100%)	3	(50%)
Urinary System								
Kidney	(50)		(40)		(59)		(50)	
Autolysis	2	(4%)			1	(2%)	4	(8%)
Cyst	4	(8%)	3	(8%)	1	(2%)		
Cyst, multiple	1	(2%)						
Fibrosis, focal			1	(3%)				
Hydronephrosis	1	(2%)						
Nephropathy	50	(100%)	40	(100%)	59	(100%)	49	(98%)
Collecting tubule, mineralization					1	(2%)		
Renal tubule, degeneration, hyaline					1	(2%)	1	(2%)
Renal tubule, hyperplasia	9	(18%)	30	(75%)	25	(42%)	19	(38%)
Renal tubule, hyperplasia, oncocytic			1	(3%)			1	(2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Urinary System (continued)				
Kidney (continued)	(50)	(40)	(59)	(50)
Renal tubule, inflammation, chronic active	14 (28%)	10 (25%)	22 (37%)	14 (28%)
Renal tubule, mineralization	1 (2%)	2 (5%)	13 (22%)	4 (8%)
Renal tubule, pigmentation	5 (10%)	40 (100%)	58 (98%)	49 (98%)
Transitional epithelium, hyperplasia	30 (60%)	40 (100%)	51 (86%)	35 (70%)
Urinary bladder	(50)	(38)	(58)	(50)
Autolysis			1 (2%)	1 (2%)
Edema		1 (3%)		
Fibrosis		1 (3%)		
Hemorrhage	2 (4%)			
Hyperplasia, lymphoid	4 (8%)			
Inflammation, chronic			1 (2%)	
Inflammation, chronic active	1 (2%)	3 (8%)		5 (10%)
Polyarteritis		1 (3%)		
Transitional epithelium, hyperplasia	1 (2%)	5 (13%)	17 (29%)	30 (60%)
Transitional epithelium, metaplasia, squamous				3 (6%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Disposition Summary				
Animals initially in study	70	50	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10			10
Early deaths				
Moribund	8	5	15	29
Natural deaths	4	3	7	8
Survivors				
Died last week of study	1			
Terminal sacrifice	37	32	38	12
Missexed				1
Animals examined microscopically	70	50	70	69
9-Month Interim Evaluation				
Genital System				
Uterus	(10)	(10)	(10)	(10)
Polyp stromal			1 (10%)	
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(10)			(10)
Polyp adenomatous				2 (20%)
Liver	(10)			(10)
Hepatocellular carcinoma				3 (30%)
Hepatocellular carcinoma, multiple				3 (30%)
Hepatocellular adenoma				3 (30%)
Hepatocellular adenoma, multiple				5 (50%)
Endocrine System				
Adrenal medulla	(10)			(1)
Pheochromocytoma benign				1 (100%)
Pituitary gland	(10)			
Pars distalis, adenoma	2 (20%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Uterus	(10)			(3)
Polyp stromal	1 (10%)			1 (33%)
Integumentary System				
Mammary gland	(7)			
Fibroadenoma	1 (14%)			
Skin	(10)			(1)
Subcutaneous tissue, fibroma				1 (100%)
Urinary System				
Kidney	(10)			(10)
Urinary bladder	(10)			(10)
Carcinoma				2 (20%)
Papilloma				1(10%)
Squamous cell carcinoma				2 (20%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(40)	(57)	(48)
Intestine large, colon	(49)	(40)	(59)	(47)
Adenocarcinoma			2 (3%)	1 (2%)
Adenocarcinoma, multiple		1 (3%)		
Polyp adenomatous			1 (2%)	1 (2%)
Polyp adenomatous, multiple		1 (3%)	1 (2%)	1 (2%)
Intestine large, rectum	(49)	(40)	(60)	(47)
Adenocarcinoma		1 (3%)	18 (30%)	6 (13%)
Adenocarcinoma, multiple			1 (2%)	1 (2%)
Polyp adenomatous		10 (25%)	8 (13%)	12 (26%)
Polyp adenomatous, multiple		17 (43%)	45 (75%)	31 (66%)
Intestine large, cecum	(50)	(40)	(60)	(47)
Polyp adenomatous			1 (2%)	
Intestine small, jejunum	(48)	(40)	(59)	(46)
Intestine small, ileum	(49)	(39)	(59)	(44)
Leiomyoma			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(40)	(60)	(48)
Cholangioma				1 (2%)
Hepatocellular carcinoma		5 (13%)	6 (10%)	4 (8%)
Hepatocellular carcinoma, multiple		7 (18%)	51 (85%)	41 (85%)
Hepatocellular adenoma		10 (25%)	8 (13%)	7 (15%)
Hepatocellular adenoma, multiple		18 (45%)	39 (65%)	22 (46%)
Hepatocholangiocarcinoma			10 (17%)	8 (17%)
Hepatocholangiocarcinoma, multiple			1 (2%)	5 (10%)
Hepatocholangioma			1 (2%)	
Hepatocholangioma, multiple			1 (2%)	
Mesentery	(4)	(6)	(1)	(4)
Hepatocellular carcinoma, metastatic, liver				3 (75%)
Pancreas	(50)	(40)	(60)	(47)
Adenoma			2 (3%)	
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Pharynx		(1)		
Palate, squamous cell papilloma, multiple		1 (100%)		
Stomach, forestomach	(49)	(40)	(60)	(47)
Squamous cell carcinoma		1 (3%)	1 (2%)	1 (2%)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(50)	(40)	(60)	(48)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Tongue				(1)
Squamous cell papilloma				1 (100%)
Tooth	(1)	(1)		(1)
Gingiva, squamous cell carcinoma				1 (100%)
Cardiovascular System				
Heart	(50)	(40)	(60)	(49)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	2 (4%)
Endocrine System				
Adrenal cortex	(47)	(40)	(59)	(47)
Adenoma	2 (4%)	1 (3%)		
Carcinoma, metastatic, kidney				1 (2%)
Adrenal medulla	(47)	(40)	(59)	(47)
Pheochromocytoma complex			1 (2%)	
Pheochromocytoma benign	2 (4%)	3 (8%)	1 (2%)	1 (2%)
Bilateral, pheochromocytoma benign				1 (2%)
Islets, pancreatic	(50)	(40)	(60)	(47)
Adenoma	1	(3%)		
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Parathyroid gland	(43)	(37)	(57)	(38)
Adenoma	1 (2%)			
Pituitary gland	(50)	(39)	(60)	(47)
Pars distalis, adenoma	27 (54%)	16 (41%)	25 (42%)	13 (28%)
Pars distalis, adenoma, multiple	5 (10%)	3 (8%)	7 (12%)	
Pars intermedia, adenoma		1 (3%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(40)	(60)	(49)
C-cell, adenoma	5 (10%)	5 (13%)	5 (8%)	
C-cell, adenoma, multiple				1 (2%)
C-cell, carcinoma	1 (2%)		1 (2%)	
Follicular cell, adenoma		1 (3%)	1 (2%)	2 (4%)
General Body System				
Tissue NOS	(2)	(1)	(1)	
Basosquamous tumor malignant		1 (100%)		
Neoplasm NOS			1 (100%)	
Sarcoma	2 (100%)			
Genital System				
Clitoral gland	(45)	(36)	(60)	(45)
Adenoma	5 (11%)	3 (8%)	3 (5%)	2 (4%)
Ovary	(50)	(40)	(60)	(47)
Granulosa cell tumor benign	1 (2%)	1 (3%)		
Hepatocellular carcinoma, metastatic, liver			1 (2%)	1 (2%)
Uterus	(50)	(40)	(60)	(47)
Adenocarcinoma	1 (2%)			
Hemangioma	1 (2%)			
Polyp stromal	7 (14%)	12 (30%)	7 (12%)	5 (11%)
Polyp stromal, multiple	1 (2%)	3 (8%)		
Sarcoma stromal			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(40)	(60)	(49)
Lymph node	(3)	(5)	(25)	(14)
Mediastinal, hepatocellular carcinoma, metastatic, liver				1 (7%)
Lymph node, mandibular	(50)	(39)	(56)	(45)
Lymph node, mesenteric	(50)	(40)	(59)	(46)
Spleen	(50)	(40)	(60)	(48)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Lipoma		1 (3%)		
Thymus	(42)	(31)	(51)	(38)
Hepatocellular carcinoma, metastatic, liver				1 (3%)
Integumentary System				
Mammary gland	(49)	(34)	(50)	(41)
Adenocarcinoma	2 (4%)			
Fibroadenoma	17 (35%)	8 (24%)	9 (18%)	5 (12%)
Fibroadenoma, multiple	4 (8%)	2 (6%)		
Fibroma	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Skin	(50)	(39)	(60)	(49)
Squamous cell papilloma	1 (2%)		1 (2%)	1 (2%)
Pinna, granular cell tumor benign			1 (2%)	
Pinna, squamous cell papilloma			2 (3%)	2 (4%)
Subcutaneous tissue, fibroma	2 (4%)	2 (5%)		
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(40)	(60)	(49)
Basosquamous tumor malignant, metastatic, tissue NOS		1 (3%)		
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Skeletal muscle		(1)		
Rhabdomyosarcoma		1 (100%)		
Nervous System				
Brain	(50)	(40)	(60)	(49)
Oligodendroglioma benign				1 (2%)
Respiratory System				
Lung	(50)	(40)	(60)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	2 (5%)	1 (2%)	
Alveolar/bronchiolar adenoma, multiple		1 (3%)		
Alveolar/bronchiolar carcinoma				1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (3%)	22 (37%)	24 (49%)
Neoplasm NOS, metastatic, uncertain primary site				1 (2%)
Sarcoma, metastatic, thymus	1 (2%)			
Squamous cell carcinoma		1 (3%)		
Nose	(50)	(40)	(60)	(49)
Special Senses System				
Ear			(8)	(3)
Zymbal's gland	(1)		(2)	
Adenoma			1 (50%)	
Carcinoma			1 (50%)	
Squamous cell carcinoma	1 (100%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(40)	(60)	(48)
Squamous cell carcinoma, metastatic, urinary bladder			1 (2%)	
Pelvis, transitional epithelium, carcinoma		1 (3%)		
Pelvis, transitional epithelium, papilloma				1 (2%)
Renal tubule, adenoma		3 (8%)	11 (18%)	11 (23%)
Renal tubule, adenoma, multiple			5 (8%)	5 (10%)
Renal tubule, carcinoma				2 (4%)
Urinary bladder	(50)	(40)	(60)	(46)
Transitional epithelium, carcinoma			8 (13%)	16 (35%)
Transitional epithelium, papilloma		2 (5%)	6 (10%)	9 (20%)
Transitional epithelium, papilloma, multiple			1 (2%)	
Transitional epithelium, squamous cell carcinoma			1 (2%)	
Transitional epithelium, squamous cell papilloma			1 (2%)	1 (2%)
Transitional epithelium, squamous cell papilloma, multiple				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(40)	(60)	(49)
Leukemia mononuclear	9 (18%)	1 (3%)	5 (8%)	1 (2%)
Lymphoma malignant histiocytic				1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
9-Month interim evaluation			1	
15-Month interim evaluation	2			9
2-Year study	46	40	60	48
Total primary neoplasms				
9-Month interim evaluation			1	
15-Month interim evaluation	4			24
2-Year study	100	148	306	228
Total animals with benign neoplasms				
9-Month interim evaluation			1	
15-Month interim evaluation	2			8
2-Year study	43	40	60	46
Total benign neoplasms				
9-Month interim evaluation			1	
15-Month interim evaluation	4			14
2-Year study	83	128	197	139
Total animals with malignant neoplasms				
15-Month interim evaluation				9
2-Year study	16	15	60	46
Total malignant neoplasms				
15-Month interim evaluation				10
2-Year study	17	20	108	89

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Neoplasm Summary (continued)				
Total animals with metastatic neoplasms				
2-Year study	1	2	22	27
Total metastatic neoplasms				
2-Year study	1	2	26	38
Total animals with malignant neoplasms of uncertain primary site				
2-Year study				2
Total animals with uncertain neoplasms - benign or malignant				
2-Year study			1	
Total uncertain neoplasms				
2-Year study			1	

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm

Number of Days on Study	268	601	606	620	642	656	658	675	704	708	716	719	731	734	734	734	734	734	734	734	734	734	734	734	734
Carcass ID Number	685	663	684	773	734	723	733	704	714	762	784	745	732	661	662	671	672	673	731	741	742	751	752	753	761
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+												+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+																	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X	X			X	X		X	X		X			X	X		X	X	X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X	X		X								
C-cell, carcinoma															X										
General Body System																									
Tissue NOS	+		+																						
Sarcoma	X		X																						
Genital System																									
Clitoral gland	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X					X							X	X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X																							
Hemangioma																				X					
Polyp stromal						X																	X		
Polyp stromal, multiple																									

+: 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 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	6811	6812	6813	6911	6912	7443	7444	7545	7722	7933	7944	7001	7002	7003	7111	7112	7113	7211	7222	7711	7811	7822	7833	7911	7912	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery					+								+													4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X																									2
Adrenal medulla	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign		X			X																					2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Adenoma														X												1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X			X	X		X	X			X	X	X	X	X				X	X			X		27
Pars distalis, adenoma, multiple				X						X	X						X								X	5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X																	X								5
C-cell, carcinoma																										1
General Body System																										
Tissue NOS																										2
Sarcoma																										2
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Adenoma				X																						5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																			X							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Hemangioma																										1
Polyp stromal	X				X		X					X			X											7
Polyp stromal, multiple																				X						1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	268	601	606	620	642	656	658	675	704	708	716	719	731	734	734	734	734	734	734	734	734	734	734	734	734
Carcass ID Number	685	663	684	773	734	723	733	704	714	762	784	745	732	661	662	671	672	673	731	741	742	751	752	753	761
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	I	M	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenocarcinoma															X										
Fibroadenoma			X						X				X					X						X	
Fibroadenoma, multiple																	X					X	X		
Fibroma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Sarcoma, metastatic, thymus									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+		+		+		+	+		+		+			+		+			+
Zymbal's gland					+																				
Squamous cell carcinoma					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X				X			X		X								X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	6811	6812	6813	6901	6902	7443	7444	7545	7722	7933	7944	7001	7002	7003	7111	7112	7113	7211	7222	7711	7811	7822	7833	7911	7912	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node															+	+										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma									X																	2
Fibroadenoma	X	X			X		X	X					X	X			X		X		X		X	X		17
Fibroadenoma, multiple															X											4
Fibroma															X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X											1
Subcutaneous tissue, fibroma											X								X							2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Sarcoma, metastatic, thymus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+					+						+													13
Zymbal's gland																										1
Squamous cell carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X												X						X		9

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm

Number of Days on Study	600	611	616	659	661	664	670	689	730	730	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734
Carcass ID Number	804	814	803	835	843	875	864	842	833	834	863	871	872	873	874	881	882	883	884	885	891	892	893	894	801
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, multiple																									
Polyp adenomatous, multiple																						X			
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp adenomatous			X				X			X	X			X					X						
Polyp adenomatous, multiple						X		X				X			X		X	X			X		X	X	X
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																						X			
Hepatocellular carcinoma, multiple											X				X			X		X					
Hepatocellular adenoma	X							X							X			X	X		X	X			
Hepatocellular adenoma, multiple		X		X		X			X	X	X	X	X	X		X	X						X		X
Mesentery						+						+									+	+		+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx										+															
Palate, squamous cell papilloma, multiple										X															
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																+									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X						X	X	X			X				X	X		X		X
Pars distalis, adenoma, multiple																	X		X						
Pars intermedia, adenoma	X																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X															
Follicular cell, adenoma													X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	802	811	812	813	821	822	823	831	832	841	851	852	853	861	862		Total Tissues/ Tumors
Alimentary System																	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Adenocarcinoma, multiple					X												1
Polyp adenomatous, multiple																	1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Adenocarcinoma											X						1
Polyp adenomatous		X				X								X	X		10
Polyp adenomatous, multiple			X	X			X	X	X	X	X						17
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		39
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Hepatocellular carcinoma					X	X							X	X			5
Hepatocellular carcinoma, multiple				X								X			X		7
Hepatocellular adenoma	X		X		X												10
Hepatocellular adenoma, multiple							X	X			X	X			X		18
Mesentery		+															6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Pharynx																	1
Palate, squamous cell papilloma, multiple																	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Squamous cell carcinoma													X				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Tooth																	1
Cardiovascular System																	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Endocrine System																	
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Adenoma	X																1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Pheochromocytoma benign											X	X					3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Adenoma																	1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+		37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		39
Pars distalis, adenoma				X				X	X		X		X	X			16
Pars distalis, adenoma, multiple										X							3
Pars intermedia, adenoma																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
C-cell, adenoma	X		X	X					X								5
Follicular cell, adenoma																	1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	600	611	616	659	661	664	670	689	730	730	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734
Carcass ID Number	804	814	803	835	843	875	864	842	833	834	863	871	872	873	874	881	882	883	884	885	891	892	893	894	801
General Body System																									
Tissue NOS																									
Basosquamous tumor malignant																									
Genital System																									
Clitoral gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X			X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal	X		X				X	X	X	X		X					X		X						
Polyp stromal, multiple														X									X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																						+		+	
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Thymus	M	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	M	+
Fibroadenoma						X								X		X		X			X				
Fibroadenoma, multiple				X																					X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant, metastatic, tissue NOS																									
Skeletal muscle																									
Rhabdomyosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar adenoma, multiple																		X							
Hepatocellular carcinoma, metastatic, liver																				X					
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	802	811	812	813	821	822	823	831	832	841	851	852	853	861	862		Total Tissues/ Tumors
General Body System																	
Tissue NOS			+														1
Basosquamous tumor malignant			X														1
Genital System																	
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+		36
Adenoma															X		3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Granulosa cell tumor benign																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Polyp stromal		X										X	X				12
Polyp stromal, multiple						X											3
Hematopoietic System																	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Lymph node		+					+			+							5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		39
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Lipoma										X							1
Thymus	+	M	+	+	+	M	+	+	+	M	M	+	M	+	+		31
Integumentary System																	
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+		34
Fibroadenoma		X			X									X			8
Fibroadenoma, multiple																	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		39
Subcutaneous tissue, fibroma						X											2
Musculoskeletal System																	
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Basosquamous tumor malignant, metastatic, tissue NOS			X														1
Skeletal muscle											+						1
Rhabdomyosarcoma											X						1
Nervous System																	
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Respiratory System																	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Alveolar/bronchiolar adenoma												X					2
Alveolar/bronchiolar adenoma, multiple																	1
Hepatocellular carcinoma, metastatic, liver																	1
Squamous cell carcinoma						X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	600	611	616	659	661	664	670	689	730	730	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734
Carcass ID Number	804	814	803	835	843	875	864	842	833	834	863	871	872	873	874	881	882	883	884	885	891	892	893	894	801
Special Senses System																									
Eye		+			+					+				+						+			+		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, carcinoma																									
Renal tubule, adenoma	X	X								X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																						X			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 2,000 ppm (continued)

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	802	811	812	813	821	822	823	831	832	841	851	852	853	861	862		Total Tissues/ Tumors
Special Senses System																	
Eye			+														7
Urinary System																	
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Pelvis, transitional epithelium, carcinoma				X													1
Renal tubule, adenoma																	3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Transitional epithelium, papilloma															X		2
Systemic Lesions																	
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		40
Leukemia mononuclear																	1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm

Number of Days on Study	575	582	601	606	609	632	642	647	649	649	660	660	667	670	691	695	696	708	714	716	719	725	729	729	729	729	729	729	729	729	729
Carcass ID Number	10005	09073	10255	09665	10044	09955	09884	10344	09444	10244	09883	10333	09905	09644	09972	10144	09963	10113	10034	09954	09343	10234	09001	09902	09903	09904	09911	09912	09913	09914	09921
Alimentary System																															
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenocarcinoma					X																										
Polyp adenomatous																															
Polyp adenomatous, multiple																						X									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X			X			X	X	X								X								X			
Adenocarcinoma, multiple																															
Polyp adenomatous			X	X						X											X	X							X		
Polyp adenomatous, multiple		X						X	X		X	X		X	X		X	X	X				X	X	X	X	X	X	X		X
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																															
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leiomyoma																															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma	X					X	X		X					X																		
Hepatocellular carcinoma, multiple		X	X					X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Hepatocellular adenoma					X		X													X						X		X			
Hepatocellular adenoma, multiple	X	X				X		X	X	X	X	X	X		X	X	X	X			X	X						X		X	X
Hepatocholangiocarcinoma																			X								X	X	X		X
Hepatocholangiocarcinoma, multiple														X																	
Hepatocholangioma																											X				
Hepatocholangioma, multiple																															
Mesentery																		+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver						X																									
Endocrine System																															
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex											X																				
Pheochromocytoma benign																															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	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	09222	09233	09244	10001	10012	10031	10032	09331	09332	09333	09341	09342	09343	09351	09352	09353	09361	09362	09371	09381	09382	09391	09392	09393	09394	10111	10121	10211	10222	Total Tissues/ Tumors
Alimentary System																														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	57
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma																													X	2
Polyp adenomatous																												X		1
Polyp adenomatous, multiple																														1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma	X	X				X	X		X			X			X			X	X	X							X			18
Adenocarcinoma, multiple																X														1
Polyp adenomatous	X														X															8
Polyp adenomatous, multiple		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Polyp adenomatous											X																			1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Leiomyoma													X																	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma																								X						6
Hepatocellular carcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	51
Hepatocellular adenoma												X						X											X	8
Hepatocellular adenoma, multiple			X		X	X	X	X	X	X			X	X	X	X	X		X	X	X	X	X	X	X	X	X			39
Hepatocholangiocarcinoma											X		X					X	X							X				10
Hepatocholangiocarcinoma, multiple																														1
Hepatocholangioma																														1
Hepatocholangioma, multiple			X																											1
Mesentery																														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Adenoma																X														2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma																														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Cardiovascular System																														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma, metastatic, liver																														1
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Pheochromocytoma complex																														1
Pheochromocytoma benign											X																			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	575	582	601	606	609	632	642	647	649	649	660	660	667	670	691	695	696	708	714	716	719	725	729	729	729	729	729	729	729	729	729
Carcass ID Number	10005	09073	10125	09065	10044	09095	09984	10334	09444	10244	09083	10333	09055	09964	09972	10144	09633	10113	10034	09544	09934	10234	09001	09902	09903	09904	09911	09912	09913	09914	09921
Endocrine System (continued)																															
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X					X	X			X		X			X		X	X	X	X	X	X		X	X		X				
Pars distalis, adenoma, multiple											X												X								X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X						X		X				
C-cell, carcinoma																							X								
Follicular cell, adenoma															X																
General Body System																															
Tissue NOS																															
Neoplasm NOS																															
Genital System																															
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X											X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X															X						X	X						
Sarcoma stromal																															
Hematopoietic System																															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+																			+			+		+	+	+	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																			X												
Thymus	+	M	M	+	I	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																															
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Fibroadenoma		X								X								X								X		X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X						
Pinna, granular cell tumor benign																															
Pinna, squamous cell papilloma																															
Musculoskeletal System																															
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																															
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	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	09222	09233	09244	10001	10002	10031	10032	09331	09332	09333	09341	09342	09343	09511	09522	09533	09611	09622	09711	09811	09822	09911	09922	09933	09944	10111	10112	10121	10122	Total Tissues/ Tumors
Endocrine System (continued)																														
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma		X	X	X				X		X				X		X						X	X						X	25
Pars distalis, adenoma, multiple					X				X																X			X		7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma			X																		X									5
C-cell, carcinoma																														1
Follicular cell, adenoma																														1
General Body System																														
Tissue NOS														+																1
Neoplasm NOS														X																1
Genital System																														
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Adenoma							X																							3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma, metastatic, liver							X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Polyp stromal			X												X													X		7
Sarcoma stromal																													X	1
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+			+	+	+				+	+	+					+	+	+	+	+	+			+	+			25
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma, metastatic, liver																														1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Integumentary System																														
Mammary gland	M	+	+	+	+	M	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	50
Fibroadenoma		X		X																X				X						9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Squamous cell papilloma																														1
Pinna, granular cell tumor benign													X																	1
Pinna, squamous cell papilloma																	X							X						2
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	575	582	601	606	609	632	642	647	649	649	660	660	667	670	691	695	696	708	714	716	719	725	729	729	729	729	729	729	729	729	729
Carcass ID Number	10005	09073	10125	09065	10044	09095	09084	10334	09444	10244	09083	10333	09055	09964	09972	10114	09963	10113	10034	09545	09934	10233	09001	09002	09003	09004	09011	09112	09113	09114	09211
Respiratory System																															
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																							
Hepatocellular carcinoma, metastatic, liver							X		X				X						X	X	X		X			X	X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																															
Ear							+		+		+																				
Eye			+																												
Zymbal's gland									+																						
Adenoma																															
Carcinoma									X																						
Urinary System																															
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, urinary bladder																										X					
Renal tubule, adenoma			X									X		X			X									X				X
Renal tubule, adenoma, multiple															X															X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma														X			X														
Transitional epithelium, papilloma															X									X				X			X
Transitional epithelium, papilloma, multiple																															
Transitional epithelium, squamous cell carcinoma																										X					
Transitional epithelium, squamous cell papilloma																															
Systemic Lesions																															
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X			X													X											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 5,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	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	09222	09233	09244	10101	10002	10311	10323	09931	09332	09333	09941	09422	09943	09951	09952	09953	09961	09962	09971	09981	09982	09991	09992	09993	09994	10111	10012	10121	10202	Total Tissues/ Tumors
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma																														1
Hepatocellular carcinoma, metastatic, liver	X		X		X	X	X		X									X	X	X	X		X			X		X		22
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Special Senses System																														
Ear													+				+						+	+		+				8
Eye						+				+			+		+		+	+												7
Zymbal's gland																							+							2
Adenoma																							X							1
Carcinoma																														1
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma, metastatic, urinary bladder																														1
Renal tubule, adenoma				X														X					X				X		X	11
Renal tubule, adenoma, multiple						X			X		X																			5
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Transitional epithelium, carcinoma					X		X								X		X	X										X		8
Transitional epithelium, papilloma				X										X																6
Transitional epithelium, papilloma, multiple																			X											1
Transitional epithelium, squamous cell carcinoma																														1
Transitional epithelium, squamous cell papilloma																										X				1
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear																		X												5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm

Number of Days on Study	367	418	460	512	543	559	566	569	576	580	598	600	610	614	616	625	635	636	636	637	638	658	662	662
Carcass ID Number	11773	10755	11143	11155	10994	11335	10044	10074	11154	10843	11133	11343	10833	11043	10545	10933	11033	10991	10902	11422	10822	11021	10633	11163
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenocarcinoma																								
Polyp adenomatous																								
Polyp adenomatous, multiple																								
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenocarcinoma																								
Adenocarcinoma, multiple																X								
Polyp adenomatous				X	X	X	X	X				X			X	X			X	X				
Polyp adenomatous, multiple									X	X			X	X				X			X	X	X	X
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	M	+	+	M	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Cholangioma																								
Hepatocellular carcinoma			X	X															X					
Hepatocellular carcinoma, multiple					X		X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Hepatocellular adenoma		X											X	X										X
Hepatocellular adenoma, multiple				X	X	X	X	X	X	X					X			X	X	X		X	X	
Hepatocholangiocarcinoma												X		X									X	
Hepatocholangiocarcinoma, multiple																					X	X		
Mesentery											+													
Hepatocellular carcinoma, metastatic, liver																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								
Salivary glands	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Squamous cell carcinoma												X												
Squamous cell papilloma																								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								
Tongue						+																		
Squamous cell papilloma						X																		
Tooth																								
Gingiva, squamous cell carcinoma																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	664	673	674	685	695	702	702	705	714	715	719	720	722	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	11162	11153	10773	10062	10043	10053	10081	11333	11112	11132	11411	10611	10072	10041	10042	10051	10052	10071	11101	11021	11111	11131	11151	11152	11161	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma													X													1
Polyp adenomatous																							X			1
Polyp adenomatous, multiple													X													1
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma		X								X				X					X	X					X	6
Adenocarcinoma, multiple																										1
Polyp adenomatous													X										X			12
Polyp adenomatous, multiple	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	31
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cholangioma											X															1
Hepatocellular carcinoma																			X							4
Hepatocellular carcinoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	41
Hepatocellular adenoma						X										X	X									7
Hepatocellular adenoma, multiple	X						X						X					X	X		X		X	X	X	22
Hepatocholangiocarcinoma				X	X										X		X	X								8
Hepatocholangiocarcinoma, multiple		X																	X	X						5
Mesentery								+						+	+											4
Hepatocellular carcinoma, metastatic, liver								X						X	X											3
Pancreas	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic, liver														X												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Squamous cell carcinoma																										1
Squamous cell papilloma																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver									X																	1
Tongue																										1
Squamous cell papilloma																										1
Tooth																				+						1
Gingiva, squamous cell carcinoma																				X						1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver							X	X																		2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	367	418	460	512	543	559	566	569	576	580	598	600	610	614	616	625	635	636	636	637	638	658	662	662
Carcass ID Number	11773	10755	11143	11155	10994	11135	10444	10074	11154	10843	11133	11343	10833	11044	10545	10943	11033	10091	10092	11422	10822	11211	10663	11163
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Bilateral, pheochromocytoma benign																			X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								
Parathyroid gland	+	+	M	+	+	M	+	M	+	M	+	+	M	+	+	+	M	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X						X					X						X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma, multiple																								
Follicular cell, adenoma																								
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Adenoma													X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Polyp stromal				X		X												X						
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+	+			+				+				+			+	
Mediastinal, hepatocellular carcinoma, metastatic, liver																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Fibroadenoma													X								X		X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X				
Pinna, squamous cell papilloma																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	664	673	674	685	695	702	702	705	714	715	719	720	722	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	11162	11553	10773	10062	10043	10053	10081	11333	11112	11323	11411	10061	10072	10041	10042	10051	10052	10071	11101	11021	11111	11331	11511	11521	11161	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Carcinoma, metastatic, kidney							X																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Pheochromocytoma benign					X																					1
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic, liver														X												1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma							X	X					X	X				X			X			X		13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma, multiple											X															1
Follicular cell, adenoma	X																		X							2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																X										2
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic, liver										X																1
Uterus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp stromal	X											X														5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node								+			+		+	+	+						+	+		+		14
Mediastinal, hepatocellular carcinoma, metastatic, liver								X																		1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	M	M	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	38
Hepatocellular carcinoma, metastatic, liver								X																		1
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	M	41
Fibroadenoma										X						X										5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Pinna, squamous cell papilloma																			X					X		2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	367	418	460	512	543	559	566	569	576	580	598	600	610	614	616	625	635	636	636	637	638	658	662	662
Carcass ID Number	11773	10755	11143	11155	10994	11135	10044	10074	11154	10843	11133	11343	10833	11043	10543	10093	11033	10991	10092	11422	10822	11021	10633	11163
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, uncertain primary site																							X	
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign																				X				
Spinal cord									+															
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								
Hepatocellular carcinoma, metastatic, liver									X		X		X	X	X					X				
Neoplasm NOS, metastatic, uncertain primary site																	X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Eye																+								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pelvis, transitional epithelium, papilloma																								
Renal tubule, adenoma																X		X	X				X	
Renal tubule, adenoma, multiple																								
Renal tubule, carcinoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A
Transitional epithelium, carcinoma	X									X	X		X	X	X	X		X			X			
Transitional epithelium, papilloma																				X			X	
Transitional epithelium, squamous cell papilloma																								
Transitional epithelium, squamous cell papilloma, multiple																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X	
Lymphoma malignant histiocytic																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	664	673	674	685	695	702	702	705	714	715	719	720	722	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	11162	11153	10773	10062	10043	10053	10081	11333	11112	11322	11411	10061	10072	10041	10042	10051	10052	10071	11101	11202	11111	11131	11151	11152	11161	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Oligodendroglioma benign																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma							X																			1
Hepatocellular carcinoma, metastatic, liver	X			X	X	X	X	X	X	X		X		X		X	X		X	X		X	X	X	X	24
Neoplasm NOS, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear														+					+					+		3
Eye						+		+			+	+				+				+						7
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pelvis, transitional epithelium, papilloma																					X					1
Renal tubule, adenoma						X	X	X	X					X										X	X	11
Renal tubule, adenoma, multiple										X			X				X		X				X			5
Renal tubule, carcinoma							X																		X	2
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Transitional epithelium, carcinoma		X					X		X									X	X	X		X				16
Transitional epithelium, papilloma	X			X	X			X			X		X		X											9
Transitional epithelium, squamous cell papilloma		X																								1
Transitional epithelium, squamous cell papilloma, multiple																X										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Lymphoma malignant histiocytic				X																						1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/47 (4%)	3/40 (8%)	1/59 (2%)	2/47 (4%)
Adjusted rate[b]	5.7%	9.4%	2.7%	7.7%
Terminal rate[c]	2/35 (6%)	3/32 (9%)	1/37 (3%)	0/11 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	636
Life table test[d]	P=0.396	P=0.459	P=0.481N	P=0.379
Logistic regression test[d]	P=0.602N	P=0.459	P=0.481N	P=0.624
Cochran-Armitage test[d]	P=0.441N			
Fisher exact test[d]		P=0.423	P=0.415N	P=0.692N
Adrenal Medulla: Benign or Complex Pheochromocytoma				
Overall rate	2/47 (4%)	3/40 (8%)	2/59 (3%)	2/47 (4%)
Adjusted rate	5.7%	9.4%	4.6%	7.7%
Terminal rate	2/35 (6%)	3/32 (9%)	1/37 (3%)	0/11 (0%)
First incidence (days)	729 (T)	729 (T)	660	636
Life table test	P=0.354	P=0.459	P=0.665N	P=0.379
Logistic regression test	P=0.583N	P=0.459	P=0.617N	P=0.624
Cochran-Armitage test	P=0.467N			
Fisher exact test		P=0.423	P=0.601N	P=0.692N
Clitoral Gland: Adenoma				
Overall rate	5/45 (11%)	3/36 (8%)	3/60 (5%)	2/45 (4%)
Adjusted rate	13.3%	10.0%	7.4%	10.8%
Terminal rate	4/36 (11%)	3/30 (10%)	2/38 (5%)	1/12 (8%)
First incidence (days)	708	729 (T)	696	610
Life table test	P=0.524N	P=0.465N	P=0.330N	P=0.664
Logistic regression test	P=0.265N	P=0.488N	P=0.263N	P=0.365N
Cochran-Armitage test	P=0.137N			
Fisher exact test		P=0.488N	P=0.212N	P=0.217N
Kidney (Renal Tubule): Adenoma				
Overall rate	0/50 (0%)	3/40 (8%)	16/60 (27%)	16/48 (33%)
Adjusted rate	0.0%	8.0%	36.0%	69.7%
Terminal rate	0/38 (0%)	1/32 (3%)	11/38 (29%)	6/12 (50%)
First incidence (days)	–[e]	600	601	625
Life table test	P<0.001	P=0.093	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.049	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.084	P<0.001	P<0.001
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/40 (8%)	16/60 (27%)	16/48 (33%)
Adjusted rate	0.0%	8.0%	36.0%	69.7%
Terminal rate	0/38 (0%)	1/32 (3%)	11/38 (29%)	6/12 (50%)
First incidence (days)	–	600	601	625
Life table test	P<0.001	P=0.093	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.049	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.084	P<0.001	P<0.001

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Large Intestine (Rectum): Adenomatous Polyp				
Overall rate	0/50 (0%)	27/40 (68%)	53/60 (88%)	43/49 (88%)
Adjusted rate	0.0%	75.0%	100.0%	100.0%
Terminal rate	0/38 (0%)	23/32 (72%)	38/38 (100%)	12/12 (100%)
First incidence (days)	–	616	582	512
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Large Intestine (Rectum): Carcinoma				
Overall rate	0/50 (0%)	1/40 (3%)	19/60 (32%)	7/49 (14%)
Adjusted rate	0.0%	3.1%	41.7%	41.9%
Terminal rate	0/38 (0%)	1/32 (3%)	13/38 (34%)	4/12 (33%)
First incidence (days)	–	729 (T)	606	625
Life table test	P<0.001	P=0.466	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.466	P<0.001	P=0.001
Cochran-Armitage test	P=0.005			
Fisher exact test		P=0.444	P<0.001	P=0.006
Large Intestine (All Sites): Adenomatous Polyp				
Overall rate	0/50 (0%)	28/40 (70%)	53/60 (88%)	43/49 (88%)
Adjusted rate	0.0%	77.7%	100.0%	100.0%
Terminal rate	0/38 (0%)	24/32 (75%)	38/38 (100%)	12/12 (100%)
First incidence (days)	–	616	582	512
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Large Intestine (All Sites): Carcinoma				
Overall rate	0/50 (0%)	2/40 (5%)	21/60 (35%)	8/49 (16%)
Adjusted rate	0.0%	6.3%	45.1%	46.3%
Terminal rate	0/38 (0%)	2/32 (6%)	14/38 (37%)	4/12 (33%)
First incidence (days)	–	729 (T)	606	625
Life table test	P<0.001	P=0.201	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.201	P<0.001	P<0.001
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.195	P<0.001	P=0.003
Liver: Hepatocellular Adenoma				
Overall rate	0/50 (0%)	28/40 (70%)	47/60 (78%)	29/48 (60%)
Adjusted rate	0.0%	75.5%	83.7%	83.6%
Terminal rate	0/38 (0%)	23/32 (72%)	29/38 (76%)	8/12 (67%)
First incidence (days)	–	600	575	418
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	0/50 (0%)	12/40 (30%)	57/60 (95%)	45/48 (94%)
Adjusted rate	0.0%	37.5%	98.3%	100.0%
Terminal rate	0/38 (0%)	12/32 (38%)	37/38 (97%)	12/12 (100%)
First incidence (days)	–	729 (T)	575	460
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	0/50 (0%)	33/40 (83%)	59/60 (98%)	47/48 (98%)
Adjusted rate	0.0%	89.1%	100.0%	100.0%
Terminal rate	0/38 (0%)	28/32 (88%)	38/38 (100%)	12/12 (100%)
First incidence (days)	–	600	575	418
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocholangiocarcinoma				
Overall rate	0/50 (0%)	0/40 (0%)	11/60 (18%)	13/48 (27%)
Adjusted rate	0.0%	0.0%	27.1%	56.9%
Terminal rate	0/38 (0%)	0/32 (0%)	9/38 (24%)	5/12 (42%)
First incidence (days)	–	–	670	600
Life table test	P<0.001	–	P<0.001	P<0.001
Logistic regression test	P<0.001	–	P=0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		–	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	3/40 (8%)	1/60 (2%)	0/49 (0%)
Adjusted rate	2.5%	9.4%	1.9%	0.0%
Terminal rate	0/38 (0%)	3/32 (9%)	0/38 (0%)	0/12 (0%)
First incidence (days)	716	729 (T)	647	–
Life table test	P=0.338N	P=0.244	P=0.739N	P=0.695N
Logistic regression test	P=0.196N	P=0.229	P=0.732N	P=0.616N
Cochran-Armitage test	P=0.154N			
Fisher exact test		P=0.229	P=0.705N	P=0.505N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/40 (8%)	1/60 (2%)	1/49 (2%)
Adjusted rate	2.5%	9.4%	1.9%	5.0%
Terminal rate	0/38 (0%)	3/32 (9%)	0/38 (0%)	0/12 (0%)
First incidence (days)	716	729 (T)	647	702
Life table test	P=0.572	P=0.244	P=0.739N	P=0.559
Logistic regression test	P=0.472N	P=0.229	P=0.732N	P=0.682
Cochran-Armitage test	P=0.380N			
Fisher exact test		P=0.229	P=0.705N	P=0.747

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Mammary Gland: Fibroadenoma				
Overall rate	21/50 (42%)	10/40 (25%)	9/60 (15%)	5/49 (10%)
Adjusted rate	52.2%	29.1%	20.7%	22.3%
Terminal rate	19/38 (50%)	8/32 (25%)	6/38 (16%)	1/12 (8%)
First incidence (days)	606	659	582	610
Life table test	P=0.058N	P=0.055N	P=0.008N	P=0.210N
Logistic regression test	P=0.001N	P=0.065N	P=0.002N	P=0.008N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.071N	P=0.002N	P<0.001N
Mammary Gland: Fibroma, Fibroadenoma, or Carcinoma				
Overall rate	23/50 (46%)	10/40 (25%)	9/60 (15%)	5/49 (10%)
Adjusted rate	57.2%	29.1%	20.7%	22.3%
Terminal rate	21/38 (55%)	8/32 (25%)	6/38 (16%)	1/12 (8%)
First incidence (days)	606	659	582	610
Life table test	P=0.030N	P=0.024N	P=0.003N	P=0.147N
Logistic regression test	P<0.001N	P=0.029N	P<0.001N	P=0.004N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.033N	P<0.001N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	32/50 (64%)	19/39 (49%)	32/60 (53%)	13/47 (28%)
Adjusted rate	74.3%	55.6%	62.3%	55.7%
Terminal rate	27/38 (71%)	17/32 (53%)	19/38 (50%)	4/11 (36%)
First incidence (days)	642	616	575	512
Life table test	P=0.285	P=0.060N	P=0.510N	P=0.431
Logistic regression test	P=0.015N	P=0.081N	P=0.208N	P=0.013N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.109N	P=0.175N	P<0.001N
Skin: Squamous Cell Papilloma				
Overall rate	1/50 (2%)	0/40 (0%)	3/60 (5%)	3/49 (6%)
Adjusted rate	2.6%	0.0%	7.9%	19.4%
Terminal rate	1/38 (3%)	0/32 (0%)	3/38 (8%)	2/12 (17%)
First incidence (days)	729 (T)	–	729 (T)	637
Life table test	P=0.007	P=0.534N	P=0.305	P=0.056
Logistic regression test	P=0.033	P=0.534N	P=0.305	P=0.171
Cochran-Armitage test	P=0.109			
Fisher exact test		P=0.556N	P=0.381	P=0.301
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	2/40 (5%)	0/60 (0%)	0/49 (0%)
Adjusted rate	5.3%	6.0%	0.0%	0.0%
Terminal rate	2/38 (5%)	1/32 (3%)	0/38 (0%)	0/12 (0%)
First incidence (days)	729 (T)	670	–	–
Life table test	P=0.148N	P=0.625	P=0.238N	P=0.513N
Logistic regression test	P=0.089N	P=0.616	P=0.238N	P=0.513N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.603	P=0.204N	P=0.253N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Skin (Subcutaneous Tissue): Fibroma or Sarcoma				
Overall rate	3/50 (6%)	2/40 (5%)	0/60 (0%)	0/49 (0%)
Adjusted rate	7.5%	6.0%	0.0%	0.0%
Terminal rate	2/38 (5%)	1/32 (3%)	0/38 (0%)	0/12 (0%)
First incidence (days)	704	670	–	–
Life table test	P=0.080N	P=0.591N	P=0.122N	P=0.355N
Logistic regression test	P=0.039N	P=0.599N	P=0.100N	P=0.247N
Cochran-Armitage test	P=0.031N			
Fisher exact test		P=0.606N	P=0.091N	P=0.125N
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/50 (10%)	5/40 (13%)	5/60 (8%)	1/49 (2%)
Adjusted rate	13.2%	15.6%	12.7%	6.7%
Terminal rate	5/38 (13%)	5/32 (16%)	4/38 (11%)	0/12 (0%)
First incidence (days)	729 (T)	729 (T)	714	719
Life table test	P=0.405N	P=0.519	P=0.627N	P=0.509N
Logistic regression test	P=0.303N	P=0.519	P=0.604N	P=0.421N
Cochran-Armitage test	P=0.058N			
Fisher exact test		P=0.481	P=0.509N	P=0.107N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	5/40 (13%)	6/60 (10%)	1/49 (2%)
Adjusted rate	13.2%	15.6%	15.2%	6.7%
Terminal rate	5/38 (13%)	5/32 (16%)	5/38 (13%)	0/12 (0%)
First incidence (days)	729 (T)	729 (T)	714	719
Life table test	P=0.469N	P=0.519	P=0.503	P=0.509N
Logistic regression test	P=0.360N	P=0.519	P=0.530	P=0.421N
Cochran-Armitage test	P=0.069N			
Fisher exact test		P=0.481	P=0.622N	P=0.107N
Urinary Bladder: Papilloma				
Overall rate	0/50 (0%)	2/40 (5%)	7/60 (12%)	9/46 (20%)
Adjusted rate	0.0%	6.3%	17.6%	39.5%
Terminal rate	0/38 (0%)	2/32 (6%)	6/38 (16%)	1/12 (8%)
First incidence (days)	–	729 (T)	691	637
Life table test	P<0.001	P=0.201	P=0.010	P<0.001
Logistic regression test	P<0.001	P=0.201	P=0.012	P=0.003
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.195	P=0.012	P<0.001
Urinary Bladder: Carcinoma				
Overall rate	0/50 (0%)	0/40 (0%)	8/60 (13%)	16/46 (35%)
Adjusted rate	0.0%	0.0%	19.5%	55.8%
Terminal rate	0/38 (0%)	0/32 (0%)	6/38 (16%)	4/12 (33%)
First incidence (days)	–	–	670	367
Life table test	P<0.001	–	P=0.006	P<0.001
Logistic regression test	P<0.001	–	P=0.008	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		–	P=0.006	P<0.001

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Urinary Bladder: Papilloma, Squamous Cell Papilloma, Carcinoma, or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	2/40 (5%)	17/60 (28%)	26/46 (57%)
Adjusted rate	0.0%	6.3%	40.9%	78.1%
Terminal rate	0/38 (0%)	2/32 (6%)	14/38 (37%)	6/12 (50%)
First incidence (days)	–	729 (T)	670	367
Life table test	P<0.001	P=0.201	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.201	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.195	P<0.001	P<0.001
Uterus: Stromal Polyp				
Overall rate	8/50 (16%)	15/40 (38%)	7/60 (12%)	5/49 (10%)
Adjusted rate	20.2%	41.4%	16.6%	17.4%
Terminal rate	7/38 (18%)	11/32 (34%)	5/38 (13%)	0/12 (0%)
First incidence (days)	656	600	601	512
Life table test	P=0.498N	P=0.030	P=0.482N	P=0.393
Logistic regression test	P=0.041N	P=0.019	P=0.371N	P=0.295N
Cochran-Armitage test	P=0.038N			
Fisher exact test		P=0.019	P=0.350N	P=0.290N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	8/50 (16%)	15/40 (38%)	8/60 (13%)	5/49 (10%)
Adjusted rate	20.2%	41.4%	19.2%	17.4%
Terminal rate	7/38 (18%)	11/32 (34%)	6/38 (16%)	0/12 (0%)
First incidence (days)	656	600	601	512
Life table test	P=0.540N	P=0.030	P=0.589N	P=0.393
Logistic regression test	P=0.050N	P=0.019	P=0.477N	P=0.295N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=0.019	P=0.449N	P=0.290N
All Organs: Mononuclear Cell Leukemia				
Overall rate	9/50 (18%)	1/40 (3%)	5/60 (8%)	1/49 (2%)
Adjusted rate	21.5%	3.0%	10.0%	3.7%
Terminal rate	6/38 (16%)	0/32 (0%)	1/38 (3%)	0/12 (0%)
First incidence (days)	620	689	601	662
Life table test	P=0.112N	P=0.026N	P=0.177N	P=0.162N
Logistic regression test	P=0.011N	P=0.023N	P=0.111N	P=0.024N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.019N	P=0.110N	P=0.009N
All Organs: Benign Neoplasms				
Overall rate	43/50 (86%)	40/40 (100%)	60/60 (100%)	46/49 (94%)
Adjusted rate	91.5%	100.0%	100.0%	100.0%
Terminal rate	34/38 (89%)	32/32 (100%)	38/38 (100%)	12/12 (100%)
First incidence (days)	606	600	575	418
Life table test	P<0.001	P=0.223	P=0.007	P<0.001
Logistic regression test	P=0.009	P=0.025	P=0.004	P=0.015
Cochran-Armitage test	P=0.164			
Fisher exact test		P=0.013	P=0.003	P=0.167

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
All Organs: Malignant Neoplasms				
Overall rate	16/50 (32%)	15/40 (38%)	60/60 (100%)	46/49 (94%)
Adjusted rate	33.9%	45.5%	100.0%	100.0%
Terminal rate	8/38 (21%)	14/32 (44%)	38/38 (100%)	12/12 (100%)
First incidence (days)	268	689	575	367
Life table test	P<0.001	P=0.424	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.341	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.373	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	40/40 (100%)	60/60 (100%)	49/49 (100%)
Adjusted rate	92.0%	100.0%	100.0%	100.0%
Terminal rate	34/38 (89%)	32/32 (100%)	38/38 (100%)	12/12 (100%)
First incidence (days)	268	600	575	367
Life table test	P<0.001	P=0.435	P=0.035	P<0.001
Logistic regression test	P=0.049	P=0.086	P=0.063	P=0.289
Cochran-Armitage test	P=0.021			
Fisher exact test		P=0.090	P=0.040	P=0.061

(T)Terminal sacrifice
[a] Number of lesion-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, kidney, liver, lung, pituitary gland, thyroid gland, urinary bladder, and uterus; 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 analysis 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 B4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	0/50	1/50	1/50
Methylphenidate Hydrochloride	0/50	0/50	0/50
Pentaerythritol Tetranitrate	0/50	0/50	0/50
Quercetin	0/50	0/50	0/50
Turmeric Oleoresin	1/50	0/50	1/50
Overall Historical Incidence			
Total	8/1,351 (0.6%)	1/1,351 (0.1%)	9/1,351 (0.7%)
Standard deviation	1.5%	0.4%	1.5%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 31 March 1993

TABLE B4b
Historical Incidence of Large Intestine Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenomatous Polyp (Adenoma)	Carcinoma	Adenomatous Polyp (Adenoma) or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	0/50	0/50	0/50
Methylphenidate Hydrochloride	0/50	0/50	0/50
Pentaerythritol Tetranitrate	0/50	0/50	0/50
Quercetin	0/50	0/50	0/50
Turmeric Oleoresin	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/1,351 (0.0%)	0/1,351 (0.0%)	0/1,351 (0.0%)

[a] Data as of 31 March 1993; the data include incidences for the colon and rectum.

TABLE B4c
Historical Incidence of Renal Tubule Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	0/49	0/49	0/49
Methylphenidate Hydrochloride	0/50	0/50	0/50
Pentaerythritol Tetranitrate	0/50	0/50	0/50
Quercetin	0/49	0/49	0/49
Turmeric Oleoresin	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/1,348 (0.1%)	0/1,348 (0.0%)	1/1,348 (0.1%)
Standard deviation	0.4%		0.4%
Range	0%-2%		0%-2%

[a] Data as of 31 March 1993

TABLE B4d
Historical Incidence of Urinary Bladder Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/44	0/44	0/44
HC Yellow 4	0/48	0/48	0/48
Methylphenidate Hydrochloride	0/47	0/47	0/47
Pentaerythritol Tetranitrate	0/49	0/49	0/49
Quercetin	1/50	0/50	1/50
Turmeric Oleoresin	0/50	0/50	0/50
Overall Historical Incidence			
Total	3/1,334 (0.2%)	0/1,334 (0.0%)	3/1,334 (0.2%)
Standard deviation	0.6%		0.6%
Range	0%-2%		0%-2%

[a] Data as of 31 March 1993

TABLE B4e
Historical Incidence of Forestomach Squamous Cell Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	0/50	0/50	0/50
Methylphenidate Hydrochloride	0/50	0/50	0/50
Pentaerythritol Tetranitrate	0/50	0/50	0/50
Quercetin	0/50	0/50	0/50
Tumeric Oleoresin	0/50	1/50	1/50
Overall Historical Incidence			
Total	0/1,351 (0%)	2/1,351 (0.2%)	2/1,351 (0.2%)
Standard deviation		0.5%	0.5%
Range		0%-2%	0%-2%

[a] Data as of 31 March 1993

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
Disposition Summary				
Animals initially in study	70	50	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10			10
Early deaths				
Moribund	8	5	15	29
Natural deaths	4	3	7	8
Survivors				
Died last week of study	1			
Terminal sacrifice	37	32	38	12
Missexed				1
Animals examined microscopically	70	50	70	69
9-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)	4 (40%)	2 (20%)	1 (10%)
Lymphoid tissue, hemorrhage				1 (10%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)		1 (10%)	
Intestine large, cecum	(10)	(10)	(10)	(10)
Parasite metazoan		1 (10%)		
Liver	(10)	(10)	(10)	(10)
Basophilic focus	1 (10%)			1 (10%)
Clear cell focus				1 (10%)
Developmental malformation				1 (10%)
Fatty change			1 (10%)	1 (10%)
Inflammation, chronic active	2 (20%)			2 (20%)
Necrosis, coagulative				4 (40%)
Pigmentation		2 (20%)	6 (60%)	6 (60%)
Bile duct, hyperplasia	1 (10%)	5 (50%)	9 (90%)	3 (30%)
Periportal inflammation, chronic active	6 (60%)	10 (100%)	10 (100%)	8 (80%)
Pancreas	(10)	(10)	(10)	(10)
Atrophy	1 (10%)	2 (20%)		
Ectopic tissue		1 (10%)		
Infiltration cellular, mononuclear cell	3 (30%)	7 (70%)	1 (10%)	1 (10%)
Infiltration cellular, mixed cell			1 (10%)	
Salivary glands	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell				2 (20%)
Infiltration cellular, lymphocyte			1 (10%)	
Stomach, forestomach	(10)	(10)	(10)	(10)
Stomach, glandular	(10)	(10)	(10)	(10)
Muscularis, mineralization	1 (10%)			
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	7 (70%)	8 (80%)	6 (60%)	3 (30%)

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
9-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Angiectasis		3 (30%)	1 (10%)	
Hyperplasia			1 (10%)	
Capsule, fibrosis	1 (10%)			
Capsule, inflammation, chronic	1 (10%)			
Zona reticularis, hyperplasia		1 (10%)		
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, angiectasis		3 (30%)		
Pars distalis, cyst	2 (20%)	1 (10%)	4 (40%)	1 (10%)
Pars distalis, hemorrhage	1 (10%)			
Pars distalis, hyperplasia	1 (10%)	1 (10%)		
Pars distalis, pars intermedia, cyst			2 (20%)	
Pars intermedia, cyst	1 (10%)		2 (20%)	
Thyroid gland	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell	1 (10%)			
Ultimobranchial cyst			1 (10%)	
C-cell, hyperplasia				1 (10%)
Follicular cell, hyperplasia			1 (10%)	
General Body System				
Tissue NOS				(1)
Hemorrhage				1 (100%)
Genital System				
Clitoral gland	(10)	(10)	(8)	(10)
Infiltration cellular, mononuclear cell	1 (10%)			
Inflammation, chronic	3 (30%)			
Inflammation, chronic active	2 (20%)	3 (30%)	4 (50%)	
Ovary	(10)	(10)	(10)	(10)
Congestion				1 (10%)
Cyst		1 (10%)		
Pigmentation		1 (10%)		
Periovarian tissue, cyst		4 (40%)	3 (30%)	
Uterus	(10)	(10)	(10)	(10)
Decidual reaction			1 (10%)	
Hydrometra	1 (10%)	2 (20%)	1 (10%)	5 (50%)
Hematopoietic System				
Lymph node	(3)	(6)	(3)	(7)
Pigmentation				1 (14%)
Lumbar, hemorrhage				1 (14%)
Lumbar, infiltration cellular, histiocyte				1 (14%)
Lumbar, pigmentation				1 (14%)
Mediastinal, hemorrhage	3 (100%)	1 (17%)	3 (100%)	3 (43%)
Mediastinal, infiltration cellular, histiocyte		1 (17%)		1 (14%)
Mediastinal, pigmentation		1 (17%)	2 (67%)	2 (29%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
9-Month Interim Evaluation (continued)				
Hematopoietic System (continued)				
Lymph node (continued)	(3)	(6)	(3)	(7)
Pancreatic, depletion lymphoid		1 (17%)		
Pancreatic, hemorrhage		2 (33%)	1 (33%)	3 (43%)
Pancreatic, infiltration cellular, histiocyte		3 (50%)		
Pancreatic, pigmentation		3 (50%)	1 (33%)	1 (14%)
Renal, hemorrhage		1 (17%)		1 (14%)
Renal, infiltration cellular, histiocyte				1 (14%)
Renal, pigmentation		1 (17%)		1 (14%)
Lymph node, mandibular	(9)	(10)	(10)	(8)
Hemorrhage	7 (78%)	3 (30%)	5 (50%)	4 (50%)
Infiltration cellular, histiocyte		1 (10%)		
Pigmentation		1 (10%)		
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Hemorrhage		4 (40%)	4 (40%)	2 (20%)
Infiltration cellular, histiocyte	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Pigmentation		7 (70%)	8 (80%)	
Spleen	(10)	(10)	(10)	(10)
Congestion				1 (10%)
Depletion lymphoid				2 (20%)
Thymus	(10)	(10)	(10)	(8)
Congestion	1 (10%)			
Depletion lymphoid			1 (10%)	
Hemorrhage	1 (10%)		1 (10%)	
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)		
Infiltration cellular, histiocyte	1 (10%)	2 (20%)	3 (30%)	2 (20%)
Alveolar epithelium, hyperplasia			1 (10%)	
Artery, mineralization	4 (40%)	3 (30%)	3 (30%)	2 (20%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Hydronephrosis	1 (10%)			
Infiltration cellular		1 (10%)		
Infiltration cellular, mononuclear cell		9 (90%)	7 (70%)	3 (30%)
Inflammation, chronic	4 (40%)			
Mineralization	3 (30%)	1 (10%)		
Pigmentation			1 (10%)	
Renal tubule, pigmentation		10 (100%)	10 (100%)	10 (100%)
Renal tubule, regeneration	4 (40%)	5 (50%)	7 (70%)	4 (40%)
Transitional epithelium, mineralization	1 (10%)			1 (10%)
Urinary bladder	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell				1 (10%)
Transitional epithelium, hyperplasia				2 (20%)
Transitional epithelium, infiltration cellular, mononuclear cell				1 (10%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
9-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
Integumentary System				
Musculoskeletal System				
Nervous Sytem				
Special Senses System				
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)			
Parasite metazoan	2 (20%)			
Intestine large, rectum	(10)			(10)
Parasite metazoan				1 (10%)
Intestine large, cecum	(10)			
Parasite metazoan	2 (20%)			
Liver	(10)			(10)
Abscess				1 (10%)
Basophilic focus	8 (80%)			9 (90%)
Clear cell focus				5 (50%)
Eosinophilic focus	2 (20%)			
Fatty change				8 (80%)
Hepatodiaphragmatic nodule	2 (20%)			1 (10%)
Inflammation, chronic, granulomatous	6 (60%)			6 (60%)
Inflammation, chronic active	1 (10%)			
Necrosis, coagulative	1 (10%)			4 (40%)
Pigmentation	1 (10%)			10 (100%)
Bile duct, hyperplasia	7 (70%)			10 (100%)
Periportal, inflammation, chronic	10 (100%)			10 (100%)
Mesentery				(1)
Inflammation, chronic				1 (100%)
Pigmentation				1 (100%)
Pancreas	(10)			(1)
Atrophy	1 (10%)			
Ectopic tissue	1 (10%)			
Inflammation, chronic	9 (90%)			1 (100%)
Pharynx				(1)
Hemorrhage				1 (100%)
Salivary glands	(10)			
Stomach, forestomach	(10)			(10)
Hyperplasia, basal cell				1 (10%)
Inflammation, chronic				1 (10%)
Stomach, glandular	(10)			(10)
Muscularis, mineralization	1 (10%)			
Cardiovascular System				
Heart	(10)			
Cardiomyopathy	10 (100%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
15-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal cortex	(10)			(1)
Angiectasis	5 (50%)			
Vacuolization cytoplasmic				1 (100%)
Adrenal medulla	(10)			(1)
Pituitary gland	(10)			
Pars distalis, cyst	8 (80%)			
Pars distalis, hyperplasia	1 (10%)			
Pars intermedia, cyst	3 (30%)			
Thyroid gland	(10)			
C-cell, hyperplasia	4 (40%)			
Genital System				
Clitoral gland	(10)			(3)
Inflammation, chronic	7 (70%)			3 (100%)
Inflammation, chronic active	1 (10%)			
Ovary	(10)			(4)
Cyst				2 (50%)
Periovarian tissue, cyst				4 (100%)
Uterus	(10)			(3)
Hydrometra	2 (20%)			3 (100%)
Endometrium, hyperplasia	1 (10%)			
Hematopoietic System				
Lymph node	(1)			(3)
Mediastinal, hemorrhage	1 (100%)			
Mediastinal, pigmentation	1 (100%)			
Pancreatic, infiltration cellular, histiocyte				3 (100%)
Pancreatic, pigmentation				3 (100%)
Lymph node, mandibular	(7)			
Hemorrhage	1 (14%)			
Lymph node, mesenteric	(10)			(4)
Hemorrhage				1 (25%)
Infiltration cellular, histiocyte	10 (100%)			4 (100%)
Pigmentation	10 (100%)			4 (100%)
Thymus	(10)			(9)
Cyst	1 (10%)			1 (11%)
Depletion lymphoid				4 (44%)
Pigmentation				1 (11%)
Integumentary System				
Mammary gland	(7)			
Hyperplasia	6 (86%)			
Musculoskeletal System				
Bone	(10)			
Osteopetrosis	1 (10%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)			(5)
Hemorrhage	1 (10%)			
Infiltration cellular, histiocyte	6 (60%)			5 (100%)
Inflammation, acute				1 (20%)
Alveolus, mineralization	1 (10%)			
Artery, mineralization	4 (40%)			2 (40%)
Nose	(10)			
Submucosa, inflammation, chronic	1 (10%)			
Urinary System				
Kidney	(10)			(10)
Nephropathy	10 (100%)			10 (100%)
Renal tubule, hyperplasia				3 (30%)
Renal tubule, mineralization	1 (10%)			
Renal tubule, pigmentation				10 (100%)
Transitional epithelium, hyperplasia	3 (30%)			4 (40%)
Transitional epithelium, mineralization	2 (20%)			1 (10%)
Urinary bladder	(10)			(10)
Inflammation, chronic				1 (10%)
Transitional epithelium, hyperplasia				9 (90%)
Systems Examined With No Lesions Observed				
General Body System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(40)	(57)	(48)
Autolysis	1 (2%)			
Intestine large, colon	(49)	(40)	(59)	(47)
Autolysis	3 (6%)		5 (8%)	3 (6%)
Parasite metazoan	14 (29%)	9 (23%)	7 (12%)	6 (13%)
Intestine large, rectum	(49)	(40)	(60)	(47)
Atypia cellular		1 (3%)	6 (10%)	
Autolysis	4 (8%)		6 (10%)	1 (2%)
Diverticulum				1 (2%)
Fibrosis		1 (3%)		
Inflammation, acute, necrotizing				3 (6%)
Parasite metazoan	10 (20%)	4 (10%)	8 (13%)	8 (17%)
Ulcer			1 (2%)	
Epithelium, hyperplasia			3 (5%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
2-Year Study (continued)								
Alimentary System (continued)								
Intestine large, cecum	(50)		(40)		(60)		(47)	
Autolysis	4	(8%)	1	(3%)	6	(10%)	4	(9%)
Hemorrhage			1	(3%)				
Mineralization					1	(2%)		
Parasite metazoan	4	(8%)	6	(15%)	5	(8%)	2	(4%)
Intestine small, duodenum	(50)		(40)		(59)		(46)	
Autolysis	2	(4%)			5	(8%)	1	(2%)
Intestine small, jejunum	(48)		(40)		(59)		(46)	
Autolysis	3	(6%)	1	(3%)	8	(14%)	3	(7%)
Intestine small, ileum	(49)		(39)		(59)		(44)	
Autolysis	3	(6%)	1	(3%)	8	(14%)	4	(9%)
Parasite metazoan			1	(3%)				
Ulcer	1	(2%)						
Liver	(50)		(40)		(60)		(48)	
Angiectasis	1	(2%)	1	(3%)				
Autolysis					4	(7%)		
Basophilic focus	39	(78%)	15	(38%)	22	(37%)	16	(33%)
Clear cell focus	3	(6%)	28	(70%)	39	(65%)	17	(35%)
Degeneration					3	(5%)		
Eosinophilic focus	7	(14%)	23	(58%)	12	(20%)	1	(2%)
Fatty change	8	(16%)			3	(5%)	5	(10%)
Hematopoietic cell proliferation					10	(17%)	2	(4%)
Hemorrhage							1	(2%)
Hepatodiaphragmatic nodule	8	(16%)	4	(10%)	1	(2%)		
Hepatodiaphragmatic nodule, multiple	1	(2%)						
Hyperplasia, focal			1	(3%)				
Infarct	1	(2%)						
Inflammation, chronic active	21	(42%)	16	(40%)	23	(38%)	5	(10%)
Mixed cell focus	1	(2%)	11	(28%)	5	(8%)	4	(8%)
Necrosis, coagulative	3	(6%)	4	(10%)	11	(18%)	9	(19%)
Pigmentation	1	(2%)	19	(48%)	51	(85%)	45	(94%)
Thrombosis	1	(2%)					1	(2%)
Bile duct, hyperplasia	33	(66%)	5	(13%)	56	(93%)	42	(88%)
Centrilobular, hemorrhage	1	(2%)						
Centrilobular, necrosis, coagulative	1	(2%)						
Periportal, inflammation, chronic active	25	(50%)	2	(5%)	54	(90%)	39	(81%)
Mesentery	(4)		(6)		(1)		(4)	
Fibrosis	2	(50%)	5	(83%)	1	(100%)	1	(25%)
Inflammation, chronic active	3	(75%)	3	(50%)	1	(100%)	1	(25%)
Necrosis, coagulative	2	(50%)	5	(83%)	1	(100%)		
Polyarteritis		1	(17%)			1	(25%)	
Pancreas		(50)		(40)		(60)		(47)
Atrophy	20	(40%)	17	(43%)	16	(27%)	15	(32%)
Autolysis	1	(2%)			1	(2%)	1	(2%)
Cytoplasmic alteration			1	(3%)	2	(3%)	1	(2%)
Ectopic liver					2	(3%)		
Ectopic tissue	1	(2%)						
Inflammation, chronic active	29	(58%)	24	(60%)	30	(50%)	22	(47%)
Polyarteritis			2	(5%)				
Vacuolization cytoplasmic	5	(10%)			12	(20%)	3	(6%)
Acinus, hyperplasia					1	(2%)	1	(2%)
Duct, hyperplasia					1	(2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		2,000 ppm		5,000 ppm		10,000 ppm	
2-Year Study (continued)								
Alimentary System (continued)								
Salivary glands	(50)		(40)		(60)		(48)	
Parotid gland, inflammation, chronic active					2	(3%)	1	(2%)
Sublingual gland, inflammation, chronic active	1	(2%)						
Submandibular gland, inflammation, chronic active	1	(2%)			1	(2%)		
Stomach, forestomach	(49)		(40)		(60)		(47)	
Autolysis	1	(2%)						
Cyst epithelial inclusion							1	(2%)
Erosion					2	(3%)	3	(6%)
Hyperkeratosis	2	(4%)	7	(18%)	23	(38%)	28	(60%)
Hyperplasia, basal cell	2	(4%)	7	(18%)	35	(58%)	28	(60%)
Hyperplasia, squamous	2	(4%)	7	(18%)	26	(43%)	33	(70%)
Inflammation, chronic active			1	(3%)	13	(22%)	10	(21%)
Ulcer	1	(2%)	2	(5%)	7	(12%)	17	(36%)
Stomach, glandular	(50)		(40)		(60)		(48)	
Autolysis	2	(4%)			3	(5%)	1	(2%)
Fibrosis					1	(2%)		
Inflammation, chronic active	3	(6%)	1	(3%)	6	(10%)	6	(13%)
Necrosis, coagulative	1	(2%)					1	(2%)
Ulcer							1	(2%)
Tongue								(1)
Foreign body							1	(100%)
Inflammation, chronic							1	(100%)
Tooth	(1)		(1)				(1)	
Cyst			1	(100%)				
Cardiovascular System								
Heart		(50)		(40)		(60)		(49)
Cardiomyopathy	46	(92%)	38	(95%)	54	(90%)	40	(82%)
Endocrine System								
Adrenal cortex	(47)		(40)		(59)		(47)	
Angiectasis	25	(53%)	29	(73%)	40	(68%)	26	(55%)
Autolysis	1	(2%)					3	(6%)
Hyperplasia	3	(6%)	4	(10%)	3	(5%)	1	(2%)
Hypertrophy	1	(2%)						
Necrosis, coagulative	1	(2%)						
Thrombosis, multiple	1	(2%)						
Vacuolization cytoplasmic	17	(36%)	16	(40%)	35	(59%)	19	(40%)
Capsule, hyperplasia	1	(2%)						
Adrenal medulla	(47)		(40)		(59)		(47)	
Autolysis	1	(2%)					1	(2%)
Hyperplasia	11	(23%)	5	(13%)	11	(19%)	14	(30%)
Islets, pancreatic	(50)		(40)		(60)		(47)	
Autolysis	1	(2%)						
Parathyroid gland		(43)		(37)		(57)		(38)
Hyperplasia			3	(8%)	1	(2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(50)	(39)	(60)	(47)
Thrombosis	1 (2%)			
Pars distalis, angiectasis			1 (2%)	
Pars distalis, autolysis			2 (3%)	1 (2%)
Pars distalis, cyst	14 (28%)	20 (51%)	19 (32%)	17 (36%)
Pars distalis, cyst, multiple				3 (6%)
Pars distalis, hyperplasia	12 (24%)	9 (23%)	15 (25%)	8 (17%)
Pars distalis, necrosis, coagulative				1 (2%)
Pars intermedia, cyst			1 (2%)	
Rathke's cleft, cyst				1 (2%)
Thyroid gland	(50)	(40)	(60)	(49)
Autolysis	2 (4%)		1 (2%)	4 (8%)
Inflammation, chronic		1 (3%)		
Inflammation, chronic active			1 (2%)	
Ultimobranchial cyst	1 (2%)			
C-cell, hyperplasia	7 (14%)	2 (5%)	3 (5%)	1 (2%)
Follicle, cyst			1 (2%)	
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(45)	(36)	(60)	(45)
Abscess	2 (4%)		3 (5%)	1 (2%)
Cyst	1 (2%)	1 (3%)		
Hyperplasia		1 (3%)		
Inflammation, chronic active	34 (76%)	18 (50%)	47 (78%)	31 (69%)
Duct, metaplasia, squamous	1 (2%)			
Ovary	(50)	(40)	(60)	(47)
Cyst	11 (22%)	2 (5%)	5 (8%)	4 (9%)
Uterus	(50)	(40)	(60)	(47)
Abscess		6 (15%)	8 (13%)	
Autolysis				1 (2%)
Cyst	1 (2%)	5 (13%)		3 (6%)
Fibrosis	3 (6%)		1 (2%)	1 (2%)
Hydrometra	5 (10%)	4 (10%)	8 (13%)	4 (9%)
Inflammation, acute	1 (2%)			
Inflammation, chronic active				1 (2%)
Endometrium, hyperplasia	4 (8%)	9 (23%)	2 (3%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(40)	(60)	(49)
Autolysis	1 (2%)			
Myelofibrosis		1 (3%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(3)	(5)	(25)	(14)
Iliac, infiltration cellular, histiocyte				1 (7%)
Lumbar, infiltration cellular, histiocyte				1 (7%)
Mediastinal, hyperplasia	1 (33%)			
Mediastinal, infiltration cellular, histiocyte	1 (33%)		2 (8%)	2 (14%)
Pancreatic, hyperplasia	2 (67%)		5 (20%)	1 (7%)
Pancreatic, infiltration cellular, histiocyte	3 (100%)	5 (100%)	21 (84%)	8 (57%)
Renal, infiltration cellular, histiocyte		1 (20%)		
Lymph node, mandibular	(50)	(39)	(56)	(45)
Autolysis				1 (2%)
Depletion lymphoid				1 (2%)
Hyperplasia		1 (3%)	2 (4%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)	1 (3%)	1 (2%)	9 (20%)
Inflammation, chronic active				1 (2%)
Lymph node, mesenteric	(50)	(40)	(59)	(46)
Autolysis	1 (2%)			2 (4%)
Depletion lymphoid	2 (4%)	1 (3%)	2 (3%)	8 (17%)
Infiltration cellular, histiocyte	49 (98%)	39 (98%)	57 (97%)	45 (98%)
Spleen	(50)	(40)	(60)	(48)
Autolysis				1 (2%)
Depletion lymphoid	8 (16%)	1 (3%)	3 (5%)	5 (10%)
Fibrosis		1 (3%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	1 (2%)			
Infiltration cellular, histiocyte	1 (2%)			
Thymus	(42)	(31)	(51)	(38)
Cyst		1 (3%)		
Hemorrhage				1 (3%)
Integumentary System				
Mammary gland	(49)	(34)	(50)	(41)
Galactocele	1 (2%)			
Hyperplasia	41 (84%)	29 (85%)	41 (82%)	26 (63%)
Inflammation, chronic active	1 (2%)			
Skin	(50)	(39)	(60)	(49)
Abscess	1 (2%)			1 (2%)
Cyst epithelial inclusion			2 (3%)	
Foreign body			1 (2%)	
Inflammation, chronic active	2 (4%)		6 (10%)	2 (4%)
Foot, acanthosis			1 (2%)	
Foot, hyperkeratosis			1 (2%)	
Foot, inflammation, chronic active		1 (3%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(40)	(60)	(49)
Cranium, osteopetrosis				1 (2%)
Femur, osteopetrosis				1 (2%)
Sternum, osteopetrosis	1 (2%)			3 (6%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(40)	(60)	(49)
Hydrocephalus	1 (2%)	2 (5%)		
Infarct			1 (2%)	
Respiratory System				
Lung	(50)	(40)	(60)	(49)
Autolysis	1 (2%)			
Fibrosis			2 (3%)	
Infiltration cellular, histiocyte	31 (62%)	31 (78%)	50 (83%)	36 (73%)
Inflammation, chronic active	4 (8%)		3 (5%)	2 (4%)
Polyarteritis				1 (2%)
Alveolar epithelium, hyperplasia				1 (2%)
Artery, mineralization	23 (46%)	6 (15%)	20 (33%)	14 (29%)
Bronchiole, epithelium, hyperplasia	1 (2%)			
Mediastinum, polyarteritis		2 (5%)		
Nose	(50)	(40)	(60)	(49)
Autolysis				1 (2%)
Foreign body	1 (2%)		4 (7%)	
Inflammation, chronic active	9 (18%)	8 (20%)	13 (22%)	12 (24%)
Metaplasia, squamous	1 (2%)	4 (10%)	4 (7%)	2 (4%)
Arteriole, thrombosis				1 (2%)
Trachea	(50)	(40)	(60)	(49)
Autolysis	1 (2%)			
Special Senses System				
Ear			(8)	(3)
External ear, inflammation, acute			2 (25%)	
Internal ear, inflammation, acute			1 (13%)	
Eye	(13)	(7)	(7)	(7)
Phthisis bulbi		1 (14%)	1 (14%)	
Synechia	1 (8%)			1 (14%)
Cornea, inflammation, acute				1 (14%)
Lens, cataract	1 (8%)		1 (14%)	
Retina, degeneration	1 (8%)		3 (43%)	1 (14%)
Zymbal's gland	(1)		(2)	
Autolysis	1 (100%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(40)	(60)	(48)
Abscess			1 (2%)	
Autolysis	2 (4%)		3 (5%)	3 (6%)
Cyst		1 (3%)	2 (3%)	
Fibrosis			1 (2%)	
Hydronephrosis	2 (4%)		2 (3%)	
Infarct		1 (3%)		
Inflammation, chronic active			1 (2%)	
Nephropathy	50 (100%)	39 (98%)	60 (100%)	46 (96%)
Polyarteritis		1 (3%)		
Artery, thrombosis			1 (2%)	
Papilla, necrosis, coagulative				2 (4%)
Pelvis, inflammation, chronic active	1 (2%)	1 (3%)	4 (7%)	6 (13%)
Pelvis, metaplasia, squamous			3 (5%)	2 (4%)
Renal tubule, hyperplasia	1 (2%)	12 (30%)	23 (38%)	27 (56%)
Renal tubule, hyperplasia, oncocytic			1 (2%)	
Renal tubule, inflammation, acute	1 (2%)	7 (18%)	3 (5%)	
Renal tubule, inflammation, chronic active			2 (3%)	7 (15%)
Renal tubule, pigmentation		40 (100%)	60 (100%)	48 (100%)
Transitional epithelium, hyperplasia	10 (20%)	16 (40%)	44 (73%)	21 (44%)
Transitional epithelium, mineralization		4 (10%)		
Urinary bladder	(50)	(40)	(60)	(46)
Autolysis	1 (2%)		2 (3%)	
Calculus, gross observation		2 (5%)		1 (2%)
Calculus, microscopic observation only				1 (2%)
Fibrosis			1 (2%)	
Hemorrhage				2 (4%)
Hyperplasia, lymphoid	15 (30%)	2 (5%)	3 (5%)	
Inflammation, chronic active	1 (2%)	1 (3%)	3 (5%)	1 (2%)
Necrosis				1 (2%)
Fat, proliferation			4 (7%)	2 (4%)
Transitional epithelium, hyperplasia	1 (2%)	2 (5%)	41 (68%)	41 (89%)
Transitional epithelium, metaplasia, squamous		1 (3%)	4 (7%)	8 (17%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	10,000 ppm	20,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	9	10
Early deaths			
Accidental death		1	
Moribund	7	23	21
Natural deaths	3	5	6
Survivors			
Terminal sacrifice	40	22	23
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(9)	(10)
Hepatocellular carcinoma		1 (11%)	
Hepatocellular adenoma		2 (22%)	4 (40%)
Stomach, forestomach	(9)	(9)	(10)
Squamous cell carcinoma			1 (10%)
Squamous cell papilloma			5 (50%)
Genital System			
Preputial gland	(5)		(1)
Squamous cell carcinoma	1 (20%)		
Respiratory System			
Lung	(10)	(9)	(10)
Alveolar/bronchiolar adenoma		3 (33%)	5 (50%)
Special Senses System			
Lacrimal gland			(1)
Adenoma			1 (100%)
Urinary System			
Urinary bladder	(10)	(9)	(10)
Papilloma			1 (10%)
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
Endocrine System			
General Body System			
Hematopoietic system			
Integumentary System			
Musculoskeletal System			
Nervous System			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study			
Alimentary System			
Gallbladder	(46)	(47)	(42)
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	1 (2%)
Intestine large, colon	(50)	(49)	(50)
Mast cell tumor malignant		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Intestine large, rectum	(48)	(49)	(48)
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Intestine large, cecum	(49)	(51)	(50)
Adenocarcinoma			1 (2%)
Mast cell tumor malignant		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Intestine small, duodenum	(50)	(50)	(46)
Mast cell tumor malignant		1 (2%)	
Polyp adenomatous	1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Intestine small, jejunum	(50)	(47)	(48)
Mast cell tumor malignant		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Intestine small, ileum	(50)	(49)	(47)
Adenocarcinoma		1 (2%)	2 (4%)
Histiocytic sarcoma		1 (2%)	
Mast cell tumor malignant		1 (2%)	
Liver	(50)	(51)	(50)
Fibrosarcoma, metastatic, stomach, forestomach			1 (2%)
Hemangiosarcoma		2 (4%)	1 (2%)
Hemangiosarcoma, multiple	3 (6%)		
Hepatoblastoma		3 (6%)	5 (10%)
Hepatocellular carcinoma	8 (16%)	15 (29%)	12 (24%)
Hepatocellular carcinoma, multiple	1 (2%)	3 (6%)	9 (18%)
Hepatocellular adenoma	4 (8%)	9 (18%)	8 (16%)
Hepatocellular adenoma, multiple	6 (12%)	29 (57%)	31 (62%)
Hepatocholangiocarcinoma, multiple			1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Squamous cell carcinoma, metastatic, tissue NOS		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		4 (8%)	4 (8%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Alimentary System (continued)			
Mesentery	(2)	(7)	(9)
Sarcoma, metastatic, stomach, forestomach		1 (14%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		2 (29%)	5 (56%)
Pancreas	(50)	(50)	(48)
Histiocytic sarcoma		1 (2%)	
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	1 (2%)
Salivary glands	(50)	(51)	(50)
Stomach, forestomach	(50)	(50)	(50)
Leiomyosarcoma		1 (2%)	
Mast cell tumor malignant		1 (2%)	
Squamous cell carcinoma		12 (24%)	13 (26%)
Squamous cell papilloma		11 (22%)	11 (22%)
Squamous cell papilloma, multiple		2 (4%)	5 (10%)
Stomach, glandular	(50)	(50)	(49)
Histiocytic sarcoma		1 (2%)	
Mast cell tumor malignant		1 (2%)	
Sarcoma		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		3 (6%)	4 (8%)
Tooth	(4)		(7)
Cardiovascular System			
Heart	(50)	(51)	(50)
Endocrine System			
Adrenal cortex	(50)	(51)	(50)
Adenoma	2 (4%)	1 (2%)	
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma benign			1 (2%)
Pituitary gland	(43)	(45)	(47)
Pars distalis, adenoma		2 (4%)	
Thyroid gland	(49)	(50)	(49)
C-cell, adenoma			1 (2%)
General Body System			
Tissue NOS	(1)	(1)	(1)
Squamous cell carcinoma		1 (100%)	
Genital System			
Coagulating gland	(1)	(1)	(1)
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (100%)	1 (100%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Genital System (continued)			
Epididymis	(49)	(51)	(50)
Fibrosarcoma, metastatic, stomach, forestomach			1 (2%)
Histiocytic sarcoma		1 (2%)	
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	1 (2%)
Preputial gland	(16)	(16)	(12)
Squamous cell carcinoma	1 (6%)		
Prostate	(47)	(46)	(48)
Histiocytic sarcoma		1 (2%)	
Squamous cell carcinoma, metastatic, preputial gland	1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Seminal vesicle	(49)	(50)	(45)
Fibrosarcoma, metastatic, stomach, forestomach			1 (2%)
Histiocytic sarcoma		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Testes	(50)	(50)	(50)
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Hematopoietic System			
Bone marrow	(49)	(50)	(49)
Mast cell tumor malignant		1 (2%)	
Lymph node	(8)	(8)	(11)
Lumbar, histiocytic sarcoma		1 (13%)	
Mediastinal, histiocytic sarcoma		1 (13%)	
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach		2 (25%)	1 (9%)
Pancreatic, histiocytic sarcoma		1 (13%)	
Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach			1 (9%)
Renal, histiocytic sarcoma		1 (13%)	
Lymph node, mandibular	(32)	(34)	(26)
Histiocytic sarcoma		1 (3%)	
Mast cell tumor malignant		1 (3%)	
Lymph node, mesenteric	(46)	(47)	(47)
Histiocytic sarcoma		1 (2%)	
Mast cell tumor malignant		1 (2%)	
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		2 (4%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Hematopoietic System (continued)			
Spleen	(50)	(51)	(50)
Hemangiosarcoma		1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)	
Mast cell tumor malignant		2 (4%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	
Thymus	(37)	(35)	(33)
Mast cell tumor malignant		1 (3%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (3%)	
Integumentary System			
Skin	(50)	(48)	(48)
Mast cell tumor malignant		1 (2%)	
Squamous cell carcinoma		1 (2%)	
Squamous cell papilloma	1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	2 (4%)	1 (2%)
Subcutaneous tissue, fibroma, multiple		1 (2%)	
Subcutaneous tissue, fibrosarcoma	3 (6%)	8 (17%)	2 (4%)
Subcutaneous tissue, sarcoma	1 (2%)		
Musculoskeletal System			
Skeletal muscle	(3)	(3)	(3)
Abdominal, squamous cell carcinoma, metastatic, stomach, forestomach			2 (67%)
Diaphragm, sarcoma, metastatic, stomach, forestomach		1 (33%)	
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach		2 (67%)	1 (33%)
Nervous System			
Brain	(50)	(51)	(50)
Respiratory System			
Lung	(50)	(51)	(50)
Alveolar/bronchiolar adenoma	7 (14%)	20 (39%)	15 (30%)
Alveolar/bronchiolar adenoma, multiple		6 (12%)	9 (18%)
Alveolar/bronchiolar carcinoma	3 (6%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	
Hepatocellular carcinoma, metastatic	1 (2%)		2 (4%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)		
Histiocytic sarcoma		1 (2%)	1 (2%)
Sarcoma, metastatic, stomach, forestomach		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		3 (6%)	
Mediastinum, hemangiosarcoma, metastatic, spleen			1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Special Senses System			
Ear	(1)	(1)	(1)
Fibrosarcoma	1 (100%)		
Harderian gland	(2)	(2)	(1)
Adenoma	2 (100%)	2 (100%)	1 (100%)
Urinary System			
Kidney	(50)	(51)	(50)
Histiocytic sarcoma		1 (2%)	
Mast cell tumor malignant		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		2 (4%)	
Urinary bladder	(49)	(50)	(49)
Histiocytic sarcoma		1 (2%)	
Mast cell tumor malignant		1 (2%)	
Systemic Lesions			
Multiple organs[b]	(50)	(51)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	7 (14%)	3 (6%)	5 (10%)
Lymphoma malignant undifferentiated cell	2 (4%)	2 (4%)	1 (2%)
Mesothelioma malignant		1 (2%)	
Neoplasm Summary			
Total animals with primary neoplasms[c]			
15-Month interim evaluation	1	4	8
2-Year study	37	49	47
Total primary neoplasms			
15-Month interim evaluation	1	6	12
2-Year study	57	162	139
Total animals with benign neoplasms			
15-Month interim evaluation		4	7
2-Year study	20	43	43
Total benign neoplasms			
15-Month interim evaluation		5	11
2-Year study	25	85	83

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone
(continued)

	0 ppm	10,000 ppm	20,000 ppm
Neoplasm Summary (continued)			
Total animals with malignant neoplasms			
15-Month interim evaluation	1	1	1
2-Year study	25	39	39
Total malignant neoplasms			
15-Month interim evaluation	1	1	1
2-Year study	32	77	56
Total animals with metastatic neoplasms			
2-Year study	4	7	9
Total metastatic neoplasms			
2-Year study	4	37	36

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm

Number of Days on Study	292	393	445	480	521	621	705	705	723	723	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	02525	03535	04545	03434	03335	01015	04343	06565	03232	06464	02121	02303	02424	04141	04441	05151	05252	05353	05454	05555	06161	06262	06363	07272	07373
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																								X	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma			X							X			X									X			
Hepatocellular carcinoma, multiple												X													
Hepatocellular adenoma									X											X					
Hepatocellular adenoma, multiple																								X	
Mesentery							+		+																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	M	M	M	M	+	+	M	M	+	+	+	+	+	+	+	M	+	+	M	M
Pituitary gland	+	+	I	+	M	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																									
Genital System																									
Coagulating gland					+																				
Epididymis	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		M	+					+	+	+			+				+					+	+	+	+
Squamous cell carcinoma																									
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, preputial gland																									
Seminal vesicle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	074	075	095	103	104	114	124	125	011	012	014	031	081	082	083	085	091	093	094	101	111	112	113	122	123	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple		X																			X			X		3
Hepatocellular carcinoma	X			X		X						X														8
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X															X								4
Hepatocellular adenoma, multiple				X			X				X					X							X			6
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth				+				+															+		+	4
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	M	M	+	+	M	+	M	M	+	+	+	+	M	M	+	M	M	+	+	+	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	43
Thyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
Tissue NOS							+																			1
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland				+		+			+	+													+	+		16
Squamous cell carcinoma																								X		1
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Squamous cell carcinoma, metastatic, preputial gland																								X		1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	0074	0075	0095	1003	1004	1014	1024	1025	0011	0012	0014	0031	0081	0082	0083	0085	0091	0093	0094	1001	1011	1012	1013	1022	1023		Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph node								+	+			+			+									+			8
Lymph node, mandibular	M	+	M	M	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+		32
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+		46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	I	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell papilloma												X															1
Subcutaneous tissue, fibroma																											2
Subcutaneous tissue, fibrosarcoma																				X							3
Subcutaneous tissue, sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Skeletal muscle																											3
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma										X	X		X										X				7
Alveolar/bronchiolar carcinoma																											3
Hepatocellular carcinoma, metastatic												X															1
Hepatocellular carcinoma, metastatic, liver	X																										2
Nose	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+		43
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Ear																			+								1
Fibrosarcoma																			X								1
Eye																	+										2
Harderian gland																	+										2
Adenoma																	X										2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic								X																			1
Lymphoma malignant mixed										X		X					X										7
Lymphoma malignant undifferentiated cell type																											2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm

Number of Days on Study	152	414	451	457	464	501	505	550	572	578	582	583	611	612	613	618	633	633	642	647	648	654	673	673	689
Carcass ID Number	185	235	165	201	195	205	135	214	164	225	224	175	204	162	145	184	155	194	245	193	183	153	133	134	144
Alimentary System																									
Esophagus	+	+	+		+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Sarcoma, metastatic, stomach, forestomach					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach																								X	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Mast cell tumor malignant																							X		
Intestine large, rectum	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																							X		
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																							X		
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	M
Mast cell tumor malignant																							X		
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Histiocytic sarcoma																			X						
Mast cell tumor malignant																							X		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Hepatoblastoma									X									X			X				
Hepatocellular carcinoma							X							X		X				X					X
Hepatocellular carcinoma, multiple																					X				
Hepatocellular adenoma			X									X					X		X		X		X		
Hepatocellular adenoma, multiple								X	X	X			X		X	X		X				X		X	X
Histiocytic sarcoma																			X						
Sarcoma, metastatic, stomach, forestomach					X																				
Squamous cell carcinoma, metastatic, tissue NOS					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach							X					X												X	X
Mesentery					+		+		+		+	+			+										
Sarcoma, metastatic, stomach, forestomach					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach												X			X										
Pancreas	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Sarcoma, metastatic, stomach, forestomach					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	7 0 6	7 0 9	7 1 5	7 1 7	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 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	2 1 3	2 0 3	2 3 4	2 2 3	1 3 1	1 3 2	1 4 1	1 4 3	1 5 1	1 5 2	1 6 1	1 7 1	1 7 2	1 7 4	1 8 2	1 9 1	1 9 2	2 0 2	2 2 1	2 2 2	2 3 1	2 3 3	2 4 1	2 4 2	2 4 3	2 4 4	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, stomach, forestomach																											1
Squamous cell carcinoma, metastatic, stomach, forestomach																											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49
Mast cell tumor malignant																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mast cell tumor malignant																											1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mast cell tumor malignant																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma						X																					1
Histiocytic sarcoma																											1
Mast cell tumor malignant																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma															X												2
Hepatoblastoma																											3
Hepatocellular carcinoma		X	X				X		X			X	X		X	X								X		X	15
Hepatocellular carcinoma, multiple																	X								X		3
Hepatocellular adenoma		X																X		X							9
Hepatocellular adenoma, multiple				X	X	X		X	X	X	X	X	X	X	X	X	X		X		X	X		X	X	X	29
Histiocytic sarcoma																											1
Sarcoma, metastatic, stomach, forestomach																											1
Squamous cell carcinoma, metastatic, tissue NOS																											1
Squamous cell carcinoma, metastatic, stomach, forestomach																											4
Mesentery	+																										7
Sarcoma, metastatic, stomach, forestomach																											1
Squamous cell carcinoma, metastatic, stomach, forestomach																											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Sarcoma, metastatic, stomach, forestomach																											1
Squamous cell carcinoma, metastatic, stomach, forestomach																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	152	414	451	457	464	501	505	550	572	578	582	583	611	612	613	618	633	633	642	647	648	654	673	673	689
Carcass ID Number	185	235	165	201	195	205	135	214	164	225	224	175	204	162	145	184	155	194	245	193	183	153	133	134	144
Alimentary System (continued)																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma					X																				
Mast cell tumor malignant																							X		
Squamous cell carcinoma							X				X	X			X								X	X	X
Squamous cell papilloma															X								X		
Squamous cell papilloma, multiple																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Mast cell tumor malignant																							X		
Sarcoma					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach											X													X	X
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Sarcoma, metastatic, stomach, forestomach					X																				
Adrenal medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M		+	+	M	+	+	M	+	+	+	+	M	+	+	M	M	+	M	M	+	+	+
Pituitary gland	+	+	+		+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pars distalis, adenoma			X																						
Thyroid gland	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS					+																				
Squamous cell carcinoma					X																				
Genital System																									
Coagulating gland																								+	
Squamous cell carcinoma, metastatic, stomach, forestomach																								X	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Sarcoma, metastatic, stomach, forestomach					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach																								X	
Penis																									
Preputial gland	+	+	+								+	+				+	+	+	+		+				
Prostate	+	+	+		+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Seminal vesicle	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, stomach, forestomach					X																				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	706	709	715	717	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	213	203	234	223	131	132	141	143	151	152	161	171	172	174	182	191	192	202	221	222	231	233	241	242	243	244	Total Tissues/ Tumors	
Alimentary System (continued)																												
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leiomyosarcoma																											1	
Mast cell tumor malignant																											1	
Squamous cell carcinoma				X	X	X											X		X								12	
Squamous cell papilloma				X	X	X	X	X			X	X	X		X												11	
Squamous cell papilloma, multiple										X									X								2	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																											1	
Mast cell tumor malignant																											1	
Sarcoma																											1	
Squamous cell carcinoma, metastatic, stomach, forestomach																											3	
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Adenoma																			X								1	
Sarcoma, metastatic, stomach, forestomach																											1	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	37	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	45	
Pars distalis, adenoma									X																		2	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
General Body System																												
Tissue NOS																											1	
Squamous cell carcinoma																											1	
Genital System																												
Coagulating gland																											1	
Squamous cell carcinoma, metastatic, stomach, forestomach																											1	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Histiocytic sarcoma																											1	
Sarcoma, metastatic, stomach, forestomach																											1	
Squamous cell carcinoma, metastatic, stomach, forestomach																											1	
Penis										+																	1	
Preputial gland		+					M							+	+		+						+		+		16	
Prostate	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Histiocytic sarcoma																											1	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																											1	
Testes	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Sarcoma, metastatic, stomach, forestomach																											1	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	1 5 2	4 1 4	4 5 1	4 5 7	4 6 4	5 0 1	5 0 5	5 5 0	5 7 2	5 7 8	5 8 2	5 8 3	6 1 1	6 1 2	6 1 3	6 1 8	6 3 3	6 3 3	6 4 2	6 4 7	6 4 8	6 5 4	6 7 3	6 7 3	6 8 9
Carcass ID Number	1 8 5	2 3 5	1 6 5	2 0 1	1 9 5	2 0 5	1 3 5	2 1 4	1 6 4	2 2 5	2 2 4	1 7 5	2 0 4	1 6 2	1 4 5	1 8 4	1 5 5	1 9 4	2 4 5	1 9 3	1 8 3	1 5 3	1 3 3	1 3 4	1 4 4
Hematopoietic System																									
Bone marrow	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									
Lymph node												+		+					+	+		+		+	
Lumbar, histiocytic sarcoma																			X						
Mediastinal, histiocytic sarcoma																			X						
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach												X												X	
Pancreatic, histiocytic sarcoma																			X						
Renal, histiocytic sarcoma																			X						
Lymph node, mandibular	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	M	M	M	+	M	M	M	+	+	M
Histiocytic sarcoma																			X						
Mast cell tumor malignant																							X		
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma																			X						
Mast cell tumor malignant																							X		
Sarcoma, metastatic, stomach, forestomach					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach							X					X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																			X						
Mast cell tumor malignant																							X		
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Thymus	+	M	+		M	+	M		M	M	+	+	+	M	M	+	+	M	+	+	+	+	M	+	M
Mast cell tumor malignant																									
Squamous cell carcinoma, metastatic, stomach, forestomach											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
Skin	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																							X		
Squamous cell carcinoma																						X			
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma						X		X		X	X						X								
Musculoskeletal System																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+		+				+														
Diaphragm, sarcoma, metastatic, stomach, forestomach					X																				
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach							X				X														

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	706	709	715	717	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	213	203	234	223	131	132	141	143	151	152	161	171	172	174	182	191	192	202	221	222	231	233	241	242	243	244	Total Tissues/ Tumors	
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Mast cell tumor malignant																X											1	
Lymph node	+						+																				8	
Lumbar, histiocytic sarcoma																											1	
Mediastinal, histiocytic sarcoma																											1	
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach																											2	
Pancreatic, histiocytic sarcoma																											1	
Renal, histiocytic sarcoma																											1	
Lymph node, mandibular	M	+	M	+	M	M	+	+	+	+	M	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	34	
Histiocytic sarcoma																											1	
Mast cell tumor malignant																											1	
Lymph node, mesenteric	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47	
Histiocytic sarcoma																											1	
Mast cell tumor malignant																											1	
Sarcoma, metastatic, stomach, forestomach																											1	
Squamous cell carcinoma, metastatic, stomach, forestomach																											2	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Hemangiosarcoma															X												1	
Histiocytic sarcoma																											1	
Mast cell tumor malignant																X											2	
Squamous cell carcinoma, metastatic, stomach, forestomach																											1	
Thymus	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	35	
Mast cell tumor malignant																X											1	
Squamous cell carcinoma, metastatic, stomach, forestomach																											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	1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Mast cell tumor malignant																											1	
Squamous cell carcinoma																											1	
Subcutaneous tissue, fibroma	X																		X								2	
Subcutaneous tissue, fibroma, multiple		X																									1	
Subcutaneous tissue, fibrosarcoma		X											X					X									8	
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Skeletal muscle																											3	
Diaphragm, sarcoma, metastatic, stomach, forestomach																											1	
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach																											2	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	152	414	451	457	464	501	505	550	572	578	582	583	611	612	613	618	633	633	642	647	648	654	673	673	689
Carcass ID Number	185	235	165	201	195	205	135	214	164	225	224	175	204	162	145	184	155	194	245	193	183	153	133	134	144
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X	X	X			X				X		X	X	X	X	X
Alveolar/bronchiolar adenoma, multiple																		X		X					
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																							X		
Histiocytic sarcoma																			X						
Sarcoma, metastatic, stomach, forestomach					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach							X																	X	X
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Trachea	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Harderian gland												+													
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Mast cell tumor malignant																							X		
Squamous cell carcinoma, metastatic, stomach, forestomach							X																	X	
Urinary bladder	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Mast cell tumor malignant																							X		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																				X					
Lymphoma malignant undifferentiated cell type														X											
Mesothelioma malignant					X																				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	706	709	715	717	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	213	203	234	223	131	132	141	143	151	152	161	171	172	174	182	191	192	202	221	222	231	233	241	242	243	244	Total Tissues/ Tumors	
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Alveolar/bronchiolar adenoma	X	X								X	X	X		X	X		X						X		X		20	
Alveolar/bronchiolar adenoma, multiple									X										X	X				X			6	
Alveolar/bronchiolar carcinoma			X																	X						X	3	
Alveolar/bronchiolar carcinoma, multiple																											1	
Histiocytic sarcoma																											1	
Sarcoma, metastatic, stomach, forestomach																											1	
Squamous cell carcinoma, metastatic, stomach, forestomach																											3	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Special Senses System																												
Ear													+														1	
Eye				+																							1	
Harderian gland				+																							2	
Adenoma				X																							2	
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Histiocytic sarcoma																											1	
Mast cell tumor malignant																											1	
Squamous cell carcinoma, metastatic, stomach, forestomach																											2	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																											1	
Mast cell tumor malignant																											1	
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Histiocytic sarcoma																											1	
Lymphoma malignant histiocytic	X																										1	
Lymphoma malignant mixed		X					X																				3	
Lymphoma malignant undifferentiated cell type						X																					2	
Mesothelioma malignant																											1	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm

Number of Days on Study	109	136	248	249	484	512	517	523	535	593	606	613	618	618	621	633	645	648	662	665	689	689	696	709	722
Carcass ID Number	355	264	335	354	263	345	321	315	325	262	295	275	334	365	294	344	285	261	324	333	284	351	305	323	364
Alimentary System																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Intestine small, duodenum	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Intestine small, ileum	M	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, forestomach								X																	
Hemangiosarcoma					X																				
Hepatoblastoma																X	X					X			
Hepatocellular carcinoma									X	X	X			X	X		X		X			X			
Hepatocellular carcinoma, multiple																				X					X
Hepatocellular adenoma								X	X				X	X					X						
Hepatocellular adenoma, multiple					X					X					X	X	X	X		X	X		X	X	X
Hepatocholangiocarcinoma, multiple																									
Histiocytic sarcoma																						X			
Squamous cell carcinoma, metastatic, stomach, forestomach																			X	X					X
Mesentery			+									+							+	+			+		+
Squamous cell carcinoma, metastatic, stomach, forestomach																			X	X					X
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma								X		X		X	X						X	X			X		X
Squamous cell papilloma														X	X										X
Squamous cell papilloma, multiple											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																			X				X		X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	724	726	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	343	304	252	253	254	255	271	272	273	274	281	283	291	292	301	303	311	312	313	314	322	331	341	361	362	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+		+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	42
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma	X																									2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, stomach, forestomach																										1
Hemangiosarcoma																										1
Hepatoblastoma																	X		X							5
Hepatocellular carcinoma			X		X							X				X										12
Hepatocellular carcinoma, multiple	X	X					X			X								X					X		X	9
Hepatocellular adenoma		X					X																X			8
Hepatocellular adenoma, multiple	X		X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X			X	X	31
Hepatocholangiocarcinoma, multiple														X												1
Histiocytic sarcoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach	X																									4
Mesentery	+																			+				+		9
Squamous cell carcinoma, metastatic, stomach, forestomach	X																			X						5
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma	X		X							X										X			X			13
Squamous cell papilloma		X					X		X				X	X	X						X		X			11
Squamous cell papilloma, multiple						X		X														X		X		5
Stomach, glandular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, stomach, forestomach																				X						4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	1 0 9	1 3 6	2 4 8	2 4 9	4 8 4	5 1 2	5 1 7	5 2 3	5 3 5	5 9 3	6 0 6	6 1 3	6 1 8	6 1 8	6 2 1	6 3 3	6 4 5	6 4 8	6 6 2	6 6 5	6 8 9	6 8 9	6 9 6	7 0 9	7 2 2
Carcass ID Number	3 5 5	2 6 4	3 3 5	3 5 4	2 6 3	3 4 5	3 2 1	3 1 5	3 2 5	2 6 2	2 9 5	2 7 5	3 3 4	3 6 5	2 9 4	3 4 4	2 8 5	2 6 1	3 2 4	3 3 3	2 8 4	3 5 1	3 0 5	3 2 3	3 6 4
Alimentary System (continued)																									
Tongue			+																						
Tooth												+							+						+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
C-cell, adenoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Coagulating gland																									+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, forestomach								X																	
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Penis																									
Preputial gland											+		+			+	+							+	+
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Seminal vesicle	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, forestomach								X																	
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+									+	+								+			+		+
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach																				X					
Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach																									
Lymph node, mandibular	M	M	+	M	+	+	M	M	M	M	M	+	+	+	+	M	+	M	M	+	M	M	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	724	726	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	34 43	30 44	25 52	25 53	25 54	25 55	27 71	27 72	27 73	27 74	28 81	28 83	29 01	29 02	30 01	30 03	31 11	31 12	31 13	31 14	32 22	33 31	34 41	36 61	36 62	Total Tissues/ Tumors
Alimentary System (continued)																										
Tongue																										1
Tooth			+			+					+														+	7
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																									X	1
General Body System																										
Tissue NOS							+																			1
Genital System																										
Coagulating gland																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, stomach, forestomach																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Penis						+																+				2
Preputial gland				+			+	+							+			M						+	+	12
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Seminal vesicle	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibrosarcoma, metastatic, stomach, forestomach																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Hematopoietic System																										
Bone marrow	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node								+												+	+			+	+	11
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach																										1
Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach																				X						1
Lymph node, mandibular	+	+	+	+	+	+	M	M	+	M	+	M	M	+	+	+	M	I	M	M	M	+	+	+	M	26
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	109	136	248	249	484	512	517	523	535	593	606	613	618	618	621	633	645	648	662	665	689	689	696	709	722
Carcass ID Number	355	264	335	354	263	445	321	315	325	262	295	275	334	365	294	344	285	261	324	333	284	351	305	323	364
Hematopoietic System (continued)																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Thymus	+	M	+	+	M	+	M	+	M	+	+	+	+	+	+	M	M	M	M	+	+	M	M	+	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Subcutaneous tissue, fibroma																									X
Subcutaneous tissue, fibrosarcoma											X		X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+								+					+
Abdominal, squamous cell carcinoma, metastatic, stomach, forestomach																				X					X
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach																									X
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X		X			X		X	X				X				X	X					
Alveolar/bronchiolar adenoma, multiple																	X						X	X	
Alveolar/bronchiolar carcinoma																		X							
Hepatocellular carcinoma, metastatic									X																
Histiocytic sarcoma																						X			
Mediastinum, hemangiosarcoma, metastatic, spleen							X																		
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Lymphoma malignant lymphocytic												X													
Lymphoma malignant mixed											X														
Lymphoma malignant undifferentiated cell type						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	724	726	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	34043	30404	25052	25053	25054	25055	27071	27072	27073	27074	28081	28083	29091	29092	30101	30103	31111	31123	31133	31144	32022	33031	34041	36061	36062		Total Tissues/ Tumors
Hematopoietic System (continued)																											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																											1
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	I	+	+	+	M	M	+	M	+	+	+	+		33
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	+	+		48
Subcutaneous tissue, fibroma																											1
Subcutaneous tissue, fibrosarcoma																											2
Musculoskeletal System																											
Bone	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Skeletal muscle																											3
Abdominal, squamous cell carcinoma, metastatic, stomach, forestomach																											2
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma				X				X			X			X		X				X					X		15
Alveolar/bronchiolar adenoma, multiple		X				X							X					X						X	X		9
Alveolar/bronchiolar carcinoma																											1
Hepatocellular carcinoma, metastatic	X																										2
Histiocytic sarcoma																											1
Mediastinum, hemangiosarcoma, metastatic, spleen																											1
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Ear																							+				1
Harderian gland									+																		1
Adenoma									X																		1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed								X	X												X				X		5
Lymphoma malignant undifferentiated cell type																											1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	10,000 ppm	20,000 ppm
Liver: Hemangiosarcoma			
Overall rate[a]	3/50 (6%)	2/51 (4%)	1/50 (2%)
Adjusted rate[b]	7.5%	6.5%	2.2%
Terminal rate[c]	3/40 (8%)	1/22 (5%)	0/23 (0%)
First incidence (days)	729 (T)	414	484
Life table test[d]	P=0.366N	P=0.658	P=0.461N
Logistic regression test[d]	P=0.189N	P=0.481N	P=0.301N
Cochran-Armitage test[d]	P=0.221N		
Fisher exact test[d]		P=0.491N	P=0.309N
Liver: Hepatocellular Adenoma			
Overall rate	10/50 (20%)	38/51 (75%)	39/50 (78%)
Adjusted rate	24.3%	94.7%	95.0%
Terminal rate	9/40 (23%)	20/22 (91%)	21/23 (91%)
First incidence (days)	723	451	484
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall rate	9/50 (18%)	18/51 (35%)	21/50 (42%)
Adjusted rate	21.1%	58.1%	58.4%
Terminal rate	7/40 (18%)	10/22 (45%)	9/23 (39%)
First incidence (days)	445	505	535
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.002	P=0.017	P=0.003
Cochran-Armitage test	P=0.007		
Fisher exact test		P=0.040	P=0.008
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	18/50 (36%)	43/51 (84%)	42/50 (84%)
Adjusted rate	41.7%	97.7%	97.7%
Terminal rate	15/40 (38%)	21/22 (95%)	22/23 (96%)
First incidence (days)	445	451	484
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatoblastoma			
Overall rate	0/50 (0%)	3/51 (6%)	5/50 (10%)
Adjusted rate	0.0%	8.2%	16.8%
Terminal rate	0/40 (0%)	0/22 (0%)	2/23 (9%)
First incidence (days)	–[e]	572	633
Life table test	P=0.011	P=0.090	P=0.011
Logistic regression test	P=0.021	P=0.151	P=0.026
Cochran-Armitage test	P=0.022		
Fisher exact test		P=0.125	P=0.028

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rate	9/50 (18%)	20/51 (39%)	24/50 (48%)
Adjusted rate	21.1%	60.2%	65.3%
Terminal rate	7/40 (18%)	10/22 (45%)	11/23 (48%)
First incidence (days)	445	505	535
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.007	P<0.001
Cochran-Armitage test	P=0.001		
Fisher exact test		P=0.016	P=0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma			
Overall rate	18/50 (36%)	43/51 (84%)	42/50 (84%)
Adjusted rate	41.7%	97.7%	97.7%
Terminal rate	15/40 (38%)	21/22 (95%)	22/23 (96%)
First incidence (days)	445	451	484
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	7/50 (14%)	26/51 (51%)	24/50 (48%)
Adjusted rate	16.8%	71.0%	66.5%
Terminal rate	6/40 (15%)	12/22 (55%)	12/23 (52%)
First incidence (days)	445	578	248
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	3/50 (6%)	4/51 (8%)	1/50 (2%)
Adjusted rate	6.9%	15.9%	3.0%
Terminal rate	2/40 (5%)	2/22 (9%)	0/23 (0%)
First incidence (days)	393	673	648
Life table test	P=0.454N	P=0.259	P=0.442N
Logistic regression test	P=0.259N	P=0.512	P=0.251N
Cochran-Armitage test	P=0.252N		
Fisher exact test		P=0.511	P=0.309N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	10/50 (20%)	28/51 (55%)	25/50 (50%)
Adjusted rate	23.3%	75.0%	67.5%
Terminal rate	8/40 (20%)	13/22 (59%)	12/23 (52%)
First incidence (days)	393	578	248
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.002
Cochran-Armitage test	P=0.002		
Fisher exact test		P<0.001	P=0.002

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Skin (Subcutaneous Tissue): Fibroma			
Overall rate	2/50 (4%)	3/51 (6%)	1/50 (2%)
Adjusted rate	5.0%	11.9%	3.8%
Terminal rate	2/40 (5%)	1/22 (5%)	0/23 (0%)
First incidence (days)	729 (T)	706	722
Life table test	P=0.578	P=0.262	P=0.679N
Logistic regression test	P=0.547N	P=0.330	P=0.650N
Cochran-Armitage test	P=0.399N		
Fisher exact test		P=0.509	P=0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rate	3/50 (6%)	8/51 (16%)	2/50 (4%)
Adjusted rate	6.9%	22.8%	5.1%
Terminal rate	1/40 (3%)	2/22 (9%)	0/23 (0%)
First incidence (days)	621	501	606
Life table test	P=0.526	P=0.037	P=0.638N
Logistic regression test	P=0.381N	P=0.136	P=0.488N
Cochran-Armitage test	P=0.429N		
Fisher exact test		P=0.106	P=0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma			
Overall rate	4/50 (8%)	8/51 (16%)	2/50 (4%)
Adjusted rate	9.3%	22.8%	5.1%
Terminal rate	2/40 (5%)	2/22 (9%)	0/23 (0%)
First incidence (days)	621	501	606
Life table test	P=0.501N	P=0.066	P=0.508N
Logistic regression test	P=0.268N	P=0.222	P=0.339N
Cochran-Armitage test	P=0.303N		
Fisher exact test		P=0.188	P=0.339N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma			
Overall rate	6/50 (12%)	10/51 (20%)	3/50 (6%)
Adjusted rate	14.1%	29.5%	8.7%
Terminal rate	4/40 (10%)	3/22 (14%)	0/23 (0%)
First incidence (days)	621	501	606
Life table test	P=0.494N	P=0.053	P=0.476N
Logistic regression test	P=0.233N	P=0.220	P=0.280N
Cochran-Armitage test	P=0.225N		
Fisher exact test		P=0.220	P=0.243N
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	0/50 (0%)	13/51 (25%)	16/50 (32%)
Adjusted rate	0.0%	51.0%	55.6%
Terminal rate	0/40 (0%)	10/22 (45%)	11/23 (48%)
First incidence (days)	–	613	606
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Stomach (Forestomach): Squamous Cell Carcinoma			
Overall rate	0/50 (0%)	12/51 (24%)	13/50 (26%)
Adjusted rate	0.0%	36.5%	37.7%
Terminal rate	0/40 (0%)	4/22 (18%)	4/23 (17%)
First incidence (days)	–	505	523
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	0/50 (0%)	19/51 (37%)	27/50 (54%)
Adjusted rate	0.0%	61.2%	73.9%
Terminal rate	0/40 (0%)	11/22 (50%)	14/23 (61%)
First incidence (days)	–	505	523
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
All Organs: Hemangiosarcoma			
Overall rate	3/50 (6%)	2/51 (4%)	2/50 (4%)
Adjusted rate	7.5%	6.5%	4.4%
Terminal rate	3/40 (8%)	1/22 (5%)	0/23 (0%)
First incidence (days)	729 (T)	414	484
Life table test	P=0.560N	P=0.658	P=0.650N
Logistic regression test	P=0.340N	P=0.481N	P=0.455N
Cochran-Armitage test	P=0.406N		
Fisher exact test		P=0.491N	P=0.500N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rate	10/50 (20%)	6/51 (12%)	7/50 (14%)
Adjusted rate	21.9%	20.8%	23.3%
Terminal rate	5/40 (13%)	2/22 (9%)	4/23 (17%)
First incidence (days)	480	612	512
Life table test	P=0.517	P=0.565N	P=0.567
Logistic regression test	P=0.282N	P=0.218N	P=0.306N
Cochran-Armitage test	P=0.243N		
Fisher exact test		P=0.195N	P=0.298N
All Organs: Benign Neoplasms			
Overall rate	20/50 (40%)	43/51 (84%)	44/50 (88%)
Adjusted rate	47.4%	100.0%	100.0%
Terminal rate	18/40 (45%)	22/22 (100%)	23/23 (100%)
First incidence (days)	445	451	248
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
All Organs: Malignant Neoplasms			
Overall rate	26/50 (52%)	39/51 (76%)	39/50 (78%)
Adjusted rate	53.1%	82.9%	88.3%
Terminal rate	17/40 (43%)	14/22 (64%)	18/23 (78%)
First incidence (days)	393	414	484
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.002	P=0.012	P=0.003
Cochran-Armitage test	P=0.003		
Fisher exact test		P=0.009	P=0.006
All Organs: Benign or Malignant Neoplasms			
Overall rate	37/50 (74%)	49/51 (96%)	48/50 (96%)
Adjusted rate	75.5%	100.0%	100.0%
Terminal rate	28/40 (70%)	22/22 (100%)	23/23 (100%)
First incidence (days)	393	414	248
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.002	P=0.002

(T)Terminal sacrifice
[a] Number of lesion-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and stomach; 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 analysis 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 C4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	10/50	9/50	18/50
Acetaminophen	11/50	7/50	16/50
HC Yellow 4	8/49	5/49	13/49
Methylphenidate Hydrochloride	18/50	10/50	24/50
Pentaerythritol Tetranitrate	9/48	3/48	11/48
Turmeric Oleoresin	25/50	12/50	30/50
Overall Historical Incidence			
Total	347/1,466 (23.7%)	241/1,466 (16.4%)	531/1,466 (36.2%)
Standard deviation	13.6%	7.0%	14.1%
Range	4%-60%	3%-29%	10%-68%

[a] Data as of 31 March 1993

TABLE C4b
Historical Incidence of Forestomach Squamous Cell Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	1/50	0/50	1/50
HC Yellow 4	3/50	0/50	3/50
Methylphenidate Hydrochloride	1/50	0/50	1/50
Pentaerythritol Tetranitrate	0/49	0/49	0/49
Turmeric Oleoresin	2/50	0/50	2/50
Overall Historical Incidence			
Total	20/1,474 (1.4%)	2/1,474 (0.1%)	22/1,474 (1.5%)
Standard deviation	2.0%	0.5%	2.0%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 31 March 1993

TABLE C4c
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	7/50	3/50	10/50
Acetaminophen	8/50	0/50	8/50
HC Yellow 4	7/50	2/50	8/50
Methylphenidate Hydrochloride	14/50	4/50	16/50
Pentaerythritol Tetranitrate	11/47	1/47	11/47
Turmeric Oleoresin	11/50	4/50	14/50
Overall Historical Incidence			
Total	201/1,469 (13.7%)	73/1,469 (5.0%)	265/1,469 (18.0%)
Standard deviation	6.2%	4.0%	7.6%
Range	4%-28%	0%-14%	4%-32%

[a] Data as of 31 March 1993

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	10,000 ppm	20,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	9	10
Early deaths			
Accidental death		1	
Moribund	7	23	21
Natural deaths	3	5	6
Survivors			
Terminal sacrifice	40	22	23
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Gallbladder	(10)	(9)	(9)
Inflammation, chronic			1 (11%)
Inflammation, chronic active	1 (10%)		
Intestine large, cecum	(10)	(9)	(10)
Ulcer, acute	1 (10%)		
Liver	(10)	(9)	(10)
Basophilic focus			1 (10%)
Fatty change	7 (70%)	3 (33%)	
Inflammation, acute	1 (10%)	9 (100%)	3 (30%)
Inflammation, chronic active	4 (40%)		5 (50%)
Necrosis, coagulative	4 (40%)	8 (89%)	8 (80%)
Pigmentation		9 (100%)	10 (100%)
Centrilobular, cytoplasmic alteration		9 (100%)	8 (80%)
Mesentery		(1)	
Inflammation, chronic		1 (100%)	
Necrosis, coagulative		1 (100%)	
Pancreas	(10)	(9)	(10)
Atrophy			1 (10%)
Cytoplasmic alteration			1 (10%)
Inflammation, chronic	2 (20%)		
Artery, inflammation, chronic active			1 (10%)
Salivary glands	(10)	(8)	(10)
Submandibular gland, inflammation, chronic	8 (80%)		4 (40%)
Stomach, forestomach	(9)	(9)	(10)
Acanthosis		2 (22%)	3 (30%)
Hyperkeratosis	1 (11%)	2 (22%)	3 (30%)
Hyperplasia, basal cell		1 (11%)	1 (10%)
Inflammation, acute			1 (10%)
Inflammation, chronic active			2 (20%)
Stomach, glandular	(9)	(9)	(10)
Inflammation, chronic	1 (11%)	5 (56%)	2 (20%)
Inflammation, chronic active	1 (11%)		1 (10%)
Muscularis, mineralization		1 (11%)	

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
15-Month Interim Evaluation (continued)			
Cardiovascular System			
Heart	(10)	(9)	(10)
Cardiomyopathy	3 (30%)		1 (10%)
Endocrine System			
Islets, pancreatic	(1)		(1)
Hyperplasia	1 (100%)		
Inflammation, chronic			1 (100%)
Pituitary gland	(9)	(9)	(9)
Pars distalis, hyperplasia			2 (22%)
Thyroid gland	(10)	(9)	(10)
Follicle, cyst			1 (10%)
Genital System			
Epididymis	(10)	(9)	(10)
Inflammation, chronic active	1 (10%)		
Penis	(1)		
Inflammation, acute	1 (100%)		
Preputial gland	(5)		(1)
Abscess			1 (100%)
Inflammation, chronic	2 (40%)		
Inflammation, chronic active	2 (40%)		
Duct, dilatation	1 (20%)		
Prostate	(10)	(9)	(9)
Inflammation, chronic	5 (50%)		2 (22%)
Inflammation, chronic active	1 (10%)		
Artery, inflammation, chronic active	1 (10%)		
Testes	(10)	(9)	(10)
Atrophy			2 (20%)
Seminiferous tubule, atrophy	6 (60%)		2 (20%)
Hematopoietic System			
Lymph node	(2)		
Inguinal, hyperplasia, lymphoid	1 (50%)		
Lumbar, hyperplasia	1 (50%)		
Lymph node, mesenteric	(8)	(9)	(8)
Hemorrhage			3 (38%)
Infiltration cellular, histiocyte			1 (13%)
Pigmentation			1 (13%)
Spleen	(10)	(9)	(8)
Hematopoietic cell proliferation	1 (10%)		
Thymus	(7)	(9)	(8)
Cyst			3 (38%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
15-Month Interim Evaluation (continued)			
Integumentary System			
Skin	(10)	(9)	(10)
Inflammation, acute	1 (10%)		
Inflammation, chronic active			1 (10%)
Subcutaneous tissue, inflammation, acute	2 (20%)		
Subcutaneous tissue, inflammation, chronic active			1 (10%)
Musculoskeletal System			
Bone	(2)	(2)	(10)
Joint, tarsal, hyperostosis	2 (100%)	2 (100%)	
Nervous System			
Brain	(10)	(9)	(10)
Thalamus, mineralization	9 (90%)		6 (60%)
Respiratory System			
Lung	(10)	(9)	(10)
Congestion	1 (10%)		
Hemorrhage	1 (10%)		1 (10%)
Inflammation, chronic active		1 (11%)	
Peribronchiolar, inflammation, chronic	1 (10%)		
Perivascular, inflammation, chronic	1 (10%)		
Nose	(10)	(9)	(10)
Crystals	1 (10%)		
Inflammation, acute	2 (20%)		
Glands, inflammation, acute			2 (20%)
Respiratory epithelium, necrosis			1 (10%)
Urinary System			
Kidney	(10)	(1)	(10)
Inflammation, chronic	10 (100%)	1 (100%)	8 (80%)
Renal tubule, regeneration			4 (40%)
Urinary bladder	(10)	(9)	(10)
Inflammation, chronic	3 (30%)	7 (78%)	5 (50%)
Inflammation, chronic active	1 (10%)		
Systems Examined With No Lesions Observed			
General Body System			
Special Senses System			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study			
Alimentary System			
Gallbladder	(46)	(47)	(42)
Autolysis	1 (2%)	2 (4%)	
Inflammation, chronic active	11 (24%)	12 (26%)	8 (19%)
Epithelium, pigmentation		1 (2%)	
Intestine large, colon	(50)	(49)	(50)
Autolysis	1 (2%)	2 (4%)	
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)
Peyer's patch, hyperplasia	1 (2%)		
Intestine large, rectum	(48)	(49)	(48)
Autolysis	2 (4%)	2 (4%)	
Intestine large, cecum	(49)	(51)	(50)
Autolysis	2 (4%)	2 (4%)	
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
Epithelium, hyperplasia		1 (2%)	
Peyer's patch, hyperplasia	1 (2%)	1 (2%)	
Serosa, inflammation, chronic active		1 (2%)	
Intestine small, duodenum	(50)	(50)	(46)
Autolysis	2 (4%)	1 (2%)	
Mesothelium, hyperplasia			1 (2%)
Peyer's patch, inflammation, chronic, granulomatous		1 (2%)	
Serosa, fibrosis			1 (2%)
Intestine small, jejunum	(50)	(47)	(48)
Autolysis	2 (4%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
Inflammation, acute		1 (2%)	
Epithelium, pigmentation			1 (2%)
Peyer's patch, inflammation, chronic, granulomatous		1 (2%)	
Intestine small, ileum	(50)	(49)	(47)
Autolysis	2 (4%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
Inflammation, acute, necrotizing	1 (2%)		
Inflammation, chronic active			1 (2%)
Peyer's patch, hyperplasia	1 (2%)	2 (4%)	1 (2%)
Peyer's patch, hyperplasia, lymphoid	1 (2%)		
Peyer's patch, inflammation, chronic, granulomatous		1 (2%)	
Liver	(50)	(51)	(50)
Angiectasis	1 (2%)		
Basophilic focus		4 (8%)	3 (6%)
Basophilic focus, focal			1 (2%)
Clear cell focus	4 (8%)	4 (8%)	2 (4%)
Cytoplasmic alteration	1 (2%)		
Eosinophilic focus		6 (12%)	1 (2%)
Fatty change	4 (8%)	3 (6%)	7 (14%)
Fibrosis		1 (2%)	
Hematopoietic cell proliferation	1 (2%)	5 (10%)	10 (20%)
Infarct			1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		10,000 ppm		20,000 ppm	
2-Year Study (continued)						
Alimentary System (continued)						
Liver (continued)	(50)		(51)		(50)	
Inflammation, chronic active	11	(22%)	10	(20%)	22	(44%)
Karyomegaly					1	(2%)
Mineralization	1	(2%)	1	(2%)		
Necrosis, coagulative	5	(10%)	12	(24%)	20	(40%)
Nuclear alteration			1	(2%)		
Pigmentation	1	(2%)	50	(98%)	47	(94%)
Thrombosis					1	(2%)
Bile duct, hyperplasia	1	(2%)	2	(4%)	1	(2%)
Hepatocyte, centrilobular, hypertrophy			17	(33%)	13	(26%)
Mesentery	(2)		(7)		(9)	
Abscess					1	(11%)
Fibrosis					1	(11%)
Inflammation, chronic active			4	(57%)	5	(56%)
Mineralization					1	(11%)
Necrosis, coagulative					2	(22%)
Thrombosis			1	(14%)		
Pancreas	(50)		(50)		(48)	
Atrophy	2	(4%)				
Autolysis	1	(2%)	1	(2%)		
Cytoplasmic alteration	4	(8%)			1	(2%)
Ectopic liver			1	(2%)		
Inflammation, chronic active	19	(38%)	12	(24%)	8	(17%)
Vacuolization cytoplasmic	20	(40%)	18	(36%)	4	(8%)
Acinus, atrophy			1	(2%)		
Salivary glands	(50)		(51)		(50)	
Inflammation, chronic	2	(4%)				
Duct, parotid gland, mineralization					1	(2%)
Parotid gland, inflammation, chronic	2	(4%)				
Sublingual gland, inflammation, chronic			1	(2%)		
Sublingual gland, submandibular gland, inflammation, chronic					1	(2%)
Submandibular gland, atrophy					1	(2%)
Submandibular gland, inflammation, chronic	37	(74%)	29	(57%)	36	(72%)
Stomach, forestomach	(50)		(50)		(50)	
Abscess			1	(2%)		
Acanthosis	1	(2%)	9	(18%)	4	(8%)
Autolysis	1	(2%)				
Cyst			1	(2%)		
Diverticulum			1	(2%)		
Edema	1	(2%)				
Erosion	1	(2%)				
Hyperkeratosis	1	(2%)	7	(14%)	6	(12%)
Hyperplasia, basal cell					2	(4%)
Inflammation, chronic active	2	(4%)	6	(12%)	12	(24%)
Inflammation, chronic active, necrotizing					1	(2%)
Ulcer			2	(4%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Alimentary System (continued)			
Stomach, glandular	(50)	(50)	(49)
Autolysis	1 (2%)		
Edema			1 (2%)
Infiltration cellular, mast cell		1 (2%)	
Inflammation, chronic active	14 (28%)	24 (48%)	22 (45%)
Mineralization	4 (8%)		3 (6%)
Tooth	(4)		(7)
Dysplasia	4 (100%)		6 (86%)
Cardiovascular System			
Heart	(50)	(51)	(50)
Inflammation, chronic	7 (14%)	17 (33%)	5 (10%)
Mineralization	1 (2%)		
Necrosis, coagulative		1 (2%)	
Coronary artery, thrombosis		1 (2%)	
Endocrine System			
Adrenal cortex	(50)	(51)	(50)
Hematopoietic cell proliferation		1 (2%)	
Hyperplasia		3 (6%)	2 (4%)
Inflammation, chronic active	3 (6%)		
Pigmentation	2 (4%)		
Vacuolization cytoplasmic			1 (2%)
Capsule, inflammation, chronic active			1 (2%)
Adrenal medulla	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	
Inflammation, acute	1 (2%)		
Pigmentation		1 (2%)	
Islets, pancreatic	(50)	(50)	(48)
Hyperplasia	8 (16%)	1 (2%)	1 (2%)
Pituitary gland	(43)	(45)	(47)
Pars distalis, cyst	5 (12%)	4 (9%)	1 (2%)
Pars distalis, hyperplasia	13 (30%)	9 (20%)	4 (9%)
Thyroid gland	(49)	(50)	(49)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Ultimobranchial cyst	1 (2%)	1 (2%)	
Follicular cell, hyperplasia	2 (4%)	3 (6%)	3 (6%)
General Body System			
None			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Genital System			
Coagulating gland	(1)	(1)	(1)
Inflammation, chronic active			1 (100%)
Epididymis	(49)	(51)	(50)
Inflammation, chronic active	29 (59%)	21 (41%)	26 (52%)
Epithelium, hyperplasia		1 (2%)	
Serosa, hyperplasia			1 (2%)
Penis		(1)	(2)
Hemorrhage		1 (100%)	
Preputial gland	(16)	(16)	(12)
Abscess	1 (6%)	3 (19%)	1 (8%)
Inflammation, chronic active	12 (75%)	7 (44%)	11 (92%)
Duct, dilatation	11 (69%)	10 (63%)	2 (17%)
Prostate	(47)	(46)	(48)
Inflammation		1 (2%)	
Inflammation, chronic active	31 (66%)	29 (63%)	20 (42%)
Epithelium, hyperplasia	1 (2%)		
Seminal vesicle	(49)	(50)	(45)
Atrophy		1 (2%)	1 (2%)
Cyst		1 (2%)	
Fibrosis		3 (6%)	
Inflammation, chronic active	4 (8%)	14 (28%)	13 (29%)
Artery, thrombosis		1 (2%)	
Testes	(50)	(50)	(50)
Inflammation, chronic active			2 (4%)
Interstitial cell, hyperplasia		1 (2%)	
Seminiferous tubule, atrophy	1 (2%)		2 (4%)
Seminiferous tubule, mineralization	2 (4%)	1 (2%)	3 (6%)
Hematopoietic System			
Bone marrow	(49)	(50)	(49)
Myeloid cell, sternal, hyperplasia	1 (2%)	2 (4%)	1 (2%)
Sternal, infiltration cellular, mast cell	1 (2%)		
Sternal, inflammation, granulomatous		1 (2%)	
Lymph node	(8)	(8)	(11)
Hyperplasia, lymphoid			1 (9%)
Lumbar, hyperplasia, lymphoid	1 (13%)	1 (13%)	
Lumbar, hyperplasia, plasma cell			2 (18%)
Lumbar, inflammation, chronic active		1 (13%)	
Mediastinal, infiltration cellular, histiocyte		1 (13%)	
Mediastinal, inflammation, chronic active			1 (9%)
Mediastinal, pigmentation		1 (13%)	
Pancreatic, angiectasis			1 (9%)
Pancreatic, hyperplasia, lymphoid	2 (25%)		
Pancreatic, infiltration cellular, histiocyte	1 (13%)		
Pancreatic, pigmentation	1 (13%)		
Renal, angiectasis	1 (13%)		
Renal, hyperplasia, lymphoid	1 (13%)		
Renal, inflammation, chronic active		1 (13%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Hematopoietic System (continued)			
Lymph node, mandibular	(32)	(34)	(26)
Depletion lymphoid	3 (9%)	1 (3%)	1 (4%)
Hyperplasia, lymphoid	3 (9%)	1 (3%)	1 (4%)
Hyperplasia, plasma cell		1 (3%)	
Infiltration cellular, histiocyte	3 (9%)		8 (31%)
Inflammation, chronic active	1 (3%)	1 (3%)	1 (4%)
Necrosis, coagulative			1 (4%)
Pigmentation	5 (16%)	4 (12%)	9 (35%)
Lymph node, mesenteric	(46)	(47)	(47)
Angiectasis	24 (52%)	11 (23%)	21 (45%)
Congestion		1 (2%)	
Depletion lymphoid	1 (2%)		1 (2%)
Hematopoietic cell proliferation		2 (4%)	
Hemorrhage	1 (2%)		1 (2%)
Hyperplasia			1 (2%)
Hyperplasia, lymphoid	6 (13%)	9 (19%)	4 (9%)
Hyperplasia, plasma cell		1 (2%)	
Infiltration cellular, histiocyte	24 (52%)	22 (47%)	21 (45%)
Inflammation, chronic active		7 (15%)	4 (9%)
Pigmentation	23 (50%)	22 (47%)	19 (40%)
Spleen	(50)	(51)	(50)
Angiectasis	1 (2%)		
Congestion			1 (2%)
Depletion lymphoid	1 (2%)	3 (6%)	3 (6%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation	5 (10%)	14 (27%)	12 (24%)
Hyperplasia, lymphoid		2 (4%)	1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)
Necrosis, coagulative		1 (2%)	
Thymus	(37)	(35)	(33)
Cyst	2 (5%)	6 (17%)	9 (27%)
Cyst, multiple	2 (5%)		
Depletion lymphoid	2 (5%)	8 (23%)	6 (18%)
Hyperplasia, lymphoid	1 (3%)		
Infiltration cellular, histiocyte		1 (3%)	
Necrosis, coagulative		1 (3%)	1 (3%)
Pigmentation	1 (3%)	1 (3%)	
Integumentary System			
Skin	(50)	(48)	(48)
Inflammation, chronic active	4 (8%)	9 (19%)	12 (25%)
Subcutaneous tissue, abscess			1 (2%)
Subcutaneous tissue, cyst		1 (2%)	
Subcutaneous tissue, fibrosis		2 (4%)	1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Musculoskeletal System			
Bone	(49)	(50)	(49)
Cartilage, tarsal, hyperplasia	1 (2%)		
Joint, tarsal, hyperostosis	10 (20%)	11 (22%)	12 (24%)
Skeletal muscle	(3)	(3)	(3)
Fibrosis	1 (33%)		
Intercostal, inflammation, chronic active			1 (33%)
Nervous System			
Brain	(50)	(51)	(50)
Cyst epithelial inclusion			1 (2%)
Cerebellum, necrosis	1 (2%)		
Cerebrum, necrosis	1 (2%)		
Thalamus, mineralization	17 (34%)	20 (39%)	13 (26%)
Respiratory System			
Lung	(50)	(51)	(50)
Bronchiectasis		1 (2%)	
Congestion			1 (2%)
Crystals		1 (2%)	
Foreign body		1 (2%)	
Granuloma		1 (2%)	
Hemorrhage	8 (16%)	9 (18%)	9 (18%)
Infiltration cellular, histiocyte	2 (4%)	2 (4%)	6 (12%)
Inflammation, acute		2 (4%)	
Inflammation, chronic active	1 (2%)	2 (4%)	1 (2%)
Mineralization	1 (2%)		
Pigmentation			1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)		4 (8%)
Bronchiole, hyperplasia	1 (2%)		
Bronchiole, metaplasia, squamous		1 (2%)	
Nose	(43)	(49)	(48)
Inflammation, acute	11 (26%)	11 (22%)	6 (13%)
Glands, crystals	2 (5%)		
Nasolacrimal duct, inflammation, acute	2 (5%)		
Trachea	(50)	(50)	(50)
Inflammation, acute	2 (4%)		3 (6%)
Special Senses System			
Eye	(2)	(1)	
Anterior, synechia		1 (100%)	
Cornea, fibrosis		1 (100%)	
Cornea, inflammation, chronic active	1 (50%)		
Harderian gland	(2)	(2)	(1)
Inflammation, chronic active	1 (50%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Urinary System			
Kidney	(50)	(51)	(50)
Autolysis		1 (2%)	
Congestion		1 (2%)	
Cyst	1 (2%)		1 (2%)
Glomerulosclerosis		3 (6%)	
Infiltration cellular, mononuclear cell		1 (2%)	
Inflammation, acute, necrotizing			1 (2%)
Inflammation, chronic active	47 (94%)	42 (82%)	47 (94%)
Metaplasia, osseous			1 (2%)
Mineralization			1 (2%)
Necrosis, coagulative		1 (2%)	
Artery, necrosis, fibrinoid		1 (2%)	
Pelvis, transitional epithelium, hyperplasia		1 (2%)	
Proximal convoluted renal tubule, hyperplasia		1 (2%)	
Proximal convoluted renal tubule, regeneration	2 (4%)	11 (22%)	1 (2%)
Proximal convoluted renal tubule, vacuolization cytoplasmic	1 (2%)		
Renal tubule, mineralization	1 (2%)	4 (8%)	1 (2%)
Renal tubule, pigmentation		42 (82%)	43 (86%)
Renal tubule, regeneration	4 (8%)	1 (2%)	
Urinary bladder	(49)	(50)	(49)
Autolysis	2 (4%)	3 (6%)	
Calculus, microscopic observation only	5 (10%)	2 (4%)	
Inflammation, chronic active	36 (73%)	31 (62%)	34 (69%)
Transitional epithelium, hyperplasia		2 (4%)	

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	10,000 ppm	20,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	5	11	11
Natural deaths	6	5	6
Survivors			
Died last week of study	1	1	
Terminal sacrifice	38	33	33
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Hepatocellular carcinoma			1 (10%)
Hepatocellular adenoma		1 (10%)	3 (30%)
Hepatocellular adenoma, multiple		1 (10%)	4 (40%)
Stomach, forestomach	(10)	(10)	(10)
Squamous cell papilloma		4 (40%)	2 (20%)
Respiratory System			
Lung	(10)	(10)	(10)
Alveolar/bronchiolar adenoma		3 (30%)	2 (20%)
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
Endocrine System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Special Senses System			
Urinary System			
2-Year Study			
Alimentary System			
Esophagus	(50)	(45)	(47)
Basosquamous tumor malignant, metastatic, uterus	1 (2%)		
Gallbladder	(49)	(47)	(44)
Basosquamous tumor malignant, metastatic, uterus	1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Alimentary System (continued)			
Intestine large, colon	(50)	(50)	(48)
Intestine small, duodenum	(48)	(50)	(46)
Intestine small, jejunum	(47)	(50)	(46)
Intestine small, ileum	(48)	(50)	(46)
Liver	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)	
Hemangioma	1 (2%)		
Hepatoblastoma			2 (4%)
Hepatocellular carcinoma		10 (20%)	14 (28%)
Hepatocellular carcinoma, multiple		13 (26%)	13 (26%)
Hepatocellular adenoma	6 (12%)	5 (10%)	4 (8%)
Hepatocellular adenoma, multiple		40 (80%)	45 (90%)
Squamous cell carcinoma, metastatic, stomach, forestomach		3 (6%)	4 (8%)
Mesentery	(6)	(9)	(8)
Basosquamous tumor malignant, metastatic, uterus	1 (17%)		
Fibrosarcoma, metastatic, skin		1 (11%)	
Sarcoma, metastatic, stomach, forestomach			1 (13%)
Squamous cell carcinoma, metastatic, stomach, forestomach		2 (22%)	3 (38%)
Pancreas	(50)	(50)	(49)
Basosquamous tumor malignant, metastatic, uterus	1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	2 (4%)
Salivary glands	(49)	(50)	(47)
Stomach, forestomach	(48)	(50)	(50)
Sarcoma			1 (2%)
Squamous cell carcinoma		12 (24%)	11 (22%)
Squamous cell papilloma	2 (4%)	12 (24%)	13 (26%)
Squamous cell papilloma, multiple		4 (8%)	14 (28%)
Stomach, glandular	(49)	(48)	(48)
Sarcoma			1 (2%)
Squamous cell carcinoma, metastatic, stomach, forestomach		3 (6%)	3 (6%)
Cardiovascular System			
Heart	(50)	(50)	(49)
Endocrine System			
Adrenal cortex	(50)	(49)	(48)
Carcinoma	1 (2%)		
Squamous cell carcinoma, metastatic			1 (2%)
Adrenal medulla	(49)	(49)	(48)
Islets, pancreatic	(49)	(50)	(48)
Adenoma	2 (4%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Endocrine System (continued)			
Pituitary gland	(43)	(45)	(43)
Pars distalis, adenoma	1 (2%)	8 (18%)	4 (9%)
Pars distalis, adenoma, multiple		1 (2%)	
Pars intermedia, adenoma	1 (2%)		
Pars nervosa, adenoma			1 (2%)
Thyroid gland	(50)	(50)	(48)
Follicular cell, adenoma	3 (6%)	1 (2%)	2 (4%)
General Body System			
Tissue NOS		(1)	
Genital System			
Ovary	(49)	(49)	(47)
Basosquamous tumor malignant, metastatic, uterus	1 (2%)		
Granulosa cell tumor benign	1 (2%)		
Hemangioma	1 (2%)		
Luteoma		1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	3 (6%)
Uterus	(49)	(50)	(49)
Leiomyoma	2 (4%)		
Polyp stromal		2 (4%)	
Sarcoma stromal		3 (6%)	
Cervix, basosquamous tumor malignant	1 (2%)		
Vagina			(1)
Squamous cell carcinoma			1 (100%)
Hematopoietic System			
Bone marrow	(50)	(49)	(49)
Lymph node	(7)	(12)	(12)
Bronchial, sarcoma, metastatic, stomach, forestomach			1 (8%)
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach		1 (8%)	1 (8%)
Renal, basosquamous tumor malignant, metastatic, uterus	1 (14%)		
Lymph node, mandibular	(32)	(45)	(31)
Lymph node, mesenteric	(49)	(46)	(44)
Basosquamous tumor malignant, metastatic, uterus	1 (2%)		
Sarcoma, metastatic, stomach, forestomach			1 (2%)
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Hematopoietic System (continued)			
Spleen	(50)	(50)	(50)
Hemangioma	1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)
Thymus	(40)	(38)	(34)
Osteosarcoma, metastatic, bone	1 (3%)		
Integumentary System			
Mammary gland	(25)	(25)	(20)
Fibroadenoma	1 (4%)		
Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)	
Subcutaneous tissue, hemangioma	1 (2%)		
Musculoskeletal System			
Bone	(50)	(48)	(49)
Rib, osteosarcoma	1 (2%)		
Skeletal muscle	(4)	(2)	(2)
Abdominal, fibrosarcoma, metastatic, skin		1 (50%)	
Diaphragm, basosquamous tumor malignant, metastatic, uterus	1 (25%)		
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach		1 (50%)	1 (50%)
Nervous System			
Brain	(49)	(50)	(50)
Respiratory System			
Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	4 (8%)	15 (30%)	12 (24%)
Alveolar/bronchiolar adenoma, multiple		2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma			2 (4%)
Basosquamous tumor malignant, metastatic, uterus	1 (2%)		
Hemangioma			1 (2%)
Hepatocellular carcinoma, metastatic, liver			1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)	
Nose	(48)	(45)	(44)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Special Senses System			
Harderian gland	(1)	(3)	(2)
Adenoma	1 (100%)	2 (67%)	2 (100%)
Carcinoma		1 (33%)	
Urinary System			
Kidney	(50)	(50)	(50)
Osteosarcoma, metastatic, bone	1 (2%)		
Urinary bladder	(49)	(50)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	9 (18%)	13 (26%)	13 (26%)
Lymphoma malignant undifferentiated cell		2 (4%)	
Neoplasm Summary			
Total animals with primary neoplasms[c]			
15-Month interim evaluation		5	9
2-Year study	32	50	50
Total primary neoplasms			
15-Month interim evaluation		9	12
2-Year study	45	149	157
Total animals with benign neoplasms			
15-Month interim evaluation		5	8
2-Year study	24	46	50
Total benign neoplasms			
15-Month interim evaluation		9	11
2-Year study	29	94	99
Total animals with malignant neoplasms			
15-Month interim evaluation			1
2-Year study	14	40	37
Total malignant neoplasms			
15-Month interim evaluation			1
2-Year study	16	55	58
Total animals with metastatic neoplasms			
2-Year study	2	4	6
Total metastatic neoplasms			
2-Year study	12	18	24

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm

Number of Days on Study	0767	4788	5922	6110	6228	6553	6885	7001	7001	7006	7008	7332	7333	7383	7393	7393	7393	7393	7393	7393	7393	7393	7393	7393	7393
Carcass ID Number	4465	3995	3885	3994	4665	4664	3975	4004	4485	4484	4463	3774	3822	3883	3991	3992	4001	4022	4003	4111	4141	4151	4221	4222	4223
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant, metastatic, uterus		X																							
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant, metastatic, uterus		X																							
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hepatocellular adenoma													X			X			X						
Mesentery		+				+		+		+									+						
Basosquamous tumor malignant, metastatic, uterus		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant, metastatic, uterus		X																							
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth					+																				
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma				X																					
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	M	+	+	M	+	+
Pituitary gland	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X																				
Pars intermedia, adenoma									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 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	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 2 4	4 2 5	4 3 1	4 3 2	4 3 3	4 3 4	4 3 5	4 4 1	4 4 2	4 4 3	4 5 1	4 5 3	4 6 1	4 7 1	4 7 3	4 7 4	3 7 3	3 8 4	4 4 4	4 5 4	4 5 5	4 6 2	4 8 1	4 8 2	4 8 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant, metastatic, uterus																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor malignant, metastatic, uterus																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma									X																	1
Hepatocellular adenoma													X											X	X	6
Mesentery																+										6
Basosquamous tumor malignant, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma														X			X									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X															1
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X																		2
Parathyroid gland	+	M	M	M	+	+	+	+	M	+	M	+	+	M	M	+	M	+	+	M	+	M	+	+	+	33
Pituitary gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	43
Pars distalis, adenoma																										1
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma	X	X	X																							3
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	0767	4788	5922	6110	6228	6553	6885	7001	7001	7006	7008	7332	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333
Carcass ID Number	44 45	39 95	38 85	39 94	46 65	46 64	37 75	40 04	48 85	48 44	46 63	37 74	38 82	38 83	39 91	39 92	40 01	40 02	40 03	41 11	41 14	41 15	42 21	42 22	42 23
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Basosquamous tumor malignant, metastatic, uterus		X																							
Granulosa cell tumor benign																									
Hemangioma																									
Uterus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Cervix, basosquamous tumor malignant		X																							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+		+		+		+			+										
Renal, basosquamous tumor malignant, metastatic, uterus		X																							
Lymph node, mandibular	M	+	M	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	M	+	+	M	+	M
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant, metastatic, uterus		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thymus	M	+	+	M	M	+	I	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone											X														
Integumentary System																									
Mammary gland	M	+	M	+	+	+	+	M	+	M	M	M	+	+	M	+	+	+	+	M	+	+	M	+	+
Fibroadenoma							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Subcutaneous tissue, fibrosarcoma		X							X																
Subcutaneous tissue, hemangioma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, osteosarcoma											X														
Skeletal muscle		+				+		+				+													
Diaphragm, basosquamous tumor malignant, metastatic, uterus		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Basosquamous tumor malignant, metastatic, uterus		X																							
Osteosarcoma, metastatic, bone											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 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	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 2 4	4 2 5	4 3 1	4 3 2	4 3 3	4 3 4	4 3 5	4 4 1	4 4 2	4 4 3	4 5 1	4 5 3	4 6 1	4 7 1	4 7 3	4 7 4	3 7 3	3 8 4	4 4 4	4 5 4	4 5 5	4 6 2	4 8 1	4 8 2	4 8 3	Total Tissues/ Tumors
Genital System																												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor malignant, metastatic, uterus																										1
Granulosa cell tumor benign													X													1
Hemangioma										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma				X						X																2
Cervix, basosquamous tumor malignant																										1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																		+								7
Renal, basosquamous tumor malignant, metastatic, uterus																										1
Lymph node, mandibular	+	+	M	M	+	+	+	+	I	+	+	M	+	M	+	M	M	+	+	+	+	M	M	+	+	32
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor malignant, metastatic, uterus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																		X								1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	40
Osteosarcoma, metastatic, bone																										1
Integumentary System																												
Mammary gland	M	M	+	+	M	M	M	M	+	M	+	+	M	+	M	M	+	M	M	M	+	M	M	M	+	25
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, hemangioma																										1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, osteosarcoma																										1
Skeletal muscle																										4
Diaphragm, basosquamous tumor malignant, metastatic, uterus																										1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																		X		X			4
Basosquamous tumor malignant, metastatic, uterus																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 ppm (continued)

Number of Days on Study	0767	4788	5922	6110	6228	6533	6885	7001	7011	7066	7083	7332	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333	7333
Carcass ID Number	4445	3995	3885	3994	4665	4664	3775	4004	4885	4884	4663	3774	3882	3883	3991	3992	4001	4022	4023	4111	4114	4115	4221	4222	4223
Special Senses System																									
Ear					+																				
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone											X														
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed						X		X		X	X	X			X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 0 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	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 2 4	4 2 5	4 3 1	4 3 2	4 3 3	4 3 4	4 3 5	4 4 1	4 4 2	4 4 3	4 5 1	4 5 3	4 6 1	4 7 1	4 7 3	4 7 4	3 7 3	3 8 4	4 4 4	4 5 4	4 5 5	4 6 2	4 8 1	4 8 2	4 8 3	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Eye				+																						1
Harderian gland				+																						1
Adenoma				X																						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic								X																		1
Lymphoma malignant lymphocytic																		X								1
Lymphoma malignant mixed		X								X										X						9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm

Number of Days on Study	202	372	442	503	555	587	652	657	671	679	706	713	713	713	716	727	730	730	730	730	730	730	730	730	730
Carcass ID Number	565	495	575	564	605	544	505	494	574	573	563	515	535	595	534	555	491	492	493	501	502	503	504	511	512
Alimentary System																									
Esophagus	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																X									
Hepatocellular carcinoma				X								X			X	X									
Hepatocellular carcinoma, multiple											X			X					X	X	X			X	
Hepatocellular adenoma				X	X						X									X					
Hepatocellular adenoma, multiple			X			X	X	X	X			X	X	X	X	X	X	X			X	X	X	X	X
Squamous cell carcinoma, metastatic, stomach, forestomach										X					X										
Mesentery							+		+	+					+	+								+	
Fibrosarcoma, metastatic, skin																X									
Squamous cell carcinoma, metastatic, stomach, forestomach										X					X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																X									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma						X				X	X				X				X				X		
Squamous cell papilloma									X			X				X				X					X
Squamous cell papilloma, multiple											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach										X					X										
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+		+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	I	M	+	+	+	+	+
Pars distalis, adenoma									X						X		X								
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	5133	5211	5222	5233	5244	5311	5322	5411	5422	5433	5533	5544	5611	5622	5722	5855	5711	5811	5833	5844	5911	5922	5933	6003	6004	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	45
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma				X	X		X												X	X					X	10
Hepatocellular carcinoma, multiple						X			X			X	X		X		X						X			13
Hepatocellular adenoma									X																	5
Hepatocellular adenoma, multiple	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	40
Squamous cell carcinoma, metastatic, stomach, forestomach																X										3
Mesentery																+			+						+	9
Fibrosarcoma, metastatic, skin																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																X										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma		X	X	X	X					X						X										12
Squamous cell papilloma				X								X	X		X			X					X		X	12
Squamous cell papilloma, multiple										X							X					X				4
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic, stomach, forestomach																X										3
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Parathyroid gland	+	+	M	+	+	+	+	M	+	M	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	39
Pituitary gland	+	+	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars distalis, adenoma							X					X						X						X	X	8
Pars distalis, adenoma, multiple													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	202	372	442	503	555	587	652	657	671	679	706	713	713	713	716	727	730	730	730	730	730	730	730	730	730
Carcass ID Number	56 65	49 55	57 55	56 04	60 05	54 44	50 55	49 44	57 44	57 33	56 33	51 55	53 55	59 55	53 34	55 55	49 91	49 92	49 23	50 01	50 02	50 03	50 04	51 11	51 12
General Body System																									
Tissue NOS														+											
Genital System																									
Clitoral gland	M																								
Ovary	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma									X																
Squamous cell carcinoma, metastatic, stomach, forestomach															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X				X															
Sarcoma stromal									X																
Hematopoietic System																									
Bone marrow	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+		+	+				+										+	
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach										X															
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	M	+	M	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	M	+	+	M	+	M	M	M	+	+	M	+	+	+	+	+	M	+	M	M	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																X									
Musculoskeletal System																									
Bone	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+	+									
Abdominal, fibrosarcoma, metastatic, skin																X									
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach															X										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X						X				X	X			X	X		X		X
Alveolar/bronchiolar adenoma, multiple																									
Squamous cell carcinoma, metastatic, stomach, forestomach															X										
Nose	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	51 13	52 11	52 22	52 23	52 24	53 11	53 12	54 11	54 12	54 13	55 13	55 14	56 11	56 12	57 22	58 25	57 11	58 11	58 13	58 14	59 11	59 12	59 13	60 13	60 14	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Luteoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										2
Sarcoma stromal							X							X												3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+			+				+	+		+										+					12
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach																										1
Lymph node, mandibular	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	M	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	38
Integumentary System																										
Mammary gland	M	M	M	M	M	M	+	M	M	+	+	M	+	+	M	+	+	+	M	+	+	M	M	M	+	25
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	48
Skeletal muscle																										2
Abdominal, fibrosarcoma, metastatic, skin																										1
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X	X	X								X			X					X				15
Alveolar/bronchiolar adenoma, multiple								X							X											2
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nose	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+		+	+	+	45
Trachea	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	202	372	442	503	555	587	652	657	671	679	706	713	713	713	716	727	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	565	495	575	604	605	444	505	494	574	573	563	515	535	595	534	555	491	492	493	501	502	503	504	511	512
Special Senses System																										
Harderian gland		+															+									
Adenoma																	X									
Carcinoma		X																								
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed								X	X					X						X				X		
Lymphoma malignant undifferentiated cell type	X		X																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 10,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	51 3	52 1	52 2	52 3	52 4	53 1	53 2	54 1	54 2	54 3	55 3	55 4	56 1	56 2	57 2	58 5	57 1	58 1	58 3	58 4	59 1	59 2	59 3	60 3	60 4	Total Tissues/ Tumors
Special Senses System																										
Harderian gland																					+					3
Adenoma																					X					2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed			X	X				X	X		X							X			X		X			13
Lymphoma malignant undifferentiated cell type																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm

Number of Days on Study	501	538	553	562	568	596	623	623	631	662	664	680	697	713	718	723	724	729	729	729	729	729	729	729	729
Carcass ID Number	634	715	674	695	714	713	633	635	725	705	712	664	694	615	614	632	724	611	612	613	621	622	623	624	631
Alimentary System																									
Esophagus	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																				X		X			
Hepatocellular carcinoma		X		X	X	X		X	X								X			X		X		X	X
Hepatocellular carcinoma, multiple											X			X	X	X					X		X		
Hepatocellular adenoma	X		X					X																	
Hepatocellular adenoma, multiple				X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Squamous cell carcinoma, metastatic, stomach, forestomach	X										X				X										X
Mesentery						+				+	+		+		+	+							+		+
Sarcoma, metastatic, stomach, forestomach						X																			
Squamous cell carcinoma, metastatic, stomach, forestomach											X				X										X
Pancreas	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach	X														X										
Salivary glands	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Squamous cell carcinoma	X								X		X			X	X		X	X			X		X		X
Squamous cell papilloma					X	X																	X	X	
Squamous cell papilloma, multiple		X													X			X	X	X		X			
Stomach, glandular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Squamous cell carcinoma, metastatic, stomach, forestomach											X				X										X
Cardiovascular System																									
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic	X																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	+	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, adenoma			X																				X		
Pars nervosa, adenoma																	X								
Thyroid gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	641	642	644	645	655	681	682	683	684	685	652	653	654	661	662	663	671	672	673	691	693	703	704	711	723	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Intestine large, colon	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																										2
Hepatocellular carcinoma							X														X				X	14
Hepatocellular carcinoma, multiple			X	X								X						X				X	X	X		13
Hepatocellular adenoma	X																									4
Hepatocellular adenoma, multiple		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Squamous cell carcinoma, metastatic, stomach, forestomach																										4
Mesentery																										8
Sarcoma, metastatic, stomach, forestomach																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, stomach, forestomach																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Squamous cell carcinoma																								X		11
Squamous cell papilloma		X	X		X				X				X							X	X	X			X	13
Squamous cell papilloma, multiple	X			X		X	X					X					X		X					X		14
Stomach, glandular	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										3
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic																										1
Adrenal medulla	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	+	M	+	+	M	+	+	+	+	+	M	+	M	+	M	+	+	M	+	+	+	M	+	33
Pituitary gland	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Pars distalis, adenoma						X																		X		4
Pars nervosa, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma				X																				X		2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	501	538	553	562	568	596	623	623	631	662	664	680	697	713	718	723	724	729	729	729	729	729	729	729	729
Carcass ID Number	634	715	674	695	714	713	633	635	725	705	712	664	694	615	614	632	724	611	612	613	621	622	623	624	631
General Body System																									
None																									
Genital System																									
Clitoral gland																+									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach	X										X														X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Vagina																+									
Squamous cell carcinoma																X									
Hematopoietic System																									
Bone marrow	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+				+	+	+	+			+						+		
Bronchial, sarcoma, metastatic, stomach, forestomach						X																			
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach											X														
Lymph node, mandibular	+	+	M	+	+	M	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Lymph node, mesenteric	+	+	M	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Sarcoma, metastatic, stomach, forestomach						X																			
Squamous cell carcinoma, metastatic, stomach, forestomach	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach											X														
Thymus	M	+	M	+	M	M	+	+	+	M	M	M	M	M	M	+	M	M	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	M	+	M	+	+	M	+	M	M	+	M	M	M	M	M	+	+	M	+	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+			+										
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach															X										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord							+																		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	641	642	644	645	655	681	682	683	684	685	652	653	654	661	662	663	671	672	673	691	693	703	704	711	723	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland																										1
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, stomach, forestomach																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Vagina																										1
Squamous cell carcinoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node									+		+		+								+					12
Bronchial, sarcoma, metastatic, stomach, forestomach																										1
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach																										1
Lymph node, mandibular	M	+	M	+	M	M	I	+	+	M	M	M	+	+	+	M	M	+	+	+	+	I	M	+	M	31
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Sarcoma, metastatic, stomach, forestomach																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	34
Integumentary System																										
Mammary gland	+	M	M	M	M	+	M	M	+	+	M	+	M	+	+	M	M	M	+	M	M	M	+	+	M	20
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										2
Diaphragm, squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	501	538	553	562	568	596	623	623	631	662	664	680	697	713	718	723	724	729	729	729	729	729	729	729	729
Carcass ID Number	634	715	674	695	714	713	633	635	725	705	712	664	694	615	614	632	724	611	612	613	621	622	623	624	631
Respiratory System																									
Lung	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X					X	X												X	X				X
Alveolar/bronchiolar adenoma, multiple						X																			
Alveolar/bronchiolar carcinoma											X														
Hemangioma																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+
Trachea	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Special Senses System																									
Eye																								+	
Harderian gland																								+	
Adenoma																								X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed												X	X	X				X	X		X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone: 20,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	641	642	644	645	655	681	682	683	684	685	652	653	654	661	662	663	671	672	673	691	693	703	704	711	712	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma							X		X	X	X					X					X					12
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma													X													2
Hemangioma																					X					1
Hepatocellular carcinoma, metastatic, liver																						X				1
Nose	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	44
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																										
Eye																										1
Harderian gland																						+				2
Adenoma																						X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed				X	X			X	X		X							X			X					13

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

	0 ppm	10,000 ppm	20,000 ppm
Harderian Gland: Adenoma or Carcinoma			
Overall rate[a]	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate[b]	2.6%	7.8%	6.1%
Terminal rate[c]	1/39 (3%)	2/34 (6%)	2/33 (6%)
First incidence (days)	729 (T)	372	729 (T)
Life table test[d]	P=0.348	P=0.271	P=0.442
Logistic regression test[d]	P=0.393	P=0.314	P=0.442
Cochran-Armitage test[d]	P=0.399		
Fisher exact test[d]		P=0.309	P=0.500
Liver: Hepatocellular Adenoma			
Overall rate	6/50 (12%)	45/50 (90%)	49/50 (98%)
Adjusted rate	15.4%	95.7%	100.0%
Terminal rate	6/39 (15%)	32/34 (94%)	33/33 (100%)
First incidence (days)	729 (T)	442	501
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall rate	0/50 (0%)	23/50 (46%)	27/50 (54%)
Adjusted rate	0.0%	57.2%	60.8%
Terminal rate	0/39 (0%)	17/34 (50%)	16/33 (48%)
First incidence (days)	–[e]	503	538
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	6/50 (12%)	46/50 (92%)	50/50 (100%)
Adjusted rate	15.4%	97.9%	100.0%
Terminal rate	6/39 (15%)	33/34 (97%)	33/33 (100%)
First incidence (days)	729 (T)	442	501
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	4/50 (8%)	17/50 (34%)	13/49 (27%)
Adjusted rate	9.8%	45.6%	33.5%
Terminal rate	3/39 (8%)	14/34 (41%)	9/33 (27%)
First incidence (days)	685	587	538
Life table test	P=0.010	P<0.001	P=0.009
Logistic regression test	P=0.017	P=0.001	P=0.015
Cochran-Armitage test	P=0.018		
Fisher exact test		P=0.001	P=0.014

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	4/50 (8%)	17/50 (34%)	15/49 (31%)
Adjusted rate	9.8%	45.6%	37.9%
Terminal rate	3/39 (8%)	14/34 (41%)	10/33 (30%)
First incidence (days)	685	587	538
Life table test	P=0.003	P<0.001	P=0.003
Logistic regression test	P=0.006	P=0.001	P=0.005
Cochran-Armitage test	P=0.006		
Fisher exact test		P=0.001	P=0.004
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	1/43 (2%)	9/45 (20%)	4/43 (9%)
Adjusted rate	2.2%	27.2%	12.2%
Terminal rate	0/34 (0%)	7/30 (23%)	3/29 (10%)
First incidence (days)	628	671	553
Life table test	P=0.145	P=0.007	P=0.151
Logistic regression test	P=0.181	P=0.009	P=0.216
Cochran-Armitage test	P=0.191		
Fisher exact test		P=0.009	P=0.180
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	2/50 (4%)	16/50 (32%)	27/50 (54%)
Adjusted rate	5.1%	41.7%	72.4%
Terminal rate	2/39 (5%)	12/34 (35%)	23/33 (70%)
First incidence (days)	729 (T)	671	538
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Stomach (Forestomach): Squamous Cell Carcinoma			
Overall rate	0/50 (0%)	12/50 (24%)	11/50 (22%)
Adjusted rate	0.0%	30.9%	27.3%
Terminal rate	0/39 (0%)	8/34 (24%)	5/33 (15%)
First incidence (days)	–	587	501
Life table test	P=0.001	P<0.001	P<0.001
Logistic regression test	P=0.002	P<0.001	P<0.001
Cochran-Armitage test	P=0.002		
Fisher exact test		P<0.001	P<0.001
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	2/50 (4%)	25/50 (50%)	34/50 (68%)
Adjusted rate	5.1%	60.7%	80.5%
Terminal rate	2/39 (5%)	18/34 (53%)	25/33 (76%)
First incidence (days)	729	587	501
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
Thyroid Gland (Follicular Cell): Adenoma			
Overall rate	3/50 (6%)	1/50 (2%)	2/48 (4%)
Adjusted rate	7.7%	2.9%	6.1%
Terminal rate	3/39 (8%)	1/34 (3%)	2/33 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table test	P=0.467N	P=0.355N	P=0.576N
Logistic regression test	P=0.467N	P=0.355N	P=0.576N
Cochran-Armitage test	P=0.415N		
Fisher exact test		P=0.309N	P=0.520N
Uterus: Stromal Sarcoma			
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	8.1%	0.0%
Terminal rate	0/39 (0%)	2/34 (6%)	0/33 (0%)
First incidence (days)	–	671	–
Life table test	P=0.597	P=0.105	–
Logistic regression test	P=0.634	P=0.116	–
Cochran-Armitage test	P=0.640		
Fisher exact test		P=0.121	–
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rate	0/50 (0%)	5/50 (10%)	0/50 (0%)
Adjusted rate	0.0%	12.4%	0.0%
Terminal rate	0/39 (0%)	2/34 (6%)	0/33 (0%)
First incidence (days)	–	587	–
Life table test	P=0.562	P=0.029	–
Logistic regression test	P=0.608	P=0.034	–
Cochran-Armitage test	P=0.610		
Fisher exact test		P=0.028	–
All Organs: Hemangioma			
Overall rate	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted rate	9.6%	0.0%	3.0%
Terminal rate	3/39 (8%)	0/34 (0%)	1/33 (3%)
First incidence (days)	478	–	729 (T)
Life table test	P=0.105N	P=0.080N	P=0.222N
Logistic regression test	P=0.082N	P=0.060N	P=0.182N
Cochran-Armitage test	P=0.082N		
Fisher exact test		P=0.059N	P=0.181N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rate	11/50 (22%)	15/50 (30%)	13/50 (26%)
Adjusted rate	25.5%	37.1%	35.7%
Terminal rate	7/39 (18%)	10/34 (29%)	10/33 (30%)
First incidence (days)	653	202	680
Life table test	P=0.237	P=0.181	P=0.268
Logistic regression test	P=0.364	P=0.254	P=0.339
Cochran-Armitage test	P=0.366		
Fisher exact test		P=0.247	P=0.408

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
All Organs: Benign Neoplasms			
Overall rate	24/50 (48%)	46/50 (92%)	50/50 (100%)
Adjusted rate	54.1%	95.8%	100.0%
Terminal rate	19/39 (49%)	32/34 (94%)	33/33 (100%)
First incidence (days)	478	442	501
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
All Organs: Malignant Neoplasms			
Overall rate	14/50 (28%)	40/50 (80%)	38/50 (76%)
Adjusted rate	30.9%	84.9%	80.7%
Terminal rate	8/39 (21%)	27/34 (79%)	24/33 (73%)
First incidence (days)	478	202	501
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms			
Overall rate	32/50 (64%)	50/50 (100%)	50/50 (100%)
Adjusted rate	66.7%	100.0%	100.0%
Terminal rate	23/39 (59%)	34/34 (100%)	33/33 (100%)
First incidence (days)	478	202	501
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001

(T)Terminal sacrifice
[a] Number of lesion-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pituitary gland, stomach, thyroid gland, and uterus; 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 analysis 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 D4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	6/50	0/50	6/50
Acetaminophen	3/49	0/49	3/49
HC Yellow 4	5/50	1/50	6/50
Methylphenidate Hydrochloride	6/49	5/49	9/49
Pentaerythritol Tetranitrate	5/49	1/49	6/49
Turmeric Oleoresin	7/50	7/50	13/50
Overall Historical Incidence			
Total	176/1,462 (12.0%)	89/1,462 (6.1%)	247/1,462 (16.9%)
Standard deviation	8.2%	5.4%	10.7%
Range	0%-33%	0%-20%	3%-42%

[a] Data as of 31 March 1993

TABLE D4b
Historical Incidence of Forestomach Squamous Cell Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	2/50	0/50	2/50
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	3/50	0/50	3/50
Methylphenidate Hydrochloride	1/49	0/49	1/49
Pentaerythritol Tetranitrate	1/50	0/50	1/50
Turmeric Oleoresin	0/50	0/50	0/50
Overall Historical Incidence			
Total	31/1,470 (2.1%)	2/1,470 (0.1%)	33/1,470 (2.2%)
Standard deviation	2.9%	0.5%	3.1%
Range	0%-14%	0%-2%	0%-14%

[a] Data as of 31 March 1993

TABLE D4c
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	4/50	0/50	4/50
Acetaminophen	1/50	0/50	1/50
HC Yellow 4	3/50	1/50	4/50
Methylphenidate Hydrochloride	1/48	0/48	1/48
Pentaerythritol Tetranitrate	2/50	1/50	3/50
Turmeric Oleoresin	4/50	1/50	5/50
Overall Historical Incidence			
Total	82/1,469 (5.6%)	30/1,469 (2.1%)	110/1,469 (7.5%)
Standard deviation	4.8%	2.2%	5.0%
Range	0%-24%	0%-8%	2%-26%

[a] Data as of 31 March 1993

TABLE D4d
Historical Incidence of Uterine Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Stromal Polyp	Stromal Sarcoma	Stromal Polyp or Stromal Sarcoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	0/50	0/50	0/50
Acetaminophen	1/50	0/50	1/50
HC Yellow 4	2/50	0/50	2/50
Methylphenidate Hydrochloride	2/49	0/49	2/49
Pentaerythritol Tetranitrate	3/50	0/50	3/50
Tumeric Oleoresin	1/50	0/50	1/50
Overall Historical Incidence			
Total	44/1,470 (3.0%)	7/1,470 (0.5%)	51/1,470 (3.5%)
Standard deviation	3.2%	0.9%	3.1%
Range	0%-16%	0%-2%	0%-16%

[a] Data as of 31 March 1993

TABLE D4e
Historical Incidence of Pituitary Gland Pars Distalis Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
1-Amino-2,4-dibromoanthraquinone	1/43		0/43
Acetaminophen	14/46	1/46	15/46
HC Yellow 4	5/42		0/42
Methylphenidate Hydrochloride	7/48		0/48
Pentaerythritol Tetranitrate	8/45		1/45
Tumeric Oleoresin	0/46		0/46
Overall Historical Incidence			
Total	212/1,392 (15.2%)	8/1,392 (0.6%)	220/1,392 (15.8%)
Standard deviation	9.9%	1.0%	10.3%
Range	0%-36%	0%-4%	0%-36%

[a] Data as of 31 March 1993

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	10,000 ppm	20,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	5	11	11
Natural deaths	6	5	6
Survivors			
Died last week of study	1	1	
Terminal sacrifice	38	33	33
Animals examined microscopically	60	60	60
15-Month Interim Evaluation			
Alimentary System			
Gallbladder	(10)	(10)	(10)
Inflammation, chronic	1 (10%)		1 (10%)
Inflammation, chronic active	1 (10%)		
Liver	(10)	(10)	(10)
Basophilic focus		1 (10%)	1 (10%)
Fatty change	1 (10%)	1 (10%)	3 (30%)
Inflammation, acute		5 (50%)	4 (40%)
Inflammation, chronic active	9 (90%)	4 (40%)	6 (60%)
Necrosis, coagulative	7 (70%)	8 (80%)	9 (90%)
Pigmentation		10 (100%)	9 (90%)
Bile duct, hyperplasia, focal		1 (10%)	
Pancreas	(10)	(10)	(10)
Inflammation, chronic	5 (50%)		1 (10%)
Vacuolization cytoplasmic	1 (10%)		
Salivary glands	(10)	(10)	(10)
Inflammation, chronic			5 (50%)
Submandibular gland, inflammation, chronic	7 (70%)		4 (40%)
Stomach, forestomach	(10)	(10)	(10)
Acanthosis		1 (10%)	8 (80%)
Hyperkeratosis		2 (20%)	7 (70%)
Hyperplasia, basal cell			2 (20%)
Inflammation, chronic			2 (20%)
Inflammation, chronic active		1 (10%)	3 (30%)
Stomach, glandular	(10)	(10)	(10)
Inflammation, chronic	2 (20%)		1 (10%)
Inflammation, chronic active	1 (10%)		
Cardiovascular System			
Heart	(10)	(10)	(10)
Cardiomyopathy	2 (20%)		
Endocrine System			
Pituitary gland	(8)	(10)	(9)
Pars distalis, cyst			1 (11%)
Pars distalis, hyperplasia	1 (13%)		1 (11%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
15-Month Interim Evaluation (continued)			
Genital System			
Ovary	(10)	(2)	(10)
Cyst	1 (10%)	1 (50%)	2 (20%)
Periovarian tissue, cyst		1 (50%)	
Periovarian tissue, inflammation, chronic	2 (20%)		
Uterus	(10)	(10)	(10)
Hydrometra	8 (80%)		3 (30%)
Endometrium, hyperplasia	6 (60%)		10 (100%)
Hematopoietic System			
Bone marrow	(10)	(10)	(10)
Myelofibrosis	2 (20%)		1 (10%)
Lymph node, mandibular	(6)	(10)	(10)
Pigmentation	1 (17%)		
Lymph node, mesenteric	(7)	(10)	(8)
Depletion lymphoid	1 (14%)		
Infiltration cellular, histiocyte	4 (57%)		7 (88%)
Pigmentation	3 (43%)		7 (88%)
Spleen	(10)	(10)	(9)
Depletion lymphoid			1 (11%)
Thymus	(9)	(10)	(8)
Cyst	6 (67%)		6 (75%)
Nervous System			
Brain	(10)	(10)	(10)
Thalamus, mineralization	3 (30%)		4 (40%)
Respiratory System			
Nose	(10)	(10)	(9)
Glands, inflammation, acute	2 (20%)		1 (11%)
Urinary System			
Kidney	(10)	(4)	(10)
Inflammation, chronic	10 (100%)	4 (100%)	9 (90%)
Renal tubule, regeneration	2 (20%)		1 (10%)
Urinary bladder	(10)	(10)	(10)
Inflammation, chronic	7 (70%)	7 (70%)	8 (80%)
Systems Examined With No Lesions Observed			
General Body System			
Integumentary System			
Musculoskeletal System			
Special Senses System			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study			
Alimentary System			
Esophagus	(50)	(45)	(47)
Autolysis			1 (2%)
Gallbladder	(49)	(47)	(44)
Autolysis	3 (6%)	2 (4%)	2 (5%)
Inflammation, chronic active	5 (10%)	6 (13%)	8 (18%)
Epithelium, hyperplasia		1 (2%)	
Intestine large, colon	(50)	(50)	(48)
Autolysis	3 (6%)	1 (2%)	
Inflammation, acute		1 (2%)	
Peyer's patch, hyperplasia		1 (2%)	1 (2%)
Intestine large, rectum	(50)	(50)	(47)
Autolysis	2 (4%)	1 (2%)	
Peyer's patch, epithelium, proliferation	1 (2%)		
Intestine large, cecum	(50)	(49)	(47)
Autolysis	4 (8%)	1 (2%)	
Peyer's patch, hyperplasia	1 (2%)	2 (4%)	
Intestine small, duodenum	(48)	(50)	(46)
Angiectasis		1 (2%)	
Autolysis	2 (4%)	2 (4%)	2 (4%)
Intestine small, jejunum	(47)	(50)	(46)
Autolysis	1 (2%)	2 (4%)	2 (4%)
Peyer's patch, hyperplasia			2 (4%)
Intestine small, ileum	(48)	(50)	(46)
Autolysis	2 (4%)	2 (4%)	2 (4%)
Inflammation, acute		1 (2%)	
Peyer's patch, hyperplasia	4 (8%)	3 (6%)	1 (2%)
Peyer's patch, inflammation, acute			1 (2%)
Liver	(50)	(50)	(50)
Autolysis	2 (4%)		1 (2%)
Basophilic focus		4 (8%)	5 (10%)
Clear cell focus		10 (20%)	9 (18%)
Eosinophilic focus		4 (8%)	2 (4%)
Fatty change	2 (4%)	3 (6%)	15 (30%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation	3 (6%)	6 (12%)	6 (12%)
Hemorrhage			1 (2%)
Inflammation, chronic active	27 (54%)	24 (48%)	23 (46%)
Mixed cell focus		2 (4%)	
Necrosis, coagulative	9 (18%)	18 (36%)	16 (32%)
Pigmentation		44 (88%)	49 (98%)
Bile duct, hyperplasia		1 (2%)	
Mesentery	(6)	(9)	(8)
Fibrosis		4 (44%)	
Inflammation, chronic active	3 (50%)	5 (56%)	4 (50%)
Mineralization	1 (17%)		
Necrosis, coagulative	1 (17%)	3 (33%)	
Pigmentation	1 (17%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Alimentary System (continued)			
Pancreas	(50)	(50)	(49)
Atrophy		1 (2%)	2 (4%)
Autolysis			2 (4%)
Cytoplasmic alteration	3 (6%)	1 (2%)	
Fibrosis			1 (2%)
Inflammation		1 (2%)	
Inflammation, chronic active	25 (50%)	24 (48%)	18 (37%)
Vacuolization cytoplasmic	19 (38%)	13 (26%)	21 (43%)
Duct, dilatation	1 (2%)	1 (2%)	1 (2%)
Duct, hyperplasia		1 (2%)	
Salivary glands	(49)	(50)	(47)
Inflammation, chronic		1 (2%)	
Parotid gland, autolysis			1 (2%)
Sublingual gland, inflammation, chronic	1 (2%)	2 (4%)	
Submandibular gland, autolysis			1 (2%)
Submandibular gland, inflammation, chronic	40 (82%)	32 (64%)	29 (62%)
Stomach, forestomach	(48)	(50)	(50)
Acanthosis	9 (19%)	15 (30%)	19 (38%)
Autolysis			1 (2%)
Erosion		1 (2%)	1 (2%)
Hyperkeratosis	10 (21%)	14 (28%)	17 (34%)
Hyperplasia, basal cell		7 (14%)	3 (6%)
Hyperplasia, squamous			2 (4%)
Inflammation, chronic active	7 (15%)	10 (20%)	21 (42%)
Ulcer	2 (4%)	1 (2%)	2 (4%)
Ulcer, multiple	1 (2%)		
Stomach, glandular	(49)	(48)	(48)
Autolysis	2 (4%)		1 (2%)
Inflammation, chronic		1 (2%)	
Inflammation, chronic active	20 (41%)	19 (40%)	21 (44%)
Mineralization	1 (2%)		1 (2%)
Tooth	(1)		
Abscess	1 (100%)		
Dysplasia	1 (100%)		
Cardiovascular System			
Heart	(50)	(50)	(49)
Autolysis			1 (2%)
Inflammation, chronic	9 (18%)	6 (12%)	8 (16%)
Mineralization		1 (2%)	1 (2%)
Thrombosis		1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Endocrine System			
Adrenal cortex	(50)	(49)	(48)
Angiectasis	2 (4%)		
Autolysis			1 (2%)
Cyst		1 (2%)	
Degeneration, fatty			1 (2%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	1 (2%)
Hyperplasia		1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	
Vacuolization cytoplasmic		1 (2%)	
Adrenal medulla	(49)	(49)	(48)
Autolysis			1 (2%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)
Hyperplasia		1 (2%)	
Islets, pancreatic	(49)	(50)	(48)
Hyperplasia	3 (6%)	1 (2%)	1 (2%)
Parathyroid gland	(33)	(39)	(33)
Cyst	1 (3%)		
Pituitary gland	(43)	(45)	(43)
Autolysis			1 (2%)
Pars distalis, angiectasis	1 (2%)		
Pars distalis, cyst	3 (7%)		
Pars distalis, hyperplasia	7 (16%)	22 (49%)	7 (16%)
Pars distalis, pigmentation	1 (2%)		
Thyroid gland	(50)	(50)	(48)
Autolysis			1 (2%)
Inflammation, chronic active	1 (2%)	2 (4%)	3 (6%)
C-cell, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Follicle, cyst	2 (4%)		2 (4%)
Follicular cell, hyperplasia	3 (6%)	19 (38%)	18 (38%)
General Body System			
None			
Genital System			
Clitoral gland			(1)
Duct, dilatation			1 (100%)
Ovary	(49)	(49)	(47)
Abscess		3 (6%)	2 (4%)
Angiectasis	2 (4%)	4 (8%)	4 (9%)
Cyst	12 (24%)	11 (22%)	7 (15%)
Cyst, multiple	1 (2%)	3 (6%)	1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute, necrotizing	1 (2%)		
Mineralization		2 (4%)	
Pigmentation	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Genital System (continued)			
Ovary (continued)	(49)	(49)	(47)
Periovarian tissue, cyst	1 (2%)	1 (2%)	
Periovarian tissue, cyst, multiple			1 (2%)
Periovarian tissue, hemorrhage			1 (2%)
Periovarian tissue, inflammation, chronic active	29 (59%)	24 (49%)	28 (60%)
Periovarian tissue, mineralization	1 (2%)		
Periovarian tissue, pigmentation			1 (2%)
Uterus	(49)	(50)	(49)
Angiectasis			1 (2%)
Fibrosis		2 (4%)	1 (2%)
Hydrometra	14 (29%)	3 (6%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic active	4 (8%)	6 (12%)	7 (14%)
Endometrium, hyperplasia	38 (78%)	36 (72%)	35 (71%)
Epithelium, metaplasia, squamous	2 (4%)	1 (2%)	1 (2%)
Hematopoietic System			
Bone marrow	(50)	(49)	(49)
Myelofibrosis		5 (10%)	
Myeloid cell, sternal, hyperplasia	2 (4%)	1 (2%)	2 (4%)
Sternal, autolysis			1 (2%)
Sternal, myelofibrosis	38 (76%)	32 (65%)	34 (69%)
Lymph node	(7)	(12)	(12)
Lumbar, hyperplasia, lymphoid	1 (14%)		1 (8%)
Lumbar, inflammation, acute	1 (14%)		
Mediastinal, hyperplasia, lymphoid			1 (8%)
Mediastinal, hyperplasia, plasma cell			1 (8%)
Mediastinal, inflammation, chronic active	1 (14%)		
Pancreatic, hyperplasia, lymphoid		1 (8%)	1 (8%)
Pancreatic, infiltration cellular, histiocyte			1 (8%)
Pancreatic, pigmentation			1 (8%)
Renal, hyperplasia, plasma cell		2 (17%)	
Renal, sinus, ectasia			1 (8%)
Lymph node, mandibular	(32)	(45)	(31)
Autolysis			1 (3%)
Congestion	1 (3%)		
Depletion lymphoid		1 (2%)	
Hyperplasia, lymphoid	3 (9%)	1 (2%)	2 (6%)
Hyperplasia, plasma cell	1 (3%)		1 (3%)
Inflammation, acute		1 (2%)	
Pigmentation	2 (6%)	2 (4%)	3 (10%)
Sinus, ectasia		2 (4%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Hematopoietic System (continued)			
Lymph node, mesenteric	(49)	(46)	(44)
Angiectasis	7 (14%)	4 (9%)	3 (7%)
Depletion lymphoid	1 (2%)	1 (2%)	
Hemorrhage		2 (4%)	
Hyperplasia, lymphoid	2 (4%)	6 (13%)	10 (23%)
Infiltration cellular, histiocyte	32 (65%)	24 (52%)	27 (61%)
Inflammation, chronic active	1 (2%)	3 (7%)	2 (5%)
Mineralization		1 (2%)	
Necrosis, coagulative	1 (2%)		
Pigmentation	31 (63%)	24 (52%)	27 (61%)
Sinus, ectasia			1 (2%)
Spleen	(50)	(50)	(50)
Autolysis	1 (2%)		1 (2%)
Depletion lymphoid	4 (8%)	2 (4%)	2 (4%)
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	6 (12%)	13 (26%)	11 (22%)
Hyperplasia, lymphoid	15 (30%)	14 (28%)	8 (16%)
Inflammation, chronic	1 (2%)		
Thymus	(40)	(38)	(34)
Angiectasis	1 (3%)		
Cyst	14 (35%)	16 (42%)	22 (65%)
Depletion lymphoid	4 (10%)	2 (5%)	6 (18%)
Hemorrhage		1 (3%)	1 (3%)
Hyperplasia, lymphoid	3 (8%)	1 (3%)	1 (3%)
Integumentary System			
Mammary gland	(25)	(25)	(20)
Hyperplasia	2 (8%)	9 (36%)	3 (15%)
Inflammation, chronic	1 (4%)		
Skin	(50)	(50)	(50)
Acanthosis	1 (2%)		
Autolysis			1 (2%)
Inflammation, acute	1 (2%)		
Epidermis, inflammation, acute			1 (2%)
Subcutaneous tissue, cyst epithelial inclusion		1 (2%)	
Subcutaneous tissue, fibrosis		1 (2%)	
Subcutaneous tissue, inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)
Subcutaneous tissue, mineralization	1 (2%)		
Musculoskeletal System			
None			
Nervous System			
Brain	(49)	(50)	(50)
Perivascular, inflammation, chronic		1 (2%)	
Thalamus, mineralization	21 (43%)	15 (30%)	21 (42%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	10,000 ppm	20,000 ppm
2-Year Study (continued)			
Respiratory System			
Lung	(50)	(50)	(49)
Autolysis			1 (2%)
Congestion	1 (2%)		
Hemorrhage	4 (8%)	4 (8%)	8 (16%)
Infiltration cellular, histiocyte			1 (2%)
Inflammation, chronic active	3 (6%)	4 (8%)	6 (12%)
Leukocytosis	1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia			1 (2%)
Pleura, inflammation, acute		1 (2%)	
Nose	(48)	(45)	(44)
Inflammation, acute	21 (44%)	9 (20%)	7 (16%)
Nasolacrimal duct, hyperplasia	1 (2%)		
Nasolacrimal duct, inflammation, acute		1 (2%)	
Trachea	(50)	(49)	(47)
Autolysis			1 (2%)
Special Senses System			
Eye	(1)		(1)
Cornea, inflammation, chronic active			1 (100%)
Cornea, neovascularization			1 (100%)
Harderian gland	(1)	(3)	(2)
Inflammation, chronic	1 (100%)		2 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Autolysis			1 (2%)
Glomerulosclerosis	2 (4%)	3 (6%)	4 (8%)
Hydronephrosis	1 (2%)	1 (2%)	
Infarct	1 (2%)		
Inflammation, chronic	43 (86%)	42 (84%)	45 (90%)
Metaplasia, osseous		3 (6%)	1 (2%)
Papilla, mineralization			1 (2%)
Pelvis, transitional epithelium, hyperplasia		1 (2%)	
Proximal convoluted renal tubule, degeneration, hyaline	1 (2%)		
Renal tubule, atrophy		1 (2%)	3 (6%)
Renal tubule, casts protein	1 (2%)		
Renal tubule, mineralization			3 (6%)
Renal tubule, pigmentation		43 (86%)	43 (86%)
Renal tubule, regeneration	1 (2%)	7 (14%)	3 (6%)
Transitional epithelium, mineralization			1 (2%)
Autolysis	3 (6%)	1 (2%)	2 (4%)
Inflammation, chronic active	42 (86%)	43 (86%)	46 (92%)
Arteriole, necrosis, fibrinoid			1 (2%)
Submucosa, proliferation	1 (2%)		

APPENDIX E
SUMMARY OF LESIONS IN MALE RATS IN THE STOP-EXPOSURE EVALUATION OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Disposition Summary			
Animals initially in study	70	10	30
9-Month interim evaluation	10		10
Early deaths			
Moribund		3	2
Natural death			1
Survivors		7	17
Animals examined microscopically	10	10	20
9-Month Interim Evaluation[b]			
Alimentary System			
Intestine large, colon	(10)		(10)
Polyp adenomatous			1 (10%)
Liver	(10)		(10)
Hepatocellular carcinoma			2 (20%)
Hepatocellular adenoma			2 (20%)
Endocrine System			
Adrenal medulla	(10)		(10)
Thyroid gland	(10)		(10)
Follicular cell, adenoma			1 (10%)
Nervous System			
Brain	(10)		(10)
Cerebrum, meningioma benign	1 (10%)		
Respiratory System			
Lung	(10)		(10)
Alveolar/bronchiolar adenoma			1 (10%)
Urinary System			
Urinary bladder	(10)		(9)
Papilloma			1 (11%)
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Special Senses System			

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation[c]						
Alimentary System						
Intestine large, rectum	(9)		(10)		(20)	
Adenocarcinoma					2	(10%)
Polyp adenomatous			2	(20%)	6	(30%)
Polyp adenomatous, multiple			1	(10%)	1	(5%)
Liver	(10)		(10)		(20)	
Hepatocellular carcinoma			4	(40%)	6	(30%)
Hepatocellular carcinoma, multiple			3	(30%)	13	(65%)
Hepatocellular adenoma			7	(70%)	3	(15%)
Hepatocholangiocarcinoma			1	(10%)	5	(25%)
Pancreas	(10)		(10)			
Adenoma	1	(10%)				
Stomach, forestomach	(10)		(10)		(20)	
Squamous cell papilloma					1	(5%)
Cardiovascular System						
Heart	(10)		(10)		(20)	
Hepatocholangiocarcinoma, metastatic, liver			1	(10%)		
Endocrine System						
Pituitary gland	(8)		(10)		(19)	
Pars distalis, adenoma	1	(13%)			1	(5%)
Thyroid gland	(10)		(10)			
Adenoma	1	(10%)				
C-cell, adenoma	1	(10%)				
General Body System						
None						
Genital System						
Epididymis					(20)	
Preputial gland	(9)				(19)	
Carcinoma					1	(5%)
Testes	(10)		(10)		(20)	
Adenoma	1	(10%)				
Bilateral, interstitial cell, adenoma			1	(10%)		
Interstitial cell, adenoma	2	(20%)	3	(30%)	3	(15%)
Hematopoietic System						
Lymph node					(3)	
Mediastinal, hepatocellular carcinoma, metastatic, liver					1	(33%)

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(10)		(10)		(20)	
Alveolar/bronchiolar adenoma	1	(10%)				
Hepatocellular carcinoma, metastatic, liver			5	(50%)	7	(35%)
Hepatocholangiocarcinoma, metastatic, liver			1	(10%)		
Special Senses System						
None						
Urinary System						
Kidney	(10)		(10)		(20)	
Hepatocellular carcinoma, metastatic, liver					1	(5%)
Renal tubule, adenoma			3	(30%)	2	(10%)
Urinary bladder	(10)		(10)		(19)	
Transitional epithelium, papilloma					3	(16%)
Squamous cell carcinoma					1	(5%)
Transitional epithelium, carcinoma					1	(5%)
Systemic Lesions						
Multiple organs[d]	(10)		(10)		(20)	
Mesothelioma malignant					1	(5%)

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Neoplasm Summary			
Total animals with primary neoplasms[e]	7	10	20
Total primary neoplasms	8	25	50
Total animals with benign neoplasms	7	10	15
Total benign neoplasms	8	17	25
Total animals with malignant neoplasms		8	19
Total malignant neoplasms		8	25
Total animals with metastatic neoplasms		6	7
Total metastatic neoplasms		7	9

[a] Number of animals examined microscopically at site and number of animals with neoplasm (includes interim and moribund animals)
[b] Controls from the 9-month interim evaluation of the 2-year core study were used for comparison.
[c] Controls from the 15-month interim evaluation of the 2-year core study were used for comparison.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 15-Month Interim Evaluation Control Group versus 9-Month and 15-Month 20,000 ppm Groups at the 15-Month Evaluation

	0 ppm (15-month interim evaluation)	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Kidney (Renal Tubule): Adenoma			
Overall rate[a]	0/10 (0%)	3/10 (30%)	2/20 (10%)
Adjusted rate[b]	0.0%	60.0%	18.2%
Interim evaluation	0/10 (0%)	3/7 (43%)	2/17 (12%)
First incidence (days)	–[d]	458 (I)	457 (I)
Life table test[c]	P=0.336	P=0.056	P=0.360
Logistic regression test[c]	P=0.336	P=0.056	P=0.360
Cochran-Armitage test[c]	P=0.385		
Fisher exact test[c]		P=0.105	P=0.437
Large Intestine (Rectum): Adenomatous Polyp			
Overall rate	0/10 (0%)	3/10 (30%)	7/20 (35%)
Adjusted rate	0.0%	38.3%	66.3%
Interim evaluation	0/10 (0%)	2/7 (29%)	7/17 (41%)
First incidence (days)	–	414	456 (I)
Life table test	P=0.030	P=0.080	P=0.031
Logistic regression test	P=0.034	P=0.232	
	P=0.031		
Cochran-Armitage test	P=0.037		
Fisher exact test		P=0.105	P=0.038
Large Intestine (Rectum): Carcinoma			
Overall rate	0/10 (0%)	0/10	2/20 (10%)
Adjusted rate	0.0%	0.0%	29.2%
Interim evaluation	0/10 (0%)	0/7 (0%)	1/17 (6%)
First incidence (days)	–	–	427
Life table test	P=0.229		P=0.369
Logistic regression test	P=0.284		P=0.502
Cochran-Armitage test	P=0.239		
Fisher exact test			P=0.437
Liver: Hepatocellular Adenoma			
Overall rate	0/10 (0%)	7/10 (70%)	8/20 (40%)
Adjusted rate	0.0%	86.3%	69.6%
Interim evaluation	0/10 (0%)	5/7 (71%)	7/17 (41%)
First incidence (days)	–	414	423
Life table test	P=0.038	P=0.002	P=0.023
Logistic regression test	P=0.049	P=0.006	P=0.026
Cochran-Armitage test	P=0.043		
Fisher exact test		P=0.002	P=0.022
Liver: Hepatocellular Carcinoma			
Overall rate	0/10 (0%)	7/10 (70%)	19/20 (95%)
Adjusted rate	0.0%	77.8%	100.0%
Interim evaluation	0/10 (0%)	5/7 (71%)	16/17 (94%)
First incidence (days)	–	442	400
Life table test	P<0.001	P=0.001	P<0.001
Logistic regression test	P<0.001	P=0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.002	P<0.001

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 15-Month Interim Evaluation Control Group versus 9-Month and 15-Month 20,000 ppm Groups at the 15-Month Evaluation (continued)

	0 ppm (15-month interim evaluation)	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	0/10 (0%)	9/10 (90%)	20/20 (100%)
Adjusted rate	0.0%	90.0%	100.0%
Interim evaluation	0/10 (0%)	6/7 (86%)	17/17 (100%)
First incidence (days)	–	414	400
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	1/8 (13%)	0/10 (0%)	1/19 (5%)
Adjusted rate	10.0%	0.0%	10.0%
Interim evaluation	1/8 (13%)	0/7 (0%)	1/16 (6%)
First incidence (days)	456 (I)	–	457 (I)
Life table test	P=0.498N	P=0.527N	P=0.601N
Logistic regression test	P=0.498N	P=0.527N	P=0.601N
Cochran-Armitage test	P=0.462N		
Fisher exact test		P=0.444N	P=0.513N
Testes: Adenoma			
Overall rate	3/10 (30%)	4/10 (40%)	3/20 (15%)
Adjusted rate	46.7%	65.0%	35.8%
Interim evaluation	3/10 (30%)	3/7 (43%)	3/17 (18%)
First incidence (days)	456 (I)	447	456 (I)
Life table test	P=0.328N	P=0.300	P=0.397N
Logistic regression test	P=0.306N	P=0.395	P=0.397N
Cochran-Armitage test	P=0.238N		
Fisher exact test		P=0.500	P=0.306N
Urinary Bladder: Papilloma			
Overall rate	0/10 (0%)	0/10 (0%)	3/19 (16%)
Adjusted rate	0.0%	0.0%	38.6%
Interim evaluation	0/10 (0%)	0/7 (0%)	3/17 (18%)
First incidence (days)	–	–	457 (I)
Life table test	P=0.126		P=0.223
Logistic regression	P=0.126		P=0.223
Cochran-Armitage test	P=0.128		
Fisher exact test			P=0.265
Urinary Bladder: Carcinoma			
Overall rate	0/10 (0%)	0/10 (0%)	1/19 (5%)
Adjusted rate	0.0%	0.0%	25.0%
Interim evaluation	0/10 (0%)	0/7 (0%)	1/17 (6%)
First incidence (days)	–	–	458 (I)
Life table test	P=0.430		P=0.606
Logistic regression	P=0.430		P=0.606
Cochran-Armitage test	P=0.442		
Fisher exact test			P=0.655

TABLE E2a
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 15-Month Interim Evaluation Control Group versus 9-Month and 15-Month 20,000 ppm Groups at the 15-Month Evaluation (continued)

	0 ppm (15-month interim evaluation)	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
All Organs: Benign Neoplasms			
Overall rate	7/10 (70%)	10/10 (100%)	15/20 (75%)
Adjusted rate	73.3%	100.0%	93.4%
Interim evaluation	7/10 (70%)	7/7 (100%)	14/17 (82%)
First incidence (days)	456 (I)	414	423
Life table test	P=0.289	P=0.024	P=0.296
Logistic regression test	P=0.420	P=0.178	P=0.388
Cochran-Armitage test	P=0.538		
Fisher exact test		P=0.105	P0.548
All Organs: Malignant Neoplasms			
Overall rate	0/10 (0%)	8/10 (80%)	19/20 (95%)
Adjusted rate	0.0%	80.0%	100.0%
Interim evaluation	0/10 (0%)	5/7 (71%)	16/17 (94%)
First incidence (days)	–	414	400
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.005	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms			
Overall rate	7/10 (70%)	10/10 (100%)	20/20 (100%)
Adjusted rate	73.3%	100.0%	100.0%
Interim evaluation	7/10 (70%)	7/7 (100%)	17/17 (100%)
First incidence (days)	456 (I)	414	400
Life table test	P=0.020	P=0.024	
	P=0.018		
Logistic regression test	P=0.015	P=0.178	P=0.042
Cochran-Armitage test	P=0.008		
Fisher exact test		P=0.105	P=0.030

(I) Interim evaluation
[a] Number of lesion-bearing animals/number of animals examined (includes interim and moribund animals). Denominator is number of animals examined microscopically for kidney, liver, pituitary gland, testes, 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] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table analysis 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 an exposure group is indicated by **N**.
[d] Not applicable; no neoplasms in animal group

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 9-Month 20,000 ppm Stop-Exposure Group versus 15-Month 20,000 ppm Exposure Group at the 15-Month Evaluation

	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Kidney (Renal Tubule): Adenoma		
Overall rate[a]	3/10 (30%)	2/20 (10%)
Adjusted rate[b]	60.0%	18.2%
Interim evaluation	3/7 (43%)	2/17 (12%)
First incidence (days)	458 (I)	457 (I)
Life table test[c]		P=0.130N
Logistic regression test[c]		P=0.130N
Fisher exact test[c]		P=0.191N
Large Intestine (Rectum): Adenomatous Polyp		
Overall rate	3/10 (30%)	7/20 (35%)
Adjusted rate	38.3%	66.3%
Interim evaluation	2/7 (29%)	7/17 (41%)
First incidence (days)	414	456 (I)
Life table test		P=0.652N
Logistic regression test		P=0.561
Fisher exact test		P=0.560
Large Intestine (Rectum): Carcinoma		
Overall rate	0/10 (0%)	2/20 (10%)
Adjusted rate	0.0%	29.2%
Interim evaluation	0/7 (0%)	1/17 (6%)
First incidence (days)	–[d]	427
Life table test		P=0.424
Logistic regression test		P=0.400
Fisher exact test		P=0.437
Liver: Hepatocellular Adenoma		
Overall rate	7/10 (70%)	8/20 (40%)
Adjusted rate	86.3%	69.6%
Interim evaluation	5/7 (71%)	7/17 (41%)
First incidence (days)	414	423
Life table test		P=0.078N
Logistic regression test		P=0.122N
Fisher exact test		P=0.123N
Liver: Hepatocellular Carcinoma		
Overall rate	7/10 (70%)	19/20 (95%)
Adjusted rate	77.8%	100.0%
Interim evaluation	5/7 (71%)	16/17 (94%)
First incidence (days)	442	400
Life table test		P=0.415
Logistic regression test		P=0.091
Fisher exact test		P=0.095

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 9-Month 20,000 ppm Stop-Exposure Group versus 15-Month 20,000 ppm Exposure Group at the 15-Month Evaluation (continued)

	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rate	9/10 (90%)	20/20 (100%)
Adjusted rate	90.0%	100.0%
Interim evaluation	6/7 (86%)	17/17 (100%)
First incidence (days)	414	400
Life table test		P=0.566N
Logistic regression test		P=0.323
Fisher exact test		P=0.333
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	0/10 (0%)	1/19 (5%)
Adjusted rate	0.0%	10.0%
Interim evaluation	0/7 (0%)	1/16 (6%)
First incidence (days)	–	457 (I)
Life table test		P=0.665
Logistic regression test		P=0.665
Fisher exact test		P=0.655
Testes: Adenoma		
Overall rate	4/10 (40%)	3/20 (15%)
Adjusted rate	65.0%	35.8%
Interim evaluation	3/7 (43%)	3/17 (18%)
First incidence (days)	447	456 (I)
Life table test		P=0.095N
Logistic regression test		P=0.120N
Fisher exact test		P=0.143N
Urinary Bladder: Papilloma		
Overall rate	0/10 (0%)	3/19 (16%)
Adjusted rate	0.0%	38.6%
Interim evaluation	0/7 (0%)	3/17 (18%)
First incidence (days)	–	457 (I)
Life table test		P=0.309
Logistic regression test		P=0.309
Fisher exact test		P=0.265
Urinary Bladder: Carcinoma		
Overall rate	0/10 (0%)	1/19 (5%)
Adjusted rate	0.0%	25.0%
Interim evaluation	0/7 (0%)	1/17 (6%)
First incidence (days)	–	458 (I)
Life table test		P=0.677
Logistic regression test		P=0.677
Fisher exact test		P=0.655

TABLE E2b
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 9-Month 20,000 ppm Stop-Exposure Group versus 15-Month 20,000 ppm Exposure Group at the 15-Month Evaluation (continued)

	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
All Organs: Benign Neoplasms		
Overall rate	10/10 (100%)	15/20 (75%)
Adjusted rate	100.0%	93.4%
Interim evaluation	7/7 (100%)	14/17 (82%)
First incidence (days)	414	423
Life table test		P=0.045N
Logistic regression test		P=0.100N
Fisher exact test		P=0.109N
All Organs: Malignant Neoplasms		
Overall rate	8/10 (80%)	19/20 (95%)
Adjusted rate	80.0%	100.0%
Interim evaluation	5/7 (71%)	16/17 (94%)
First incidence (days)	414	400
Life table test		P=0.608
Logistic regression test		P=0.203
Fisher exact test		P=0.251
All Organs: Benign or Malignant Neoplasms		
Overall rate	10/10 (100%)	20/20 (100%)
Adjusted rate	100.0%	100.0%
Interim evaluation	7/7 (100%)	17/17 (100%)
First incidence (days)	414	400
Life table test		P=0.332N
Logistic regression test		—[e]
Fisher exact test		P=1.000

(I) Interim evaluation
[a] Number of lesion-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for kidney, liver, pituitary gland, testes, 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] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between both exposed groups. The life table analysis 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 an exposure group is indicated by **N**.
[d] Not applicable; no neoplasms in animal group
[e] Value of the statistic cannot be computed.

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
Disposition Summary						
Animals initially in study	70		10		30	
9-Month interim evaluation	10				10	
Early deaths						
Moribund			3		2	
Natural death					1	
Survivors			7		17	
Animals examined microscopically	10		10		20	
9-Month Interim Evaluation[b]						
Alimentary System						
Intestine large, colon	(10)				(10)	
Parasite metazoan	2	(20%)				
Intestine large, rectum	(10)				(10)	
Intestine large, cecum					(9)	
Parasite metazoan	(10)				1	(11%)
Liver	(10)				(10)	
Basophilic focus					6	(60%)
Clear cell focus					4	(40%)
Cytomegaly					2	(20%)
Fatty change	3	(30%)				
Inflammation, chronic active	1	(10%)				
Mixed cell focus					1	(10%)
Necrosis, coagulative	1	(10%)			2	(20%)
Pigmentation					10	(100%)
Bile duct, hyperplasia	1	(10%)			7	(70%)
Periportal, inflammation, chronic active	9	(90%)			10	(100%)
Pancreas	(10)				(10)	
Atrophy	2	(20%)				
Ectopic tissue					1	(10%)
Infiltration cellular, mononuclear cell	3	(30%)			1	(10%)
Infiltration cellular, mixed cell					1	(10%)
Inflammation, chronic	1	(10%)				
Inflammation, chronic active	1	(10%)				
Necrosis, coagulative	2	(20%)				
Pigmentation	1	(10%)			1	(10%)
Acinus, atrophy	1	(10%)				
Salivary glands	(10)				(10)	
Sublingual gland, atrophy					1	(10%)
Sublingual gland, pigmentation					1	(10%)
Cardiovascular System						
Heart	(10)					(10)
Cardiomyopathy	9	(90%)			6	(60%)

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
9-Month Interim Evaluation (continued)						
Endocrine System						
Adrenal cortex	(10)				(10)	
Angiectasis					1	(10%)
Adrenal medulla	(10)				(10)	
Hyperplasia	1	(10%)				
Pituitary gland	(9)				(10)	
Pars distalis, cyst	1	(11%)				
Pars distalis, hyperplasia	3	(33%)			4	(40%)
Thyroid gland	(10)				(10)	
Genital System						
Preputial gland	(9)				(10)	
Inflammation, chronic	2	(22%)			2	(20%)
Inflammation, chronic active	7	(78%)			8	(80%)
Prostate	(10)				(10)	
Inflammation, acute	1	(10%)			6	(60%)
Inflammation, chronic active					1	(10%)
Testes (10)					(10)	
Atrophy					1	(10%)
Infarct					1	(10%)
Inflammation, chronic active					1	(10%)
Interstitial cell, hyperplasia	1	(10%)			2	(20%)
Hematopoietic System						
Lymph node	(2)				(3)	
Mediastinal, hemorrhage	1	(50%)			1	(33%)
Mediastinal, pigmentation	1	(50%)			1	(33%)
Pancreatic, pigmentation					1	(33%)
Renal, hemorrhage	1	(50%)				
Renal, pigmentation	1	(50%)				
Lymph node, mandibular	(10)				(10)	
Hemorrhage	9	(90%)			1	(10%)
Infiltration cellular, histiocyte					1	(10%)
Lymph node, mesenteric	(10)				(10)	
Hemorrhage					1	(10%)
Infiltration cellular, histiocyte	10	(100%)			10	(100%)
Pigmentation					8	(80%)
Spleen(10)					(10)	
Thymus	(9)				(10)	
Depletion lymphoid	3	(33%)			8	(80%)
Hemorrhage					1	(10%)
Integumentary System						
Mammary gland	(8)				(5)	
Hyperplasia	7	(88%)			5	(100%)

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
9-Month Interim Evaluation (continued)						
Respiratory System						
Lung	(10)				(10)	
Infiltration cellular, histiocyte	1	(10%)				
Artery, mineralization	6	(60%)			4	(40%)
Nose	(10)				(10)	
Glands, inflammation, acute					1	(10%)
Nasolacrimal duct, inflammation, chronic active					1	(10%)
Special Senses System						
Ear	(1)					
Inflammation, chronic active	1	(100%)				
Ulcer	1	(100%)				
Urinary System						
Kidney	(10)				(10)	
Granuloma	1	(10%)				
Infiltration cellular, mononuclear cell					7	(70%)
Infiltration cellular, mixed cell					1	(10%)
Inflammation, chronic	4	(40%)				
Renal tubule, degeneration, hyaline					10	(100%)
Renal tubule, pigmentation					10	(100%)
Renal tubule, regeneration	10	(100%)			10	(100%)
Urinary bladder	(10)				(9)	
Calculus microscopic observation only	2	(20%)			2	(22%)
Serosa, mineralization	1	(10%)				
Systems Examined With No Lesions Observed						
General Body System						
Musculoskeletal System						
Nervous System						
15-Month Evaluation[c]						
Alimentary System						
Intestine large, colon	(10)		(10)		(20)	
Parasite metazoan	4	(40%)			1	(5%)
Intestine large, rectum	(9)		(10)			(20)
Parasite metazoan	1	(11%)			1	(10%)
Intestine large, cecum	(10)		(10)			(19)
Inflammation, chronic active					1	(5%)
Parasite metazoan	3	(30%)	3	(30%)		
Intestine small, ileum					(19)	
Inflammation, chronic active					1	(5%)

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Alimentary System (continued)						
Liver	(10)		(10)		(20)	
Anisokaryosis			1	(10%)		
Basophilic focus	1	(10%)	4	(40%)	13	(65%)
Clear cell focus			6	(60%)	13	(65%)
Degeneration	2	(20%)			4	(20%)
Eosinophilic focus	1	(10%)			2	(10%)
Fatty change	6	(60%)	9	(90%)	10	(50%)
Hemmorrhage					1	(5%)
Hematopoietic cell proliferation	2	(20%)				
Hepatodiaphragmatic nodule			1	(10%)		
Inflammation, chronic, granulomatous	2	(20%)				
Inflammation, chronic active	6	(60%)			2	(10%)
Necrosis, coagulative	6	(60%)	1	(10%)	2	(10%)
Pigmentation			8	(80%)	18	(90%)
Bile duct, hyperplasia	10	(100%)	7	(70%)	19	(95%)
Periportal, inflammation, chronic	10	(100%)	7	(70%)	17	(85%)
Periportal, inflammation, chronic active					1	(5%)
Mesentery			(1)		(1)	
Hemorrhage			1	(100%)		
Inflammation, chronic			1	(100%)		
Inflammation, chronic active					1	(100%)
Necrosis, coagulative					1	(100%)
Thrombosis			1	(100%)		
Pancreas	(10)		(10)		(20)	
Atrophy	4	(40%)	2	(20%)	4	(20%)
Hyperplasia					1	(5%)
Inflammation, chronic	8	(80%)	5	(50%)	11	(55%)
Inflammation, chronic active					1	(5%)
Vacuolization cytoplasmic			1	(10%)		
Artery, inflammation, chronic active					1	(5%)
Salivary glands					(19)	
Duct, parotid gland, mineralization					1	(5%)
Stomach, forestomach	(10)		(10)		(20)	
Acanthosis					2	(10%)
Hyperkeratosis			2	(20%)	1	(5%)
Hyperplasia, basal cell			2	(20%)	3	(15%)
Hyperplasia, squamous			2	(20%)		
Inflammation, chronic active			1	(10%)	1	(5%)
Ulcer			2	(20%)		
Muscularis, mineralization	1	(10%)				
Stomach, glandular	(10)		(10)		(20)	
Inflammation, chronic	1	(10%)	1	(10%)	1	(5%)
Inflammation, chronic active			1	(10%)		
Arteriole, mineralization					1	(5%)
Muscularis, mineralization	1	(10%)			1	(5%)

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Cardiovascular System						
Heart	(10)		(10)		(20)	
Cardiomyopathy	10	(100%)	8	(80%)	17	(85%)
Endocrine System						
Adrenal cortex	(10)		(10)		(20)	
Hyperplasia	1	(10%)	1	(10%)		
Bilateral, vacuolization cytoplasmic	1	(10%)			6	(30%)
Adrenal medulla	(9)		(10)		(20)	
Bilateral, hyperplasia	1	(11%)			1	(5%)
Islets, pancreatic	(4)		(3)			
Hemorrhage	1	(25%)				
Pituitary gland	(8)		(10)		(19)	
Pars distalis, cyst			1	(10%)	3	(16%)
Pars distalis, hyperplasia	8	(100%)	6	(60%)	16	(84%)
Pars nervosa, cyst					1	(5%)
Pars nervosa, hyperplasia					1	(5%)
Thyroid gland	(10)		(10)		(20)	
Ultimobranchial cyst			1	(10%)	1	(5%)
C-cell, hyperplasia	1	(10%)	1	(10%)	1	(5%)
General Body System						
None						
Genital System						
Epididymis	(10)		(10)		(20)	
Inflammation, chronic					1	(5%)
Vacuolization cytoplasmic			1	(10%)		
Preputial gland	(9)		(10)		(19)	
Inflammation, chronic	5	(56%)	2	(20%)	6	(32%)
Inflammation, chronic active	4	(44%)	7	(70%)	9	(47%)
Prostate	(10)		(10)		(20)	
Inflammation, acute	1	(10%)	4	(40%)	5	(25%)
Inflammation, chronic					1	(5%)
Inflammation, chronic active	6	(60%)	4	(40%)	6	(30%)
Epithelium, hyperplasia					1	(5%)
Testes	(10)		(10)		(20)	
Abscess			1	(10%)		
Abscess, chronic					1	(5%)
Inflammation, chronic					2	(10%)
Interstitial cell, hyperplasia	10	(100%)	8	(80%)	17	(85%)
Seminiferous tubule, atrophy	2	(20%)	3	(30%)	7	(35%)
Seminiferous tubule, mineralization			2	(20%)		

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Hematopoietic System						
Bone marrow	(10)		(10)		(20)	
Myelofibrosis			1	(10%)		
Lymph node			(2)		(3)	
Mediastinal, hemorrhage			1	(50%)	2	(67%)
Pancreatic, hemorrhage			1	(50%)		
Pancreatic, infiltration cellular, histiocyte			1	(50%)	2	(67%)
Pancreatic, pigmentation					2	(67%)
Lymph node, mandibular	(10)		(8)		(17)	
Hemorrhage	3	(30%)	1	(13%)	3	(18%)
Hyperplasia, plasma cell					1	(6%)
Infiltration cellular, histiocyte					1	(6%)
Pigmentation					1	(6%)
Lymph node, mesenteric	(10)		(9)		(20)	
Depletion lymphoid	1	(10%)				
Hemorrhage	1	(10%)			1	(5%)
Infiltration cellular, histiocyte	10	(100%)	9	(100%)	20	(100%)
Pigmentation	9	(90%)	7	(78%)	15	(75%)
Spleen				(20)		
Depletion lymphoid					1	(5%)
Thymus	(10)		(9)		(16)	
Cyst	1	(10%)				
Depletion lymphoid			4	(44%)	12	(75%)
Integumentary System						
Mammary gland	(4)		(7)		(10)	
Hyperplasia	2	(50%)	7	(100%)	9	(90%)
Skin					(19)	
Inflammation, chronic					1	(5%)
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(10)		(10)		(20)	
Infiltration cellular, histiocyte	2	(20%)	2	(20%)	7	(35%)
Alveolar epithelium, hyperplasia	3	(30%)			1	(5%)
Alveolus, mineralization	1	(10%)			1	(5%)
Artery, mineralization	8	(80%)	7	(70%)	9	(45%)

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Respiratory System (continued)						
Nose	(10)		(10)		(20)	
Glands, inflammation, acute	3	(30%)	3	(30%)	7	(35%)
Glands, inflammation, chronic active	1	(10%)			3	(15%)
Lumen, inflammation, acute			1	(10%)		
Nasolacrimal duct, inflammation, chronic active	1	(10%)				
Respiratory epithelium, metaplasia, squamous					1	(5%)
Special Senses System						
Eye					(1)	
Conjunctiva, inflammation, chronic active					1	(100%)
Cornea, fibrosis					1	(100%)
Cornea, neovascularization					1	(100%)
Urinary System						
Kidney	(10)		(10)		(20)	
Autolysis					1	(5%)
Cyst			1	(10%)		
Nephropathy	10	(100%)	10	(100%)	20	(100%)
Renal tubule, hyperplasia			1	(10%)	1	(5%)
Renal tubule, inflammation, chronic active					1	(5%)
Renal tubule, pigmentation			9	(90%)	20	(100%)
Transitional epithelium, hyperplasia			1	(10%)	11	(55%)
Urinary bladder	(10)		(10)		(19)	
Inflammation, chronic					1	(5%)
Fat, proliferation					1	(5%)
Muscularis, mineralization					1	(5%)
Transitional epithelium, hyperplasia					9	(47%)

[a] Number of animals examined microscopically at site and number of animals with lesion (includes interim and moribund animals)
[b] Controls from the 9-month interim evaluation of the 2-year core study were used for comparison.
[c] Controls from the 15-month interim evaluation of the 2-year core study were used for comparison.

APPENDIX F
SUMMARY OF LESIONS IN FEMALE RATS IN THE STOP-EXPOSURE EVALUATION OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Disposition Summary			
Animals initially in study	70	10	30
9-Month interim evaluation	10		10
Early deaths			
Moribund		1	5
Natural deaths			3
Survivors		9	11
Missexed			1
Animals examined microscopically	10	10	18[b]
9-Month Interim Evaluation[c]			
Alimentary System			
Liver	(10)		(10)
Hepatocellular carcinoma			1 (10%)
Hepatocellular adenoma			2 (20%)
Endocrine System			
Pituitary gland	(10)		(10)
Pars distalis, adenoma			1 (10%)
Urinary System			
Kidney	(10)		(10)
Adenoma			1 (10%)
Systems Examined With No Neoplasms Observed			
Cardiovascular System			
General Body System			
Genital System			
Hematopoietic System			
Integumentary System			
Musculoskeletal System			
Nervous System			
Respiratory System			
Special Senses System			
15-Month Evaluation[d]			
Alimentary System			
Intestine large, rectum	(10)	(10)	(17)
Polyp adenomatous		5 (50%)	2 (12%)
Polyp adenomatous, multiple			1 (6%)

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Alimentary System (continued)						
Liver	(10)		(10)		(18)	
Hepatocellular carcinoma			3	(30%)	7	(39%)
Hepatocellular carcinoma, multiple			3	(30%)	8	(44%)
Hepatocellular adenoma			5	(50%)	3	(17%)
Hepatocellular adenoma, multiple			1	(10%)	7	(39%)
Cardiovascular System						
None						
Endocrine System						
Pituitary gland	(10)		(10)		(18)	
Pars distalis, adenoma	2	(20%)	2	(20%)	1	(6%)
Thyroid gland	(10)		(10)		(18)	
Adenoma			1	(10%)		
General Body System						
None						
Genital System						
Uterus	(10)		(10)		(18)	
Polyp stromal	1	(10%)	1	(10%)	1	(6%)
Hematopoietic System						
None						
Integumentary System						
Mammary gland	(7)		(7)			
Fibroadenoma	1	(14%)				
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(10)		(10)		(18)	
Hepatocellular carcinoma, metastatic, liver			1	(10%)	1	(6%)

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
15-Month Evaluation (continued)			
Special Senses System			
None			
Urinary System			
Kidney	(10)	(10)	(18)
Renal tubule, adenoma		3 (30%)	1 (6%)
Renal tubule, adenoma, multiple			1 (6%)
Urinary bladder	(10)	(10)	(18)
Squamous cell, carcinoma			4 (22%)
Squamous cell, papilloma			1 (6%)
Transitional epithelium, carcinoma			1 (6%)
Transitional epithelium, papilloma			1 (6%)
Neoplasm Summary			
Total animals with primary neoplasms[e]	2	9	17
Total primary neoplasms	4	25	39
Total animals with benign neoplasms	2	9	13
Total benign neoplasms	4	18	19
Total animals with malignant neoplasms		6	16
Total malignant neoplasms		7	20
Total animals with metastatic neoplasms		1	1
Total metastatic neoplasms		1	1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm (includes interim and moribund animals)
[b] One animal not examined microscopically
[c] Controls from the 9-month interim evaluation of the 2-year core study were used for comparison.
[d] Controls from the 15-month interim evaluation of the 2-year core study were used for comparison.
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE F2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 15-Month Interim Evaluation Control Group versus 9-Month and 15-Month 20,000 ppm Groups at the 15-Month Evaluation

	0 ppm (15-month interim evaluation)	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Kidney (Renal Tubule): Adenoma			
Overall rate[a]	0/10 (0%)	3/10 (30%)	2/18 (11%)
Adjusted rate[b]	0.0%	40.7%	24.2%
Interim evaluation	0/10 (0%)	3/9 (33%)	2/11 (18%)
First incidence (days)	–[d]	462 (I)	462 (I)
Life table test[c]	P=0.189	P=0.093	P=0.256
Logistic regression test[c]	P=0.189	P=0.093	P=0.256
Cochran-Armitage test[c]	P=0.345		
Fisher exact test[c]		P=0.105	P=0.405
Large Intestine (Rectum): Adenomatous Polyp			
Overall rate	0/10 (0%)	5/10 (50%)	3/18 (17%)
Adjusted rate	0.0%	61.1%	20.5%
Interim evaluation	0/10 (0%)	5/9 (56%)	1/11 (9%)
First incidence (days)	–	462 (I)	306
Life table test	P=0.136	P=0.015	P=0.186
Logistic regression test	P=0.320	P=0.015	P=0.367
Cochran-Armitage test	P=0.266		
Fisher exact test		P=0.016	P=0.249
Liver: Hepatocellular Adenoma			
Overall rate	0/10 (0%)	6/10 (60%)	10/18 (56%)
Adjusted rate	0.0%	65.0%	100.0%
Interim evaluation	0/10 (0%)	5/9 (56%)	9/11 (82%)
First incidence (days)	–	456	306
Life table test	P<0.001	P=0.009	P<0.001
Logistic regression test	P=0.002	P=0.015	P=0.003
Cochran-Armitage test	P=0.005		
Fisher exact test		P=0.005	P=0.003
Liver: Hepatocellular Carcinoma			
Overall rate	0/10 (0%)	6/10 (60%)	15/18 (83%)
Adjusted rate	0.0%	66.7%	100.0%
Interim evaluation	0/10 (0%)	6/9 (67%)	11/11 (100%)
First incidence (days)	–	462 (I)	426
Life table test	P<0.001	P=0.005	P<0.001
Logistic regression test	P<0.001	P=0.005	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.005	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	0/10 (0%)	8/10 (80%)	16/18 (89%)
Adjusted rate	0.0%	80.0%	100.0%
Interim evaluation	0/10 (0%)	7/9 (78%)	11/11 (100%)
First incidence (days)	–	456	306
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.002	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001

TABLE F2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 15-Month Interim Evaluation Control Group versus 9-Month and 15-Month 20,000 ppm Groups at the 15-Month Evaluation (continued)

	0 ppm (15-month interim evaluation)	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	2/10 (20%)	2/10 (20%)	1/18 (6%)
Adjusted rate	20.0%	25.0%	8.3%
Interim evaluation	2/10 (20%)	1/9 (11%)	0/11 (0%)
First incidence (days)	462 (I)	456	461
Life table test	P=0.387N	P=0.670	P=0.456N
Logistic regression test	P=0.319N	P=0.539N	P=0.427N
Cochran-Armitage test	P=0.222N		
Fisher exact test		P=0.709N	P=0.284N
Urinary Bladder: Papilloma			
Overall rate	0/10 (0%)	0/10 (0%)	2/18 (11%)
Adjusted rate	0.0%	0.0%	22.2%
Interim evaluation	0/10 (0%)	0/9 (0%)	1/11 (9%)
First incidence (days)	–	–	426
Life table test	P=0.174		P=0.295
Logistic regression test	P=0.215		P=0.357
Cochran-Armitage test	P=0.220		
Fisher exact test			P=0.405
Urinary Bladder: Carcinoma			
Overall rate	0/10 (0%)	1/10 (10%)	5/18 (28%)
Adjusted rate	0.0%	11.1%	48.7%
Interim evaluation	0/10 (0%)	1/9 (11%)	4/11 (36%)
First incidence (days)	–	462 (I)	299
Life table test	P=0.022	P=0.479	P=0.044
Logistic regression test	P=0.061	P=0.479	P=0.105
Cochran-Armitage test	P=0.051		
Fisher exact test		P=0.500	P=0.087
All Organs: Benign Neoplasms			
Overall rate	2/10 (20%)	9/10 (90%)	13/18 (72%)
Adjusted rate	20.0%	90.0%	100.0%
Interim evaluation	2/10 (20%)	8/9 (89%)	10/11 (91%)
First incidence (days)	462 (I)	456	306
Life table test	P<0.001	P=0.004	P<0.001
Logistic regression test	P=0.001	P=0.007	P=0.004
Cochran-Armitage test	P=0.008		
Fisher exact test		P=0.003	P=0.011
All Organs: Malignant Neoplasms			
Overall rate	0/10 (0%)	6/10 (60%)	16/18 (89%)
Adjusted rate	0.0%	66.7%	100.0%
Interim evaluation	0/10 (0%)	6/9 (67%)	11/11 (100%)
First incidence (days)	–	462 (I)	299
Life table test	P<0.001	P=0.005	P<0.001
Logistic regression test	P<0.001	P=0.005	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.005	P<0.001

TABLE F2a
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 15-Month Interim Evaluation Control Group versus 9-Month and 15-Month 20,000 ppm Groups at the 15-Month Evaluation (continued)

	0 ppm (15-month interim evaluation)	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
All Organs: Benign or Malignant Neoplasms			
Overall rate	2/10 (20%)	9/10 (90%)	17/18 (94%)
Adjusted rate	20.0%	90.0%	100.0%
Interim evaluation	2/10 (20%)	8/9 (89%)	11/11 (100%)
First incidence (days)	462	456	299
Life table test	P<0.001	P=0.004	P<0.001
Logistic regression test	P<0.001	P=0.007	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.003	P<0.001

(I) Interim evaluation
[a] Number of lesion-bearing animals/number of animals examined (includes interim and moribund animals). Denominator is number of animals examined microscopically for kidney, liver, pituitary 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] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table analysis 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 an exposure group is indicated by **N**.
[d] Not applicable; no neoplasms in animal group

TABLE F2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 9-Month 20,000 ppm Stop-Exposure Group versus 15-Month 20,000 ppm Exposure Group at the 15-Month Evaluation

	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Kidney (Renal Tubule): Adenoma		
Overall rates[a]	3/10 (30%)	2/18 (11%)
Adjusted rates[b]	40.7%	24.2%
Interim evaluation	3/9 (33%)	2/11 (18%)
First incidence (days)	462 (I)	462 (I)
Life table tests[c]		P=0.400N
Logistic regression tests[c]		P=0.400N
Fisher exact test[c]		P=0.228N
Large Intestine (Rectum): Adenomatous Polyp		
Overall rates	5/10 (50%)	3/18 (17%)
Adjusted rates	61.1%	20.5%
Interim evaluation	5/9 (56%)	1/11 (9%)
First incidence (days)	462 (I)	306
Life table tests		P=0.209N
Logistic regression tests		P=0.057N
Fisher exact test		P=0.077N
Liver: Hepatocellular Adenoma		
Overall rates	6/10 (60%)	10/18 (56%)
Adjusted rates	65.0%	100.0%
Interim evaluation	5/9 (56%)	9/11 (82%)
First incidence (days)	456	306
Life table tests		P=0.305
Logistic regression tests		P=0.595
Fisher exact test		P=0.570N
Liver: Hepatocellular Carcinoma		
Overall rates	6/10 (60%)	15/18 (83%)
Adjusted rates	66.7%	100.0%
Interim evaluation	6/9 (67%)	11/11 (100%)
First incidence (days)	462 (I)	426
Life table tests		P=0.014
Logistic regression tests		P=0.010
Fisher exact test		P=0.181
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rates	8/10 (80%)	16/18 (89%)
Adjusted rates	80.0%	100.0%
Interim evaluation	7/9 (78%)	11/11 (100%)
First incidence (days)	456	306
Life table tests		P=0.063
Logistic regression tests		P=0.126
Fisher exact test		P=0.452

TABLE F2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 9-Month 20,000 ppm Stop-Exposure Group versus 15-Month 20,000 ppm Exposure Group at the 15-Month Evaluation (continued)

	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
Pituitary Gland (Pars Distalis): Adenoma		
Overall rates	2/10 (20%)	1/18 (6%)
Adjusted rates	25.0%	8.3%
Interim evaluation	1/9 (11%)	0/11 (0%)
First incidence (days)	456	461
Life table tests		P=0.423N
Logistic regression tests		P=0.385N
Fisher exact test		P=0.284N
Urinary Bladder: Papilloma		
Overall rates	0/10 (0%)	2/18 (11%)
Adjusted rates	0.0%	22.2%
Interim evaluation	0/9 (0%)	1/11 (9%)
First incidence (days)	–[d]	426
Life table tests		P=0.308
Logistic regression tests		P=0.357
Fisher exact test		P=0.405
Urinary Bladder: Carcinoma		
Overall rates	1/10 (10%)	5/18 (28%)
Adjusted rates	11.1%	48.7%
Interim evaluation	1/9 (11%)	4/11 (36%)
First incidence (days)	462 (I)	299
Life table tests		P=0.154
Logistic regression tests		P=0.292
Fisher exact test		P=0.277
All Organs: Benign Neoplasms		
Overall rates	9/10 (90%)	13/18 (72%)
Adjusted rates	90.0%	100.0%
Interim evaluation	8/9 (89%)	10/11 (91%)
First incidence (days)	456	306
Life table tests		P=0.412
Logistic regression tests		P=0.539N
Fisher exact test		P=0.277N
All Organs: Malignant Neoplasms		
Overall rates	6/10 (60%)	16/18 (89%)
Adjusted rates	66.7%	100.0%
Interim evaluation	6/9 (67%)	11/11 (100%)
First incidence (days)	462 (I)	299
Life table tests		P=0.010
Logistic regression tests		P=0.015
Fisher exact test		P=0.098

TABLE F2b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone: 9-Month 20,000 ppm Stop-Exposure Group versus 15-Month 20,000 ppm Exposure Group at the 15-Month Evaluation (continued)

	20,000 ppm (9-month stop-exposure)	20,000 ppm (15-month exposure)
All Organs: Benign or Malignant Neoplasms		
Overall rates	9/10 (90%)	17/18 (94%)
Adjusted rates	90.0%	100.0%
Interim evaluation	8/9 (89%)	11/11 (100%)
First incidence (days)	456	299
Life table tests		P=0.082
Logistic regression tests		P=0.396
Fisher exact test		P=0.595

(I) Interim evaluation
[a] Number of lesion-bearing animals/number of animals examined (includes interim and moribund animals). Denominator is number of animals examined microscopically for kidney, liver, pituitary 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] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between both exposed groups. The life table analysis 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 an exposure group is indicated by **N**.
[d] Not applicable; no neoplasms in animal group

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
Disposition Summary						
Animals initially in study	70		10		30	
9-Month interim evaluation	10				10	
Early deaths						
Moribund			1		5	
Natural deaths					3	
Survivors			9		11	
Missexed					1	
Animals examined microscopically	10		10		18[b]	
9-Month Interim Evaluation[c]						
Alimentary System						
Intestine large, colon	(10)				(10)	
Parasite metazoan	1	(10%)				
Intestine large, rectum	(10)				(10)	
Parasite metazoan	2	(20%)				
Intestine large, cecum	(10)				(10)	
Liver	(10)				(10)	
Angiectasis					2	(20%)
Basophilic focus	1	(10%)			3	(30%)
Clear cell focus					1	(10%)
Fatty change					7	(70%)
Inflammation, chronic active	2	(20%)				
Necrosis, coagulative					8	(80%)
Pigmentation					10	(100%)
Bile duct, hyperplasia	1	(10%)			9	(90%)
Periportal, inflammation, chronic active	6	(60%)			10	(100%)
Pancreas	(10)				(10)	
Atrophy	1	(10%)			2	(20%)
Infiltration cellular, mononuclear cell	3	(30%)			4	(40%)
Salivary glands	(10)				(10)	
Stomach, forestomach	(10)				(10)	
Muscularis, mineralization					1	(10%)
Stomach, glandular	(10)				(10)	
Muscularis, mineralization	1	(10%)			1	(10%)
Cardiovascular System						
Heart	(10)				(10)	
Cardiomyopathy	7	(70%)			5	(50%)
Endocrine System						
Adrenal cortex	(10)				(10)	
Capsule, fibrosis	1	(10%)				
Capsule, inflammation, chronic	1	(10%)				

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
9-Month Interim Evaluation (continued)						
Endocrine System (continued)						
Pituitary gland	(10)				(10)	
Pars distalis, angiectasis					1	(10%)
Pars distalis, cyst	2	(20%)			3	(30%)
Pars distalis, hemorrhage	1	(10%)				
Pars distalis, hyperplasia	1	(10%)				
Pars intermedia, cyst	1	(10%)			1	(10%)
Thyroid gland	(10)				(10)	
Infiltration cellular, mononuclear cell	1	(10%)				
Genital System						
Clitoral gland	(10)				(9)	
Infiltration cellular, mononuclear cell	1	(10%)				
Inflammation, chronic	3	(30%)			1	(11%)
Inflammation, chronic active	2	(20%)			2	(22%)
Ovary	(10)				(10)	
Periovarian tissue					1	(10%)
Uterus	(10)				(10)	
Hydrometra	1	(10%)			1	(10%)
Hematopoietic System						
Lymph node	(3)				(5)	
Mediastinal, hemorrhage	3	(100%)				
Mediastinal, pigmentation					3	(60%)
Pancreatic, infiltration cellular, histiocyte					4	(80%)
Pancreatic, pigmentation					5	(100%)
Lymph node, mandibular	(9)				(10)	
Hemorrhage	7	(78%)			2	(20%)
Hyperplasia					1	(10%)
Infiltration cellular, histiocyte					1	(10%)
Lymph node, mesenteric	(10)				(10)	
Hemorrhage					5	(50%)
Infiltration cellular, histiocyte	10	(100%)			10	(100%)
Pigmentation					1	(10%)
Spleen	(10)				(10)	
Congestion					1	(10%)
Thymus	(10)				(9)	
Congestion	1	(10%)				
Hemorrhage	1	(10%)			2	(22%)
Respiratory System						
Lung	(10)				(10)	
Infiltration cellular, histiocyte	1	(10%)			5	(50%)
Artery, mineralization	4	(40%)			2	(20%)

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Evaluaton of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
9-Month Interim Evaluation (continued)						
Special Senses System						
Eye					(1)	
Anterior chamber, inflammation, acute					1	(100%)
Posterior chamber, inflammation, acute					1	(100%)
Retina, degeneration					1	(100%)
Harderian gland					(1)	
Hyperplasia					1	(100%)
Urinary System						
Kidney	(10)				(10)	
Fibrosis, focal					1	(10%)
Hydronephrosis	1	(10%)				
Infiltration cellular, mononuclear cell					7	(70%)
Inflammation, chronic	4	(40%)				
Mineralization	3	(30%)			1	(10%)
Mineralization, focal					1	(10%)
Renal tubule, pigmentation					10	(100%)
Renal tubule, regeneration	4	(40%)			7	(70%)
Transitional epithelium, mineralization	1	(10%)				
Urinary bladder	(10)				(10)	
Transitional epithelium, hyperplasia					4	(40%)
Systems Examined With No Lesions Observed						
General Body System						
Integumentary System						
Musculoskeletal System						
Nervous System						
15-Month Evaluation[d]						
Alimentary System						
Intestine large, colon	(10)		(10)		(18)	
Parasite metazoan	2	(20%)	1	(10%)		
Intestine large, rectum	(10)		(10)		(17)	
Parasite metazoan			1	(10%)		
Intestine large, cecum	(10)		(10)		(18)	
Parasite metazoan	2	(20%)	2	(20%)		

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Alimentary System (continued)						
Liver	(10)		(10)		(18)	
Basophilic focus	8	(80%)	6	(60%)	13	(72%)
Clear cell focus			5	(50%)	13	(72%)
Cyst			1	(10%)		
Cytomegaly			1	(10%)	2	(11%)
Cytoplasmic alteration			1	(10%)		
Eosinophilic focus	2	(20%)	2	(20%)	3	(17%)
Fatty change					10	(56%)
Hematopoietic cell proliferation					1	(6%)
Hepatodiaphragmatic nodule	2	(20%)				
Inflammation, chronic, granulomatous	6	(60%)	2	(20%)	1	(6%)
Inflammation, chronic active	1	(10%)			1	(6%)
Mixed cell focus			2	(20%)	3	(17%)
Necrosis, coagulative	1	(10%)			4	(22%)
Pigmentation	1	(10%)	10	(100%)	17	(94%)
Bile duct, hyperplasia	7	(70%)	10	(100%)	18	(100%)
Periportal, inflammation, chronic	10	(100%)	9	(90%)	11	(61%)
Periportal, inflammation, chronic active			1	(10%)	7	(39%)
Mesentery					(1)	
Inflammation, chronic, granulomatous					1	(100%)
Necrosis, coagulative					1	(100%)
Pancreas	(10)		(10)		(18)	
Atrophy	1	(10%)	3	(30%)	3	(17%)
Ectopic tissue	1	(10%)			1	(6%)
Inflammation, chronic	9	(90%)	6	(60%)	6	(33%)
Inflammation, chronic, active					2	(11%)
Salivary glands	(10)		(10)		(18)	
Duct, submandibular gland, dilatation					1	(6%)
Parotid gland, atrophy					1	(6%)
Parotid gland, inflammation, chronic					2	(11%)
Parotid gland, inflammation, chronic active					2	(11%)
Submandibular gland, atrophy					1	(6%)
Submandibular gland, inflammation, chronic					1	(6%)
Submandibular gland, inflammation, chronic active					5	(28%)
Submandibular gland, metaplasia, squamous					2	(11%)
Submandibular gland, pigmentation					1	(6%)
Stomach, forestomach	(10)		(10)		(18)	
Acanthosis					1	(6%)
Erosion					1	(6%)
Hyperkeratosis					1	(6%)
Hyperplasia, basal cell					6	(33%)
Hyperplasia, squamous					2	(11%)
Ulcer					1	(6%)
Stomach, glandular	(10)		(10)		(18)	
Inflammation, chronic					1	(6%)
Mineralization			1	(10%)		
Artery, mineralization					1	(6%)
Muscularis, mineralization	1	(10%)			1	(6%)

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Cardiovascular System						
Blood vessel			(1)			
Aorta, inflammation, chronic			1	(100%)		
Heart	(10)		(10)		(18)	
Cardiomyopathy	10	(100%)	10	(100%)	13	(72%)
Endocrine System						
Adrenal cortex	(10)		(10)		(17)	
Angiectasis	5	(50%)	2	(20%)	3	(18%)
Hyperplasia			1	(10%)		
Vacuolization, cytoplasmic					1	(6%)
Adrenal medulla	(10)		(10)		(17)	
Hyperplasia			1	(10%)	2	(12%)
Parathyroid gland	(10)		(10)		(15)	
Hyperplasia			1	(10%)		
Pituitary gland	(10)		(10)		(18)	
Pars distalis, angiectasis			5	(50%)		
Pars distalis, cyst	8	(80%)	6	(60%)	8	(44%)
Pars distalis, hyperplasia	1	(10%)			2	(11%)
Pars intermedia, cyst	3	(30%)	1	(10%)	3	(17%)
Thyroid gland	(10)		(10)			
C-cell, hyperplasia	4	(40%)				
General Body System						
None						
Genital System						
Clitoral gland	(10)		(10)		(18)	
Cyst					1	(6%)
Inflammation, chronic	7	(70%)	6	(60%)	3	(17%)
Inflammation, chronic active	1	(10%)	1	(10%)	8	(44%)
Ovary					(18)	
Periovarian tissue, cyst					3	(17%)
Uterus	(10)		(10)		(18)	
Hydrometra	2	(20%)	2	(20%)	5	(28%)
Inflammation, chronic active					1	(6%)
Endometrium, hyperplasia	1	(10%)	1	(10%)	1	(6%)
Submucosa, hyperplasia					1	(6%)
Hematopoietic System						
Lymph node	(1)		(1)		(4)	
Mediastinal, hemorrhage	1	(100%)	1	(100%)		
Mediastinal, pigmentation	1	(100%)				
Pancreatic, infiltration cellular, histiocyte			1	(100%)	4	(100%)
Pancreatic, pigmentation			1	(100%)	2	(50%)

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Hematopoietic System (continued)						
Lymph node, mandibular	(7)		(9)		(17)	
Hemorrhage	1	(14%)	3	(33%)	1	(6%)
Infiltration cellular, hystiocyte					6	(35%)
Lymph node, mesenteric	(10)		(9)		(18)	
Depletion lymphoid					1	(6%)
Hemorrhage			2	(22%)		
Infiltration cellular, histiocyte	10	(100%)	9	(100%)	18	(100%)
Pigmentation	10	(100%)	8	(89%)	11	(61%)
Spleen					(18)	
Fibrosis					1	(6%)
Thymus (10)		(10)		(13)		
Cyst	1	(10%)				
Depletion lymphoid			1	(10%)	6	(46%)
Hemorrhage			1	(10%)		
Integumentary System						
Mammary gland	(7)		(7)		(14)	
Hyperplasia	6	(86%)	4	(57%)	5	(36%)
Musculoskeletal System						
Bone	(10)		(10)			
Osteopetrosis	1	(10%)				
Nervous System						
None						
Respiratory System						
Lung	(10)		(10)		(18)	
Congestion			1	(10%)		
Hemorrhage	1	(10%)				
Infiltration cellular, histiocyte	6	(60%)	7	(70%)	12	(67%)
Inflammation, chronic active					1	(6%)
Alveolus, mineralization	1	(10%)				
Artery, mineralization	4	(40%)	5	(50%)	10	(56%)
Nose	(10)		(10)		(18)	
Inflammation, chronic active					2	(11%)
Submucosa, inflammation, chronic	1	(10%)				
Special Senses System						
None						

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm		20,000 ppm (9-month stop-exposure)		20,000 ppm (15-month exposure)	
15-Month Evaluation (continued)						
Urinary System						
Kidney	(10)		(10)		(18)	
Fibrosis					1	(6%)
Inflammation, chronic active					1	(6%)
Nephropathy	10	(100%)	10	(100%)	18	(100%)
Papilla, necrosis, coagulative					2	(11%)
Pelvis, inflammation, chronic active					1	(6%)
Renal tubule, hyperplasia			2	(20%)	2	(11%)
Renal tubule, inflammation, chronic active			1	(10%)		
Renal tubule, mineralization	1	(10%)				
Renal tubule, pigmentation			10	(100%)	18	(100%)
Transitional epithelium, hyperplasia	3	(30%)	1	(10%)	5	(28%)
Transitional epithelium, mineralization	2	(20%)	1	(10%)		
Urinary bladder	(10)		(10)		(18)	
Hemorrhage					4	(22%)
Necrosis					1	(6%)
Fat, proliferation					2	(11%)
Transitional epithelium, hyperplasia			4	(40%)	17	(94%)
Transitional epithelium, metaplasia, squamous					3	(17%)

[a] Number of animals examined microscopically at site and number of animals with lesion (includes interim and moribund animals)
[b] One animal not examined microscopically
[c] Controls from the 9-month interim evaluation of the 2-year core study were used for comparison.
[d] Controls from the 15-month interim evaluation of the 2-year core study were used for comparison.

APPENDIX G
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). 1-Amino-2,4-dibromoanthraquinone was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of five doses of 1-amino-2,4-dibromoanthraquinone. The high dose was limited to 10,000 µg/plate. All positive trials were repeated under the conditions that elicited the positive response. If no positive responses were seen, all negative trials 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 that is not dose related, not reproducible, or is 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. There was no minimum percentage or fold increase required for a chemical to the judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Loveday *et al.* (1990). 1-Amino-2,4-dibromoanthraquinone was sent to each of two testing laboratories as a coded aliquot by Radian Corporation. The aliquots were 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 1-amino-2,4-dibromoanthraquinone. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with 1-amino-2,4-dibromoanthraquinone in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing 1-amino-2,4-dibromoanthraquinone 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 1-amino-2,4-dibromoanthraquinone, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no 1-amino-2,4-dibromoanthraquinone and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Usually, 50 second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. The high dose was limited by toxicity.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). 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. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P \leq 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with 1-amino-2,4-dibromoanthraquinone for 8 to 10 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 1-amino-2,4-dibromoanthraquinone and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 10 to 11 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The high dose was limited to 100 µg/mL.

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. Two hundred first-division metaphase cells were scored at each dose level. 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).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) are considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

RESULTS

1-Amino-2,4-dibromoanthraquinone (100 to 10,000 µg/plate) was tested for induction of gene mutations in four strains of *Salmonella typhimurium* in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table G1; Haworth *et al.*, 1983). 1-Amino-2,4-dibromoanthraquinone was positive in the absence of S9 in the frameshift strains TA98 and TA1537; with S9, an equivocal response was obtained in TA1537, and TA98 was negative. In TA100, 1-amino-2,4-dibromoanthraquinone gave equivocal responses with and without S9, and all trials were negative in TA1535. The equivocal calls were the results of positive or weakly positive responses that were not duplicated in a second trial. Precipitation of 1-amino-2,4-dibromoanthraquinone occurred at concentrations of 100 µg/plate and above, and this may have been a factor in the nonreproducibility of the results.

1-Amino-2,4-dibromoanthraquinone was tested in two laboratories for induction of SCEs and Abs in cultured CHO cells, with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9. In the SCE test, Environmental Health Research & Testing observed a significant increase in SCEs only in the absence of S9, while Bioassay Systems Corporation recorded positive responses with and without S9 (Table G2; Loveday *et al.*, 1990). The discrepancy with S9 cannot be explained by a difference in dose levels employed at the two laboratories because positive responses were seen at 3, 10, 15, and 30 µg/mL at Bioassay Systems Corporation, whereas negative trials resulted from testing doses up to 100 µg/mL at

Environmental Health Research & Testing. In the Abs test, Environmental Health Research & Testing observed a weakly positive response only in the absence of S9 (Table G3). Bioassay Systems Corporation obtained a positive response in the first trial without S9 but did not duplicate the positive response in the second trial (Table G3), and the overall call without S9 was concluded to be equivocal (Loveday *et al.*, 1990). Neither laboratory observed an increase in Abs with 1-amino-2,4-dibromoanthraquinone in the presence of S9.

TABLE G1
Mutagenicity of 1-Amino-2,4-dibromoanthraquinone in *Salmonella typhimurium*[a]

Strain	Dose μg/plate	Revertants/plate[b] −S9 Trial 1	−S9 Trial 2	+10 hamster S9 Trial 1	+10 hamster S9 Trial 2	+10 rat S9 Trial 1	+10 rat S9 Trial 2
TA100	0	119 ± 4.2	170 ± 2.6	112 ± 6.7	138 ± 10.6	121 ± 7.8	156 ± 12.0
	100	115 ± 5.0	146 ± 6.2[c]	143 ± 11.8	157 ± 10.2	202 ± 8.0	182 ± 3.5
	333	136 ± 7.5[c]	140 ± 13.0[c]	136 ± 2.9[c]	218 ± 11.8	194 ± 3.8[c]	184 ± 10.7
	1,000	154 ± 6.4[c]	177 ± 6.4[c]	151 ± 8.5[c]	209 ± 7.2[c]	191 ± 4.4[c]	181 ± 9.1[c]
	3,333	158 ± 6.2c	184 ± 8.8[c]	190 ± 18.4[c]	194 ± 12.9[c]	185 ± 7.8[c]	159 ± 5.4[c]
	10,000	218 ± 24.5c	233 ± 27.0[c]	178 ± 12.5[c]	215 ± 10.7[c]	205 ± 14.0[c]	184 ± 11.0[c]
Trial summary		Weakly Positive	Equivocal	Weakly Positive	Equivocal	Equivocal	Negative
Positive control[d]		420 ± 7.0	365 ± 4.7	1,027 ± 43.5	1,978 ± 31.5	612 ± 14.7	1,703 ± 202.1
TA1535	0	29 ± 0.9	26 ± 6.4	11 ± 1.8	16 ± 0.6	13 ± 0.6	16 ± 0.9
	100	22 ± 2.1	25 ± 3.8[c]	9 ± 2.3	14 ± 2.7	11 ± 3.0	13 ± 2.7
	333	27 ± 1.5[c]	22 ± 3.1[c]	10 ± 0.9[c]	11 ± 0.9	13 ± 1.7[c]	16 ± 3.0
	1,000	28 ± 5.6[c]	30 ± 7.6[c]	13 ± 2.1[c]	14 ± 0.7[c]	8 ± 1.5[c]	12 ± 1.9[c]
	3,333	25 ± 3.5[c]	30 ± 3.5[c]	11 ± 1.7[c]	14 ± 3.0[c]	10 ± 2.0[c]	13 ± 2.4[c]
	10,000	26 ± 6.0[c]	25 ± 5.0[c]	10 ± 2.3[c]	11 ± 0.9[c]	7 ± 1.5[c]	11 ± 0.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		554 ± 6.7	359 ± 12.5	377 ± 16.4	606 ± 23.6	346 ± 24.7	528 ± 24.8
TA1537	0	5 ± 0.7	5 ± 1.2	9 ± 1.8	16 ± 2.1	8 ± 1.0	12 ± 3.2
	100	11 ± 1.2	9 ± 1.2[c]	8 ± 0.9	13 ± 3.2	10 ± 1.2	12 ± 2.5
	333	11 ± 0.6[c]	8 ± 1.2[c]	15 ± 2.0[c]	13 ± 1.2	16 ± 2.7[c]	19 ± 4.5
	1,000	13 ± 1.8[c]	8 ± 1.2[c]	17 ± 2.7[c]	12 ± 2.6[c]	20 ± 1.7[c]	18 ± 2.5[c]
	3,333	19 ± 5.3[c]	17 ± 2.3[c]	21 ± 2.9[c]	21 ± 2.1[c]	24 ± 3.8[c]	19 ± 2.7[c]
	10,000	28 ± 0.7[c]	32 ± 0.9[c]	30 ± 3.0[c]	27 ± 4.0[c]	28 ± 0.3[c]	30 ± 3.5[c]
Trial summary		Positive	Positive	Positive	Negative	Positive	Equivocal
Positive control		141 ± 3.2	147 ± 18.7	324 ± 8.8	367 ± 4.4	234 ± 14.0	308 ± 36.0
TA98	0	23 ± 4.9	19 ± 1.5	28 ± 2.0	29 ± 0.7	36 ± 3.3	36 ± 3.2
	100	20 ± 3.2	18 ± 3.6[c]	24 ± 3.2	30 ± 1.8	40 ± 1.5	44 ± 7.4
	333	19 ± 2.1[c]	29 ± 1.5[c]	33 ± 8.3[c]	21 ± 3.2	41 ± 3.5[c]	36 ± 6.1
	1,000	33 ± 1.7[c]	24 ± 4.6[c]	30 ± 4.6[c]	33 ± 3.8[c]	38 ± 4.2[c]	46 ± 3.3[c]
	3,333	46 ± 6.0[c]	37 ± 1.2[c]	43 ± 4.4[c]	47 ± 1.8[c]	38 ± 4.4[c]	50 ± 2.7[c]
	10,000	73 ± 10.6[c]	86 ± 9.5[c]	53 ± 3.8[c]	46 ± 0.7[c]	45 ± 2.9[c]	41 ± 2.9[c]
Trial summary		Positive	Positive	Equivocal	Negative	Negative	Negative
Positive control		536 ± 43.2	591 ± 76.8	1,048 ± 40.5	1,503 ± 69.9	507 ± 21.0	1,080 ± 15.6

[a] The detailed protocol and these data are presented in Haworth *et al*. (1983).
[b] Revertants are presented as mean ± the standard error from three plates.
[c] Precipitate on plate
[d] The positive controls in the absence of metabolic activation were sodium azide (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE G2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 1-Amino-2,4-dibromoanthraquinone[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
Study Performed at Environmental Health Research & Testing								
–S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,049	435	0.41	8.7	26.0	
Mitomycin-C	0.0008	50	1,039	591	0.56	11.8	26.0	37.17
	0.0050	10	210	194	0.92	19.4	26.0	122.77
1-Amino-2,4-dibromoanthraquinone								
	1.6	50	1,043	516	0.49	10.3	26.0	19.30
	5.0	50	1,041	526	0.50	10.5	26.0	21.85*
	16.0	50	1,048	565	0.53	11.3	26.0	30.01*
	50.0	14[c]	290	171	0.58	12.2	26.0	42.19*
					P<0.001[d]			
Trial 2								
Summary: Weakly Positive								
Dimethylsulfoxide		50	1,047	468	0.44	9.4	26.0	
Mitomycin-C	0.0005	50	1,043	574	0.55	11.5	26.0	23.12
	0.0050	10	210	273	1.30	27.3	26.0	190.83
1-Amino-2,4-dibromoanthraquinone								
	1.6	50	1,046	515	0.49	10.3	26.0	10.15
	5.0	50	1,044	538	0.51	10.8	26.0	15.29
	16.0	50	1,047	554	0.52	11.1	26.0	18.38
	50.0	13[c]	267	147	0.55	11.3	26.0	23.17*
					P=0.001			
+S9								
Summary: Negative								
Dimethylsulfoxide		50	1,051	432	0.41	8.6	26.0	
Cyclophosphamide	0.1	50	1,046	546	0.52	10.9	26.0	26.99
	0.6	10	210	193	0.91	19.3	26.0	123.59
1-Amino-2,4-dibromoanthraquinone								
	5.0	50	1,049	412	0.39	8.2	26.0	–4.45
	16.0	50	1,050	465	0.44	9.3	26.0	7.74
	50.0	50	1,040	489	0.47	9.8	26.0	14.39
	100.0	50	1,050	480	0.45	9.6	26.0	11.22
					P=0.003			

* Significant positive response (P≤0.01)
[a] A detailed description of the protocol and these data are presented by Loveday *et al.* (1990). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine.

TABLE G2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 1-Amino-2,4-dibromoanthraquinone (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
Study Performed at Bioassay Systems Corporation								
–S9								
Summary: Weakly Positive								
Dimethylsulfoxide		50	1,046	335	0.32	6.7	26.0	
Mitomycin-C	0.002	50	1,041	567	0.54	11.3	26.0	70.07
	0.010	10	208	243	1.16	24.3	26.0	264.78
1-Amino-2,4-dibromoanthraquinone								
	2.5	50	1,037	355	0.34	7.1	26.0	6.89
	5.0	50	1,040	395	0.37	7.9	26.0	18.59
	10.0	50	1,043	436	0.41	8.7	26.0	30.53*
					P<0.001			
+S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,047	420	0.40	8.4	26.0	
Cyclophosphamide	0.5	50	1,038	642	0.61	12.8	26.0	54.18
	2.5	10	206	291	1.41	29.1	26.0	252.15
1-Amino-2,4-dibromoanthraquinone								
	3.01	50	1,044	528	0.50	10.6	26.0	26.08*
	10.10	50	1,047	581	0.55	11.6	26.0	38.33*
	30.10	50	1,048	597	0.56	11.9	26.0	42.01*
					P<0.001			
Trial 2								
Summary: Weakly Positive								
Dimethylsulfoxide		50	1,032	402	0.38	8.0	26.0	
Cyclophosphamide	0.5	50	1,044	593	0.56	11.9	26.0	45.82
	2.5	10	207	248	1.19	24.8	26.0	207.57
1-Amino-2,4-dibromoanthraquinone								
	7.5	50	1,041	440	0.42	8.8	26.0	8.51
	10.0	50	1,041	452	0.43	9.0	26.0	11.47
	15.0	50	1,043	501	0.48	10.0	26.0	23.31*
					P<0.001			

[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Decreased number of metaphases available for evaluation due to the cytostatic nature of 1-amino-2,4-dibromoanthraquinone
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE G3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 1-Amino-2,4-dibromoanthraquinone[a]

−S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Study Performed at Environmental Health Research & Testing									
Trial 1 – Harvest Time: 12.0 hours Summary: Weakly Positive					Harvest Time: 13.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	3	0.02	1.5		200	4	0.02	2.0
Mitomycin-C					Cyclophosphamide				
0.0625	200	23	0.12	10.0	5.0	200	15	0.08	7.0
0.2500	50	18	0.36	32.0	7.5	50	19	0.38	36.0
1-Amino-2,4-dibromoanthraquinone					1-Amino-2,4-dibromoanthraquinone				
5	200	7	0.04	3.5	16	200	3	0.02	0.5
16	200	9	0.05	4.0	50	200	2	0.01	1.0
50	200	12	0.06	5.5*	100	200	4	0.02	2.0
				P=0.017[b]					P=0.467
Trial 2 – Harvest Time: 12.0 hours Summary: Weakly Positive									
Dimethylsulfoxide									
	200	4	0.02	2.0					
Mitomycin-C									
0.0625	200	25	0.13	12.5					
0.2500	50	21	0.42	36.0					
1-Amino-2,4-dibromoanthraquinone									
16	200	12	0.06	5.0					
30	200	9	0.05	4.5					
50	200	13	0.07	6.0					
				P=0.039					

TABLE G3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 1-Amino-2,4-dibromoanthraquinone (continued)

−S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Study Performed at Bioassay Systems Corporation									
Trial 1 – Harvest Time: 10.5 hours Summary: Positive					Harvest Time: 12.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	0	0.00	0.0		200	4	0.02	2.0
Mitomycin-C					Cyclophosphamide				
1	200	51	0.26	20.5	50	50	25	0.50	34.0
5	50	47	0.94	56.0					
1-Amino-2,4-dibromoanthraquinone					1-Amino-2,4-dibromoanthraquinone				
3.02	200	7	0.04	3.0*	3.02	200	9	0.05	4.0
10.10	200	5	0.03	2.5*	10.10	200	13	0.07	5.5
30.20	200	4	0.02	1.5	30.20	200	7	0.04	3.5
				P=0.164					P=0.153
Trial 2 – Harvest Time: 10.0 hours Summary: Negative									
Dimethylsulfoxide									
	200	5	0.03	2.0					
Mitomycin-C									
1	200	171	0.86	40.5					
5	50	41	0.82	56.0					
1-Amino-2,4-dibromoanthraquinone									
1	200	12	0.06	5.0					
3	200	18	0.09	6.0					
10	200	11	0.06	4.5					
30	200	6	0.03	2.0					
				P=0.550					

* Significant positive response (P<0.05)
[a] The detailed protocol and these data are presented in Loveday *et al*. (1990). Abs = aberrations.
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

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

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
n	10	10	9	9	10	7
Necropsy body wt	359 ± 4	327 ± 4**	332 ± 4**	305 ± 2**	232 ± 3**	161 ± 6**
Brain						
Absolute	1.924 ± 0.021	1.942 ± 0.014	1.945 ± 0.016	1.914 ± 0.019	1.798 ± 0.016**	1.708 ± 0.015**
Relative	5.36 ± 0.08	5.95 ± 0.06**	5.86 ± 0.07**	6.26 ± 0.05**	7.77 ± 0.07**	10.69 ± 0.37**
Heart						
Absolute	0.953 ± 0.019	0.964 ± 0.042	0.923 ± 0.026	0.895 ± 0.019	0.683 ± 0.008**[b]	0.579 ± 0.050**
Relative	2.65 ± 0.05	2.95 ± 0.12	2.78 ± 0.08	2.90 ± 0.05	2.94 ± 0.06[b]	3.59 ± 0.26**
R. Kidney						
Absolute	1.102 ± 0.017	1.094 ± 0.023	1.121 ± 0.018	1.096 ± 0.015[c]	0.892 ± 0.011**	0.708 ± 0.026**
Relative	3.07 ± 0.04	3.35 ± 0.06**	3.37 ± 0.06**	3.58 ± 0.03**[c]	3.86 ± 0.04**	4.40 ± 0.09**
Liver						
Absolute	12.513 ± 0.288	14.374 ± 0.381**	16.172 ± 0.309**	16.295 ± 0.370**	13.661 ± 0.206	12.333 ± 0.562
Relative	34.84 ± 0.71	43.96 ± 0.95**	48.64 ± 0.67**	52.67 ± 1.02**	59.03 ± 0.76**	76.58 ± 1.70**
Lung						
Absolute	1.322 ± 0.042	1.338 ± 0.026	1.329 ± 0.047	1.259 ± 0.011	1.067 ± 0.038**	0.861 ± 0.014**
Relative	3.68 ± 0.12	4.10 ± 0.07	4.00 ± 0.14	4.13 ± 0.05*	4.62 ± 0.18**	5.40 ± 0.22**
R. Testis						
Absolute	1.468 ± 0.020[b]	1.506 ± 0.020	1.508 ± 0.014	1.479 ± 0.020	1.390 ± 0.026*	1.082 ± 0.037**
Relative	4.08 ± 0.08[b]	4.61 ± 0.05**	4.54 ± 0.06**	4.82 ± 0.07**	6.01 ± 0.11**	6.73 ± 0.12**
Thymus						
Absolute	0.235 ± 0.014	0.193 ± 0.009*	0.163 ± 0.018**	0.146 ± 0.008**	0.112 ± 0.010**[b]	0.065 ± 0.010**
Relative	0.65 ± 0.04	0.59 ± 0.03	0.49 ± 0.05*	0.48 ± 0.03**	0.48 ± 0.04**[b]	0.42 ± 0.07**

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Female						
n	10	10	10	10	10	9
Necropsy body wt	209 ± 3	195 ± 3**	188 ± 3**	184 ± 2**	157 ± 2**	129 ± 4**
Brain						
Absolute	1.809 ± 0.019	1.757 ± 0.014*	1.727 ± 0.016**[b]	1.710 ± 0.012**	1.683 ± 0.018**	1.598 ± 0.017**
Relative	8.66 ± 0.13	9.02 ± 0.19	9.20 ± 0.10[b]	9.32 ± 0.11*	10.71 ± 0.15**	12.49 ± 0.39**
Heart						
Absolute	0.616 ± 0.010	0.605 ± 0.015	0.580 ± 0.016	0.557 ± 0.014**	0.473 ± 0.012**[b]	0.439 ± 0.016**
Relative	2.94 ± 0.03	3.10 ± 0.09	3.09 ± 0.08	3.04 ± 0.07	3.03 ± 0.06[b]	3.42 ± 0.11**
R. Kidney						
Absolute	0.629 ± 0.013	0.684 ± 0.015	0.667 ± 0.012	0.656 ± 0.014	0.590 ± 0.007*	0.532 ± 0.011**
Relative	3.01 ± 0.04	3.51 ± 0.07**	3.55 ± 0.04**	3.57 ± 0.05**	3.75 ± 0.06**	4.15 ± 0.15**
Liver						
Absolute	6.561 ± 0.095	7.674 ± 0.202**	8.335 ± 0.213**	8.509 ± 0.159**	8.090 ± 0.158**	8.243 ± 0.236**
Relative	31.39 ± 0.41	39.28 ± 0.77**	44.35 ± 1.06**	46.33 ± 0.60**	51.45 ± 0.77**	64.12 ± 1.45**
Lung						
Absolute	1.001 ± 0.018	1.010 ± 0.043[b]	0.937 ± 0.029	0.930 ± 0.020	0.855 ± 0.023**[b]	0.702 ± 0.022**
Relative	4.79 ± 0.06	5.15 ± 0.17[b]	4.98 ± 0.12	5.07 ± 0.11	5.47 ± 0.16**[b]	5.46 ± 0.12**
Thymus						
Absolute	0.221 ± 0.007	0.179 ± 0.008**[b]	0.155 ± 0.006**	0.145 ± 0.008**	0.130 ± 0.016**[b]	0.062 ± 0.006**
Relative	1.06 ± 0.03	0.91 ± 0.04[b]	0.82 ± 0.03**	0.79 ± 0.04**	0.84 ± 0.11**[b]	0.48 ± 0.04**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights 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
[c] n=8

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	2,000 ppm	5,000 ppm	10,000 ppm	20,000 ppm (15-month exposure)
Male					
n	10	10	10	10	10
Necropsy body wt	435 ± 11	424 ± 9	398 ± 4**	388 ± 7**	372 ± 10**
R. Kidney					
Absolute	1.247 ± 0.040	1.362 ± 0.047	1.300 ± 0.022	1.259 ± 0.026	1.294 ± 0.044
Relative	2.87 ± 0.06	3.21 ± 0.07**	3.27 ± 0.06**	3.25 ± 0.04**	3.47 ± 0.05**
Liver					
Absolute	13.934 ± 0.391	16.876 ± 0.506**	16.578 ± 0.441**	18.009 ± 0.594**	17.925 ± 0.901**
Relative	32.04 ± 0.54	39.80 ± 0.72**	41.60 ± 0.85**	46.37 ± 0.80**	48.06 ± 1.92**
Female					
n	10	10	10	10	10
Necropsy body wt	251 ± 7	236 ± 4*	229 ± 5**	218 ± 3**	208 ± 3**
R. Kidney					
Absolute	0.710 ± 0.014[b]	0.786 ± 0.020*	0.770 ± 0.019	0.775 ± 0.016*	0.739 ± 0.016
Relative	2.90 ± 0.06[b]	3.35 ± 0.09**	3.37 ± 0.07**	3.56 ± 0.06**	3.56 ± 0.09**
Liver					
Absolute	7.378 ± 0.400	8.753 ± 0.240**	9.361 ± 0.253**	9.313 ± 0.124**	9.651 ± 0.241**
Relative	29.17 ± 0.95	37.20 ± 0.88**	40.89 ± 0.74**	42.83 ± 0.43**	46.38 ± 0.94**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights 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 H3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	10,000 ppm	20,000 ppm (15-month exposure)	20,000 ppm (9-month stop-exposure)
Male				
n	10	10	10	7
Necropsy body wt	481 ± 6	394 ± 7**	361 ± 11**	374 ± 22**
R. Kidney				
Absolute	1.431 ± 0.032	1.472 ± 0.044	1.543 ± 0.041	1.319 ± 0.032
Relative	2.98 ± 0.07	3.73 ± 0.07**	4.34 ± 0.25**	3.61 ± 0.26**
Liver				
Absolute	16.348 ± 0.522	20.110 ± 1.296	26.448 ± 2.340**	25.495 ± 5.628*
Relative	34.00 ± 1.01	50.88 ± 2.84	75.40 ± 8.94**	74.37 ± 20.34**
Female				
n	10	10	8	9
Necropsy body wt	318 ± 6	234 ± 11**	216 ± 4**	260 ± 9**
R. Kidney				
Absolute	0.941 ± 0.028	0.971 ± 0.035	0.994 ± 0.037	0.917 ± 0.035
Relative	2.96 ± 0.06	4.18 ± 0.08**	4.67 ± 0.17**	3.55 ± 0.13**
Liver				
Absolute	9.394 ± 0.276	11.986 ± 0.644**	13.738 ± 0.358**	10.804 ± 0.679**
Relative	29.59 ± 0.85	51.31 ± 1.29**	64.66 ± 2.34**	41.65 ± 2.43**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights 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 H4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
n	10	10	9	10	9	10
Necropsy body wt	30.0 ± 0.6	30.2 ± 0.5	30.0 ± 0.7	31.2 ± 0.5	30.4 ± 0.6	30.5 ± 0.4
Brain						
Absolute	0.454 ± 0.005[b]	0.450 ± 0.006	0.452 ± 0.004	0.446 ± 0.007	0.446 ± 0.007	0.437 ± 0.017[b]
Relative	15.26 ± 0.28[b]	14.98 ± 0.38	15.12 ± 0.32	14.33 ± 0.28	14.68 ± 0.27	14.35 ± 0.56[b]
Heart						
Absolute	0.146 ± 0.004	0.141 ± 0.005	0.148 ± 0.004	0.147 ± 0.004	0.139 ± 0.003	0.148 ± 0.004
Relative	4.88 ± 0.10	4.68 ± 0.10	4.92 ± 0.10	4.70 ± 0.10	4.57 ± 0.06	4.85 ± 0.10
R. Kidney						
Absolute	0.266 ± 0.005	0.257 ± 0.010	0.250 ± 0.004	0.251 ± 0.008	0.231 ± 0.006*	0.250 ± 0.008*
Relative	8.90 ± 0.20	8.51 ± 0.28	8.35 ± 0.17	8.03 ± 0.20**	7.59 ± 0.17**	8.19 ± 0.24**
Liver						
Absolute	1.593 ± 0.041	1.738 ± 0.039	1.765 ± 0.052*	2.011 ± 0.077**[b]	2.002 ± 0.069**	2.381 ± 0.061**
Relative	53.11 ± 0.94	57.60 ± 0.65*	58.94 ± 1.59**	63.92 ± 1.94**[b]	65.73 ± 1.79**	78.05 ± 1.84**
Lung						
Absolute	0.215 ± 0.006	0.201 ± 0.006[b]	0.195 ± 0.005	0.196 ± 0.008	0.197 ± 0.004	0.205 ± 0.011
Relative	7.17 ± 0.10	6.71 ± 0.21[b]	6.55 ± 0.25	6.26 ± 0.21	6.47 ± 0.09	6.75 ± 0.40
R. Testis						
Absolute	0.114 ± 0.002	0.113 ± 0.008[b]	0.110 ± 0.002	0.110 ± 0.003[b]	0.108 ± 0.002[c]	0.111 ± 0.002[b]
Relative	3.81 ± 0.11	3.74 ± 0.22[b]	3.69 ± 0.08	3.51 ± 0.09[b]	3.53 ± 0.04[c]	3.66 ± 0.09[b]
Thymus						
Absolute	0.031 ± 0.001	0.038 ± 0.003[d]	0.031 ± 0.004	0.034 ± 0.003	0.033 ± 0.002	0.029 ± 0.002
Relative	1.05 ± 0.04	1.24 ± 0.07[d]	1.05 ± 0.14	1.09 ± 0.07	1.09 ± 0.06	0.96 ± 0.06

TABLE H4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 1-Amino-2,4-dibromoanthraquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Female						
n	10	10	10	9	10	10
Necropsy body wt	23.8 ± 0.3	24.6 ± 0.6	24.0 ± 0.7	24.5 ± 0.4	23.1 ± 0.3	24.2 ± 0.4
Brain						
Absolute	0.461 ± 0.005	0.456 ± 0.006	0.452 ± 0.004	0.446 ± 0.005	0.450 ± 0.004	0.438 ± 0.006**
Relative	19.37 ± 0.24	18.65 ± 0.36	19.01 ± 0.62	18.20 ± 0.31	19.50 ± 0.30	18.14 ± 0.31
Heart						
Absolute	0.109 ± 0.002	0.112 ± 0.002	0.111 ± 0.003	0.117 ± 0.003	0.110 ± 0.002	0.116 ± 0.003
Relative	4.56 ± 0.12	4.59 ± 0.07	4.63 ± 0.08	4.75 ± 0.12	4.78 ± 0.10	4.81 ± 0.11
R. Kidney						
Absolute	0.152 ± 0.004	0.166 ± 0.004*	0.156 ± 0.004	0.163 ± 0.003	0.158 ± 0.003	0.158 ± 0.003
Relative	6.36 ± 0.11	6.77 ± 0.13	6.51 ± 0.15	6.64 ± 0.15	6.84 ± 0.14*	6.55 ± 0.07
Liver						
Absolute	1.146 ± 0.022	1.453 ± 0.053**	1.529 ± 0.055**	1.666 ± 0.030**	1.613 ± 0.043**	1.904 ± 0.043**
Relative	48.16 ± 1.27	59.10 ± 1.30**	63.92 ± 2.11**	67.94 ± 1.16**	69.83 ± 1.49**	78.72 ± 1.02**
Lung						
Absolute	0.184 ± 0.008	0.175 ± 0.007	0.186 ± 0.006	0.185 ± 0.009	0.174 ± 0.006	0.187 ± 0.007
Relative	7.73 ± 0.35	7.15 ± 0.32	7.81 ± 0.31	7.52 ± 0.30	7.55 ± 0.25	7.77 ± 0.32
Thymus						
Absolute	0.036 ± 0.001	0.037 ± 0.002	0.038 ± 0.003	0.038 ± 0.002	0.029 ± 0.002	0.034 ± 0.003
Relative	1.51 ± 0.06	1.52 ± 0.08	1.60 ± 0.11	1.55 ± 0.08	1.25 ± 0.09	1.39 ± 0.12

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights 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
[c] n=7
[d] n=8

TABLE H5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone[a]

	0 ppm	10,000 ppm	20,000 ppm
Male			
n	10	9	10
Necropsy body wt	42.9 ± 1.2	39.9 ± 0.9	35.5 ± 1.1**
R. Kidney			
Absolute	0.334 ± 0.014	0.289 ± 0.011*	0.288 ± 0.011*
Relative	7.81 ± 0.32	7.26 ± 0.23	8.18 ± 0.40
Liver			
Absolute	1.979 ± 0.146	2.022 ± 0.051	1.932 ± 0.092
Relative	46.69 ± 4.43	50.85 ± 1.59	54.45 ± 2.13
Female			
n	10	10	10
Necropsy body wt	38.5 ± 1.5	34.5 ± 1.9	33.6 ± 0.9*
R. Kidney			
Absolute	0.215 ± 0.005	0.209 ± 0.005	0.208 ± 0.006[b]
Relative	5.66 ± 0.25	6.21 ± 0.36	6.24 ± 0.23[b]
Liver			
Absolute	1.373 ± 0.038	1.657 ± 0.042**	1.805 ± 0.043**
Relative	35.96 ± 1.06	48.92 ± 2.20**	53.86 ± 1.13**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights 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

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

1-Amino-2,4-dibromoanthraquinone was obtained from American Color and Chemical Corporation (Charlotte, NC) (lot 1076-C) and Mobay Corporation (Pittsburgh, PA). Lot 1076-C was used in the 13-week studies and for 2 months of the 2-year studies. For tracking purposes, the lot from Mobay Corporation was assigned the number M061583 and was used throughout the remainder of the 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 1-amino-2,4-dibromoanthraquinone studies are on file at the National Institute of Environmental Health Sciences.

The two lots of the study chemical, a reddish brown to orange powder, were identified as 1-amino-2,4-dibromoanthraquinone by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with those expected for the structure or with the literature spectra, as shown in Figures I1 and I2.

The purity of both lots was determined by elemental analysis, Karl Fischer water analysis, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). TLC was performed with two systems: A) aluminum oxide F-254 Type E plates using a solvent system of hexanes:diethylether (50:50) and B) Whatman RP KC_{18} F-254 plates using methanol as the solvent. Visualization was accomplished with visible light and shortwave (254 nm) ultraviolet light for both lots; longwave (366 nm) ultraviolet light was also used for visualization of lot M061583. HPLC was performed with a Waters μBondapak C_{18} column with ultraviolet detection at 254 nm using a solvent system of water: tetrahydrofuran (65:35 for lot 1076-C and 61:39 for lot M061583) and a flow rate of 1.0 mL/minute.

For lot 1076-C, elemental analyses for hydrogen and nitrogen were in agreement with theoretical values; the elemental analysis for carbon was high and the analysis for bromine was low. Karl Fischer water analysis indicated 0.21% ± 0.05% water. TLC indicated a major spot and two slight trace impurities by system A and a major spot and one trace impurity by system B. HPLC indicated a major peak and six impurities, with a total impurity area of approximately 20% relative to the major peak area.

The impurities in lot 1076-C were further identified and quantified using HPLC and direct-inlet mass spectrometry. A filtered solution of 0.57 mg/mL 1-amino-2,4-dibromoanthraquinone in *N,N*-dimethylformamide was analyzed by HPLC with a Waters μBondapak C_{18} column with a solvent system of water:acetonitrile (52:48) at a flow rate of 1.0 mL/minute. A major peak and eight impurities with areas of 0.1% or larger were detected by ultraviolet light (254 nm). No additional impurities were observed when the ratio of the solvent was increased linearly from 48% to 100%. Three impurities had areas larger than 1% of the total peak area. Aliquots of 5.0 mg/mL 1-amino-2,4-dibromoanthraquinone in *N,N*-dimethylformamide were analyzed using the same HPLC system as was used in the impurity profile analysis, but with a solvent ratio of 53:47. The fractions were then evaporated to dryness, reconstituted in 5 mL *n*-hexane, and concentrated under purified nitrogen to a volume of 200 μL. The samples were then analyzed using direct-inlet mass spectrometry. The three impurities with areas greater than 1% of the major peak area were identified as anthraquinone, a monoamino-monobromoanthraquinone, and an isomer of the major component. Further analysis of the second and third of these impurities using proton Fourier transform NMR spectroscopy indicated that the structure of the second impurity, a monoamino-monobromoanthraquinone, was consistent with that of 1-amino-2-bromoanthraquinone, and that the isomer was probably 2-amino-1,3-dibromoanthraquinone. Quantitation of the impurity identified as anthraquinone using HPLC with a Dupont Zorbax ODS column using a solvent system of water: acetonitrile (30:70) and 0.3 mg/mL butyrophenone as an internal standard indicated approximately 5.0% anthraquinone. Quantitation of the impurities identified as 1-amino-2-bromoanthraquinone and an isomer of the major component by the HPLC system described for the impurity profile analysis indicated approximately 4.3% 1-amino-2-bromoanthraquinone and approximately 2.2% isomer. The overall purity of lot 1076-C was determined to be approximately 87%.

For lot M061583, elemental analyses for carbon, hydrogen, nitrogen, and bromine were in agreement with theoretical values. Karl Fischer water analysis indicated 0.32% ± 0.04% water. TLC indicated a major spot and one trace and one slight trace impurity by system A and a major spot and one slight trace impurity by system B. HPLC indicated a major peak and six impurities with the same retention times as found for lot 1076-C and a total impurity area of 3% relative to the major peak area. Additionally, when the tetrahydrofuran in the solvent was increased to 60%, two impurity peaks with areas less than 1% of the peak area were observed. A concomitant analysis of lot 1076-C with lot M061583 with the same high-performance liquid chromatography system described for the purity analyses, but with a solvent ratio of 50:50 and with octanophenone as an internal standard, indicated a 1-amino-2,4-dibromoanthraquinone concentration of approximately 112% in lot M061583 relative to lot 1076-C. The overall purity of lot M061583 was determined to be approximately 97%.

Stability studies were performed using the same HPLC system described for the purity determination of lot 1076-C but with a solvent ratio of 55:45 and with octanophenone added as an internal standard. The studies indicated that 1-amino-2,4-

dibromoanthraquinone, when stored protected from light, was stable as a bulk chemical for 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the dark at 4° ± 3° C throughout the studies. During the 2-year studies, the stability of the bulk chemical was monitored periodically by the study laboratory using the same HPLC system; no degradation of 1-amino-2,4-dibromoanthraquinone was seen throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate quantities of 1-amino-2,4-dibromoanthraquinone with feed (Table I1). Dosed feed formulations for chronic toxicity testing were made by preparing a 1-amino-2,4-dibromoanthraquinone/feed premix by hand, which was then blended with plain feed in a Patterson-Kelly twin-shell blender for 15 minutes using an intensifier bar. Dose formulations were prepared weekly.

Homogeneity and stability analyses of the dosed feed preparations were conducted by the analytical chemistry laboratory. For the homogeneity analyses, the formulations were extracted with 100 mL of acetonitrile, centrifuged, and then further diluted with acetonitrile. The absorbance of the samples was determined versus acetonitrile using ultraviolet spectroscopy at 249 nm. For the stability studies, 2,000 ppm feed samples were extracted with 100 mL of an acetonitrile hydrochloride solution (999:1) and centrifuged; the extracts were then mixed with 0.5 mg/mL octanophenone (internal standard) in aceto-nitrile and further diluted with acetonitrile. The samples were injected into an HPLC system equipped with a µBondapak C_{18} column and a 254 nm filtered detector, with a mobile phase of water:acetonitrile (57:43) at 1 mL/minute. Homogeneity of these formulations was confirmed; stability was established for at least 2 weeks when dose formulations were stored in the dark at temperatures up to 25° C.

Periodic analyses of the dose formulations of 1-amino-2,4-dibromoanthraquinone were conducted at the study laboratory and at the analytical chemistry laboratory using ultraviolet/visible spectroscopy at 460 nm. For the 13-week studies, dose formulations were analyzed at the beginning, midpoint, and end of the studies (Table I2). During the 2-year studies, the first set of dose formulations and one randomly selected preparation every 8 weeks were analyzed (Table I3). All dose formulations for rats and mice were within 10% of the target concentrations during the 13-week and 2-year studies. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table I4).

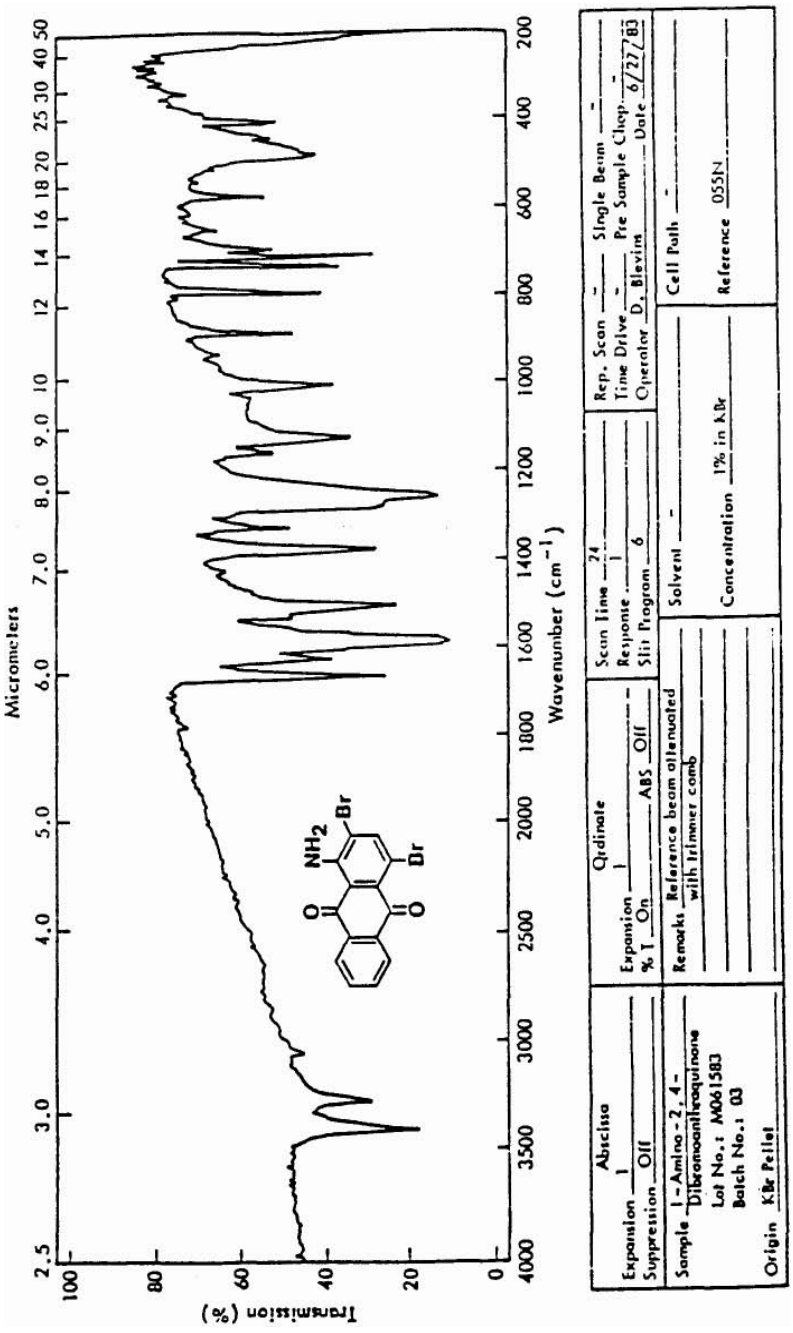

FIGURE I1
Infrared Absorption Spectrum of 1-Amino-2,4-dibromoanthraquinone

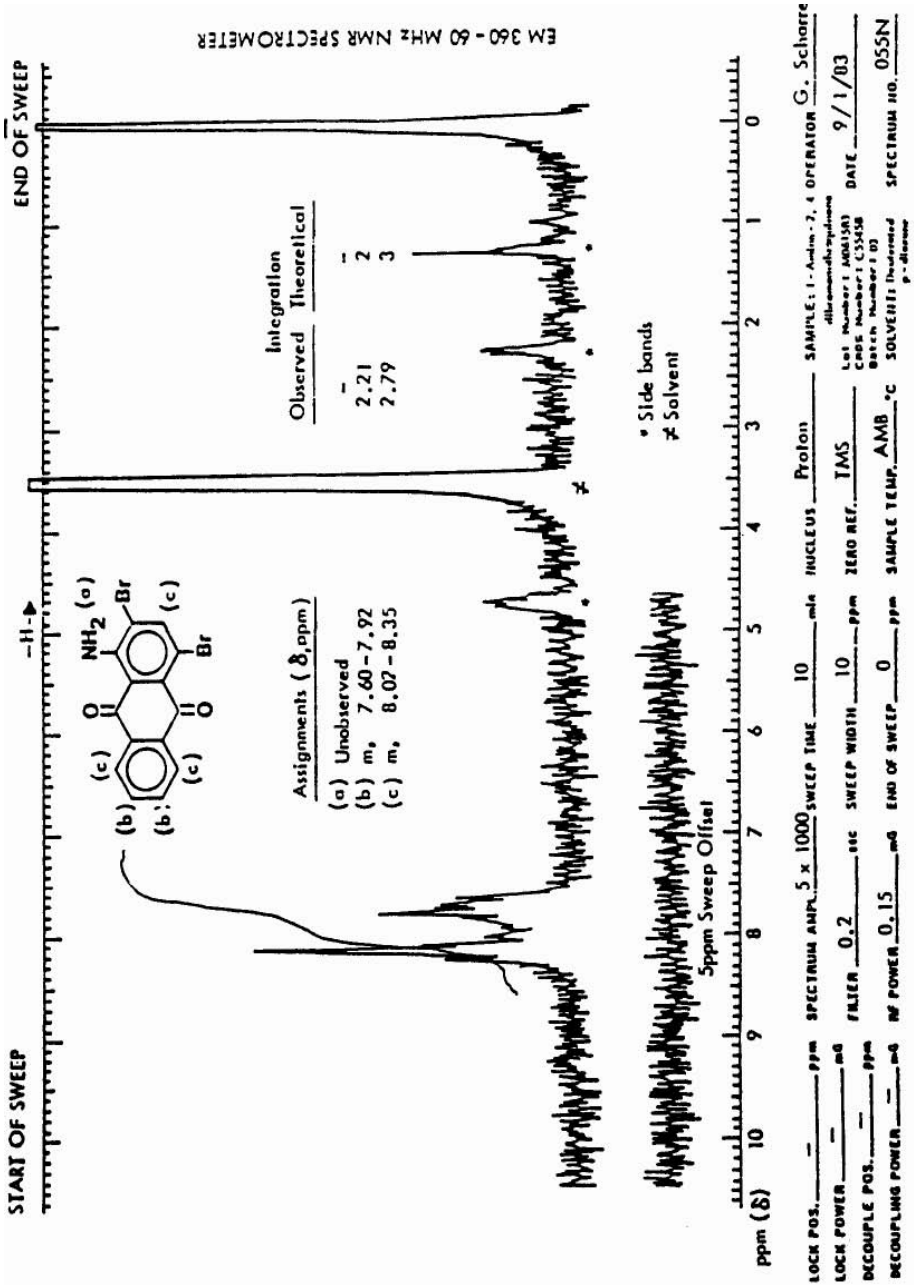

FIGURE I2
Nuclear Magnetic Resonance Spectrum of 1-Amino-2,4-dibromoanthraquinone

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of 1-Amino-2,4-dibromoanthraquinone

13-Week Studies	2-Year Studies
Preparation A premix with feed and 1-amino-2,4-dibromoanthraquinone was prepared with a mortar and pestle; premix and remainder of feed were layered into a blender with a intensifier bar and mixed for 15 minutes with the bar on. Doses were prepared weekly.	Same as 13-week studies
Chemical Lot Number 1076-C	1076-C and M061583
Maximum Storage Time 14 days	14 days
Storage Conditions In double, clear plastic bags, in the dark, at 4° C	In double, clear plastic bags, in the dark, at 4° ± 3° C
Study Laboratory EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)
Referee Laboratory Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of 1-Amino-2,4-dibromoanthraquinone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
14 April 1982	16 April 1982	2,500[b]	2,500	0
		2,500[c]	2,620	+5
		2,500[d]	2,400	−4
		5,000	4,780	−4
	20 April 1982	10,000	10,200	+2
		25,000	24,800	−1
		50,000[b]	50,100	0
		50,000[c]	49,500	−1
		50,000[d]	48,600	−3
9 June 1982	11 June 1982	2,500	2,500	0
		5,000	4,690	−6
		10,000	9,700	−3
		25,000	25,000	0
		50,000	50,400	+1
21 July 1982	22 July 1982	2,500	2,400	−4
		5,000	4,670	−7
		10,000	10,000	0
		25,000	24,500	−2
		50,000	50,200	0

[a] Results of duplicate analyses
[b] Sample selection from top left of twin-shell blender
[c] Sample selection from top right of twin-shell blender
[d] Sample selection from bottom of twin-shell blender

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 1-Amino-2,4-dibromoanthraquinone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
13 June 1983	14 June 1983[b]	10,000	9,920	−1
		20,000	19,700	−2
6 July 1983	7 July 1983	2,000	1,980	−1
		5,000	4,950	−1
		10,000	9,760	−2
		20,000	20,100	+1
15 August 1983	16 August 1983	2,000	1,990	−1
		5,000	5,000	0
		10,000	9,900	−1
		20,000	19,600	−2
17 October 1983	19 October 1983	2,000	1,910	−5
		5,000	4,920	−2
		10,000	9,800	−2
		20,000	20,000	0
19 December 1983	21 December 1983	2,000	1,980	−1
		5,000	4,870	−3
		10,000	9,800	−2
		20,000	20,700	+4
21 February 1984	22 February 1984	2,000	1,960	−2
		5,000	4,780	−4
		10,000	10,100	+1
		20,000	19,900	−1
9 April 1984	10 April 1984	2,000	1,900	−5
		5,000	4,980	0
		10,000	9,800	−2
		20,000	19,400	−3
29 May 1984	30 May 1984	2,000	1,970	−2
		5,000	4,870	−3
		10,000	10,100	+1
		20,000	20,000	0
9 July 1984	10 July 1984	2,000	1,880	−6
		5,000	4,930	−1
		10,000	10,000	0
		20,000	20,100	+1
17 September 1984	18 September 1984	2,000	1,910	−5
		5,000	5,120	+2
		10,000	10,100	+1
		20,000	19,800	−1

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 1-Amino-2,4-dibromoanthraquinone (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
19 November 1984	20 November 1984	2,000	1,910	−5
		5,000	4,900	−2
		10,000	10,200	+2
		20,000	19,900	−1
21 January 1985	23 January 1985	2,000	1,930	−4
		5,000	4,970	−1
		10,000	10,200	+2
		20,000	20,100	+1
1 April 1985	2 April 1985	2,000	1,920	−4
		5,000	5,150	+3
		10,000	10,200	+2
		20,000	20,200	+1
3 June 1985	4 June 1985	2,000	1,970	−2
		5,000	4,830	−3
		10,000	10,100	+1
		20,000	19,500	−3

[a] Results of duplicate analyses
[b] Doses mixed on this date were administered to mice only.

TABLE I4
Results of Referee Analysis of Dose Formulations in the 13-Week and 2-Year Feed Studies of 1-Amino-2,4-dibromoanthraquinone

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
14 April 1982	5,000	4,780	5,050 ± 130
2-Year Studies			
13 June 1983	10,000	9,920	10,500 ± 100
19 December 1983	2,000	1,980	1,960 ± 20
9 April 1984	20,000	19,400	19,600 ± 100
17 September 1984	5,000	5,120	5,250 ± 110
1 April 1985	2,000	1,920	2,030 ± 40

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF 1-AMINO-2,4-DIBROMOANTHRAQUINONE

TABLE J1
Feed and Compound Consumption by Male Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone

	20,000 ppm (9-month stop-exposure)			20,000 ppm (15-month exposure)		
Week	Feed (g/day)[a]	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	11.2	130	1,718	10.9	136	1,605
2	15.1	144	2,096	15.9	149	2,136
4	22.8	169	2,700	20.0	173	2,303
5	17.7	169	2,095	17.0	177	1,922
8	20.3	211	1,924	20.8	217	1,919
12	20.2	267	1,511	18.5	277	1,336
13	17.8	267	1,328	17.7	271	1,308
14	19.6	284	1,381	18.9	292	1,292
17	16.9	305	1,110	17.8	318	1,117
21	17.9	327	1,092	18.9	334	1,133
25	14.1	341	827	14.5	351	829
29	15.8	338	932	15.9	355	898
33	16.8	351	957	15.4	364	844
37	18.0	352	1,019	18.9	364	1,038
41[c]	17.6	374	0	15.6	377	825
45	16.0	384	0	15.2	381	799
49	17.3	395	0	15.4	383	805
53	15.5	398	0	16.3	389	840
57	15.3	393	0	15.7	377	833
61	14.9	379	0	15.1	370	817
65				15.3	364	841
Mean for weeks						
1-13	17.9	194	1,910	17.3	200	1,790
14-40	17.0	328	1,045	17.1	340	1,022
41-61 or 65	16.1	387	0	15.5	377	823

[a] Grams of feed consumed per animal per day
[b] Milligrams of compound consumed per kilogram body weight per day
[c] 9-Month stop-exposure animals switched to undosed feed

TABLE J2
Feed and Compound Consumption by Female Rats in the Stop-Exposure Evaluation of 1-Amino-2,4-dibromoanthraquinone

	20,000 ppm (9-month stop-exposure)			20,000 ppm (15-month exposure)		
Week	Feed (g/day)[a] (g/day)	Body Weight Weight (g)	Dose/ Day[b] Day (mg/kg)	Feed	Body (g)	Dose/ (mg/kg)
1	8.1	90	1,810	7.3	94	1,543
2	10.6	93	2,259	10.0	97	2,079
4	14.6	113	2,591	14.6	114	2,563
5	13.2	117	2,240	13.8	121	2,296
8	14.0	141	1,982	14.7	150	1,955
9	12.9	146	1,764	11.6	157	1,474
12	15.1	168	1,794	12.8	171	1,497
13	14.6	172	1,688	14.2	175	1,628
14	15.0	177	1,694	15.8	179	1,764
17	18.8	188	2,000	16.8	190	1,770
21	17.1	194	1,771	16.4	196	1,666
25	14.5	198	1,462	12.9	200	1,290
29	16.5	200	1,653	14.9	203	1,469
33	21.0	201	2,083	21.0	203	2,071
37	10.9	207	1,052	11.0	211	1,048
41[c]	9.7	207	0	10.9	210	1,040
49	12.1	231	0	10.2	213	959
53	11.0	248	0	11.6	219	1,062
57	11.9	252	0	11.2	220	1,022
61	11.1	258	0	10.3	217	953
65				10.9	220	992
Mean for weeks						
1-13	12.9	130	2,016	12.4	135	1,879
14-40	16.3	195	1,673	15.5	197	1,582
41-61 or 65	11.2	239	0	10.9	217	1,005

[a] Grams of feed consumed per animal per day
[b] Milligrams of compound consumed per kilogram body weight per day
[c] 9-Month stop-exposure animals switched to undosed feed

TABLE J3
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Week	0 ppm		2,000 ppm			5,000 ppm			10,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	20.1	139	16.2	136	238	15.0	136	549	12.6	134	937
2	17.2	161	16.6	165	202	16.5	164	504	14.9	155	961
4	21.4	235	20.3	225	180	20.7	222	466	19.3	204	943
5	17.5	240	16.9	233	145	17.0	230	369	15.9	215	742
8	22.5	302	20.7	285	145	21.3	280	380	20.0	260	769
12	18.5	338	18.8	323	116	20.2	318	317	16.9	300	563
13	17.9	332	17.8	321	111	17.8	309	288	17.6	298	589
14	22.4	356	19.9	339	117	18.5	330	281	17.7	314	561
17	22.9	387	20.1	363	111	19.3	350	275	19.7	335	589
21	20.9	406	20.8	382	109	18.7	368	254	17.3	356	486
25	19.0	423	18.0	398	91	15.8	383	206	15.8	369	427
29	20.8	435	18.5	403	92	17.9	384	232	19.5	376	520
33	19.9	445	17.6	413	85	16.8	398	210	16.9	383	441
37	21.8	453	21.6	420	103	21.9	401	273	19.9	388	514
41	17.1	468	16.7	433	77	16.2	415	196	15.5	397	392
45	16.2	473	16.0	440	73	16.1	424	190	15.7	403	389
49	15.5	479	17.4	452	77	16.7	428	195	15.6	409	382
53	16.7	489	17.8	457	78	17.7	439	201	16.6	415	399
57	17.4	486	16.9	453	75	16.8	430	195	15.9	409	389
61	16.3	484	15.3	445	69	15.4	430	179	14.3	405	352
65	15.8	484	16.8	448	75	15.5	426	182	16.5	408	405
69	15.6	479	15.1	442	68	15.7	417	188	14.6	398	368
72	16.0	472	15.1	429	70	14.8	407	182	15.8	389	407
77	15.1	460	13.8	412	67	14.3	392	183	15.2	381	400
80	15.3	462	14.9	418	71	14.5	390	187	14.7	373	393
85	14.3	467	14.8	419	71	14.2	388	183	13.9	365	382
89	13.8	455	13.8	405	68	14.7	378	194	14.8	357	414
93	14.4	445	14.9	396	75	14.6	363	202	16.0	347	462
97	12.9	432	15.7	380	82	16.4	355	231	16.9	332	508
101	14.5	422	16.2	380	85	15.6	343	227	17.0	301	565
103	14.7	406	14.7	349	84	16.6	341	244	18.6	283	656
Mean for weeks											
1-13	19.3	249	18.2	241	163	18.4	237	411	16.7	224	786
14-52	19.6	433	18.7	404	93	17.8	388	231	17.4	373	470
53-103	15.2	460	15.4	417	74	15.5	393	198	15.8	369	436

[a] Grams of feed consumed per animal per day
[b] Milligrams of compound consumed per kilogram body weight per day

TABLE J4
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Week	0 ppm		2,000 ppm			5,000 ppm			10,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	12.4	93	10.2	93	219	9.3	94	493	8.5	94	911
2	14.6	114	11.8	110	216	12.2	107	571	11.1	102	1,091
4	15.5	147	14.0	141	198	14.5	136	534	14.3	128	1,119
5	15.7	157	14.5	151	192	15.0	146	514	13.4	137	984
8	16.4	180	15.2	174	175	18.4	167	552	13.9	158	882
9	16.9	186	11.8	178	133	12.5	173	362	12.5	167	749
12	17.0	203	13.3	194	137	13.3	188	352	13.5	181	747
13	19.2	208	14.6	195	149	15.2	192	396	14.0	185	758
14	19.2	212	14.8	201	147	14.6	196	372	14.5	189	767
17	20.0	222	14.7	209	141	16.7	205	409	16.9	200	846
21	17.1	228	15.0	216	139	14.7	213	346	14.8	205	723
25	15.3	237	11.0	219	100	12.1	216	280	11.3	208	545
29	18.6	246	13.7	223	123	13.7	219	312	13.1	212	619
33	19.8	251	18.7	227	165	19.3	222	434	20.1	213	943
37	10.4	258	10.3	233	89	12.9	230	282	10.7	218	492
41	9.8	265	9.6	233	82	9.1	227	201	9.2	217	425
45	10.6	272	10.4	239	87	10.0	231	216	10.2	221	461
49	11.8	284	11.4	246	93	10.8	237	228	10.7	227	474
53	11.0	299	11.3	257	88	10.7	245	218	10.8	232	467
57	12.4	311	11.5	264	88	11.0	249	222	10.9	238	457
61	12.0	315	12.0	267	90	11.4	251	228	10.9	238	456
65	12.6	328	11.6	276	84	11.6	257	226	10.9	242	452
68	12.0	333	11.8	277	85	11.5	257	224	11.4	241	471
73	12.4	343	12.4	286	87	12.1	263	230	11.8	245	481
77	11.7	347	11.2	289	78	11.2	269	208	10.9	243	449
81	11.9	351	11.7	296	79	11.2	270	206	10.9	239	457
85	11.7	354	11.2	295	76	10.8	268	201	10.8	234	463
89	12.3	354	11.8	298	79	11.2	262	213	11.5	229	500
93	11.6	356	10.9	299	73	10.4	251	208	11.6	224	518
97	11.9	358	12.5	298	84	11.7	250	233	11.6	213	543
100	11.7	361	12.0	293	82	11.5	243	237	12.3	202	607
103	12.3	362	12.6	290	87	11.6	234	249	12.9	194	663
Mean for weeks											
1-13	16.0	161	13.2	154	177	13.8	150	472	12.7	144	905
14-52	15.3	248	13.0	225	117	13.4	219	308	13.2	211	629
53-103	12.0	341	11.8	285	83	11.3	255	222	11.4	230	499

[a] Grams of feed consumed per animal per day
[b] Milligrams of compound consumed per kilogram body weight per day

TABLE J5
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1						6.6	21.2	6,260
2	5.8	23.5	5.9	23.2	2,525	6.0	23.9	5,000
5	6.0	27.3	6.2	26.9	2,297	6.0	27.3	4,380
9	6.2	30.2	5.8	30.1	1,916	5.4	30.5	3,561
13	5.7	33.7	5.6	32.5	1,732	5.5	33.0	3,326
17	5.9	36.3	5.8	34.4	1,689	5.7	34.4	3,339
21	5.8	38.8	6.4	34.0	1,890	5.7	34.6	3,292
25	6.0	39.2	6.1	37.0	1,653	6.1	35.6	3,445
29	5.5	39.9	5.8	35.6	1,617	5.5	36.2	3,064
33	5.7	41.3	5.8	38.5	1,496	5.0	36.4	2,757
37	5.3	42.1	5.1	39.6	1,281	5.1	37.9	2,697
41	5.3	42.8	4.9	39.8	1,242	5.2	38.2	2,703
45	5.9	42.1	5.9	39.5	1,492	5.8	37.4	3,097
49	5.5	43.5	5.5	40.1	1,373	6.1	38.9	3,119
53	6.2	44.4	5.1	41.8	1,215	5.5	39.6	2,792
57	5.4	44.0	5.4	41.6	1,294	5.1	39.3	2,630
61	6.6	44.8	5.8	42.3	1,383	6.4	40.2	3,165
65	6.8	45.2	5.5	41.6	1,323	6.0	39.4	3,046
69	6.5	43.6	6.1	40.7	1,501	6.5	37.7	3,468
73	4.1	42.1	6.4	39.8	1,600	6.0	39.2	3,052
77	6.3	44.2	6.0	40.0	1,507	6.3	38.7	3,257
81	5.1	43.0	6.0	39.5	1,530	6.1	38.4	3,200
85	5.6	44.1	6.2	38.9	1,584	6.3	38.0	3,306
89	6.2	44.0	6.4	37.7	1,694	6.7	37.1	3,600
93	4.7	42.3	6.3	38.1	1,656	5.8	36.2	3,191
97	7.8	43.8	9.4	37.4	2,505	9.5	36.8	5,179
101	8.3	43.7	8.9	37.4	2,394	8.5	36.7	4,668
104	9.1	43.6	11.2	37.0	3,016	9.6	36.3	5,315
Mean for weeks								
1-13	5.9	28.7	5.9	28.2	2,117	5.9	27.2	4,506
14-52	5.6	40.7	5.7	37.6	1,526	5.6	36.6	3,057
53-104	6.3	43.8	6.7	39.6	1,702	6.7	38.1	3,519

[a] Grams of feed consumed per animal per day
[b] Milligrams of compound consumed per kilogram body weight per day

TABLE J6
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of 1-Amino-2,4-dibromoanthraquinone

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
2	5.4	18.1	4.8	18.4	2,628	4.8	18.0	5,385
5	6.4	20.8	5.5	21.3	2,597	5.7	20.8	5,487
9	5.9	22.9	5.9	22.9	2,579	5.1	23.3	4,402
13	6.0	24.8	5.0	24.8	2,023	6.7	25.0	5,339
17	5.8	26.0	5.8	26.6	2,190	6.2	26.0	4,789
21	5.6	27.7	5.1	27.3	1,866	5.7	27.3	4,189
25	6.0	29.2	5.6	28.6	1,941	6.3	28.1	4,507
29	6.4	30.2	5.8	28.8	2,002	6.8	28.9	4,737
33	6.0	32.1	5.7	30.7	1,854	5.3	28.8	3,681
37	6.5	32.9	5.5	31.9	1,726	6.1	30.5	4,029
41	6.7	34.2	6.3	33.0	1,910	6.6	30.1	4,365
45	5.9	35.2	5.5	32.8	1,687	5.6	31.2	3,588
49	6.8	36.6	6.4	34.5	1,844	6.7	32.5	4,124
53	5.3	36.8	4.9	35.0	1,389	5.2	32.5	3,190
56	6.7	38.2	6.8	36.3	1,881	6.7	33.1	4,086
61	6.9	39.1	6.2	36.2	1,704	6.4	33.8	3,796
65	6.7	38.4	6.2	36.1	1,722	6.3	33.5	3,754
69	6.6	37.6	6.4	35.4	1,798	6.6	32.4	4,075
73	5.1	37.3	7.4	35.7	2,062	7.2	32.7	4,374
77	5.1	39.3	5.7	35.8	1,581	5.7	33.1	3,427
81	5.5	39.9	5.7	36.4	1,575	6.1	33.8	3,597
85	6.3	39.5	6.4	36.7	1,754	6.6	33.6	3,905
89	7.0	41.1	7.2	36.1	1,985	7.3	33.7	4,347
93	7.8	41.4	7.5	35.3	2,137	8.5	33.3	5,121
97	8.3	40.0	6.8	33.6	2,019	7.8	31.9	4,902
101	8.6	38.5	9.6	34.1	2,833	10.2	31.5	6,521
104	9.1	39.2	10.2	33.6	3,021	11.1	31.9	6,985
Mean for weeks								
1-13	5.9	21.7	5.3	21.9	2,457	5.6	21.8	5,153
14-52	6.2	31.6	5.5	30.5	1,798	6.2	29.3	4,223
53-104	6.8	39.0	6.8	35.5	1,935	7.2	32.9	4,415

[a] Grams of feed consumed per animal per day
[b] Milligrams of compound consumed per kilogram body weight per day

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

TABLE K1
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 K2
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
dl-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 K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.29 ± 0.86	21.00 – 24.30	22
Crude fat (% by weight)	5.38 ± 0.59	4.40 – 6.30	22
Crude fiber (% by weight)	3.72 ± 0.47	3.10 – 5.40	22
Ash (% by weight)	6.67 ± 0.29	5.96 – 7.27	22
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.060	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)	10,459 ± 4,285	4,200 – 17,800	22
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α–Tocopherol (ppm)	37.95 ± 9.406	22.5 – 48.90	8
Thiamine (ppm)	20.73 ± 5.08	12.0 – 37.0	22
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)	0.25 ± 0.04	0.19 – 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 – 65.0	8
Choline (ppm)	3,089 ± 328	2,400 – 3,430	8
Minerals			
Calcium (%)	1.20 ± 0.14	0.91 – 1.43	22
Phosphorus (%)	0.94 ± 0.06	0.84 – 1.10	22
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	8.09 – 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 K4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.56 ± 0.19	0.18 – 0.80	22
Cadmium (ppm)[c]	0.11 ± 0.03	0.10 – 0.20	22
Lead (ppm)	0.57 ± 0.19	0.24 – 1.00	22
Mercury (ppm)	<0.05		22
Selenium (ppm)	0.33 ± 0.06	0.23 – 0.45	22
Aflatoxins (ppb)	<5.00		22
Nitrate nitrogen (ppm)[d]	11.57 ± 5.85	2.50 – 22.0	22
Nitrite nitrogen (ppm)[d]	0.69 ± 1.42	<0.10 – 6.10	22
BHA (ppm)[e]	<2		22
BHT (ppm)[e]	2.36 ± 1.00	<1.00 – 4.00	22
Aerobic plate count (CFU/g)	144,259 ± 157,664	6,200 – 443,800	22
Coliform (MPN/g)	317 ± 567	<3.00 – 2,400	22
Escherichia coli (MPN/g)[f]	9.73 ± 31.33	<3.00 – 150	22
Escherichia coli (MPN/g)[g]	3.04 ± 0.22	<3.00 – 4.0	21
Total nitrosoamines (ppb)[h]	6.44 ± 6.26	0.80 – 30.30	22
N–Nitrosodimethylamine (ppb)[h]	5.91 ± 6.21	0.50 – 30.00	22
N–Nitrosopyrrolidine (ppb)[h]	0.53 ± 0.58	0.30 – 2.70	22
Pesticides (ppm)			
α–BHC	<0.01		22
β–BHC	<0.02		22
γ–BHC	<0.01		22
δ–BHC	<0.01		22
Heptachlor	<0.01		22
Aldrin	<0.01		22
Heptachlor epoxide	<0.01		22
DDE	<0.01		22
DDD	<0.01		22
DDT	<0.01		22
HCB	<0.01		22
Mirex	<0.01		22
Methoxychlor	<0.05		22
Dieldrin	<0.01		22
Endrin	<0.01		22
Telodrin	<0.01		22
Chlordane	<0.05		22
Toxaphene	<0.1		22
Estimated PCBs	<0.2		22
Ronnel	<0.01		22
Ethion	<0.02		22
Trithion	<0.05		22
Diazinon	<0.1		22
Methyl parathion	<0.02		22
Ethyl parathion	<0.02		22
Malathion[i]	0.32 ± 0.68	0.05 – 3.20	22
Endosulfan I	<0.01		22
Endosulfan II	<0.01		22
Endosulfan sulfate	<0.03		22

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] CFU = colony forming units, MPN = most probable number, BHC is hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Three lots milled 22 February 1984, 14 March 1984, and 9 May 1984 contained 0.20 ppm. All other lots measured less than or equal to the detection limit.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] Mean, standard deviation, and range include one high value of 150 MPN/g from the lot milled on 17 October 1984.
[g] Mean, standard deviation, and range exclude the high value of 150 MPN/g from the lot milled on 17 October 1984.
[h] All values were corrected for percent recovery.
[i] Mean, standard deviation, and range include one high value of 3.20 ppm.

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. 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 and the study animals are all subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected, allowed to clot, and the serum separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method of Analysis	Time of Analysis
Rats	
13-Week Study	
Complement Fixation	
RCV (rat coronavirus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
PVM (pneumonia virus of mice)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthritidis	18 and 24 months
Mycoplasma pulmonis	18 and 24 months
PVM	18 and 24 months
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	6, 12, 18, and 24 months
Sendai	18 and 24 months
Hemagglutination Inhibition	
H-1	
6, 12, 18, and 24 months	
KRV	6, 12, 14, 15, 18, and 24 months
PVM	6 and 12 months
Sendai	6 and 12 months

Mice

13-Week Study

Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus	Study termination
Sendai	Study termination
ELISA	
MHV (mouse hepatitis virus)	Study termination
Hemagglutination Inhibition	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
PVM	Study termination
Polyoma virus	Study termination
Reovirus 3	Study termination

2-Year Study

Complement Fixation	
LCM	6, 12, 18, and 24 months
Mouse adenoma virus	6 and 12 months
ELISA	
Ectromelia virus	18 and 24 months
GDVII	12, 18, and 24 months
Mouse adenoma virus	18 and 24 months
MHV	6, 12, 18, and 24 months
M. arthritidis	18 and 24 months
M. pulmonis	18 and 24 months
PVM	18 and 24 months
Reovirus 3	18 and 24 months
Sendai	18 and 24 months
Hemagglutination Inhibition	
Ectromelia virus	6 and 12 months
GDVII	6 months
K (papovavirus)	18 and 24 months
MVM	6, 12, 18, and 24 months
PVM	6 and 12 months
Polyoma virus	6, 12, 18, and 24 months
Reovirus 3	6 and 12 months
Sendai	6 and 12 months
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	18 and 24 months

Results of serology tests for rats are presented in Table L1. All test results for mice were negative.

TABLE L1
Murine Virus Antibody Determinations for Rats in the 13-Week and 2-Year Feed Studies of 1-Amino-2,4-dibromoanthraquinone

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Study		
Study termination	0/10	None positive
2-Year Study		
Male		
6 Months	0/5	None positive
12 Months	0/5	None positive
18 Months	0/4	None positive
24 Months	0/5	None positive
Female		
6 Months	5/5	Sendai
12 Months	1/5	KRV
	5/5	Sendai
14 Months	1/5	KRV
15 Months	0/10	None positive
18 Months	1/5	KRV
	5/5	Sendai
24 Months	5/5	Sendai