NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 422

TOXICOLOGY AND CARCINOGENESIS STUDIES OF COUMARIN (CAS NO. 91-64-5) IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

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

FOREWORD

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

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

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

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

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-1371).

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF COUMARIN

(CAS NO. 91-64-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

September 1993

NTP TR 422

NIH Publication No. 93-3153

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

CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.A. Bridge, B.S.
J.K. Dunnick, Ph.D.
S.L. Eustis, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
R.A. Griesemer, D.V.M., Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
G.N. Rao, D.V.M., Ph.D.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

International Research and Development Corporation
Conducted 16-day and 13-week studies, evaluated pathology findings

P.L. Lang, Ph.D., Study Director
D. Rajasekaran, D.V.M., M.V.S.C., F.R.V.C.S.

American Biogenics Corporation
Conducted 2-year studies, evaluated pathology findings

I.A. Muni, Ph.D., Principal Investigator
R. Dahlgren, D.V.M.
E.B. Gordon, Ph.D.
D.S. Wyand, D.V.M.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
B.F. Hamilton, D.V.M., Ph.D.
K. Yoshitomi, D.V.M., Ph.D.

Integrated Laboratory Systems
Prepared quality assurance audits

S.L. Smith, J.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides, prepared pathology report on rats (28 November 1990)

J.R. Leininger, D.V.M., Ph.D., Chair
Pathology Associates, Inc.
J.M. Cullen, V.M.D., Ph.D.
North Carolina State University
S.L. Eustis, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M. (observer)
Purdue University
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

Evaluated slides, prepared pathology report on mice (20 December 1990)

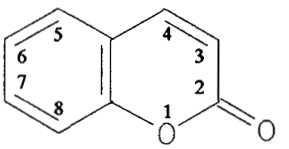
P. Hildebrandt, D.V.M., Chair
PATHCO, Inc.
B.F. Hamilton, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
M.P. Jokinen, D.V.M.
National Toxicology Program
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program
J.A. Popp, D.V.M., Ph.D.
Chemical Industry Institute of Toxicology
C.C. Shackelford, D.V.M., M.S., Ph.D.
National Toxicology Program

Biotechnical Services, Inc.
Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
P. Chaffin, M.S.
G.F. Corley, D.V.M.
A.B. James-Stewart, B.S.

CONTENTS

ABSTRACT



COUMARIN

CAS No. 91-64-5

Chemical Formula: $C_9H_6O_2$ Molecular Weight: 146.5

Synonyms: 5,6-benzo-alpha-pyrone, 2H-1-benzopyran-2-one, 2H-benzo[b]pyran-2-one, 1,2-oxo-1,2-benzopyran, 1,2-benzopyrone, *cis-o*-coumarinic acid lactone, coumarinic anhydride, cumarin, *o*-hydroxycinnamic acid lactone, kumarin, [2-propenoic acid, 3-(2-hydroxyphenyl)-delta-lactone], Rattex, tonka bean camphor

Coumarin is the basic structure of numerous naturally occurring compounds with important and diverse physiological activities. More than a thousand coumarin derivatives have been described, varying from simple coumarins containing alkyl and hydroxyl side chains to complex coumarins with benzoyl, furanoyl, pyranoyl, or alkylphosphorothionyl substituents. Coumarin and 3,4-dihydrocoumarin were nominated by the Food and Drug Administration and the National Cancer Institute for study because of the widespread use of coumarin in perfumes, cosmetics, and other products as a fragrance, continued interest in coumarin compounds as flavor-enhancing agents for foods, and the interest in structure-activity relationships of this important group of compounds. Coumarin is believed to be metabolized to a 3,4-epoxide intermediate, which may be responsible for its toxic effects, while 3,4-dihydrocoumarin, which lacks the 3,4-double bond, is not considered likely to form an epoxide intermediate.

Toxicity and carcinogenicity studies were conducted by administering coumarin (97% pure) in corn oil by gavage to groups of male and female F344/N rats and $B6C3F_1$ mice for 16 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, and $B6C3F_1$ mice.

16-Day Study in Rats

Groups of five male and five female rats received coumarin in corn oil by gavage at doses of 0, 25, 50, 100, 200, or 400 mg per kg body weight, 5 days a week for a total of 12 doses in a 16-day period. All female rats and four male rats receiving 400 mg/kg died. The mean body weight gains and final mean body weights of surviving dosed male and female rats were similar to those of the controls. There were no clinical signs of organ-specific toxicity, and there was no evidence of impaired blood coagulation from measurements of capillary clotting time or prothrombin and activated partial thromboplastin time.

16-Day Study in Mice

Groups of five male and five female mice received coumarin in corn oil by gavage at doses of 0, 40, 75, 150, 300, or 600 mg per kg body weight, 5 days a week for a total of 12 doses in a 16-day period. All mice receiving 600 mg/kg, two male mice receiving 300 mg/kg, and one male mouse receiving 75 mg/kg died. The mean body weight gains and final mean body weights of surviving dosed male and female mice were similar to those of the controls. Clinical findings of inactivity, excessive lacrimation, piloerection, bradypnea, ptosis, or ataxia were observed in some mice from the 300 and 600 mg/kg groups

within the first several hours after dosing. Capillary clotting time and platelet counts of dosed mice were similar to those of controls.

13-Week Study in Rats

Groups of 10 male and 10 female rats received coumarin in corn oil by gavage at doses of 0, 19, 38, 75, 150, or 300 mg per kg body weight. Three male and three female rats receiving 300 mg/kg died. The mean body weight gains and final mean body weights of male rats that received 150 and 300 mg/kg were significantly lower than those of the controls. There were no clinical signs related to specific organ toxicity.

Male and female rats receiving coumarin exhibited dose-related decreases in mean erythrocyte volume and mean erythrocyte hemoglobin, and dose-related increases in erythrocyte counts. Serum levels of total bilirubin and one or more cytoplasmic enzymes including alanine aminotransferase, aspartate aminotransferase, ornithine carbamoyltransferase, and/or sorbitol dehydrogenase in males and females receiving 300 mg/kg were higher than those of controls.

The absolute and relative liver weights of male and female rats that received 150 and 300 mg/kg were significantly greater than those of the controls. Centrilobular hepatocellular degeneration and necrosis, chronic active inflammation, and bile duct hyperplasia were observed in the liver of rats receiving 150 or 300 mg/kg.

The high dose selected for the 2-year study was 100 mg/kg, which was just below the level at which mortality, lower final mean body weights, and treatment-related liver lesions were observed in the 13-week study.

13-Week Study in Mice

Groups of 10 male and 10 female mice received coumarin in corn oil by gavage at doses of 0, 19, 38, 75, 150, or 300 mg per kg body weight. Two male mice receiving 300 mg/kg died. The mean body weight gain and final mean body weight of surviving male mice that received 300 mg/kg were significantly lower than those of the controls. No clinical signs of toxicity were observed.

Male and female mice receiving coumarin exhibited dose-related decreases in mean erythrocyte volume and mean erythrocyte hemoglobin. The absolute and relative liver weights of males and females that received 150 and 300 mg/kg were significantly greater than those of the controls. Centrilobular hepatocellular hypertrophy was observed in male and female mice receiving 300 mg/kg.

The high dose selected for the 2-year study was 200 mg/kg, which was just below the level at which mortality and liver lesions were observed in the 13-week study.

2-Year Study in Rats

Groups of 60 male and 60 female rats were administered coumarin in corn oil by gavage at doses of 0, 25, 50, or 100 mg per kg body weight. After 15 months, 10 animals from each group were evaluated.

Survival, Body Weights, and Clinical Findings

None of the male rats receiving 100 mg/kg and only two males receiving 50 mg/kg survived until the end of the study (vehicle control, 28/50; 25 mg/kg, 9/50; 50 mg/kg, 2/51; 100 mg/kg, 0/50). Survival of dosed female rats was similar to that of the controls (29/50, 38/50, 36/50, 30/50). The reduced survival in dosed male rats was primarily attributed to chemical-related exacerbation of spontaneously occurring renal disease. Final mean body weights of female rats that received 100 mg/kg and all dosed groups of male rats were lower than those of the controls. There were no clinical signs of toxicity in rats, other than nonspecific signs relating to debilitation as a result of renal or other spontaneous disease.

Hematology and Clinical Chemistry

At the 15-month interim evaluation, the values for one or more hematologic parameters including mean erythrocyte volume, mean erythrocyte hemoglobin in 50 and 100 mg/kg rats, and hematocrit or hemoglobin in 100 mg/kg rats were significantly lower than those of controls. Activated partial thromboplastin times were also significantly lower in 50 and 100 mg/kg males, while platelet counts were significantly higher. Activities of alanine aminotransferase, sorbitol dehydrogenase, or γ-glutamyltransferase in 50 and 100 mg/kg male and 100 mg/kg female rats were significantly higher than those of the controls at the 15-month interim evaluation.

Pathology Findings

The principal lesions associated with the administration of coumarin to rats for up to 2 years occurred in the liver, kidney, and forestomach. While the hepatic lesions were seen in all groups of males, they occurred only in the 50 and 100 mg/kg females. The lesions consisted of a spectrum of changes including hepatocellular necrosis, fibrosis, cytologic alteration, and increased severity of bile duct hyperplasia. The incidences of hepatocellular neoplasms were not increased in dosed rats.

There was a chemical-related increase in the average severity of nephropathy in all groups of dosed male and female rats. There were corresponding increased incidences of parathyroid gland hyperplasia in all groups of dosed males, probably as a result of compromised renal function. In the standard evaluation of single kidney sections, a low incidence of renal adenomas was seen in all groups of males and in 100 mg/kg females (males: vehicle control, 1/49; 25 mg/kg, 2/50; 50 mg/kg, 2/51; 100 mg/kg, 1/50; females: 0/49, 0/50, 0/50, 2/49). An evaluation of step sections identified additional individuals with renal tubule focal hyperplasia (males: 2/49, 12/50, 10/51, 6/50; females: 1/49, 0/50, 4/50, 2/49) and adenoma (males: 0/49, 4/50, 5/51, 4/50; females: 0/49, 0/50, 1/50, 1/49) in the dosed groups.

The incidences of forestomach ulcers in all groups of dosed male rats and in 100 mg/kg female rats were significantly greater than those of the controls (males: 7/48, 24/50, 35/51, 34/50; females: 1/48, 1/49, 6/50, 9/48).

Stop-Exposure Evaluation

A group of 40 male rats received 100 mg/kg coumarin in corn oil by gavage for 9 months, when 20 of the animals were necropsied and evaluated. The remainder of the male rats received only the corn oil vehicle during the 15-month recovery period. Similarly, a group of 30 male rats received 100 mg/kg coumarin in corn oil by gavage for 15 months, when 10 of the rats were necropsied and evaluated. The remaining 20 rats received only corn oil during the 9-month recovery period. A group of 20 vehicle control male rats were necropsied at 9 months, and another 10 vehicle control male rats were necropsied at 15 months.

While chemical-related hepatic lesions were seen at both the 9- and 15-month interim evaluations, the incidences and severities of these lesions following the recovery period were generally similar to controls. Thus, the hepatic lesions produced by 9 or 15 months of exposure were reversible. In contrast to the liver lesions, the severity of nephropathy in male rats following the recovery period was significantly greater than that of males examined at the 9- and 15-month interim evaluations. This is not unexpected, since nephropathy is a progressive degenerative disease that naturally increases in severity with age.

The incidence of renal tubule hyperplasia in the 15-month stop-exposure group (dosed for 15 months followed by the recovery period) and the incidence of renal tubule adenoma in the 9-month stop-exposure group were significantly greater than those of the control group.

2-Year Study in Mice

Groups of 70 male and 70 female mice were administered coumarin in corn oil by gavage at doses of 0, 50, 100, or 200 mg per kg body weight for up to 2 years. After 15 months, 19 or 20 mice from each group were evaluated.

Survival, Body Weights, and Clinical Findings

Survival of dosed male and female mice was similar to that of the controls (males: vehicle control, 43/50; 50 mg/kg, 47/50; 100 mg/kg, 42/50; 200 mg/kg, 37/51; females: 33/50, 40/50, 42/51, 28/51). The mean body weights of 200 mg/kg male and female mice were lower than those of controls throughout much of the study. There were no clinical findings related to chemical administration.

Hematology and Clinical Chemistry

Mean erythrocyte volume, mean erythrocyte hemoglobin, and hematocrit of 200 mg/kg males and mean erythrocyte volume of 200 mg/kg females were significantly lower than those of the controls. Blood platelet counts of 200 mg/kg males and females were significantly higher than those of controls. There were no biologically significant differences in enzyme activities between dosed and control mice.

Pathology Findings

The principal toxic lesions associated with the administration of coumarin to mice occurred in the liver. The incidences of centrilobular hypertrophy in 100

and 200 mg/kg males and 200 mg/kg females were significantly greater than those of controls. The incidences of syncytial alteration in all male dose groups and in 200 mg/kg females were also significantly greater than controls.

The incidences of eosinophilic foci, a putative preneoplastic lesion, and of hepatocellular adenoma were significantly greater in the 50 and 100 mg/kg females. Hepatocellular carcinomas occurred with low incidences in the dosed females, but none occurred in the controls. The overall incidence of hepatocellular neoplasms (benign and malignant combined) in the 50 and 100 mg/kg females (control, 8/50; 50 mg/kg, 27/49; 100 mg/kg, 31/51; 200 mg/kg, 13/50) exceeds the range in historical controls (range 2%-34%; 129/898, 14.4%) from recent NTP studies. The reason for a lack of liver response in 200 mg/kg female mice is not known, but may be due in part to the decrease in body weight. While the incidences of eosinophilic foci were marginally greater in dosed male mice, the incidences of hepatocellular neoplasms were similar among the dosed and control groups.

The incidences of alveolar/bronchiolar adenomas were significantly greater in 200 mg/kg male and female mice than in the controls. Further, the incidence of alveolar/bronchiolar carcinoma in 200 mg/kg females was also significantly greater than in controls. The overall incidence of pulmonary neoplasms (benign and malignant combined) in the 200 mg/kg groups (males: 14/50, 9/50, 15/50, 25/51; females: 2/51, 5/49, 7/49, 27/51) exceeds the range in historical controls (males: range 6%-28%; 166/900, 18.4%; females: range 0%-14%; 58/899, 6.5%) from recent NTP studies.

The incidence of squamous cell papilloma of the forestomach in 50 mg/kg males was greater than that of the controls (2/50, 8/50, 2/50, 0/51) and also exceeds the range of this neoplasm in control male mice from recent NTP studies (range 0%-14%; 27/902, 3.0%). The incidence of squamous cell papilloma of the forestomach in 50 mg/kg female mice was also slightly increased (1/52, 5/50, 2/51, 2/51); however, the incidence did not exceed the NTP historical range (27/901, 3%; range, 0%-10%).

GENETIC TOXICOLOGY

Coumarin induced gene mutations in *Salmonella typhimurium* strain TA100 in the presence, but not in the absence, of exogenous metabolic activation (S9); no mutations were induced in strains TA98, TA1535, or TA1537, with or without S9. In Chinese hamster ovary cells, coumarin induced sister chromatid exchanges in the absence of S9, and chromosomal aberrations in the presence of S9. Coumarin did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* treated either as adults by feeding or injection, or as larvae by feeding. No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood of male and female B6C3F$_1$ mice administered coumarin by gavage for 13 weeks.

CONCLUSIONS

Under the conditions of these 2-year gavage studies there was *some evidence of carcinogenic activity** of coumarin in male F344/N rats based on increased incidences of renal tubule adenomas. There was *equivocal evidence of carcinogenic activity* of coumarin in female F344/N rats based on a marginally increased incidence of renal tubule adenomas. There was *some evidence of carcinogenic activity* of coumarin in male B6C3F$_1$ mice based on the increased incidence of alveolar/bronchiolar adenomas. There was *clear evidence of carcinogenic activity* of coumarin in female B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and hepatocellular adenomas. The marginally increased incidences of squamous cell papillomas of the forestomach in male and female mice receiving 50 mg/kg may have been related to coumarin administration.

The administration of coumarin to rats was also associated with an increased severity of nephropathy in the kidney and of bile duct hyperplasia in the liver, increased incidences of ulcers of the forestomach, and necrosis, fibrosis, and cytologic alteration of the liver. Administration of coumarin to mice was also associated with centrilobular hypertrophy, syncytial alteration, and eosinophilic focus in the liver.

---

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

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

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 25, 50, or 100 mg/kg in corn oil by gavage	0, 25, 50, or 100 mg/kg in corn oil by gavage	0, 50, 100, or 200 mg/kg in corn oil by gavage	0, 50, 100, or 200 mg/kg in corn oil by gavage
Body weights			
Dosed groups lower than controls	High-dose group lower than controls	High-dose group lower than controls	High-dose group lower than controls
2-Year survival rates			
28/50, 9/50, 2/51, 0/50	29/50, 38/50, 36/50, 30/50	43/50, 47/50, 42/50, 37/51	33/50, 40/50, 42/51, 28/51
Nonneoplastic effects			
Liver: cytologic alterations (0/49, 0/50, 28/51, 29/50); fibrosis (0/49, 3/50, 41/51, 42/50); necrosis (1/49, 13/50, 38/51, 40/50); bile duct hyperplasia severity grades (1.6, 1.8, 2.2, 2.1) Forestomach: ulcer (7/48, 24/50, 35/51, 34/50) Nephropathy severity grades (2.0, 3.1, 3.7, 3.6)	Liver: fibrosis (0/50, 0/50, 1/50, 12/50); necrosis (3/50, 3/50, 4/50, 15/50); degeneration (0/50, 0/50, 8/50, 30/50); bile duct hyperplasia severity grades (1.2, 1.3, 1.3, 1.5) Forestomach: ulcer (1/48, 1/49, 6/50, 9/48) Nephropathy severity grades (1.2, 1.4, 1.8, 2.3)	Liver: syncytial alteration (0/50, 6/50, 35/50, 47/51); centrilobular hypertrophy (1/50, 2/50, 23/50, 44/51); eosinophilic focus (6/50, 15/50, 13/50, 15/51)	Liver: syncytial alteration (0/50, 0/49, 2/51, 19/50); centrilobular hypertrophy (0/50, 0/49, 0/51, 17/50); eosinophilic focus (4/50, 20/49, 20/51, 9/50)
Neoplastic effects			
Kidney: renal tubule adenoma (single sections – 1/49, 2/50, 2/51, 1/50); renal tubule adenoma (step sections – 0/49, 4/50, 5/51, 4/50)	None	Lung: alveolar/bronchiolar adenoma (14/50, 8/50, 14/50, 24/51); alveolar/bronchiolar adenoma or carcinoma (combined) (14/50, 9/50, 15/50, 25/51)	Lung: alveolar/bronchiolar adenoma (2/51, 5/49, 7/49, 20/51); alveolar/bronchiolar carcinoma (0/51, 0/49, 0/49, 7/51); alveolar/bronchiolar adenoma or carcinoma (combined) (2/51, 5/49, 7/49, 27/51) Liver: hepatocellular adenoma (8/50, 26/49, 29/51, 12/50)
Uncertain findings			
None	Kidney: renal tubule adenoma (single sections – 0/49, 0/50, 0/50, 2/49); renal tubule adenoma (step sections – 0/49, 0/50, 1/50, 1/49)	Forestomach: squamous cell papilloma (2/50, 8/50, 2/50, 0/51)	Forestomach: squamous cell papilloma (1/52, 5/50, 2/51, 2/51)
Level of evidence of carcinogenic activity			
Some evidence	Equivocal evidence	Some evidence	Clear evidence
Genetic toxicology			
Salmonella typhimurium gene mutation:	Positive with S9 in TA100; negative with or without S9 in TA98, TA1535, and TA1537		
Sister chromatid exchanges			
Chinese hamster ovary cells *in vitro*:	Positive without S9		
Chromosomal aberrations			
Chinese hamster ovary cells *in vitro*:	Positive with S9		
Sex-linked recessive lethal mutations			
Drosophila melanogaster:	Negative when administered in feed or by injection		
Micronucleated erythrocytes			
B6C3F$_1$ mouse peripheral blood:	Negative at 13 weeks		

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 coumarin on June 23, 1992, 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.

Gary P. Carlson, Ph.D., Chair
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Paul T. Bailey, Ph.D., Principal Reviewer
Toxicology Division
Mobil Oil Corporation
Princeton, NJ

Louis S. Beliczky, M.S., M.P.H.*
Department of Industrial Hygiene
United Rubber Workers International Union
Akron, OH

Kowetha A. Davidson, Ph.D., Principal Reviewer
Health and Safety Research Division
Oak Ridge National Laboratory
Oak Ridge, TN

Harold Davis, D.V.M., Ph.D.
School of Aerospace Medicine
Brooks Air Force Base, TX

Jay I. Goodman, Ph.D.
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

David W. Hayden, D.V.M., Ph.D., Principal Reviewer
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

Curtis D. Klaassen, Ph.D.*
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Daniel S. Longnecker, M.D.*
Department of Pathology
Dartmouth Medical School
Lebanon, NH

Barbara McKnight, Ph.D.*
Department of Biostatistics
University of Washington
Seattle, WA

Ellen K. Silbergeld, Ph.D.
University of Maryland Medical School
Baltimore, MD

Lauren Zeise, Ph.D.
California Department of Health Services/RCHAS
Berkeley, CA

Matthew J. van Zwieten, D.V.M., Ph.D
Department of Safety Assessment
Merck, Sharp & Dohme Research Laboratories
West Point, PA

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 23, 1992, the draft Technical Report on the toxicology and carcinogenesis studies of coumarin received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of coumarin by discussing the uses and rationale for study, describing the experimental design including an additional 2-year stop-exposure evaluation in male rats, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in male and female rats and mice.

The proposed conclusions were *some evidence of carcinogenic activity* of coumarin in male F344/N rats and male $B6C3F_1$ mice, *equivocal evidence of carcinogenic activity* of coumarin in female F344/N rats, and *clear evidence of carcinogenic activity* of coumarin in female $B6C3F_1$ mice.

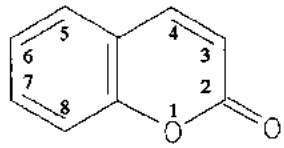
Dr. Bailey, a principal reviewer, agreed with the proposed conclusions. He said it would be useful to have pharmacokinetic or metabolism data on the fate of coumarin in the Fischer rat and $B6C3F_1$ mouse. Dr. Bailey said he would also like to see included in the report a discussion on the relevancy of these carcinogenicity studies to humans since there are data indicating that humans metabolize coumarin differently than do rodents. Dr. Dunnick said the available data on human and rodent metabolism of coumarin had been cited in the Introduction, but would also be integrated into the Discussion. Dr. Bailey reported that Rhone Poulenc, Inc., had evaluated the carcinogenic potential of coumarin in Swiss (CD-1®) mice and Sprague-Dawley rats, and suggested that the data be obtained and included after NTP review. Dr. Dunnick responded that the FDA had some of the Rhone Poulenc information under review and that, if available, it would be cited in the report.

Dr. Hayden, the second principal reviewer, agreed with the proposed conclusions. He asked why only male and not female rats were used in the stop-exposure evaluation. Dr. Dunnick said the liver lesions reported in the literature were observed in male rats. Dr. Hayden requested an explanation for the high incidence of bile duct hyperplasia in the absence of fibrosis in male vehicle control rats. Dr. S.L. Eustis, NIEHS, said that mild bile duct hyperplasia is a common spontaneous degenerative lesion of aging rats. Dr. Hayden said that the inclusion of a table comparing the toxic and carcinogenic effects of coumarin with those of 3,4-dihydrocoumarin would be useful.

Dr. Davidson, the third principal reviewer, agreed with the proposed conclusions for male rats and male and female mice, but disagreed with the conclusion for female rats. Based on the low incidences of hyperplasia and renal tubule adenomas, Dr. Davidson said she believed the conclusion for female rats should be *no evidence of carcinogenic activity*. Dr. Dunnick said that the incidence of two renal tubule adenomas in 100 mg/kg female rats was greater than the incidence in historical controls and added that renal tubule adenomas are rare neoplasms. Thus, an association between the occurrence of the neoplasm and the administration of coumarin could not be ruled out. Dr. Davidson asked if the stop-exposure evaluation was done in rats to determine if there was a relationship between progression and regression of liver neoplasms and the occurrence of cholangiofibrosis and bile duct carcinomas. Dr. Eustis said the primary purpose of the stop-exposure study was to examine the biological behavior of cholangiofibrosis and to determine if the lesions would progress to cholangiocarcinomas. He noted that the lesions progressed to carcinomas during the NTP studies on furan and that they had been reported in German studies. However, they were not induced in the present studies.

Dr. Bailey moved that the Technical Report on coumarin be accepted with the revisions discussed and with the conclusions as written, *some evidence of carcinogenic activity* for male rats and mice, *equivocal evidence of carcinogenic activity* for female rats, and *clear evidence of carcinogenic activity* for female mice. Dr. Hayden seconded the motion. Dr. Davidson offered an amendment that the level of evidence for female rats be changed to *no evidence of carcinogenic activity*. Dr. Goodman seconded the amendment, which was defeated by two yes (Drs. Davidson and Goodman) to six no votes. The original motion by Dr. Bailey was then accepted unanimously with eight votes.

INTRODUCTION



COUMARIN

CAS No. 91-64-5

Chemical Formula: $C_9H_6O_2$ Molecular Weight: 146.5

Synonyms: 5,6-benzo-alpha-pyrone, 2H-1-benzopyran-2-one, 2H-benzo[b]pyran-2-one, 1,2-oxo-1,2-benzopyran, 1,2-benzopyrone, *cis-o*-coumarinic acid lactone, coumarinic anhydride, cumarin, *o*-hydroxycinnamic acid lactone, kumarin, [2-propenoic acid, 3-(2-hydroxyphenyl)-delta-lactone], Rattex, tonka bean camphor

CHEMICAL AND PHYSICAL PROPERTIES

Coumarin is a colorless crystal, flake, or powder, with a fragrant odor similar to vanilla, and a bitter, aromatic burning taste. It is slightly soluble in water and freely soluble in hot ethanol. The ultraviolet absorption spectrum of coumarin in alcohol shows a strong band at 265 to 275 nm. The melting point of coumarin is 70.6° C, with a boiling point of 297° to 299° C. Coumarin is found naturally in plants and may also be synthesized from salicylaldehyde and acetic anhydride in the presence of sodium acetate (*Fenaroli's*, 1971; Hawley, 1977; *Kirk-Othmer*, 1978).

USE AND HUMAN EXPOSURE

Coumarin is the odoriferous principle of the tonka bean and sweet clover, and occurs in oil of lavender, oil of cassia, citrus oils, and in some 60 other species of plants. Coumarins are also found in the water-soluble fractions of cigarette smoke (Schumacher *et al.*, 1977) and in certain tobaccos and alcoholic beverages (Cohen, 1979). Coumarin was first isolated from tonka beans in 1820, and is now widely used in perfumes, cosmetics, and related products owing to its pleasant bitter-sweet and characteristic odor (*Kirk-Othmer*, 1978; Murray *et al.*, 1982). In addition, coumarin is used as an agent to mask the odor of other chemicals including iodoform, phenolic, and quinoline odors, and as such may be found in paints, printing inks, insecticides, plastics, and synthetic rubbers. It is also used in the electroplating industry to reduce porosity and increase brightness of electroplated metals, especially nickel, zinc, and cadmium (*Kirk-Othmer*, 1978). At one time coumarin was an important food-flavoring material, but in 1954 the FDA withdrew approval for the use of coumarin in foods because of reported liver toxicity in rodents (FDA, 1954). The annual production of coumarin has been estimated at greater than 544 tons (*Kirk-Othmer*, 1978).

Typical concentrations of coumarin found in common household products range from 0.03% to 0.2% in soaps, 0.003% to 0.02% in detergents, 0.015% to 0.1% in creams and lotions, and 0.3% to 0.8% in perfumes (Cohen, 1979).

The National Institute for Occupational Safety and Health estimated that approximately 240,000 workers are potentially exposed to coumarin (NIOSH, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

The metabolism and excretion of coumarin have been studied in several different species, including man. Coumarin metabolites identified and the percentages of dose excreted in the urine and feces of rat, rabbit, and man are shown in Table 1. Probable pathways for the metabolism of coumarin are shown in Figure 1.

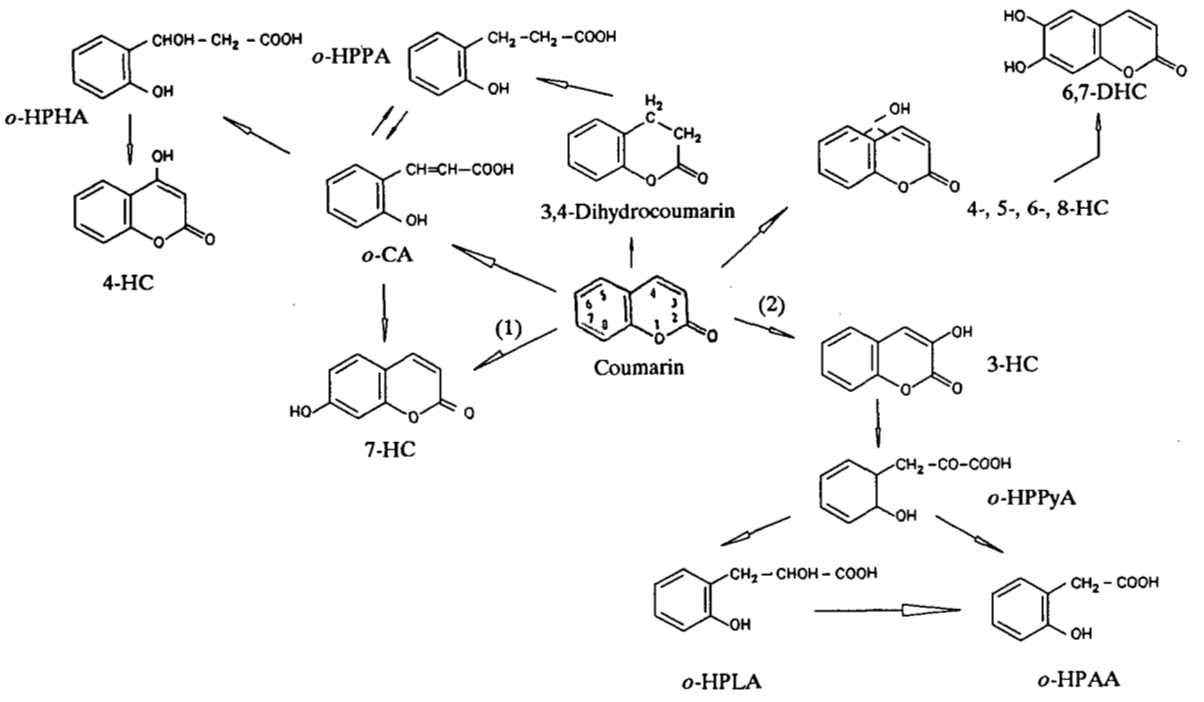
Coumarin is rapidly absorbed from the intestinal tract after oral administration. In rats given a single oral dose of [3-^{14}C]-coumarin, ^{14}C appeared in the serum, liver, and kidney within 5 minutes and attained a maximum concentration after 45 to 60 minutes (Feuer *et al.*, 1966). Within 48 hours, 70% of the oral dose was eliminated in the urine and 10% was eliminated in the feces. Similarly, in a group of four men and two women given 0.857 mg/kg coumarin *per os*, the parent compound and its major metabolite, 7-hydroxycoumarin, were detected in the blood within minutes while peak concentrations were reached in about 10 to 20 minutes (Ritschel *et al.*, 1977). More than 80% of the administered dose was excreted in the urine within 24 hours.

Coumarin and its metabolites do not accumulate to a significant extent in any rat (Kaighen and Williams, 1961; Feuer *et al.*, 1966) or rabbit tissues (Kaighen and Williams, 1961) following oral exposure or in any rat tissues following intraperitoneal administration (Van Sumere and Tuechy, 1971). Following administration of a single intraperitoneal dose of [3-^{14}C]-coumarin, ^{14}C was detected in various organs, particularly the liver and kidney, at levels much higher than that of the blood at any given period (Piller, 1977). The blood and tissue ^{14}C levels declined steadily over a 100-hour post-administration period, with a biological half-life of approximately 43 hours. Ritschel *et al.* (1976) reported a half-life of about 1.5 hours in the blood of humans given intravenous doses of 0.125 to 0.25 mg/kg.

TABLE 1
Coumarin Metabolites Identified in the Urine and Feces of Various Species[a]

	Rabbit[b]	Rat[b]	Human[c]
Metabolites in Urine			
Coumarin, Unchanged	12.3–16.7	3.1–7.4	–[d]
3-Hydroxycoumarin	18.1–28.2	1.7–1.8	–
4-Hydroxycoumarin	0.3–0.9	0.0–0.5	–
5-Hydroxycoumarin	0.3–0.5	–	–
6-Hydroxycoumarin	2.0–4.7	0.3	–
7-Hydroxycoumarin	10.0–16.0	0.3–0.5	68–92
8-Hydroxycoumarin	1.3–2.5	0.3–0.5	–
o-Coumaric	Trace	Trace	–
o-Hydroxyphenyllactic acid	2.6–3.5	0.6–0.9	–
o-Hydroxyphenylacetic acid	18.1–22.1	12.5–27.2	1–6
o-Hydroxyphenylpropionic acid	Trace	Trace	–
Total in Urine	80.3–92.4	47.0–60.5	80–100
Total in Feces	0.2–0.7	32.4–38.8	–

[a] Expressed as percentage of dose administered
[b] From Kaighen and Williams, 1961
[c] From Shilling *et al.*, 1969
[d] Metabolite not measured for this species



(1)	7-Hydroxylase
(2)	3-Hydroxylase
o-CA	*o*-Coumaric acid
6,7-DHC	6,7-Dihydroxycoumarin
3-HC	3-Hydroxycoumarin
4-HC	4-Hydroxycoumarin
5-HC	5-Hydroxycoumarin
6-HC	6-Hydroxycoumarin
7-HC	7-Hydroxycoumarin
8-HC	8-Hydroxycoumarin
o-HPAA	*o*-Hydroxyphenylacetic acid
o-HPHA	*o*-Hydroxyphenylhydracrylic acid
o-HPLA	*o*-Hydroxyphenyllactic acid
o-HPPA	*o*-Hydroxyphenylpropionic acid
o-HPPyA	*o*-Hydroxyphenylpyruvic acid

FIGURE 1
Pathways of Coumarin Metabolism *In Vivo* and *In Vitro* from Cohen (1979)

Coumarin is metabolized primarily in the liver by microsomal enzymes associated with the endoplasmic reticulum (Feuer *et al.*, 1965a,b; Peters *et al.*, 1991). Coumarin is metabolized first by cytochrome P-450 enzymes, resulting in hydroxylation prior to conjugation with glucuronide. Hydroxylation occurs primarily at the number 3 and 7 positions to yield 3-hydroxycoumarin or 7-hydroxycoumarin, respectively. 3-Hydroxycoumarin can be further metabolized by nonenzymatic ring opening to form *o*-hydroxyphenylacetic acid and *o*-hydroxyphenyllactic acid.

There are substantial qualitative differences in the metabolism of coumarin among various species. Studies with rat hepatic microsomes have shown that coumarin is metabolized by isoenzymes of the cytochrome P-450 IA and IIB subfamilies, resulting in hydroxylation primarily at the number 3 position with subsequent ring opening and further metabolism to *o*-hydroxyphenylacetic acid and *o*-hydroxyphenyllactic acid (Feuer, 1970a,b; Lake, 1984; Peters *et al.*, 1991). During this process, reactive metabolites are generated which covalently bind to microsomal proteins and glutathione (Peters *et al.*, 1991). Based on these studies, Peters *et al.* (1991), postulated that a coumarin 3,4-epoxide intermediate is formed which may rearrange to 3-hydroxycoumarin with subsequent ring opening, or form a glutathione conjugate. While hydroxylation also apparently occurs at other ring positions, the extent of activity at the 4, 5, 6, 7, or 8 positions is low in rats.

In contrast to rats, coumarin metabolism in humans results principally in the hydroxylation at the number 7 position with the formation of 7-hydroxycoumarin and 7-hydroxycoumarin glucuronide (Ritschel *et al.*, 1977). Further, Miles *et al.* (1990) have shown that the isoenzyme responsible for most, if not all, of the coumarin 7-hydroxylase activity in the human liver belongs to the cytochrome P-450 IIA subfamily.

The differences in metabolism of coumarin among various species is largely reflected by the quantitative differences in hydroxylation at the 3 and 7 positions. Gangolli *et al.* (1974) showed that the amount of 7-hydroxycoumarin found in the urine of various species, as a percentage of the administered dose of coumarin, was 1% in the squirrel monkey, ferret, and guinea pig; 3% in the mouse and dog; 5% in the hamster; 12% in the pig; 19% in the cat; and 60% in the baboon.

The metabolites of coumarin identified in various species are shown in Table 1. In rats, the metabolites are excreted in significant amounts in both the urine and feces. Following the oral administration of [3-^{14}C]-coumarin to rats, the amount of labeled metabolites in the urine varied from 47% to 60% of the administered dose, while that in the feces varied from 32% to 38% (Kaighen and Williams, 1961). Although some of the orally administered coumarin may be metabolized by intestinal microflora (Scheline, 1968), the significant level of metabolites found in the feces may reflect the high level of biliary excretion observed in the rat. Within 24 hours of an oral or intraperitoneal dose of 50 mg/kg, about 50% of the dose was excreted in the bile of rats as unidentified ring-opened compounds (Williams *et al.*, 1965). By contrast, in humans more than 80% of the metabolites of coumarin are found in the urine, suggesting that enterohepatic circulation of coumarin in humans is substantially less than that in rats.

TOXICITY

Experimental Animals

The oral LD_{50} value for coumarin is reported as 420 mg/kg in C3H/HeJ mice and 780 mg/kg in DBA/2J mice (Endell and Seidel, 1978). The oral LD_{50} for coumarin in rats is reported as 292 to 680 mg/kg (Hazleton *et al.*, 1956).

Osborne-Mendel rats fed coumarin in the diet at a level of 1,000 ppm for up to 4 weeks showed no evidence of toxicity, while rats fed 10,000 ppm coumarin for 4 weeks or 2,500 ppm for 29 weeks had growth retardation and liver alterations characterized as slight midzonal fatty change (Hagan *et al.*, 1967). In Sprague-Dawley rats given a single oral dose of 125 to 500 mg/kg coumarin, hepatotoxic changes consisting of centrilobular hepatic necrosis occurred within 24 hours (Lake, 1984). The mechanism for liver toxicity is thought to be due to the production of one or more coumarin metabolites by cytochrome P-450-dependent mixed-function oxidase enzymes. It has been hypothesized that a 3,4-epoxide intermediate may be responsible for coumarin-induced hepatotoxicity in the rat. 3,4-Dihydrocoumarin, which lacks the 3,4-double bond, does not produce liver toxicity when given to Sprague-Dawley rats intraperitoneally at doses of 127 or 254 mg/kg, although coumarin at these doses does produce hepatotoxicity (Lake *et al.*, 1989).

In another study, Sprague-Dawley rats were fed either a control diet or a diet containing 5,000 ppm coumarin for 1, 3, 6, 9, 12, or 18 months with estimated coumarin intakes of 50 mg/kg per day for 2 weeks, 360 mg/kg per day for 3 months, and 200 mg/kg per day for 1 year. After 1 month the liver showed extensive vacuolation of hepatocytes with some necrosis; the effect was diffuse and affected all lobes. After 3 months the bile duct proliferation was more extensive. After 9 or more months of coumarin treatment there were large areas of fibrosis in the liver. In addition, there were irregular ducts formed of pale staining cells in a heavy fibrous stroma. There was no evidence of local invasion or metastasis (Evans *et al.*, 1989).

Humans

Information on the toxicity of coumarin in humans is limited to Phase I and II toxicity studies in cancer patients given coumarin in combination with cimetidine. These studies found no major organ toxicity attributable to the use of coumarin, given at doses of 100 to 400 mg/day for several weeks to 1 month (Dexeus *et al.*, 1990).

Reproductive and Developmental Toxicity

Experimental Animals

No malformations were found in the offspring of mice fed diets containing 500 to 2,500 ppm coumarin on days 6 through 17 of gestation, but increased numbers of stillbirths and delayed ossification were seen at the 2,500 ppm level, and increased mortality up to 3 weeks of age was seen at all levels (Roll and Bär, 1967). The purity of the coumarin used in these studies was not given.

Humans

No information on the reproductive and developmental toxicity of coumarin in humans is reported in the literature.

Carcinogenicity

Experimental Animals

Coumarin administered in feed at a level of 5,000 ppm to six male and six female Osborne-Mendel rats for 2 years caused liver damage characterized as focal proliferation of bile ducts with cholangiofibrosis, fatty metamorphosis, and focal necrosis, but produced no carcinogenic effect (Hagan *et al.*, 1967). In addition, Evans *et al.* (1989) reported that long-term administration of coumarin at dietary levels of 5,000 ppm produced cholangiofibrosis in Sprague-Dawley rats, but no treatment-related tumors. Groups of Syrian golden hamsters fed diets containing 0, 1,000, or 5,000 ppm coumarin for up to 2 years showed no evidence of hepatotoxicity or hepatocarcinogenicity (Ueno and Hirono, 1981). Baboons receiving doses of 0, 2.5, 7.5, 22.5, or 67.5 mg/kg coumarin for 16 or 24 months showed no evidence of dose-related tumors. Liver toxicity was observed at the high dose and was characterized as dilatation of the endoplasmic reticulum (Evans *et al.*, 1979).

Bär and Griepentrog (1967) and Griepentrog (1973) characterized liver lesions in rats as bile duct carcinomas after long-term administration of coumarin. In these studies five groups of rats were fed diets containing 1,000 to 6,000 ppm coumarin for up to 2 years. Of the animals surviving to the end of the studies, 12 rats that received 5,000 ppm and five rats that received 6,000 ppm developed bile duct carcinomas. No carcinomas were seen in the rats fed 1,000 or 2,500 ppm coumarin (Bär and Griepentrog, 1967; Griepentrog, 1973). Cohen (1979) reported that a review of the bile duct lesions in the Griepentrog study showed that the cytologic changes in the bile duct were more consistent with fatty degeneration, necrosis, and proliferation than with the original diagnosis of carcinoma. These studies provided little information on the purity of the coumarin used, and little consistent information on other toxic endpoints such as clinical findings and body weights.

In a study of 3,4-dihydrocoumarin, administered by subcutaneous injection twice a week for 51 or 57 weeks at a dose of 0.5 mg to mice and 2 mg to rats, no tumors were found. Only a few animals were included in each treatment group (Dickens and Waynforth, 1968). In addition, no tumors were observed in dogs administered 3,4-dihydrocoumarin orally at a dose of 150 mg/kg per day for 2 years (Hagan *et al.*, 1967).

No tumors were observed in Osborne-Mendel rats that received diets containing 500 to 15,000 ppm 6-methylcoumarin for up to 2 years (Hagan *et al.*, 1967).

Humans

Some coumarin derivatives have been reported to have antitumor activity against human cancer (Nair *et al.*, 1991). The precise mechanism is not understood, but it has been suggested that this antitumor activity may be due to immune modulation. At this time coumarin is not approved by the FDA for use as an anticancer agent. Compounds structurally related to coumarin, such as Warfarin (3-α-phenyl-ß-acetyl-ethyl-4-hydroxy-coumarin), are used as anticoagulants, but coumarin itself has no anticoagulant properties and is not approved for use as a licensed drug in the United States (Thornes *et al.*, 1989). At the 1991 meeting of the American Cancer Society there were several reports on the antitumor properties of coumarin, nitrocoumarin derivatives, and 6,7-OH coumarin derivatives in a variety of model systems. When MTV-H-*ras* transgenic mice were given 200 μM coumarin in drinking water for 6 months, tumor incidence was decreased and tumor onset was delayed (Tseng, 1991). Coumarin has also been reported to inhibit the effects of 7,12-dimethylbenz(a)anthracene-induced neoplasia in the rat mammary gland (Wattenberg *et al.*, 1979).

Coumarin administered to humans at a dose of 1 g/m^2 per day for 8 days significantly increased lymphocyte response to phytohaem-agglutinin, indicating that coumarin can activate lymphocytes and stimulate some immunologic functions (Berkarda *et al.*, 1983). Other studies on the ability of coumarin to restore cellular immunity in patients with chronic brucellosis have been reported by Thornes (1983). Cellular immunity was partially restored in patients given 25 mg coumarin daily for 6 months or 100 mg daily for 1 month as evidenced by increased numbers of lymphocytes and activated T cells, and a restoration of the delayed hypersensitivity reaction which is often decreased in patients with brucellosis. Other *in vitro* studies also suggest that coumarin may enhance the lymphocytic mitogenic response (Marshall *et al.*, 1989b).

Liver toxicity was not reported in humans where coumarin and related compounds were used as experimental anticancer agents with a typical oral dose of approximately 100 mg/day (Marshall *et al.*, 1987a,b; 1989a).

GENETIC TOXICITY

Coumarin induced gene mutations in *Salmonella typhimurium* strain TA100 in the presence of S9 activation; no mutagenic activity was noted in any other test strains, with and without S9 (Stoltz and Scott, 1980; Norman and Wood, 1981; Haworth *et al.*, 1983). No induction of sex-linked recessive lethal mutations was observed in germ cells of male *Drosophila melanogaster* treated with coumarin as adults, by feeding or injection (Yoon *et al.*, 1985), or as larvae by feeding (Valencia *et al.*, 1989). No increase in unscheduled DNA synthesis was reported in rat tracheal epithelium cultures treated with 1.46 mg/mL coumarin in the absence of S9 (Ide *et al.*, 1981).

Chromosomal effects have been reported in mammalian cells following treatment with coumarin. Cytogenetic tests with Chinese hamster ovary cells demonstrated induction of sister chromatid exchanges by 100 to 300 μg/mL coumarin in the absence, but not the presence, of S9; a dose-related increase in chromosomal aberrations was also observed in Chinese hamster ovary cells after treatment with coumarin, but only in the presence of S9 (Galloway *et al.*, 1987).

Studies of the cytogenetic effects of coumarin in plants are difficult to interpret due to the presentation of the experimental protocols and the data. However, there seems to be agreement that mitotic inhibition and increases in the frequencies of acentric fragments, anaphase bridges, and other chromosomal abnormalities in plants were consequences of coumarin exposures (D'Amato and D'Amato-Avanzi, 1954; Riley and Hoff, 1960; Sarma and Tripathi, 1976).

The only metabolites for which genotoxicity information is available are 7-hydroxycoumarin and 3,4-dihydrocoumarin. 7-Hydroxycoumarin did not induce gene mutations in *Salmonella typhimurium* strains TA98, TA100, or TA1537, with and without S9, at doses up to 2 mg/mL, but it was reported to induce mutations in *Klebsiella pneumoniae* in the absence of S9 (Voogd *et al.*, 1980). Previously

published genotoxicity data for 3,4-dihydrocoumarin are limited to two *Salmonella* gene mutation assays, conducted with and without S9; results from both studies were negative for TA98, TA100, TA1535, and TA1537 (Prival *et al.*, 1982; Haworth *et al.*, 1983). In the companion NTP studies of 3,4-dihydrocoumarin, chemical administration induced sister chromatid exchanges, but not chromosomal aberrations in cultured Chinese hamster ovary cells, with and without S9. No induction of micronuclei was observed in peripheral blood erythrocyte samples obtained from male and female B6C3F$_1$ mice at the end of the 13-week toxicity study (NTP, 1993).

Study Rationale

Coumarin was nominated by the FDA and NCI for toxicity and carcinogenicity studies because it is widely distributed in perfumes, soaps, and other common household products; because of continued interest in using coumarin compounds as flavor-enhancing agents for foods; and because complete comparative toxicity and carcinogenicity studies in rats and mice had not previously been performed. The oral route of exposure was used to mimic exposure in foods. Due to minimal solubility in water and unpalatability in feed, coumarin was administered by gavage in corn oil.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF COUMARIN

Coumarin was obtained from Rhone Poulenc, Incorporated (Monmouth Junction, NJ), in two lots (7971 and 5H2003). Lot 7971 was used throughout the 16-day and 13-week studies and lot 5H2003 was used throughout the 2-year studies. Identity, purity, and stability analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and confirmed by the study laboratory (Appendix I).

Both lots of the chemical, a white crystalline powder, were identified as coumarin by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of the lots was found to be greater than 97% by Karl Fischer water analysis, titration of the free acid, lactone hydrolysis, thin-layer chromatography, and gas chromatography. Thin-layer chromatography of both lots indicated only one major spot. Gas chromatography of both lots indicated one major peak and no impurities with total areas greater than 0.1% relative to the major peak area. Stability studies performed at the analytical chemistry laboratory indicated that coumarin was stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically at the study laboratory with gas chromatography and free acid titration methods; no change in purity was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulation suspensions for gavage administration were prepared by mixing coumarin and corn oil (Table I1). Studies to determine stability of the gavage preparations were conducted by the analytical chemistry laboratory. The stability studies of the dose formulations were performed using a gas chromatographic method. The findings of the studies indicated that the dose formulations were stable for at least 3 weeks at room temperature, when stored in the dark, and under simulated dosing conditions (exposed to light and air for 3 hours). No special handling was required during dosing.

Periodic analyses of the dose formulations of coumarin were conducted at the study laboratory and the analytical chemistry laboratory using ultraviolet spectroscopy. During the 16-day studies all dose formulations were analyzed. During the 13-week studies, the dose formulations were analyzed every 6 weeks (Tables I2 and I3). During the 2-year studies, the dose formulations were analyzed every 6 to 10 weeks (Table I4). In the 2-year studies, 100% of the dose formulations were within 10% of the target concentrations. Periodic analyses of the corn oil vehicle by the study laboratory indicated that peroxide levels were within the acceptable limit of 10 mEq/kg. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table I5).

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, MI). At receipt the rats and mice were 35 to 42 days old. The animals were quarantined for 14 days before dosing began. During this time two males and two females of each species were randomly selected and evaluated for evidence of disease.

Groups of five male and five female rats received coumarin in corn oil by gavage at doses of 0, 25, 50, 100, 200, or 400 mg/kg body weight; groups of five male and five female mice received coumarin in corn oil by gavage at doses of 0, 40, 75, 150, 300, or 600 mg/kg body weight. All doses were given once daily for 5 days per week, with at least two consecutive dosing days at the end of the studies. Animals were housed five per cage; water and feed were available *ad libitum*. Clinical findings were recorded twice daily. The animals were weighed at study initiation, at day 7, and at the end of the studies. Details of study design and animal maintenance are summarized in Table 2.

At the end of the 16-day studies, blood was collected from the orbital sinus of all animals for clinical pathology analyses. The clinical pathology parameters measured are listed in Table 2. A gross necropsy was performed on all rats and mice, and complete histopathologic examinations were conducted on all animals. The tissues routinely examined microscopically are listed in Table 2.

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to coumarin and to determine the appropriate doses 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 rats were 29 to 36 days old and the mice were 36 to 43 days old. The animals were quarantined for 23 (rats) or 24 (mice) days before dosing began. At this time, five males and five females of each species were randomly selected and evaluated for evidence of disease. At the end of the studies, serologic analyses were performed on 5 rats and 10 mice of each sex using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats and mice received coumarin in corn oil by gavage at doses of 0, 19, 38, 75, 150, or 300 mg/kg body weight 5 days per week for 13 weeks. Animals were housed five per cage; water and feed were available *ad libitum*. Clinical findings were recorded twice daily. The animals were weighed at the beginning of the studies and weekly thereafter. Further details of study design and animal maintenance are summarized in Table 2.

At the end of the 13-week studies, blood was collected from all animals and urine was collected from rats for clinical pathology analyses. The parameters measured are listed in Table 2. A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of rats were weighed. The left kidney, liver, and left testis of mice were weighed. Tissues for microscopic examination were 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 control animals, animals killed moribund, and all animals from the 300 mg/kg dose groups that lived to the end of the studies. The livers from all dosed rats and mice were examined microscopically. Table 2 lists the tissues and organs routinely examined microscopically.

2-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats received coumarin in corn oil by gavage at doses of 0, 25, 50, or 100 mg/kg body weight for 103 weeks; groups of 70 male and 70 female mice received coumarin in corn oil by gavage at doses of 0, 50, 100, or 200 mg/kg body weight for 103 weeks. Ten rats and 20 mice per dose group were designated for interim evaluations after 15 months of chemical administration.

Stop-Exposure Evaluation

Groups of male rats receiving 100 mg/kg coumarin for 9 or 15 months followed by a recovery period were evaluated to assess the potential for coumarin-induced liver lesions to progress or regress. This stop-exposure evaluation was conducted based on literature reports of hepatic cholangiofibrosis and cholangiocarcinomas occurring in rats given coumarin for 2 years (Bär and Griepentrog, 1967).

A group of 40 male rats received 100 mg/kg coumarin in corn oil by gavage for 9 months, when 20 of the animals were necropsied and evaluated. The remainder of the male rats received only the corn oil vehicle until they died or the end of the study was reached. Similarly, a group of 30 male rats received 100 mg/kg coumarin in corn oil by gavage for 15 months, when 10 of the rats were necropsied and evaluated. The remaining 20 rats received only corn oil until the end of the study. A group of 20 vehicle control male rats were necropsied at 9 months, and another 10 vehicle control male rats were necropsied at 15 months for comparison with those receiving coumarin and killed at these time points. The incidences of lesions in male rats receiving coumarin and evaluated at 9 or 15 months were compared with those in male rats receiving coumarin for 9 or 15 months, respectively, followed by the recovery period.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD) for use in the 2-year studies. Rats were quarantined for 15 (males) or 16 (females) days, and mice were quarantined for 16 (males) or

17 (females) days before the beginning of the studies. Five rats and five mice of each sex were randomly selected and evaluated for evidence of disease. Serology samples were collected for viral screening. Rats and mice in the 2-year studies were 44 (males) and 45 (females) days old at the beginning of the studies. The health of the animals was monitored during the studies according to the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Feed and water were available *ad libitum*. Cages were rotated every 2 weeks. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded weekly for the first 13 weeks, and monthly thereafter. Animals were weighed at the beginning of the studies, weekly for the initial 13 weeks, and monthly thereafter. Blood was collected by cardiac puncture from all animals at the 9- and 15-month interim evaluations to determine hematology and clinical chemistry parameters. The clinical pathology parameters measured are listed in Table 2. The brain, left kidney, right kidney, and liver were weighed at the 9- and 15-month interim evaluations.

A complete necropsy was performed on all animals. 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 gross lesions. 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 microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. A quality assessment pathologist reviewed the kidney in rats, the clitoral gland and thyroid gland in female rats, and the liver and lung in mice for accuracy and consistency of lesion diagnosis.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the kidney in rats and mice, clitoral gland and nose in rats, forestomach, lung, lymph node, salivary gland, skeletal muscle, skin, and uterus in mice, and any tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of disagreements in diagnosis between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chair to the PWG for review. 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 dose groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that 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, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses if they were found dead of other than natural causes or were found to be missing; 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, and E4 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, and E3) and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) 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.

Analysis of Neoplasm Incidences

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 it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When 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 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 neoplasm-bearing animals. Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of 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 method used was a logistic regression analysis in which lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of neoplasm incidence. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry and hematology data, which typically have skewed distributions, were analyzed using the nonparametric multiple comparison methods of Dunn (1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with 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, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of coumarin was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and *Drosophila melanogaster*, chromosome damage in Chinese hamster ovary cells, and micronuclei in the peripheral blood cells of mice. The protocols for these studies and the results are given in Appendix F.

The genetic toxicity studies of coumarin 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 of the chemical and its responses in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-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 predicitivty of the *Salmonella* alone. The predictivity of carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

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

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Study Laboratory			
International Research and Development Corporation, Mattawan, MI	International Research and Development Corporation, Mattawan, MI	American Biogenics Corporation, Woburn, MA	American Biogenics Corporation, Woburn, MA
Strain and Species			
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Male Rats: F344/N	Rats: F344/N Mice: $B6C3F_1$
Animal Source			
Charles River Breeding Laboratories, Inc., Portage, MI	Charles River Breeding Laboratories, Inc., Portage, MI	Frederick Cancer Research Center, Frederick, MD	Frederick Cancer Research Center, Frederick, MD
Time Held Before Studies			
14 days	Rats: 23 days Mice: 24 days	15 days	Rats: 15 days (males) and 16 days (females) Mice: 16 days (males) and 17 days (females)
Average Age When Studies Began			
49-56 days	Rats: 52-59 days Mice: 60-67 days	44 days	44 days (males) and 45 days (females)
Date of First Dose			
5 January 1981	Rats: 9 April 1981 Mice: 10 April 1981	6 September 1984	Rats: 6 September 1984 (males) 7 September 1984 (females) Mice: 8 November 1984 (males) 9 November 1984 (females)
Duration of Dosing			
16 days	91 days	9-Month stop-exposure group: 39-40 weeks 15-Month stop-exposure group: 65 weeks	103 weeks
Date of Last Dose			
21 January 1981	Rats: 9 July 1981 Mice: 10 July 1981	27 August 1986	Rats: 27 August 1986 (males) 28 August 1986 (females) Mice: 29 October 1986 (males) 30 October 1986 (females)

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

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Necropsy Dates			
21 January 1981	Rats: 9 July 1981 Mice: 10 July 1981	9-Month interim: 6-7 June 1985 15-Month interim: 2-5 December 1985 Terminal: 4-5 September 1986	Rats: 15-Month interim – 2-6 December 1985 Terminal – 4-10 September 1986 Mice: 15-Month interim – 5-7 and 10-11 February 1986 Terminal – 6-7 and 10-12 November 1986
Average Age at Necropsy			
65-72 days	Rats: 143-150 days Mice: 151-158 days	9-Month interim: 46 weeks 15-Month interim: 71-72 weeks	15-Month interim: 71-72 weeks 2-year study 110-111 weeks
Size of Study Groups			
5 males and 5 females	10 males and 10 females	9-Month stop-exposure: 20 dosed and 20 control rats evaluated at 9 months; 20 dosed rats evaluated after recovery period. 15-Month stop-exposure: 10 dosed and 10 control rats evaluated at 15 months; 20 dosed rats evaluated after recovery period.	Rats: 60 males and 60 females Mice: 70 males and 70 females
Method of Distribution			
Animals assigned by random numbers; average cage weights were approximately equal.	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Animals per Cage			
5	5	5	Rats: 5 Mice: 1
Method of Animal Identification			
Rats: Metal tag Mice: Toe clip	Rats: Metal tag Mice: Toe clip	Toe clip	Toe clip
Diet			
NIH-07 open formula mash diet (Zeigler Brothers, Inc., Gardners, PA); available *ad libitum*	Same as 16-day studies	NIH-07 pelleted diet (Zeigler Brothers, Inc., Gardners, PA); available *ad libitum*	Same as stop-exposure evaluation

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

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Maximum Storage Time for Feed			
120 days from the date of milling	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Water			
Automatic watering system, available *ad libitum*	Same as 16-day studies	Hardco Automatic Watering System, available *ad libitum*	Same as stop-exposure evaluation
Cages			
Clear polycarbonate, changed twice weekly	Same as 16-day studies	Polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice weekly	Same as stop-exposure evaluation
Bedding			
BetaChips®, hardwood laboratory bedding (Northeastern Products Corp., Warrensburg, NY), changed twice weekly	Same as 16-day studies	Sani-chip heat-treated hardwood chips (Old Mother Hubbard, Lowell, MA), changed twice weekly	Same as stop-exposure evaluation
Cage Filters			
Nonwoven polyester, changed every other week	Nonwoven polyester, changed once weekly	Nonwoven polyester (Snow Filtration Co., Cincinnati, OH), changed once every 2 weeks	Same as stop-exposure evaluation
Racks			
Stainless steel, changed every other week	Stainless steel, changed once weekly	Stainless steel (Lab Products, Inc., Maywood, NJ), changed once every 2 weeks	Same as stop-exposure evaluation
Animal Room Environment			
Temperature: 22° C Relative humidity: 36% Fluorescent light: 12 hours/day Room air: not available	Temperature: Rats – 24° C Mice – 23° C Relative humidity: Rats – 47.1% Mice – 50.8% Fluorescent light: 12 hours/day Room air: not available	Temperature: 22.7° C ± 1.2° C Relative humidity: 55.7% ± 8.6% Fluorescent light: 12 hours/day Room air: not available	Temperature: Rats – 22.7° C ± 1.2° C Mice – 21.9° C ± 0.8° C Relative humidity: Rats – 55.7% ± 8.6% Mice – 56.7% ± 7.4% Fluorescent light: 12 hours/day Room air: not available
Doses			
Rats: 0, 25, 50, 100, 200, or 400 mg/kg coumarin in corn oil by gavage; once daily, 5 days per week Mice: 0, 40, 75, 150, 300, or 600 mg/kg coumarin in corn oil by gavage; once daily, 5 days per week	Rats: 0, 19, 38, 75, 150, or 300 mg/kg coumarin in corn oil by gavage; once daily, 5 days per week Mice: 0, 19, 38, 75, 150, or 300 mg/kg coumarin in corn oil by gavage; once daily, 5 days per week	0 or 100 mg/kg coumarin in corn oil by gavage; once daily, 5 days per week for 9 or 15 months; followed by administration of only corn oil by gavage until the end of the 2-year study	Rats: 0, 25, 50 or 100 mg/kg coumarin in corn oil by gavage; once daily, 5 days per week Mice: 0, 50, 100, or 200 mg/kg coumarin in corn oil by gavage; once daily, 5 days per week

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

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Type and Frequency of Observation			
Animals observed for mortality twice daily; animals weighed initially, weekly, and at the end of the studies; clinical observations recorded daily	Animals observed for mortality twice daily; animals weighed initially, weekly, and at the end of the studies; clinical observations recorded daily and once weekly at the following intervals: pre-dosing, 30-60 minutes post-dosing, and 2 hours post-dosing	Animals observed for mortality twice daily; animal weights and clinical findings recorded weekly through week 13, monthly thereafter, and at interim evaluations or at the end of the studies.	Same as stop-exposure evaluation
Method of Sacrifice			
Carbon dioxide asphyxiation	Same as 16-day studies	9- and 15-month interims: Anesthetized with methoxyflurane followed by exsanguination Terminal: Carbon dioxide asphyxiation	Same as stop-exposure evaluation
Necropsy			
Necropsy performed on all animals.	Necropsy performed on all animals. Organs weighed included: Rats – brain, heart, right kidney, liver, lung, right testis, and thymus Mice – left kidney, liver, and left testis	Necropsy performed on all animals. Organ weights recorded for brain, left kidney, right kidney, and liver.	Necropsy performed on all animals. Organ weights recorded for brain, left kidney, right kidney, and liver.
Clinical Pathology			
Blood samples were collected from the orbital sinus of all animals. *Hematology:* platelets, capillary clotting time, fibrinogen (rats), prothrombin time (rats), activated partial thromboplastin time (rats)	Blood from the orbital sinus was collected from all animals surviving to the end of the studies. Urine samples were collected from rats only. *Hematology:* hematocrit, hemoglobin, erythrocytes, leukocyte count and differential, platelets, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, prothrombin time, and clotting time (mice) (continued)	Blood samples were obtained by cardiac puncture from all animals at the interim evaluations. *Hematology:* hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, reticulocytes, leukocyte count and differential, nucleated erythrocytes, activated partial thromboplastin time, and thromboplastin time (continued)	Blood samples were obtained by cardiac puncture from all animals at the interim evaluations. *Hematology:* hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, reticulocytes, leukocytes count and differential, nucleated erythrocytes, activated partial thromboplastin time (rats), and thromboplastin time (rats) (continued)

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

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Clinical Pathology (continued)			
	Clinical chemistry (rats only): sodium, potassium, chloride, calcium, alanine aminotransferase, aspartate aminotransferase, ornithine carbamoyltransferase, lactate dehydrogenase, sorbitol dehydrogenase, blood urea nitrogen, creatinine, total protein, albumin, A/G ratio, bilirubin, cholinesterase, and phosphorus ***Urinalysis (rats only):*** specific gravity	***Clinical chemistry:*** calcium, alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, and gamma-glutamyltransferase	***Clinical chemistry:*** calcium (rats), alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, and gamma-glutamyltransferase
Histopathology			
None	Complete histopathology was performed on all controls, all animals killed moribund, and all high-dose animals surviving to the end of the studies. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland, mandibular lymph node, mesenteric lymph node, muscle, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, small intestine (duodenum, ileum, jejunum), spleen, sternum (including marrow), stomach (mice), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the liver was examined in all dosed groups.	Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (including marrow), brain, epididymis, esophagus, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph node (mandibular and mesenteric), mammary gland, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, ileum, jejunum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, and urinary bladder.	Complete histopathology was performed on all animals. In addition, to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph node (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, ileum, jejunum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

16-DAY STUDY

All female rats and four male rats that received 400 mg/kg died within the first 3 days of the study (Table 3). One male receiving 50 mg/kg also died on day 3, but the death was caused by gavage error rather than chemical toxicity. There were no clinical signs relating to specific organ toxicity, although one or more male or female rats in the 400 mg/kg group exhibited excessive lacrimation, decreased activity, prostration, ataxia, or bradypnea in the first several days prior to death. The final mean body weights and mean body weight gains of rats that received 200 mg/kg or less were similar to those of the controls. There was no evidence of impaired blood coagulation from measurements of capillary clotting time, prothrombin and activated partial thromboplastin time, and blood fibrinogen at the end of the study (Table H1). Histopathology was not performed in the 16-day study. Because of the chemical-related deaths in rats receiving 400 mg/kg in the 16-day study, 300 mg/kg was selected as the high dose for the 13-week study.

TABLE 3
Survival and Mean Body Weights of Rats in the 16-Day Gavage Study of Coumarin

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	134 ± 5	183 ± 6	49 ± 3	
25	5/5	137 ± 7	192 ± 7	55 ± 3	105
50	4/5[c]	139 ± 10	191 ± 9	51 ± 4	104
100	5/5	137 ± 6	191 ± 7	54 ± 2	104
200	5/5	135 ± 5	181 ± 5	47 ± 2	99
400	1/5[d]	136 ± 5	159	24	87
Female					
0	5/5	109 ± 3	136 ± 4	27 ± 2	
25	5/5	110 ± 4	140 ± 5	30 ± 2	103
50	5/5	112 ± 3	141 ± 4	29 ± 1	104
100	5/5	109 ± 3	138 ± 3	29 ± 1	102
200	5/5	111 ± 3	136 ± 3	25 ± 2	100
400	0/5[e]	110 ± 2	–	–	–

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No data were collected for groups with 100% mortality. Differences from the control group are not significant by Williams' or Dunnett's tests.
[c] Day of death: 3
[d] Day of death: 2, 2, 2, 3
[e] Day of death: 2, 2, 3, 3, 3

13-WEEK STUDY

Three females and one male receiving 300 mg/kg died during the first week of the study, and two additional males in the 300 mg/kg group died during weeks 8 and 9 (Table 4). There were no other chemical-related deaths. There were no clinical signs related to specific organ toxicity.

Swelling in the ventral neck region, presumably due to edema and inflammation of the subcutaneous tissue, salivary glands and/or lymph nodes, was observed in one or more rats in each of the dosed and control groups, except for the 19 and 150 mg/kg groups of females. These observations were made during weeks 7 and 8 of the study and were likely due to infection with sialodacryoadenitis virus, although serology analyses were not performed. Diffuse inflammation of the salivary gland, consistent with sialodacryoadenitis virus infection, was observed microscopically in two 300 mg/kg male rats that died in weeks 8 and 9. In the weeks that followed, some rats also exhibited excessive lacrimation and porphyrin-stained crusts around the eyes and mouth. These observations were also likely related to viral infection.

The final mean body weights and body weight gains of male rats that received 150 or 300 mg/kg were significantly lower than those of controls (Table 4). In contrast, mean body weight gains of females receiving coumarin, except for the 300 mg/kg group, were higher than those of the controls. While the increased body weights are likely related to increased feed consumption, the cause is not readily apparent.

Male and female rats receiving coumarin exhibited dose-related decreases in mean erythrocyte volume and mean erythrocyte hemoglobin, and dose-related increases in erythrocyte counts (Table H2). The differences in these parameters between the dosed groups and controls were significant primarily in rats that received 75 mg/kg or more, although some were significant at lower doses. Although these changes

TABLE 4
Survival and Mean Body Weights of Rats in the 13-Week Gavage Study of Coumarin

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	179 ± 6	335 ± 9	156 ± 7	
19	10/10	178 ± 4	321 ± 5	143 ± 4	96
38	10/10	176 ± 4	336 ± 7	161 ± 5	100
75	10/10	177 ± 5	322 ± 6	145 ± 5	96
150	10/10	181 ± 6	310 ± 5**	129 ± 3**	92
300	7/10[c]	181 ± 5	278 ± 6**	101 ± 5**	83
Female					
0	10/10	132 ± 3	191 ± 2	59 ± 3	
19	10/10	132 ± 3	204 ± 3*	72 ± 2**	107
38	10/10	128 ± 4	202 ± 3	74 ± 3**	106
75	10/10	132 ± 3	200 ± 3	68 ± 1	105
150	10/10	133 ± 3	205 ± 2*	72 ± 2**	107
300	7/10[d]	130 ± 3	190 ± 7	62 ± 5	100

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Week of death: 1, 8, 9
[d] Week of death: 1, 1, 1

are statistically significant and chemical related, the actual differences are slight and are not clinically important. The hematocrit and hemoglobin concentration of dosed groups were similar to those of controls, and there was no chemical-related effect on activated partial thromboplastin time.

The serum levels of total bilirubin and several cytoplasmic enzymes including alanine aminotransferase, aspartate aminotransferase, ornithine carbamoyltransferase, and sorbitol dehydrogenase were markedly higher in many male and female rats receiving 300 mg/kg than in controls (Table H2). The values of some of these enzymes were also higher in rats, particularly males, receiving 150 mg/kg. These changes are consistent with the liver toxicity observed histologically.

At necropsy the absolute and relative liver weights of male and female rats receiving 150 or 300 mg/kg coumarin were significantly greater than those of the controls (Table G1). The increased relative weights of testis (males), lungs, kidney, heart, and brain of male and female rats were the result of lower body weights rather than organ toxicity. The absolute and relative thymus weights of 300 mg/kg male and female rats were significantly lower than those of controls, presumably as a result of debilitation and stress associated with liver toxicity.

Consistent with the elevations in serum enzymes and increases in liver weights, the principal morphologic lesion associated with the administration of coumarin occurred in the liver of male and female rats receiving 150 or 300 mg/kg (Table 5). The toxic lesion,

TABLE 5
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Gavage Study of Coumarin

Dose	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male						
Liver[a]	10	10	10	10	10	10
Centrilobular Hepatitis[b]	0	0	0	1	7°°(1.6)[c]	10°°(2.7)
Kidney	10	10	10	10	10	10
Nephropathy	0	0	0	0	8°° (1.0)	6°°(1.0)
Necrosis	0	0	0	0	0	3 (2.3)
Female						
Liver	10	10	10	10	10	10
Centrilobular Hepatitis	0	0	0	0	5°(1.4)	10°°(2.8)
Kidney	10	–[d]	–	–	–	10
Nephropathy	1					5 (1.0)
Necrosis	0					5° (1.1)

° Significantly different (P≤0.05) from the control group by the Fisher exact test
°° P≤0.01
a Number of animals with organ examined microscopically.
b Number of animals with lesion.
c Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
d Kidney not examined microscopically at these dose levels.

recorded as centrilobular hepatitis, consisted of a spectrum of changes including centrilobular hepatocyte degeneration and necrosis, chronic active inflammation, and bile duct hyperplasia. The lesions varied in severity from animal to animal as well as from lobule to lobule within the liver of any particular animal. In general, however, the lesions varied from minimal to mild in rats receiving 150 mg/kg and mild to marked in rats receiving 300 mg/kg.

Degeneration of hepatocytes was the most frequent change and varied from minimal cell injury to overt necrosis. Hepatocyte degeneration consisted of swollen cells with granular or vacuolated cytoplasm (Plate 1). Ultrastructural examination of these hepatocytes revealed accumulations of small- to moderate-sized lipid droplets within the cytoplasm. Hepatocellular necrosis varied in severity from necrosis of a few widely scattered individual cells to confluent necrosis of centrilobular hepatocytes (Plate 2). The necrosis was characterized by nuclear pyknosis or karyorrhexis, or complete loss of nuclear and cytoplasmic detail. Chronic active inflammation was associated with hepatocellular degeneration and necrosis and consisted of accumulations of neutrophils, monocytes, and macrophages in sinusoids and portal triads. The bile duct hyperplasia was characterized by increased numbers of small ductules with prominent epithelium, and occurred in rats with the more severe hepatocellular changes (Plate 3).

Although not reported by the laboratory pathologist, a blind reevaluation of the kidneys revealed minimal nephropathy with tubular casts in many of the high-dose males and females and minimal to marked focal necrosis of proximal convoluted tubule epithelium in others (Table 5). Kidneys from control rats were generally normal. The nephropathy consisted of one or several scattered proximal convoluted tubules with thickened basement membranes and basophilic epithelial cells. In rats that died during the study, the necrosis was characterized by increased cytoplasmic eosinophilia and nuclear pyknosis or karyorrhexis. The lesions in rats that survived generally consisted of atrophic tubules with scattered necrotic cells and regenerating epithelium.

Dose Selection Rationale: Based on the mortality observed in rats receiving 300 mg/kg and the hepatic toxicity observed in rats receiving 150 mg/kg or more in the 13-week study, the doses selected for the 2-year study in rats were 25, 50, and 100 mg/kg.

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier curves in Figure 2. Survival of male dosed groups was significantly lower than that of controls, primarily as a result of chemical-related increased severity of renal disease in dosed animals. None of the 100 mg/kg males and only two of the 50 mg/kg males survived until the end of the study. Survival of dosed female rats was similar to that of the controls.

Body Weights and Clinical Findings

The mean body weights of male rats receiving 50 or 100 mg/kg were lower than those of the controls throughout the study (Figure 3 and Table 7). The decrement in the body weight of 100 mg/kg males ranged from 9% at week 2 to 22% at week 89, while that of 50 mg/kg males ranged from 5% at week 2 to 20% at the end of the study. The mean body weights of 100 mg/kg female rats were consistently lower than, but within 10% of, those of controls throughout the study (Figure 3 and Table 8).

TABLE 6
Survival of Rats in the 2-Year Gavage Study of Coumarin

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	9	10
Natural deaths	6	7	13	17
Moribund kills	14	31	34	31
Accidental deaths[a]	2	3	2	2
Animals surviving to study termination	28	9	2	0
Percent probability of survival at end of study[b]	59	19	4	0
Mean survival (days)[c]	619	592	553	530
Survival analysis[d]	P<0.001	P<0.001	P<0.001	P<0.001
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Natural deaths	5	4	2	6
Moribund kills	14	7	7	14
Accidental deaths[a]	2	1	5	0
Animals surviving to study termination	29	38	36[e]	30
Percent probability of survival at end of study	61	78	80	60
Mean survival (days)	630	646	614	645
Survival analysis	P=0.616	P=0.133N	P=0.070N	P=0.990

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[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 dosed columns. A lower mortality in a dose group is indicated by N.
[e] Includes one animal that died during the last week of the study.

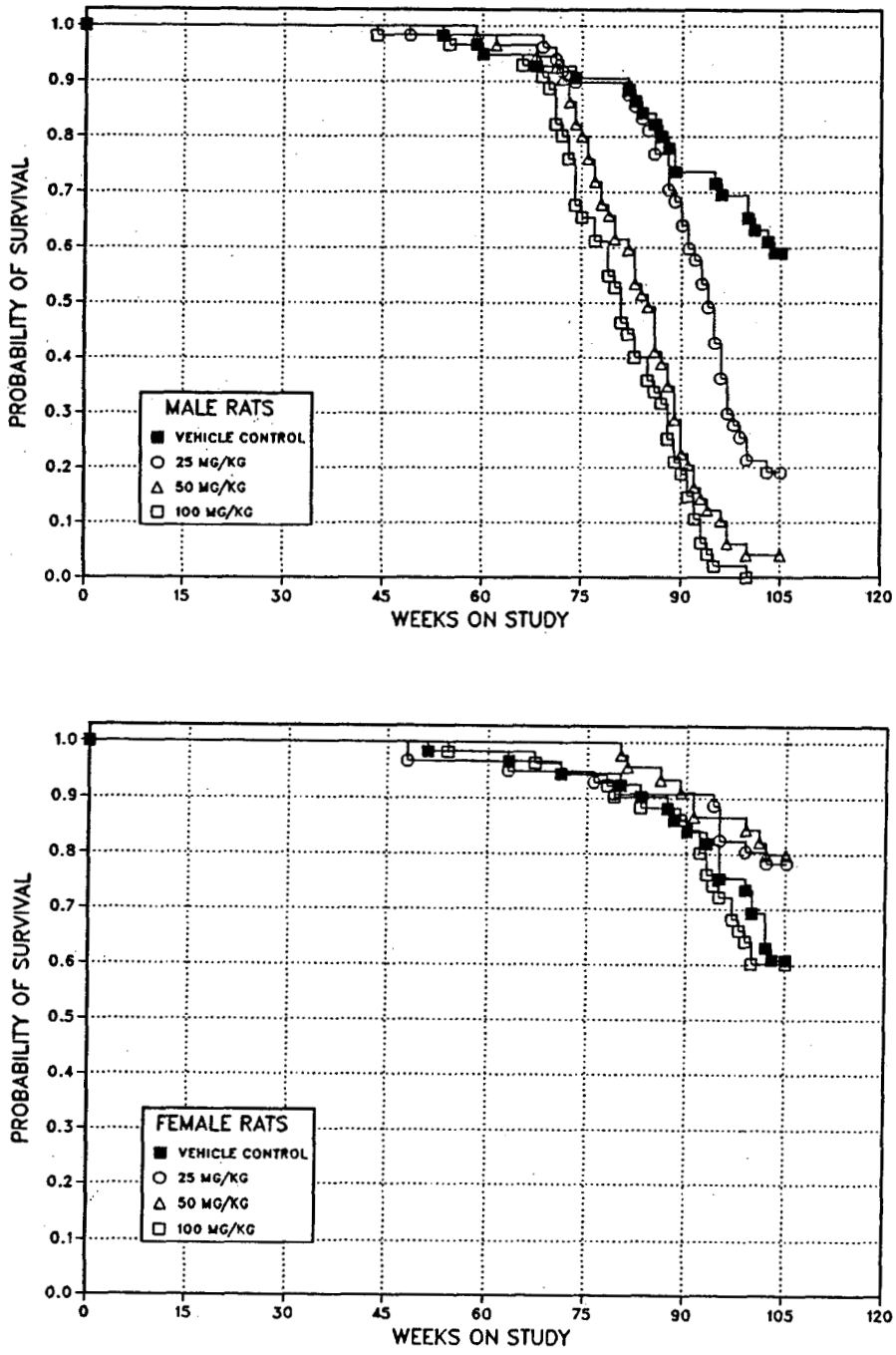


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Coumarin by Gavage for 2 Years

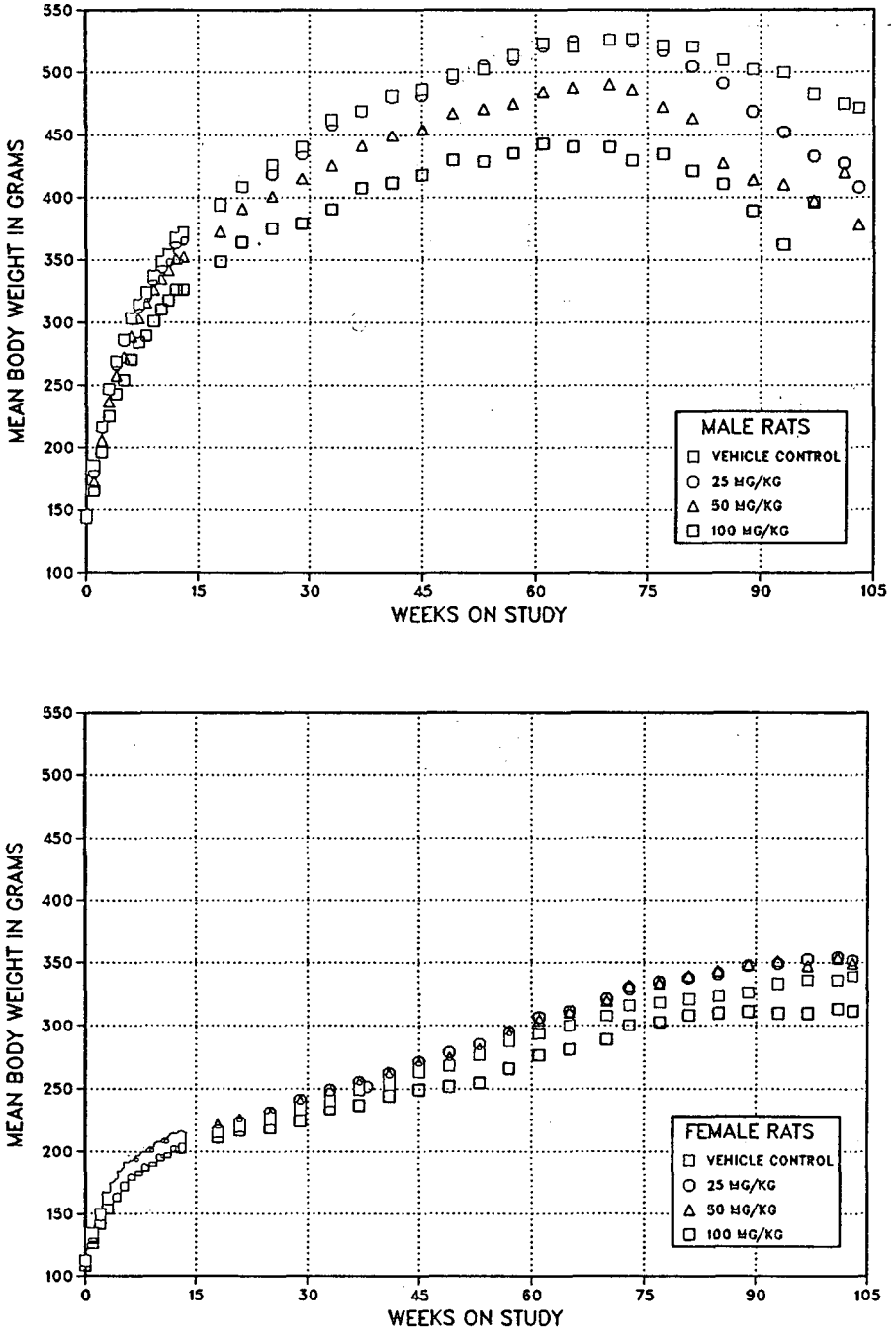


FIGURE 3
Growth Curves for Male and Female Rats Administered Coumarin by Gavage for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Coumarin

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	25 mg/kg Av. Wt. (g)	25 mg/kg Wt. (% of controls)	25 mg/kg No. of Survivors	50 mg/kg Av. Wt. (g)	50 mg/kg Wt. (% of controls)	50 mg/kg No. of Survivors	100 mg/kg Av. Wt. (g)	100 mg/kg Wt. (% of controls)	100 mg/kg No. of Survivors
1	145	60	146	101	60	143	99	60	144	100	60
2	216	59	215	100	60	206	95	60	196	91	60
3	247	59	247	100	60	237	96	60	225	91	59
4	269	59	267	99	60	258	96	60	243	91	59
5	286	59	285	100	60	273	95	60	254	89	59
6	304	59	303	100	60	289	95	60	270	89	59
7	315	59	312	99	60	303	96	60	284	90	59
8	324	59	321	99	60	316	98	60	290	89	59
9	338	59	334	99	60	326	97	60	301	89	59
10	349	59	344	99	60	335	96	59	311	89	59
11	355	59	350	99	60	342	96	59	318	90	59
12	368	59	363	99	60	351	95	59	327	89	59
13	372	59	367	99	59	353	95	59	326	88	59
18	394	59	395	100	59	373	95	59	349	89	59
21	409	59	409	100	59	392	96	59	364	89	59
25	426	59	419	98	59	401	94	59	375	88	59
29	441	59	435	99	59	415	94	59	379	86	59
33	462	59	458	99	59	426	92	59	391	85	59
37	469	59	469	100	59	442	94	59	410	87	59
41	481	59	480	100	59	450	93	59	412	86	59
45	486	59	482	99	59	455	94	59	418	86	58
49	498	58	495	99	59	468	94	59	430	86	58
53	502	58	505	101	57	471	94	59	429	85	58
57	514	57	510	99	56	475	93	59	436	85	57
61	523	55	521	100	56	485	93	58	443	85	55
65	521	46	525	101	48	488	94	48	441	85	47
70[a]	526	44	526	100	45	491	93	46	441	84	43
73	527	44	525	100	43	486	92	42	430	82	37
77	522	43	518	99	42	473	91	36	435	83	29
81	521	43	505	97	42	464	89	30	422	81	22
85	510	40	491	96	38	428	84	24	411	81	17
89	502	35	469	93	32	414	82	14	389	78	10
93	500	35	452	91	25	410	82	7			
97	483	33	433	90	14						
101	475	30	428	90	10						
103	471	29	401	85	9	378	80	2			
Mean for weeks											
1-13	299		296	99		287	96		268	90	
14-52	452		449	99		425	94		392	87	
53-103	507		486	96		455	90		428	84	

[a] Interim evaluation occurred during week 65.

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Coumarin

Weeks on Study	Vehicle Control		25 mg/kg			50 mg/kg			100 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	112	60	112	100	60	112	100	60	109	97	60
2	150	60	149	99	60	149	100	59	142	95	60
3	163	60	161	99	60	164	100	59	154	95	60
4	171	60	172	101	60	174	102	58	164	96	60
5	180	60	180	100	60	183	102	57	173	96	60
6	187	60	186	100	60	189	101	57	182	97	60
7	188	60	191	101	60	193	103	57	185	99	60
8	194	60	195	101	60	196	101	57	188	97	60
9	195	60	199	102	60	199	102	57	193	99	60
10	202	60	204	101	60	204	101	56	197	98	60
11	203	60	206	102	60	207	102	56	199	98	60
12	208	60	210	101	60	211	102	56	204	98	60
13	211	60	212	101	60	213	101	56	203	96	60
18	215	59	218	101	60	222	103	56	212	98	60
21	220	59	224	102	60	226	103	56	218	99	60
25	227	59	232	102	60	230	102	56	220	97	60
29	234	58	241	103	60	240	102	55	225	96	60
33	241	58	249	103	60	249	104	55	234	97	60
37	249	58	255	103	59[a]	255	102	55	237	95	60
41	255	58	262	103	59	261	103	55	245	96	60
45	264	58	271	103	59	270	102	55	249	95	60
49	268	58	279	104	57	275	103	55	252	94	60
53	277	57	285	103	57	282	102	55	255	92	60
57	288	57	295	103	57	294	102	55	266	92	59
61	294	57	307	105	57	305	104	55	277	94	59
65	300	51	312	104	53	311	104	51	281	94	56
70[b]	308	46	321	104	46	320	104	45	289	94	48
73	316	45	330	104	46	332	105	45	300	95	47
77	319	45	334	105	45	333	105	45	303	95	47
81	322	44	338	105	44	339	106	43	308	96	45
85	324	43	341	105	44	343	106	43	310	96	44
89	326	41	348	107	44	348	107	41	311	95	43
93	333	39	349	105	44	351	106	39	310	93	40
97	336	36	353	105	40	348	103	39	310	92	34
101	336	33	354	105	39	354	105	37	314	93	30
103	339	29	352	104	38	350	103	36	312	92	30
Mean for weeks											
1-13	182		183	101		184	101		176	97	
14-52	241		248	103		248	103		232	96	
53-103	316		330	104		329	104		296	94	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.
[b] Interim evaluation occurred during week 65.

There were no clinical signs of toxicity in rats, other than nonspecific signs relating to debilitation as a result of renal or other spontaneous disease. Male rats receiving coumarin were noted to resist the gavage procedure.

Hematology and Clinical Chemistry

The results of hematology and clinical chemistry evaluations at 15 months are shown in Table H5. The values of several hematologic parameters for 50 and 100 mg/kg groups of male and female rats were significantly lower than those of controls. While mean erythrocyte volume and mean erythrocyte hemoglobin were significantly lower in the 50 and 100 mg/kg groups than in the controls, significantly lower values for hematocrit and hemoglobin were observed only in the 100 mg/kg groups. Although the differences between the dosed and control groups were slight and not clinically important, they are characteristic of a microcytic normochromic anemia. In 50 and 100 mg/kg males, activated partial thromboplastin times were significantly lower and platelet counts were significantly higher than controls, suggesting that the microcytic normochromic anemia was due to chronic blood loss from impaired blood coagulation.

Activities of alanine aminotransferase, sorbitol dehydrogenase, or γ-glutamyltransferase in 50 and 100 mg/kg males and 100 mg/kg females were significantly higher than those of controls (Table H5). Activities of these cytoplasmic enzymes are characteristically elevated due to hepatocellular degeneration and necrosis, consistent with the liver toxicity observed histologically.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the liver, kidney, parathyroid gland, pharynx, forestomach, thyroid gland, nose, testis, and pituitary gland. Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal tumor diagnoses, the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group, and historical control incidences for the biologically significant neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Liver: The absolute and relative liver weights of male and female rats that received 100 mg/kg were significantly greater than those of controls at the 15-month interim evaluation (Table G4). Consistent with the increase in organ weight, a spectrum of degenerative lesions occurred with a dose-related increase in incidence and/or average severity in male and female rats receiving coumarin by gavage (Table 9). Despite the wide variability in extent and severity of the liver lesions among individual animals, the lesions were generally more frequent and more severe in males.

Hepatocellular degeneration was usually minimal to mild in severity and occurred in randomly distributed lobules within an affected lobe. The affected hepatocytes were usually located in the centrilobular region (zone 3 of the liver acinus) and were characterized by the presence of multiple small, clear, intracytoplasmic vacuoles which gave the cytoplasm a granular appearance, or fewer larger vacuoles typical of lipid accumulation (Plates 5 and 6). The latter was recorded as fatty change at the 15-month interim evaluation. Hepatocellular degeneration was often accompanied by minimal to mild necrosis of individual cells or small clusters of cells, usually in the centrilobular or midzonal area of the hepatic lobule. Moderate to marked necrosis, which occurred in only a few rats, was zonal (generally centrilobular) to massive with the latter showing only a few viable hepatocytes near the portal area and blood filling the necrotic lobules (Plate 4). In many rats with mild to marked centrilobular necrosis, the hepatocytes in the peripheral regions of the liver lobules were enlarged and exhibited increased cytoplasmic basophilia. These peripherolobular hepatocytes also had enlarged, vesicular nuclei and cells in mitosis were more frequent than normally seen. This change was diagnosed as cytologic alteration. Liver fibrosis was characterized by bands of connective tissue running between lobules and connecting central areas to each other and to portal areas (Plates 7 and 8). This lesion was considered a sequel of necrosis.

The severity of bile duct hyperplasia, a naturally occurring age-related lesion in rats, increased with increasing dose in rats administered coumarin. The lesion was characterized by increased profiles of well-differentiated bile ductules in the portal areas (Plates 9 and 10). These lesions did not exhibit the mucus cell metaplasia or epithelial dysplasia typical of cholangiofibrosis.

TABLE 9
Incidences of Nonneoplastic Lesions of the Liver of Rats in the 2-Year Gavage Study of Coumarin

Dose	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Male				
15-Month Interim Evaluation				
Liver[a]	10	10	9	10
Fatty Change[b]	0	8**(1.8)[c]	8**(1.1)	5*(1.4)
Hepatocyte Degeneration	0	7**(1.3)	8**(1.9)	5*(1.0)
Coagulative Necrosis	0	0	0	1 (1.0)
Bile Duct Hyperplasia	6 (1.0)	8 (1.8)	9 (1.7)	9 (1.7)
2-Year Study				
Liver	49	50	51	50
Hepatocyte Degeneration	0	1 (2.0)	0	1 (3.0)
Coagulative Necrosis	1 (3.0)	13**(1.5)	38**(1.7)	40**(2.4)
Fibrosis	0	3 (1.3)	41**(1.6)	42**(1.9)
Bile Duct Hyperplasia	41 (1.6)	41 (1.8)	45 (2.2)	47**(2.1)
Cytologic Alteration	0	0	28**(1.8)	29**(2.4)
Female				
15-Month Interim Evaluation				
Liver	10	8	8	10
Fatty Change	0	0	5*(1.2)	9**(2.3)
Hepatocyte Degeneration	0	0	3 (1.0)	9**(1.0)
Coagulative Necrosis	0	0	1 (1.0)	0
Bile Duct Hyperplasia	1 (1.0)	3 (1.0)	1 (1.0)	3 (1.0)
2-Year Study				
Liver	50	50	50	50
Hepatocyte Degeneration	0	0	8*(1.5)	30**(2.0)
Coagulative Necrosis	3 (2.3)	3 (1.0)	4 (2.0)	15**(1.7)
Fibrosis	0	0	1 (1.0)	12**(1.8)
Bile Duct Hyperplasia	26 (1.2)	27 (1.3)	29 (1.3)	20 (1.5)
Cytologic Alteration	0	0	0	9**(2.4)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grade of lesion in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

There was a decreased incidence of basophilic focus in dosed male and female rats. In males this decrease was due in part to the decreased survival in the dosed groups. There were no chemical-related increased incidences of liver neoplasms.

Kidney: The relative kidney weights of male and female rats receiving 100 mg/kg were significantly greater than those of controls at the 15-month interim evaluation (Table G4). The absolute kidney weights of 100 mg/kg rats were not increased, apparently because of the marked decrement in mean body weight. While nephropathy was observed in nearly all dosed and control rats, particularly males, the average severity of renal disease increased with increasing dose at the 15-month interim evaluation and at the end of the 2-year study (Tables 10 and 11). The more frequent occurrence of moderate or marked nephropathy in 50 and 100 mg/kg males was the principal cause of reduced survival of these groups.

Nephropathy was characterized by glomerulosclerosis, thickening of tubule basement membrane, degeneration and atrophy of tubule epithelium, dilatation of tubule lumens by pale pink acellular material (hyaline casts), interstitial fibrosis, and chronic inflammation. Regeneration of tubule epithelium was also observed frequently, and the extent and severity of this process paralleled the overall severity of the degenerative changes. In general, the severity grades were based upon the extent of tubular and glomerular involvement: minimal — less than 25%; mild — 25% to 50%; moderate — 50% to 75%; marked — greater than 75%.

The kidneys were initially sampled for histopathology by preparing a single hematoxylin and eosin stained section of each kidney. In addition to the nephropathy previously described, low numbers of renal tubule adenomas were seen in all groups of male rats and in the 100 mg/kg female rats (Tables 10, 11, A1, and B1). The incidences in the 25 and 50 mg/kg males and in 100 mg/kg female rats (two per group) were not significantly greater than those of the controls. However, no more than one per group has been observed in historical NTP 2-year control F344/N rats (Tables A4a and B4a). Renal tubule hyperplasia, a possible precursor of adenoma, occurred in male rats in the control and 25 mg/kg groups (Tables 10 and A5); hyperplasia was not observed in female rats.

Primarily because of the occurrence of this rare neoplasm in 100 mg/kg female rats and in the male groups, additional step sections of kidney were prepared from the remaining formalin-fixed tissue. Approximately 6 to 8 additional sections taken at 1 μm intervals were prepared for each male and female rat. Additional rats, primarily dosed males, were identified with focal hyperplasia or adenoma. A carcinoma was also seen in one 25 mg/kg male rat. The incidences of these proliferative lesions in the step sections and in the single and step sections combined are shown in Tables 10 and 11. While hyperplasia or adenoma clearly occurred more frequently in the dosed male rats, the incidences did not increase with increasing dose. In female rats, the lesions occurred much less frequently, but the adenomas were seen in the 50 and 100 mg/kg groups.

Renal tubule hyperplasia, as defined in this study, was distinguished from the common regenerative epithelial changes commonly seen as a part of nephropathy and was considered a preneoplastic lesion. Hyperplasia, adenoma, and carcinoma were part of a morphological continuum and occurred in the cortex of the kidney. Hyperplasia of the tubule epithelium was characterized by single or multiple profiles of a single tubule partially or completely filled with normal or slightly enlarged epithelial cells. The renal tubule adenomas were discrete, sometimes multinodular masses at least three times greater in diameter than an average tubule and composed of somewhat pleomorphic epithelial cells arranged in complex tubular structures and solid clusters. The carcinoma was larger than the adenomas and exhibited cellular pleomorphism and atypia and central necrosis.

Oncocytomas were observed in two 25 mg/kg male rats (Table 10). These were small, discrete nodules of uniform cells with dense, hyperchromatic nuclei and granular eosinophilic cytoplasm. While these lesions also occurred in the cortex, they appear to be morphologically distinct from renal tubule hyperplasia, adenoma, or carcinoma.

TABLE 10
Incidences of Kidney Lesions in Male Rats in the 2-Year Gavage Study of Coumarin

Dose	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Single Sections (Standard Evaluation)				
15-Month Interim Evaluation				
Kidney[a]	10	10	9	10
Nephropathy[b]	10 (1.0)[c]	10 (1.7) **	9 (2.3)**	10 (2.5)**
Renal Tubule Adenoma	0	0	1	0
2-Year Study				
Kidney	49	50	51	50
Nephropathy	48 (2.0)	48 (2.9)**	50 (3.6)**	50 (3.6)**
Renal Tubule Hyperplasia	1	3	0	0
Renal Tubule Adenoma[d]	1	2	2	1
Step Sections (Extended Evaluation)				
15-Month Interim Evaluation				
Kidney	10	10	9	10
Renal Tubule Hyperplasia	0	0	1	1
Renal Tubule Adenoma	0	0	0	0
2-Year Study				
Kidney	49	50	51	50
Renal Tubule Hyperplasia	2	12**	10**	6
Renal Tubule Adenoma	0	4	5*	4
Renal Tubule Carcinoma	0	1	0	0
Renal Tubule Adenoma or Carcinoma	0	5*	5*	4
Renal Tubule Oncocytoma	0	2	0	0
Single and Step Sections Combined				
15-Month Interim Evaluation				
Kidney	10	10	9	10
Renal Tubule Hyperplasia	0	0	1	1
Renal Tubule Adenoma	0	0	1	0
2-Year Study				
Kidney	49	50	51	50
Renal Tubule Hyperplasia	3	15**	10**	6
Renal Tubule Adenoma	1	6*	7**	5
Renal Tubule Carcinoma	0	1	0	0
Renal Tubule Adenoma or Carcinoma	1	6*	7**	5
Renal Tubule Oncocytoma	0	2	0	0

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test (2-year study) or Mann-Whitney U test (severity grades)
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Group average severity grade of lesion: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 8/1,019 (0.8% ± 1.0%); range 0%-2%

TABLE 11
Incidences of Kidney Lesions in Female Rats in the 2-Year Gavage Study of Coumarin

Dose	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Single Sections (Standard Evaluation)				
15-Month Interim Evaluation				
Kidney[a]	10	8	10	10
Nephropathy[b]	4 (0.4)[c]	8*(1.0)*	10*(1.0)**	10*(1.5)**
2-Year Study				
Kidney	49	50	50	49
Nephropathy	34 (0.9)	44*(1.2)*	44*(1.6)**	49**(2.3)**
Renal Tubule Adenoma[d]	0	0	0	2
Step Sections (Extended Evaluation)				
15-Month Interim Evaluation				
Kidney	10	8	10	10
Renal Tubule Hyperplasia	0	0	0	0
Renal Tubule Adenoma	0	0	0	0
2-Year Study				
Kidney	49	50	50	49
Renal Tubule Hyperplasia	1	0	4	2
Renal Tubule Adenoma	0	0	1	1[e]
Single and Step Sections Combined				
15-Month Interim Evaluation				
Kidney	10	8	10	10
Renal Tubule Hyperplasia	0	0	0	0
Renal Tubule Adenoma	0	0	0	0
2-Year Study				
Kidney	49	50	50	49
Renal Tubule Hyperplasia	1	0	4	2
Renal Tubule Adenoma	0	0	1	2

* Significantly different (P≤0.05) from the control group by the Fisher exact test (15-month interim), logistic regression test (2-year study), or Mann-Whitney U test (severity grades)
** P≤0.01
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Group average severity grade of lesion: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 2/1,018 (0.2% ± 0.6%); range 0%-2%
[e] The adenoma in the step section is the same adenoma seen in the original single section.

Parathyroid gland: The incidences of bilateral, diffuse hyperplasia of the parathyroid gland in 25, 50, and 100 mg/kg male rats were significantly greater than that of controls (0 mg/kg, 3/41; 25 mg/kg, 20/47; 50 mg/kg, 31/49; 100 mg/kg, 29/47; Table A5). This increased incidence of hyperplasia was considered to be secondary to the increased severity of renal disease and characteristic of renal secondary hyperparathyroidism. Consistent with the overall lower severity of renal disease in females as compared with males, parathyroid hyperplasia occurred infrequently but only in dosed female rats (Table B5).

Pharynx: Squamous cell papillomas occurred in one control, one 25 mg/kg, and one 50 mg/kg male and in two 100 mg/kg female rats (Tables A1 and B1). Further, a squamous cell carcinoma was seen in another 50 mg/kg male rat. No more than one squamous cell neoplasm (papilloma or carcinoma) has been observed in an individual control group of male or female rats from recent NTP 2-year gavage studies (Tables A4b and B4b). Because of the overall low incidences, the lack of increasing incidence over a fourfold range of doses in males, and the lack of statistical significance, these neoplasms were not considered chemical related.

Forestomach: Ulcers of the forestomach occurred frequently in dosed male rats, and the incidences in dosed male rats were significantly greater than that of controls (Tables 12 and A5). While ulcers occurred much less frequently in dosed females, the incidence in the 100 mg/kg group was also significantly greater than controls. The forestomach ulcers were characterized by focal necrosis of the mucosa and adjacent muscularis mucosa. A few of the forestomach ulcers had perforated, resulting in a secondary peritonitis which was considered to be the cause of death. The squamous epithelium at the margin of the ulcers was usually thickened by an increase in cells (hyperplasia) and keratin (hyperkeratosis); the adjacent submucosa was infiltrated with acute and chronic inflammatory cells.

Squamous cell papillomas of the forestomach occurred in several male and female rats (Tables 12, A1, and B1). The incidence of three papillomas in the 25 mg/kg females contrasts with the historical incidence of 3/1,020 in control female F344/N rats from recent NTP 2-year studies (Table B4c). However, since there were no increased incidences in the 50 and 100 mg/kg females, the squamous cell papillomas in the 25 mg/kg females were not considered to be chemical related.

Thyroid gland: Follicular cell carcinomas were seen in one control and one 25 mg/kg male, while follicular cell adenomas were seen in three additional 25 mg/kg males (Table A1). No follicular cell neoplasms were observed in 50 or 100 mg/kg males. Follicular cell hyperplasia, a precursor to follicular cell neoplasia, did not occur in any male rat groups. The incidence of four thyroid gland follicular cell neoplasms in 25 mg/kg male rats exceeds the range observed in control male rats from recent NTP 2-year studies (range 0%-6%; 22/1,009, 2.2%; Table A4c). The marginally greater incidence of thyroid neoplasms in 25 mg/kg males is difficult to evaluate because of the early deaths of dosed male rats. However, the absence of thyroid gland follicular cell hyperplasia suggests this is not a chemical-related response.

Nose: The incidences of suppurative inflammation in the nose in 50 and 100 mg/kg male and 100 mg/kg female rats were significantly greater than those of controls (males: 13/49, 20/50, 27/51, 41/50; females: 4/50, 2/50, 0/50, 13/49; Tables A5 and B5). Inflammation generally consisted of accumulations of neutrophils in the nasal cavity, often associated with globules of yellow refractile material compatible with corn oil or fragments of plant material. Inflammation in the nose is frequently observed in corn oil gavage studies and appears to be due to reflux of corn oil into the nasal cavity following dosing. The increased incidence in dosed animals may be related to the greater degree of irritation caused by the coumarin-corn oil mixture than by corn oil alone.

Testis: The incidences of testicular interstitial cell adenomas in dosed groups of male rats were marginally greater than those of controls (38/45, 43/49, 42/49, 46/50; Table A3), but the incidence in each group is within the historical range of controls from recent NTP studies (range 88%-94%; 886/1,012, 85.6%; Table A4d) and is not considered chemical related.

Pituitary gland: The incidence of adenomas of the pituitary gland pars distalis in the 100 mg/kg male rats was marginally lower than that of the controls (19/48, 12/48, 16/49, 6/50; Table A3).

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach of Rats in the 2-Year Gavage Study of Coumarin

Dose	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Male				
15-Month Interim Evaluation				
Forestomach[a]	10	10	9	10
Squamous Cell Papilloma[b]	0	1	0	1
2-Year Study				
Forestomach	48	50	51	50
Ulcer	7	24**	35**	34**
Squamous Cell Papilloma[c]				
Overall rate[d]	0/49 (0%)	1/50 (2%)	0/51 (0%)	1/50 (2%)
Logistic regression test[e]	P=0.219	P=0.275	–[f]	P=0.543
Female				
2-Year Study				
Forestomach	48	49	50	48
Ulcer	1	1	6	9**
Squamous Hyperplasia	0	2	0	0
Squamous Cell Papilloma[g]				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Logistic regression test	P=0.407N	P=0.406	P=0.457N	P=0.749

** Significantly different (P≤0.01) from the control group by the logistic regression test
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 5/1,020 (0.5% ± 1.1%); range 0%-4%
[d] Number of animals with neoplasm per number of animals necropsied.
[e] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or lower incidence in a dose group is indicated by N.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence: 3/1,020 (0.3% ± 0.7%); range 0%-2%

STOP-EXPOSURE EVALUATION

Stop-exposure groups of male rats were included in the NTP 2-year study to evaluate the potential for chemical-related liver lesions to progress or regress during a recovery period, based on reports that coumarin produced cholangiofibrosis and bile duct carcinomas in male rats (Bär and Griepentrog, 1967; Griepentrog, 1973). Groups of 20 male rats each were given 100 mg/kg coumarin for 9 or 15 months followed by administration of only the gavage vehicle until the end of the study (2 years). To determine progression or regression of chemical-related lesions during the recovery period, the incidences of neoplasms and nonneoplastic lesions in these stop-exposure groups were compared with those of male rats scheduled for 9- and 15-month interim evaluations. To provide an additional measure of dose response relative to duration of exposure, the incidences of neoplasms in rats in the 9- and 15-month stop-exposure groups were compared with the incidences in rats receiving 100 mg/kg for the entire 2 years (the latter group was part of the regular 2-year study).

Survival

Estimates of the survival probability for male rats in the stop-exposure groups are shown in Table 13. Nine of the 20 males that received 100 mg/kg for 9 months (9-month stop-exposure group) and two of the 20 males that received 100 mg/kg for 15 months (15-month stop-exposure group) survived until week 104. The decreased survival of each of the stop-exposure groups was attributed primarily to a chemical-related increased severity of renal disease.

Body Weights

The mean body weights of male rats in the 9- and 15-month stop-exposure groups are compared with the controls of the regular 2-year study in Table 14. The mean body weights of the 9-month stop-exposure group ranged from 8% less than controls at week 2 to about 15% less at week 40, when the administration of coumarin to this group ceased. Thereafter, body weight gain of this group improved slightly and the weight deficit diminished to about 12% for much of the study.

The weight gain of the 15-month stop-exposure group followed a similar pattern. The mean body weights of the 15-month stop-exposure group ranged from 7% to 15% less than controls during the period that the rats received coumarin. After week 65, when the administration of coumarin to this group was stopped, the weight deficit diminished slightly to about 12%.

TABLE 13
Survival of Male Rats in the Stop-Exposure Gavage Evaluation of Coumarin

	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Animals initially in study	40	30
9-Month interim evaluation[a]	20	0
15-Month interim evaluation[a]	0	10
Natural deaths	4	2
Moribund kills	6	13
Accidental deaths[a]	1	3
Animals surviving to study termination	9	2
Percent probability of survival at end of study[b]	47	12
Mean survival (days)[c]	629	511

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)

TABLE 14
Mean Body Weight and Survival of Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of Coumarin

Weeks on Study	Vehicle Control		100 mg/kg (9-month)			100 mg/kg (15-month)		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	145	60	145	101	20	148	102	20
2	216	59	199	92	20	202	93	20
3	247	59	223	90	20	227	92	20
4	269	59	247	92	20	251	93	20
5	286	59	260	91	20	265	93	20
6	304	59	275	91	20	279	92	18
7	315	59	284	90	20	289	92	18
8	324	59	290	90	19	294	91	18
9	338	59	298	88	19	304	90	18
10	349	59	308	88	19	315	90	18
11	355	59	314	89	19	322	91	17
12	368	59	322	88	19	329	90	17
13	372	59	329	88	19	338	91	17
18	394	59	344	87	19	354	90	17
21	409	59	358	88	19	367	90	17
25	426	59	376	88	19	384	90	17
29	441	59	380	86	19	392	89	17
33	462	59	392	85	19	397	86	17
37	469	59	405	86	19	415	88	16
41	481	59	404	84	19	416	86	16
45	486	59	418	86	18	425	87	16
49	498	58	428	86	18	437	88	16
53	502	58	442	88	18	432	86	16
57	514	57	454	88	18	444	86	16
61	523	55	459	88	18	444	85	16
65[a]	521	46	457	88	18	446	86	16
70	526	44	463	88	18	456	87	16
73	527	44	461	88	18	456	87	14
77	522	43	466	89	17	452	87	14
81	521	43	456	88	17	425	82	12
85	510	40	451	89	15	446	88	9
89	502	35	444	88	13	451	90	5
93	500	35	435	87	13	441	88	3
97	483	33	392	81	13	431	89	3
101	475	30	423	89	9	390	82	3
103	471	29	401	85	9	366	78	3
Mean for weeks								
1-13	299		269	90		274	92	
14-52	452		389	86		399	88	
53-103	507		443	87		434	86	

[a] Interim evaluation occurred during week 65.

Pathology and Statistical Analyses of Results

Summaries of the incidences of neoplasms and nonneoplastic lesions and the individual animal diagnoses for male rats of the stop-exposure groups are shown in Appendix E. For statistical analyses, the incidences of neoplasms in the stop-exposure groups were compared with the controls of the regular 2-year study (Table E3a) and with the group receiving 100 mg/kg for the entire study (Table E3b).

Progression or Regression of Chemical-Induced Lesions

Consistent with the findings of the 2-year study in male rats, chemical-related lesions were observed in the liver and kidney at the 9- and 15-month interim evaluations of the stop-exposure groups (Tables 15 and 16). Comparisons of the incidences of hepatic lesions at the interim evaluations with their corresponding stop-exposure groups show that the incidences and/or severity of the lesions returned to levels similar to those of controls following cessation of exposure at 9 or 15 months (Tables 17 and 18). Thus, the hepatocellular and biliary lesions produced by 9 or 15 months of exposure were reversible. For completeness, Table 19 compares the incidences of liver lesions among male rats receiving 100 mg/kg in the 9- and 15-month stop-exposure groups and in the 2-year study group. These comparisons also show that continued administration is necessary for the manifestation of these lesions at the end. Since coumarin administered by gavage to F344/N rats failed to produce cholangiofibrosis or bile duct carcinomas, as suggested by reports in the literature, the primary purpose of the stop-exposure groups was largely confounded.

In contrast to the liver lesions, the severity of nephropathy in male rats of the two stop-exposure groups was significantly greater at the end of 2 years than that in the male rats at the respective interim evaluations (Tables 17 and 18). This is not unexpected, since nephropathy is a progressive degenerative disease that naturally increases in severity with age. However, it does indicate that renal damage caused by 9 or 15 months of exposure to coumarin was largely irreversible. Consistent with the increased average severity of renal disease, the incidence of parathyroid hyperplasia was greater in the stop-exposure groups than in the 9- and 15-month interim evaluation groups (Tables 17 and 18). The severity of nephropathy and incidence of parathyroid hyperplasia in male rats receiving 100 mg/kg coumarin for the entire 2-year study were significantly greater than those in the stop-exposure groups (Table 19).

In the standard evaluation of single sections, renal tubule adenomas were seen in one male in the 9-month 100 mg/kg stop-exposure group and in two males in the 15-month 100 mg/kg stop-exposure group (Table 16). Further, renal tubule oncocytomas were also seen in two males in the 15-month 100 mg/kg stop-exposure group. Microscopic examination of the additional step sections revealed additional males with hyperplasia and adenoma in these stop-exposure groups (Table 16).

TABLE 15
Incidences of Nonneoplastic Liver Lesions in Male Rats in the Stop-Exposure Gavage Evaluation of Coumarin

Dose	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
9-Month Interim Evaluation			
Liver[a]	17	18	
Necrosis[b]	0	17**(1.6)[c]	
Bile Duct Hyperplasia	7 (1.0)	17**(1.6)	
15-Month Interim Evaluation[d]			
Liver	17		20
Fatty Change	1 (1.0)		14**(1.6)
Necrosis	0		3 (1.0)
Hepatocyte Degeneration	0		13**(1.2)
Bile Duct Hyperplasia	11 (1.0)		19*(1.8)
Stop-Exposure			
Liver	49	20	20
Necrosis	1 (3.0)[c]	2 (2.0)	3 (2.3)
Hepatocyte Degeneration	0	0	1 (1.0)
Bile Duct Hyperplasia	41 (1.6)	17 (1.9)	14 (1.4)
Fibrosis	0	0	2 (1.5)

* Significantly different (P≤0.01) from the control group by the Fisher exact test (interims)
** (P≤0.01)
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grade of lesion in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Includes data from the 15-month interim in the 2-year core study and the 15-month interim in the stop-exposure evaluation.

TABLE 16
Incidences of Selected Lesions of the Kidney, Forestomach, and Parathyroid Gland in Male Rats in the Stop-Exposure Gavage Evaluation of Coumarin

Dose	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Single Sections (Standard Evaluation)			
9-Month Interim Evaluation			
Kidney[a]	17	18	
Nephropathy[b]	17 (1.0)[c]	18 (2.3)**	
15-Month Interim Evaluation[d]			
Kidney	17		20
Nephropathy	17 (1.3)		20 (2.7)**
Stop-Exposure			
Kidney	49[e]	20	20
Nephropathy	48 (2.0)	20 (3.1)**	20 (3.4)**
Renal Tubule Hyperplasia	1	0	3
Renal Tubule Adenoma	1	1	2
Renal Tubule Oncocytoma	0	0	2
Parathyroid Gland	41	19	18
Hyperplasia	3	4	8**
Forestomach	48	19	19
Ulcer	7	3	5
Step Sections (Extended Evaluation)			
15-Month Interim Evaluation			
Kidney	17		20
Hyperplasia	0		1
Renal Tubule Adenoma	0		1
Stop-Exposure			
Kidney	49	20	20
Renal Tubule Hyperplasia	2	2	5**
Renal Tubule Adenoma	0	3*	1

(continued)

TABLE 16
Incidences of Selected Lesions of the Kidney, Forestomach, and Parathyroid Gland in Male Rats in the Stop-Exposure Gavage Evaluation of Coumarin (continued)

Dose	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Single and Step Sections Combined			
15-Month Interim Evaluation			
Kidney	17		20
Renal Tubule Hyperplasia	0		1
Renal Tubule Adenoma	0		1
Stop-Exposure			
Kidney	49	20	20
Renal Tubule Hyperplasia	3	2	7**
Renal Tubule Adenoma	1	4*	2

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test (stop-exposure) or Mann-Whitney U test (severity grades).
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Group average severity grade of lesion: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Includes data from the 15-month interim in the 2-year core study and the 15-month interim in the stop-exposure evaluation.
[e] For comparison the data for the vehicle control group of the regular 2-year study is included here.

TABLE 17
Comparison of the 9-Month Interim Evaluation with the 9-Month Stop-Exposure Group in the Stop-Exposure Gavage Evaluation of Coumarin

Dose (100 mg/kg)	9-Month Interim Evaluation	9-Month Stop-Exposure Group
Liver[a]	18	20
Necrosis[b]	17 (1.6)[c]	2**(2.0)
Bile Duct Hyperplasia	17 (1.6)	17 (1.9)
Kidney	18	20
Nephropathy	18 (2.3)	20 (3.1)**
Parathyroid Gland	18	19
Hyperplasia	0	4
Stomach, Forestomach	18	19
Ulcer	0	3

** Significantly different (P≤0.01) from the 9-month interim group by the logistic regression test (incidence data) or Mann-Whitney U test (severity grades)
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grade of lesion in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

TABLE 18
Comparison of the 15-Month Interim Evaluation with the 15-Month Stop-Exposure Group in the Stop-Exposure Gavage Evaluation of Coumarin

Dose (100 mg/kg)	15-Month Interim Evaluation[a]	15-Month Stop-Exposure Group
Liver[b]	20	20
Fatty Change[c]	14 (1.6)[d]	3**(1.0)
Necrosis	3 (1.0)	3 (1.7)
Hepatocyte Degeneration	13 (1.2)	1**(1.0)
Fibrosis	0	3 (1.7)
Bile Duct Hyperplasia	19 (1.8)	14 (1.4)
Kidney	20	20
Nephropathy	20 (2.7)	20 (3.4)**
Parathyroid Gland	20	18
Hyperplasia	0	8**
Stomach, Forestomach	20	19
Ulcer	0	5*

* Significantly different (P≤0.05) from the 15-month interim group by the logistic regression test (incidence data) or Mann-Whitney U test (severity grades)
** P≤0.01
[a] Includes data from the 15-month interim in the 2-year core study and the 15-month interim in the stop-exposure evaluation.
[b] Number of animals with organ examined microscopically.
[c] Number of animals with lesion.
[d] Average severity grade of lesion in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

TABLE 19
Incidences of Selected Lesions of the Liver and Kidney of Male Rats: Comparison of the 9- and 15-Month Stop-Exposure Groups with the 2-Year Core Group in the Stop-Exposure Gavage Evaluation of Coumarin

Dose (100 mg/kg)	9-Month Stop-Exposure Group	15-Month Stop-Exposure Group	2-Year Core Group
Liver[a]	20	20	50
Hepatocyte Degeneration[b]	0	1 (1.0)[c]	1 (3.0)
Necrosis	2 (2.0)	3 (1.7)	40**(2.4)
Fibrosis	0	3 (1.7)	42**(1.9)
Bile Duct Hyperplasia	17 (1.9)	14 (1.4)	47 (2.1)
Kidney	20	20	50
Nephropathy	20 (3.1)	20 (3.4)	50 (3.6)*
Renal Tubule Hyperplasia[d]	2	7	6
Renal Tubule Adenoma[d]	4	2	5
Parathyroid Gland	19	18	47
Hyperplasia	4	8	29**
Stomach, Forestomach	19	19	50
Ulcer	3	5	34**

* Significantly different ($P \leq 0.05$) from the 9-month stop-exposure group by the logistic regression test (incidence data) or Mann-Whitney U test (severity grades)
** ($P \leq 0.01$)
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grade of lesion in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Includes standard (single section) and extended (step sections) evaluations.

MICE

16-DAY STUDY

All male and female mice receiving 600 mg/kg died within the first 3 days of the study (Table 20). Of the mice that received 300 mg/kg, one female died on day 1 and one male died on day 6. While the deaths of mice in the 300 and 600 mg/kg groups were considered chemical related, the cause of death of one 75 mg/kg male on day 3 was uncertain. There were no clinical findings related to specific organ toxicity. One or more clinical findings of inactivity, excessive lacrimation, piloerection, bradypnea, ptosis, or ataxia were observed in one or more mice from the 300 and 600 mg/kg groups within the first several hours after dosing. These signs were generally seen during the first week of the study.

The mean body weight gains and final mean body weights of all surviving mice that received coumarin were similar to those of the controls. Further, the platelet counts and capillary clotting time of mice receiving coumarin were also similar to those of the controls (Table H6). Histopathology examinations were not performed in the 16-day study.

TABLE 20
Survival and Mean Body Weights of Mice in the 16-Day Gavage Study of Coumarin

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	22.6 ± 0.9	24.6 ± 1.4	2.0 ± 0.8	
40	5/5	21.8 ± 0.9	24.4 ± 0.8	2.6 ± 0.2	99
75	4/5[c]	22.4 ± 0.5	25.3 ± 0.5	2.5 ± 0.3	103
150	5/5	22.2 ± 0.8	24.6 ± 0.8	2.4 ± 0.2	100
300	4/5[d]	21.2 ± 0.7	23.5 ± 1.2	2.0 ± 0.4	96
600	0/5[e]	23.2 ± 0.7	–	–	–
Female					
0	5/5	18.6 ± 0.5	21.0 ± 1.0	2.4 ± 0.5	
40	5/5	17.4 ± 0.6	20.2 ± 0.6	2.8 ± 0.2	96
75	5/5	18.4 ± 0.8	20.4 ± 0.8	2.0 ± 0.3	97
150	5/5	17.6 ± 0.7	20.4 ± 0.5	2.8 ± 0.6	97
300	4/5[f]	18.2 ± 0.5	20.0 ± 0.7	1.8 ± 0.3	95
600	0/5[g]	18.4 ± 1.2	–	–	–

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No data were collected for groups with 100% mortality. Differences from the control group are not significant by Williams' or Dunnett's tests.
[c] Day of death: 3
[d] Day of death: 6
[e] Day of death: 1, 1, 2, 2, 3
[f] Day of death: 1
[g] Day of death: 1, 1, 1, 1, 3

13-WEEK STUDY

Two male mice that received 300 mg/kg died during the first week (Table 21). One female mouse receiving 75 mg/kg died in week 12 and one female receiving 19 mg/kg died in week 2. While the cause of death of the latter two mice was not reported by the laboratory, the deaths were more likely related to gavage error than to toxicity. There were no clinical signs of toxicity observed. The mean body weight gain and final mean body weight of males that received 300 mg/kg were significantly lower than those of controls (Table 21).

Hematology evaluations revealed a dose-related decrease in mean erythrocyte volume and mean erythrocyte hemoglobin in male and female mice receiving coumarin (Table H7). The mean erythrocyte volume of males receiving 38 mg/kg or more and of females receiving 75 mg/kg or more was significantly lower than that of controls. The hematocrit of male mice receiving 300 mg/kg was also significantly lower than controls. While these changes were not clinically important, they are characteristic of a microcytic, normochromic anemia.

At necropsy, the absolute and relative liver weights of male and female mice receiving 150 or 300 mg/kg were significantly greater than those of the controls (Table G5). Significantly increased relative brain and testis weights of 300 mg/kg male mice were considered to be due to the significantly lower body weight of this group. The principal lesion observed in mice receiving 300 mg/kg was minimal to mild centrilobular hepatocellular hypertrophy, consistent with the significant increase in liver weight. The hepatocellular hypertrophy was seen in seven males and seven females in the 300 mg/kg group; hypertrophy was not seen in the next lower dose group.

Dose Selection Rationale: Based on the mortality observed in the 300 mg/kg group in the 16-day and 13-week studies and the lack of significant toxicity at lower doses, the high dose selected for the 2-year study was 200 mg/kg.

TABLE 21
Survival and Mean Body Weights of Mice in the 13-Week Gavage Study of Coumarin

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	25.0 ± 0.6	32.3 ± 0.8	7.3 ± 0.6	
19	10/10	24.4 ± 0.5	32.6 ± 0.9	8.2 ± 0.4	101
38	10/10	24.7 ± 0.6	32.7 ± 0.8	8.0 ± 0.5	101
75	10/10	24.6 ± 0.6	32.1 ± 0.7	7.5 ± 0.7	99
150	10/10	24.6 ± 0.6	31.6 ± 0.5	7.0 ± 0.4	98
300	8/10[c]	24.2 ± 0.5	28.3 ± 0.7**	4.4 ± 0.4**	87
Female					
0	10/10	19.1 ± 0.5	25.3 ± 0.6	6.2 ± 0.5	
19	9/10[d]	19.0 ± 0.2	25.1 ± 0.4	6.1 ± 0.4	99
38	10/10	19.4 ± 0.3	25.0 ± 0.7	5.6 ± 0.5	99
75	9/10[e]	19.3 ± 0.4	25.8 ± 0.7	6.3 ± 0.4	102
150	10/10	19.1 ± 0.4	24.8 ± 0.6	5.7 ± 0.3	98
300	10/10	18.6 ± 0.5	23.5 ± 0.7	4.9 ± 0.4*	93

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's tests
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Week of death: 1, 1
[d] Week of death: 2
[e] Week of death: 12

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female mice are shown in Table 22 and in the Kaplan-Meier curves in Figure 4. Survival of all dosed groups of male and female mice was similar to that of the controls.

Body Weights and Clinical Findings

The mean body weights of 200 mg/kg male mice were about 3% to 10% lower than those of controls from week 10 to week 81 of the study. Thereafter, the body weight differences between the 200 mg/kg and control males diminished, and at the end of the study the mean body weights were similar. The mean body weights of 200 mg/kg female mice followed a pattern similar to males and varied from about 3% to 18% lower than controls from week 11 until week 49. The body weight differences diminished slightly thereafter, but remained about 12% lower at the end of the study (Figure 5 and Tables 23 and 24).

Hematology and Clinical Chemistry

Chemical-related changes in hematology parameters were more apparent in male mice than in females (Table H8). Mean erythrocyte volume, mean erythrocyte hemoglobin, and hematocrit of 200 mg/kg males were significantly lower than those of the controls. Of these parameters, only mean erythrocyte volume of 200 mg/kg females was significantly lower than controls. The platelet counts of both males and females in the 200 mg/kg groups were significantly higher than controls. Of the clinical chemistry parameters evaluated, only the value of alkaline phosphatase in 200 mg/kg males was significantly different from controls. The lower mean value of alkaline phosphatase for 200 mg/kg males is of uncertain significance, since increases in this enzyme are usually seen with certain disease processes.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the lung, liver, and forestomach. Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal tumor diagnoses, the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group, and historical control incidences for the biologically significant neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

TABLE 22
Survival of Mice in the 2-Year Gavage Study of Coumarin

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Male				
Animals initially in study	70	70	70	70
15-Month interim evaluation[a]	20	20	20	19
Natural deaths	5	3	1	11
Moribund kills	1	0	6	3
Accidental deaths[a]	1	0	1	0
Animals surviving to study termination	43	47	42	37
Percent probability of survival at end of study[b]	88	94	87	74
Mean survival (days)[c]	642	647	618	619
Survival analysis[d]	P=0.008	P=0.476N	P=0.927	P=0.075
Female				
Animals initially in study	70	70	70	70
15-Month interim evaluation[a]	18	20	19	19
Natural deaths	7	5	3	13
Moribund kills	8	5	5	8
Accidental deaths[a]	4	0	1	2
Animals surviving to study termination	33	40[e]	42	28
Percent probability of survival at end of study	70	80	85	61
Mean survival (days)	577	639	618	577
Survival analysis	P=0.105	P=0.240N	P=0.124N	P=0.330

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[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 dosed columns. A lower mortality in a dose group is indicated by N.
[e] Includes one animal killed moribund the last week of the study.

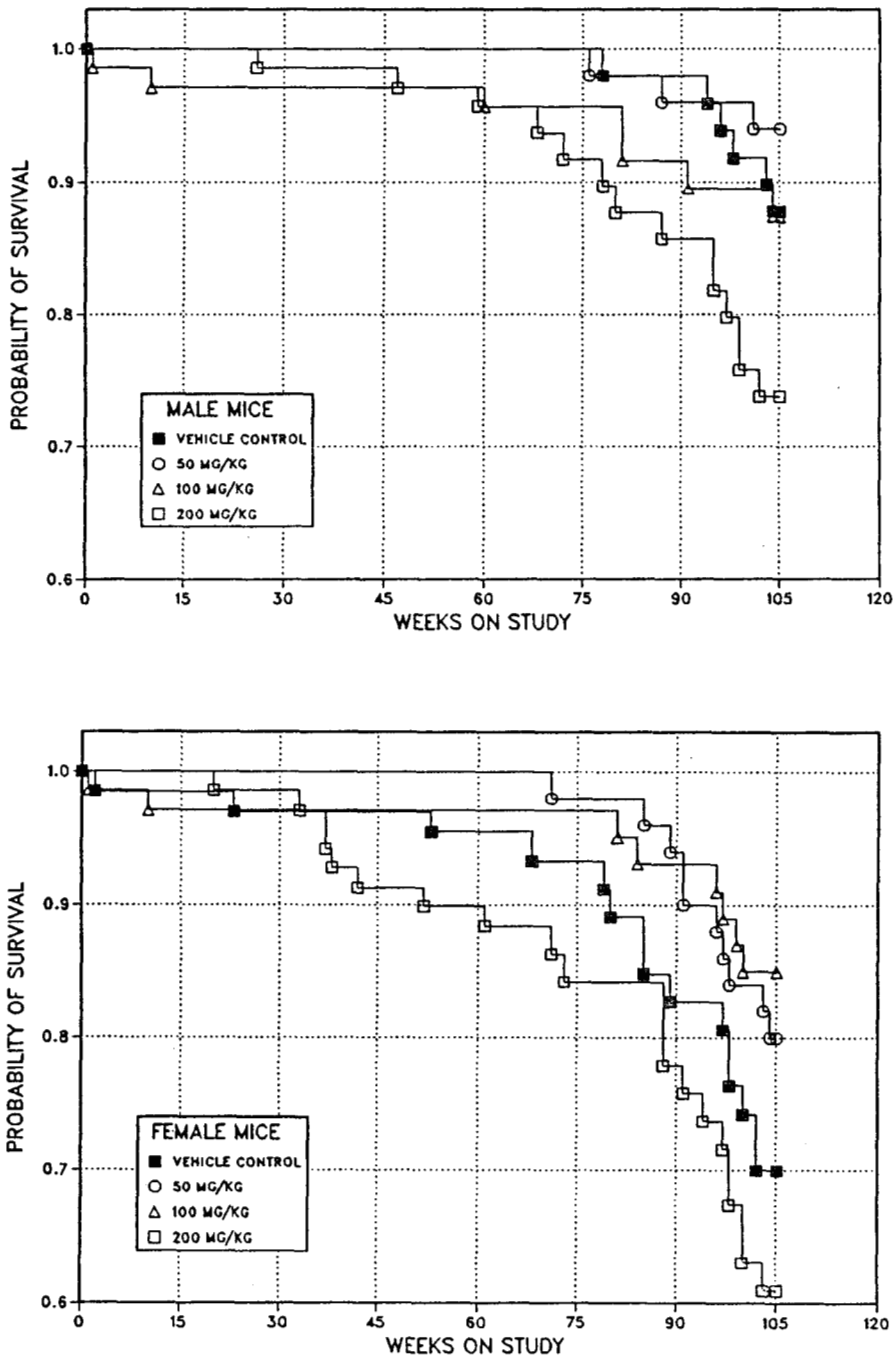


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Coumarin by Gavage for 2 Years

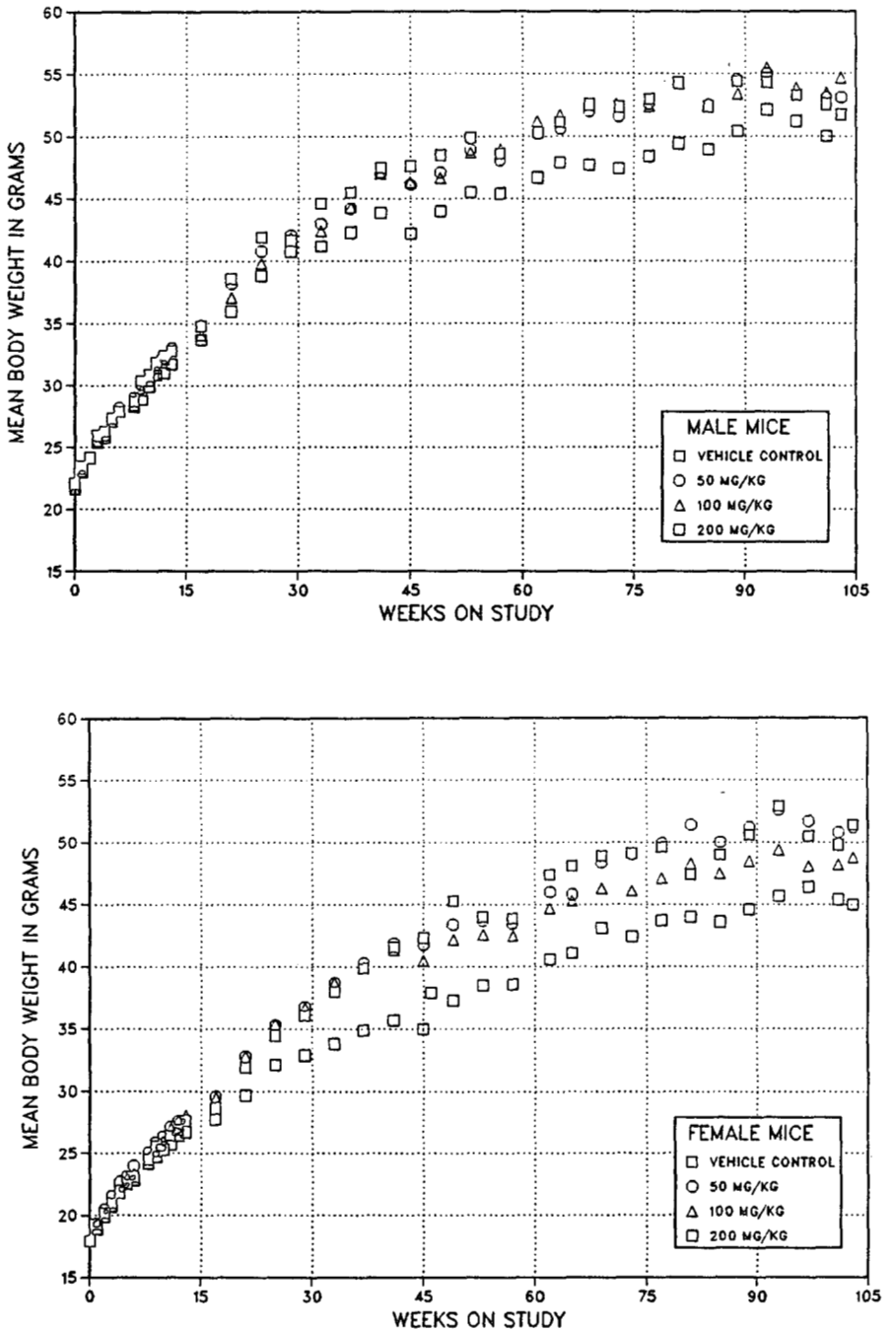


FIGURE 5
Growth Curves for Male and Female Mice Administered Coumarin by Gavage for 2 Years

TABLE 23
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Coumarin

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg			200 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	22.8	70	22.4	98	70	22.3	98	69	22.6	99	70
2	24.1	70	24.0	100	70	24.2	100	69	24.1	100	70
3	25.9	70	25.9	100	70	25.3	98	70	25.5	99	70[a]
4	26.3	70	26.3	100	70	25.9	99	70	25.8	98	70
5	27.4	70	27.3	100	70	27.1	99	70	27.3	100	70
6	27.9	70	28.2	101	70	27.9	100	70	27.9	100	70
8	28.7	70	29.0	101	70	28.4	99	70	28.3	99	70
9	30.2	70	29.8	99	70	29.4	97	70	29.0	96	70
10	30.9	70	30.9	100	70	30.3	98	69	29.9	97	70
11	31.9	70	31.9	100	70	31.4	98	69	30.8	97	70
12	32.4	70	32.2	99	70	32.1	99	69	31.0	96	70
13	32.8	70	33.0	101	70	32.7	100	69	31.7	97	70
17	34.8	70	34.9	100	70	34.0	98	68	33.7	97	70
21	38.6	70	38.2	99	70	36.9	96	68	36.0	93	70
25	41.9	70	40.8	97	70	39.8	95	68	38.8	93	70
29	41.7	70	42.1	101	70	41.8	100	68	40.8	98	69
33	44.6	70	43.0	96	70	42.3	95	68	41.2	92	69
37	45.5	70	44.2	97	70	44.2	97	68	42.3	93	69
41	47.5	70	47.1	99	70	46.8	99	68	43.9	92	69
45	47.6	70	46.1	97	70	46.2	97	68	42.2	89	69
49	48.5	70	47.1	97	70	46.6	96	68	44.0	91	68
53	49.9	70	48.9	98	70	48.5	97	68	45.5	91	68
57	48.6	70	48.1	99	70	48.8	100	68	45.4	93	68
62	50.3	70	50.2	100	70	51.1	102	67	46.7	93	67
65	51.1	65	50.6	99	65	51.6	101	62	47.9	94	62
69[b]	52.6	49	52.0	99	50	52.3	99	47	47.7	91	47
73	52.4	49	51.6	99	50	52.1	99	47	47.4	91	46
77	53.0	49	52.6	99	49	52.2	99	46	48.4	91	46
81	54.3	48	54.2	100	49	54.0	99	44	49.4	91	44
85	52.4	48	52.5	100	49	52.2	100	44	48.9	93	44
89	54.4	48	54.6	100	48	53.2	98	44	50.4	93	43
93	54.3	48	55.0	101	48	55.4	102	43	52.1	96	43
97	53.3	46	53.3	100	48	53.8	101	43	51.2	96	40
101	52.5	45	53.1	101	47	53.4	102	43	50.0	95	38
103	51.8	44	53.1	103	47	54.7	106	43	51.7	100	37
Mean for weeks											
1-13	28.4		28.4	100		28.1	99		27.8	98	
14-52	43.4		42.6	98		42.1	97		40.3	93	
53-103	52.2		52.1	100		52.4	100		48.8	93	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.
[b] Interim evaluation occurred during week 65.

TABLE 24
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Coumarin

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg			200 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.5	70	18.7	101	70	18.6	101	70	18.5	100	70
2	20.2	65	20.5	102	70	20.2	100	70	19.9	99	70
4	22.0	65	22.7	103	70	21.9	100	68	21.8	99	70
5	22.5	65	23.1	103	70	23.0	102	68	22.5	100	70
6	23.1	65	24.0	104	70	23.4	101	68	22.8	99	70
8	24.5	65	25.1	102	70	24.7	101	68	24.2	99	69
9	25.3	65	25.6	101	70	25.1	99	68	24.5	97	69
10	25.3	65	26.4	104	70	26.0	103	67	25.3	100	69
11	26.4	65	27.1	103	70	27.0	102	67	25.7	97	69
12	26.9	65	27.6	103	70	27.6	103	67	26.4	98	69
13	27.6	65	27.7	100	70	28.1	102	67	26.7	97	69
17	28.6	65	29.6	104	70	29.5	103	67	27.7	97	69
21	31.9	65	32.8	103	70	32.8	103	67	29.7	93	68
25	34.4	64	35.3	103	70	35.4	103	67	32.1	93	68
29	36.1	64	36.8	102	70	36.7	102	67	32.9	91	68
33	38.0	64	38.7	102	70	38.7	102	67	33.8	90	67
37	39.9	64	40.3	101	70	40.0	100	67	34.9	88	65
41	41.6	64	41.9	101	70	41.4	100	67	35.7	86	64
45	42.3	64	41.8	99	70	40.5	96	67	35.0	83	63
49	45.3	64	43.4	96	70	42.2	93	67	37.3	82	63
53	44.0	63	43.7	99	70	42.6	97	67	38.5	88	62
57	43.9	63	43.5	99	70	42.5	97	67	38.6	88	62
62	47.4	63	46.0	97	70	44.7	94	67	40.6	86	61
65	48.1	60	45.8	95	68	45.3	94	64	41.1	85	59
69[a]	48.9	44	48.4	99	50	46.3	95	48	43.1	88	42
73	49.1	44	49.0	100	49	46.1	94	48	42.4	86	40
77	49.6	44	49.9	101	49	47.1	95	48	43.7	88	39
81	47.4	42	51.4	108	49	48.3	102	47	44.0	93	40
85	49.0	40	50.0	102	48	47.5	97	46	43.6	89	40
89	50.6	40	51.2	101	47	48.5	96	46	44.6	88	37
93	52.9	39	52.6	99	45	49.4	93	46	45.7	86	36
97	50.5	38	51.7	102	43	48.1	95	45	46.4	92	34
101	49.8	35	50.8	102	42	48.2	97	42	45.4	91	30
103	51.4	33	51.2	100	41	48.8	95	42	45.0	88	28
Mean for weeks											
1-13	23.6		24.2	103		23.9	101		23.3	99	
14-52	37.6		37.8	101		37.5	100		33.2	88	
53-103	48.8		48.9	100		46.7	96		43.1	88	

[a] Interim evaluation occurred during week 65.

Lung: Alveolar/bronchiolar adenomas were seen in two 50 mg/kg and three 200 mg/kg male mice and in one 100 mg/kg and two 200 mg/kg female mice at the 15-month interim evaluation, while none were seen in controls (Tables 25, C1, and D1). In the 2-year study, the incidences of alveolar/bronchiolar adenomas in the 200 mg/kg male and female mice were significantly greater than those of the controls. Further, the incidence of alveolar/bronchiolar carcinomas in 200 mg/kg females, but not in males, was also significantly greater than controls. The incidences of pulmonary neoplasms in 200 mg/kg male and female mice are well above the range of historical control groups in recent NTP studies (Tables C4a and D4a).

No nonneoplastic lesions of the lungs of dosed mice were considered chemical related. Low incidences of focal alveolar epithelial hyperplasia, generally considered a precursor of alveolar/bronchiolar neoplasms, occurred at low incidence in all groups of male mice and all but the control group of female mice (Tables 25, C5, and D5).

Alveolar epithelial hyperplasia, alveolar/bronchiolar adenoma, and alveolar/bronchiolar carcinoma constitute a morphologic continuum. Alveolar epithelial hyperplasia consisted of focal areas with normal alveolar architecture lined by cuboidal or low columnar epithelial cells. Adenomas were discrete expansile masses that compressed adjacent tissue. The adenomas lacked normal architecture and consisted of somewhat pleomorphic cuboidal to columnar cells arranged in regular or papillary patterns. No single morphological criterion distinguished carcinomas from adenomas. As the neoplasms became larger they generally exhibited greater heterogeneity of growth pattern and cellular pleomorphism and atypia. Neoplasms diagnosed as carcinomas consisted of cells that were moderately to highly pleomorphic and, in some areas, appeared to grow in solid clusters. Mitotic figures were frequently observed.

TABLE 25
Incidences of Lung Lesions in Mice in the 2-Year Gavage Study of Coumarin

Dose	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Male				
15-Month Interim Evaluation				
Lung[a]	10	2	1	9
Alveolar/bronchiolar Adenoma[b]	0	2	0	3
2-Year Study				
Lung	50	50	50	51
Alveolar Epithelium Hyperplasia	3	1	4	5
Alveolar/bronchiolar Adenoma[c]				
Overall rate[d]	14/50 (28%)	8/50 (16%)	14/50 (28%)	24/51 (47%)
Adjusted rate[e]	29.7%	17.0%	33.3%	58.3%
Terminal rate[f]	10/43 (23%)	8/47 (17%)	14/42 (33%)	20/37 (54%)
First incidence (days)	653	729 (T)	729 (T)	558
Logistic regression test[g]	P=0.004	P=0.114N	P=0.588N	P=0.038
Alveolar/bronchiolar Carcinoma[h]				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	1/51 (2%)
Adjusted rate	2.2%	2.1%	4.8%	2.7%
Terminal rate	0/43 (23%)	1/47 (2%)	2/42 (5%)	1/37 (3%)
First incidence (days)	716	729 (T)	729 (T)	729 (T)
Logistic regression test	P=0.579	P=0.619	P=0.332	P=0.758N
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	14/50 (28%)	9/50 (18%)	15/50 (30%)	25/51 (49%)
Adjusted rate	29.7%	19.1%	35.7%	60.8%
Terminal rate	10/43 (23%)	9/47 (19%)	15/42 (36%)	21/37 (57%)
First incidence (days)	653	729 (T)	729 (T)	558
Logistic regression test	P=0.003	P=0.171N	P=0.500N	P=0.025

(continued)

TABLE 25
Incidences of Lung Lesions in Mice in the 2-Year Gavage Study of Coumarin (continued)

Dose	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Female				
15-Month Interim Evaluation				
Lung	8	1	1	9
Alveolar Epithelium Hyperplasia	0	1	0	0
Alveolar/bronchiolar Adenoma	0	0	1	2
2-Year Study				
Lung	51	49	49	51
Alveolar Epithelium Hyperplasia	0	3	4	4
Alveolar/bronchiolar Adenoma[j]				
Overall rate	2/51 (4%)	5/49 (10%)	7/49 (14%)	20/51 (39%)
Adjusted rate	5.8%	11.8%	16.3%	64.2%
Terminal rate	1/33 (3%)	3/40 (8%)	6/42 (14%)	17/28 (61%)
First incidence (days)	708	673	694	684
Logistic regression test	P<0.001	P=0.201	P=0.072	P<0.001
Alveolar/bronchiolar Carcinoma[k]				
Overall rate	0/51 (0%)	0/49 (0%)	0/49 (0%)	7/51 (14%)
Adjusted rate	0.0%	0.0%	0.0%	22.3%
Terminal rate	0/33 (0%)	0/40 (0%)	0/42 (0%)	5/28 (18%)
First incidence (days)	–[l]	–	–	615
Logistic regression test	P<0.001	–	–	P=0.007
Alveolar/bronchiolar Adenoma or Carcinoma[m]				
Overall rate	2/51 (4%)	5/49 (10%)	7/49 (14%)	27/51 (53%)
Adjusted rate	5.8%	11.8%	16.3%	81.5%
Terminal rate	1/33 (3%)	3/40 (8%)	6/42 (14%)	22/28 (79%)
First incidence (days)	708	673	694	615
Logistic regression test	P<0.001	P=0.201	P=0.072	P<0.001

(T)Terminal sacrifice
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 141/900 (15.7% ± 5.7%); range 4%-28%
[d] Number of animals with neoplasm per number of animals with organ examined microscopically.
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[f] Observed incidence in animals surviving until the end of the study.
[g] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A lower incidence in a dose group is indicated by N.
[h] Historical incidence: 34/900 (3.8% ± 3.6%); range 0%-12%
[i] Historical incidence: 166/900 (18.4% ± 5.9%); range 6%-28%
[j] Historical incidence: 40/899 (4.4% ± 2.4%); range 0%-10%
[k] Historical incidence: 19/899 (2.1% ± 2.0%); range 0%-6%
[l] Not applicable; no neoplasms in animal group
[m] Historical incidence: 58/899 (6.5% ± 3.7%); range 0%-14%

Liver: The administration of coumarin to mice was associated with increased incidences of several nonneoplastic lesions of the liver in mice evaluated at 15 months and at the end of the study (Tables 26, C5, and D5). At the 15-month interim evaluation, the incidences of syncytial alteration and centrilobular hypertrophy in 200 mg/kg mice were significantly greater than those of controls. At the end of the study, the incidences of these lesions were significantly greater in 100 and 200 mg/kg males and 200 mg/kg females. Coagulative necrosis of hepatocytes also occurred more frequently in the 200 mg/kg mice.

Syncytial alteration was generally minimal to mild in severity and consisted of widely scattered, enlarged, individual hepatocytes with 3 to 10 nuclei (Plate 11). The term syncytial alteration may be a misnomer since the alteration is likely not the result of cell fusion, but rather a failure of cell division. Centrilobular hypertrophy was also minimal to mild in severity and characterized by generalized, centrilobular hepatocellular enlargement (Plate 12). The affected cells usually had cytoplasm that stained more homogeneous and densely eosinophilic than cells in the periportal region. About a third or less of the liver lobule was affected in minimal lesions, while one-third to one-half the liver lobule was affected in mild lesions. Coagulative necrosis was focal and randomly distributed in some mice or located within or adjacent to hepatocellular neoplasms in others. In a few mice, it consisted of massive necrosis of an entire liver lobe and was judged the cause of death. Thus, the coagulative necrosis, while increased in incidence in the dosed groups, was not clearly chemical related.

The incidences of eosinophilic focus were significantly greater in all groups of dosed mice, except for the 100 mg/kg males and 200 mg/kg females, than in controls (Table 26). Consistent with the increased incidences of foci in females, the incidences of hepatocellular adenoma in the 50 and 100 mg/kg female mice were also significantly greater than controls. A few hepatocellular carcinomas occurred in dosed females, but none were seen in controls. The incidences of benign and malignant neoplasms combined in the 50 and 100 mg/kg females (55% and 61%) exceeds the range of historical controls from recent NTP studies (range 2%-34%; 129/898, 14.4%; Table D4b). The absence of a significant increased incidence of hepatocellular neoplasms in the 200 mg/kg group may be related to the reduced body weights of this group.

In contrast to female mice, the incidences of hepatocellular adenoma in dosed males were similar to that of controls, while the incidence of hepatocellular carcinoma in the 200 mg/kg group was lower than controls. The incidences of hepatocellular neoplasms in all male groups were high (57%-70%) but within the range of historical controls (range 14%-72%; 370/901, 41.1%; Table C4b).

Hepatic foci of cytoplasmic alteration, hepatocellular adenoma, and hepatocellular carcinoma constituted a morphologic continuum. The foci generally consisted of enlarged cells with eosinophilic, basophilic, or clear cytoplasm and were classified based on the predominant staining characteristics of the cytoplasm. The staining characteristics of the cytoplasm generally reflect increased amounts of smooth endoplasmic reticulum (eosinophilic), rough endoplasmic reticulum or ribosomes (basophilic), or glycogen (clear). The architecture of the hepatic plates was generally normal within foci of cytoplasmic alteration. Hepatocellular adenomas were discrete masses with distorted or absent lobular architecture consisting of plates one to two cells thick, similar to the normal liver. The hepatocytes often had staining properties similar to those found in foci of cytoplasmic alteration. In contrast to the adenomas, hepatocellular carcinomas had heterogeneous growth patterns with hepatocytes arranged in plates two to six cells thick or with glandular structures. Carcinomas exhibited a greater degree of cellular pleomorphism and atypia than did adenomas. Hepatoblastomas usually consisted predominantly of neoplastic cells similar to those of carcinomas, but with an added component of small, undifferentiated cells with intensely basophilic cytoplasm.

TABLE 26
Incidences of Liver Lesions in Mice in the 2-Year Gavage Study of Coumarin

Dose	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Male				
15-Month Interim Evaluation				
Liver[a]	10	4	6	9
Syncytial Alteration[b]	0	1 (1.0)[c]	4 (1.8)	9**(2.0)
Centrilobular Hypertrophy	0	0	0	8**(2.9)
Hepatocellular Adenoma	0	2	1	3
2-Year Study				
Liver	50	50	50	51
Eosinophilic Focus	6	15*	13	15**
Syncytial Alteration	0	6*(1.2)	35**(1.2)	47**(1.9)
Centrilobular Hypertrophy	1 (2.0)	2 (2.0)	23**(1.7)	44**(1.6)
Coagulative Necrosis	3 (2.3)	1 (3.0)	0	8 (3.3)
Hepatocellular Adenoma[d]				
Overall rate[e]	26/50 (52%)	29/50 (58%)	29/50 (58%)	27/51 (53%)
Terminal rate[f]	56.5%	59.2%	67.4%	64.0%
Adjusted rate[g]	23/43 (50%)	27/47 (57%)	28/42 (67%)	22/37 (59%)
First incidence (days)	680	607	567	476
Logistic regression test[h]	P=0.519N	P=0.344	P=0.344	P=0.542
Hepatocellular Carcinoma[i]				
Overall rate	11/50 (22%)	11/50 (22%)	5/50 (10%)	3/51 (6%)
Terminal rate	23.6%	22.0%	11.6%	7.5%
Adjusted rate	8/43 (19%)	8/47 (17%)	4/42 (10%)	2/37 (5%)
First incidence (days)	541	532	636	558
Logistic regression test	P=0.003N	P=0.505	P=0.099N	P=0.011N
Hepatocellular Adenoma or Carcinoma[j]				
Overall rate	35/50 (70%)	34/50 (68%)	31/50 (62%)	29/51 (57%)
Adjusted rate	71.4%	68.0%	70.4%	67.2%
Terminal rate	29/43 (67%)	31/47 (66%)	29/42 (69%)	23/37 (62%)
First incidence (days)	541	532	567	476
Logistic regression tests	P=0.080N	P=0.500N	P=0.263N	P=0.122N
Hepatoblastoma[k]				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	1/51 (2%)
Adjusted rate	0.0%	0.0%	11.3%	2.7%
Terminal rate	0/43 (0%)	0/47 (0%)	4/42 (10%)	1/37 (3%)
First incidence (days)	–[l]	–	1	729 (T)
Logistic regression test	P=0.299	–	P=0.060	P=0.470
Hepatocellular Carcinoma or Hepatoblastoma[m]				
Overall rate	11/50 (22%)	11/50 (22%)	9/50 (18%)	3/51 (6%)
Adjusted rate	23.6%	22.0%	20.2%	7.5%
Terminal rate	8/43 (19%)	8/47 (17%)	7/42 (17%)	2/37 (5%)
First incidence (days)	541	532	1	558
Logistic regression tests	P=0.004N	P=0.505	P=0.347N	P=0.011N

(continued)

TABLE 26
Incidences of Liver Lesions in Mice in the 2-Year Gavage Study of Coumarin (continued)

Dose	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Female				
15-Month Interim Evaluation				
Liver	8	1	2	9
Eosinophilic Focus	0	1 (2.0)	2 (1.5)	0
Syncytial Alteration	0	0	0	4**(1.0)
Centrilobular Hypertrophy	0	0	0	8**(1.6)
Coagulative Necrosis	1 (2.0)	0	0	0
Hepatocellular Adenoma	1	0	0	0
2-Year Study				
Liver	50	49	51	50
Eosinophilic Focus	4 (2.5)	20**(2.3)	20**(2.4)	9 (1.9)
Syncytial Alteration	0	0	2 (1.0)	19**(1.4)
Centrilobular Hypertrophy	0	0	0	17**(1.2)
Coagulative Necrosis	2 (2.5)	2 (3.0)	2 (2.0)	11**(3.3)
Hepatocellular Adenoma[n]				
Overall rate	8/50 (16%)	26/49 (53%)	29/51 (57%)	12/50 (24%)
Adjusted rate	23.4%	63.4%	62.9%	39.7%
Terminal rate	7/33 (21%)	25/40 (63%)	25/42 (60%)	10/28 (36%)
First incidence (days)	694	722	564	684
Logistic regression test	P=0.525	P<0.001	P<0.001	P=0.227
Hepatocellular Carcinoma[o]				
Overall rate	0/50 (0%)	3/49 (6%)	3/51 (6%)	1/50 (0%)
Adjusted rate	0.0%	7.3%	6.7%	2.8%
Terminal rate	0/33 (0%)	2/40 (5%)	1/42 (2%)	0/28 (0%)
First incidence (days)	–	715	672	655
Logistic regression test	P=0.570N	P=0.132	P=0.101	P=0.594
Hepatocellular Adenoma or Carcinoma[p]				
Overall rate	8/50 (16%)	27/49 (55%)	31/51 (61%)	13/50 (26%)
Adjusted rate	23.4%	64.3%	65.9%	41.4%
Terminal rate	7/33 (21%)	25/40 (63%)	26/42 (62%)	10/28 (36%)
First incidence (days)	694	715	564	655
Logistic regression tests	P=0.447	P<0.001	P<0.001	P=0.163
Hepatoblastoma[q]				
Overall rate	0/50 (0%)	1/49 (2%)	0/51 (0%)	0/50 (0%)
Adjusted rate	0.0%	2.5%	0.0%	0.0%
Terminal rate	0/33 (0%)	1/40 (3%)	0/42 (0%)	0/28 (0%)
First incidence (days)	–	729 (T)	–	–
Logistic regression test	P=0.601N	P=0.538	–	–
Hepatocellular Carcinoma or Hepatoblastoma[r]				
Overall rate	0/50 (0%)	4/49 (8%)	3/51 (6%)	1/50 (2%)
Adjusted rate	0.0%	9.7%	6.7%	2.8%
Terminal rate	0/33 (0%)	3/40 (8%)	1/42 (2%)	0/28 (0%)
First incidence (days)	–	715	672	655
Logistic regression tests	P=0.502N	P=0.076	P=0.101	P=0.594

(continued)

TABLE 26
Incidences of Liver Lesions in Mice in the 2-Year Gavage Study of Coumarin (continued)

* Significantly different (P≤0.05) from the control group by the Fisher exact test (15-month interim) or logistic regression test (2-year study)
** P≤0.01
(T)Terminal sacrifice
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grade of lesion in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 249/901 (27.6% ± 15.0%); range 4%-58%
[e] Number of animals with neoplasm per number of animals with organ examined microscopically.
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[g] Observed incidence in animals surviving until the end of the study.
[h] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or lower incidence in a dose group is indicated by N.
[i] Historical incidence: 155/901 (17.2% ± 5.8%); range 8%-32%
[j] Historical incidence: 370/901 (41.1% ± 15.5%); range 14%-72%
[k] Historical incidence: 2/901 (0.2% ± 0.7%); range 0%-2%
[l] Not applicable; no neoplasms in animal group
[m] Historical incidence: 155/901 (17.2% ± 5.8%); range 8%-32%
[n] Historical incidence: 94/898 (10.5% ± 7.2%); range 2%-26%
[o] Historical incidence: 41/898 (4.6% ± 3.6%); range 0%-14%
[p] Historical incidence: 129/898 (14.4% ± 8.1%); range 2%-34%
[q] Historical incidence: 0/898
[r] Historical incidence: 41/898 (4.6% ± 3.6%); range 0%-14%

Forestomach: Squamous hyperplasia of the forestomach was seen in one control male, three 50 mg/kg males, and three 100 mg/kg males. Squamous cell papillomas of the forestomach occurred more frequently in 50 mg/kg male mice than in controls; the incidence in the 100 mg/kg group was similar to controls and none were seen in the 200 mg/kg group (Tables 27 and C1). Squamous cell carcinomas were seen in one 50 mg/kg and two 100 mg/kg males as well, and none were observed in the controls. The incidence of squamous cell papilloma in the 50 mg/kg males slightly exceeds the range in historical controls from recent NTP studies; further, no more than one squamous cell carcinoma has been observed in a group of 50 historical control male mice (Table C4c).

The incidence of forestomach hyperplasia was significantly increased in 100 mg/kg female mice. Similar to the pattern seen in male mice, the incidence of squamous cell papilloma in the 50 mg/kg females was slightly greater than that of the controls. However, the incidence is within the range of NTP historical controls (Table D4c). Squamous cell carcinomas were seen in one 50 mg/kg and one 100 mg/kg female (Tables 27 and D1).

Focal hyperplasia of the forestomach epithelium, squamous cell papilloma, and squamous cell carcinoma constitute a morphologic continuum. Hyperplasia was characterized by focally thickened stratified squamous epithelium forming rugose folds that extended into the stomach lumen. Papillomas also consisted of thickened, folded epithelium, but the folds were more complex and had a fibrovascular core. Differentiation of the epithelium within papillomas was normal and there was no cellular atypia. Squamous cell carcinomas consisted of cords of stratified squamous epithelium which invaded the submucosa and muscularis.

GENETIC TOXICOLOGY

Positive results were obtained with *in vitro* mutagenicity tests, but no mutagenic responses were observed *in vivo*. Coumarin (33 to 3,333 μg/plate) was tested for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat and Syrian hamster liver S9; a positive response was obtained only in TA100 with S9 (Table F1; Haworth *et al.*, 1983).

In Chinese hamster ovary cells, coumarin induced sister chromatid exchanges in the absence, but not the presence, of Aroclor 1254-induced male Sprague-Dawley rat liver S9; the lowest effective dose was 100 μg/mL (Table F2; Galloway *et al.*, 1987). In both sister chromatid exchange trials without S9, the increases in sister chromatid exchanges were significant, but did not correlate with dose. Coumarin was also tested for induction of chromosomal aberrations in Chinese hamster ovary cells with and without S9. A dose-related positive response was also observed, but only in the presence of S9 (Table F3; Galloway *et al.*, 1987). A significant increase in chromosomal aberrations was seen at the highest dose tested (1,600 μg/mL) with S9; at this dose, 37% of cells showed chromosomal damage.

Coumarin did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* exposed either as adults, by feeding (70 ppm) or by injection (500 ppm), or as larvae, treated by feeding (194 and 200 ppm) (Table F4; Yoon *et al.*, 1985; Valencia *et al.*, 1989).

Peripheral blood erythrocytes of male and female $B6C3F_1$ mice administered coumarin at doses up to 300 mg/kg for 13 weeks by gavage were examined for frequencies of micronuclei; no increases in micronucleated normochromatic erythrocytes were observed (Table F5).

TABLE 27
Incidences of Forestomach Lesions in Mice in the 2-Year Gavage Study of Coumarin

Dose	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Male				
Forestomach[a]	48	49	49	47
Squamous Hyperplasia[b]	1	3	3	0
Squamous Cell Papilloma[c]				
Overall rate[d]	2/50 (4%)	8/50 (16%)	2/50 (4%)	0/51 (0%)
Adjusted rate[e]	4.7%	17.0%	4.8%	0.0%
Terminal rate[f]	2/43 (5%)	8/47 (17%)	2/42 (5%)	0/37 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	–[h]
Logistic regression test[g]	P=0.051N	P=0.048	P=0.695	P=0.233N
Squamous Cell Carcinoma[i]				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	0/51 (0%)
Adjusted rate	0.0%	2.1%	4.1%	0.0%
Terminal rate	0/43 (0%)	1/47 (2%)	0/42 (0%)	0/37 (0%)
First incidence (days)	–	729 (T)	1	–
Logistic regression test	P=0.289N	P=0.518	–	–
Squamous Cell Papilloma or Carcinoma (combined)[j]				
Overall rate	2/50 (4%)	9/50 (18%)	4/50 (8%)	0/51 (0%)
Adjusted rate	4.7%	19.1%	8.7%	0.0%
Terminal rate	2/43 (5%)	9/47 (19%)	2/42 (5%)	0/37 (0%)
First incidence (days)	729 (T)	729 (T)	1	–
Logistic regression test	P=0.042N	P=0.039	P=0.686	P=0.272N
Female				
Forestomach	48	49	49	46
Squamous Hyperplasia	0	2	5*	0
Squamous Cell Papilloma[k]				
Overall rate	1/52 (2%)	5/50 (10%)	2/51 (4%)	2/51 (4%)
Adjusted rate	2.4%	12.5%	4.8%	7.1%
Terminal rate	0/33 (0%)	5/40 (13%)	2/42 (5%)	2/28 (7%)
First incidence (days)	589	729 (T)	729 (T)	729 (T)
Logistic regression test	P=0.548N	P=0.095	P=0.493	P=0.493
Squamous Cell Carcinoma[l]				
Overall rate	0/52 (0%)	1/50 (2%)	1/51 (2%)	0/51 (0%)
Adjusted rate	0.0%	2.5%	2.3%	0.0%
Terminal rate	0/33 (0%)	1/40 (3%)	0/42 (0%)	0/28 (0%)
First incidence (days)	–	729 (T)	694	–
Logistic regression test	P=0.573N	P=0.538	P=0.419	–
Squamous Cell Papilloma or Carcinoma[m]				
Overall rate	1/52 (2%)	6/50 (12%)	3/51 (6%)	2/51 (4%)
Adjusted rate	2.4%	15.0%	7.0%	7.1%
Terminal rate	0/33 (0%)	6/40 (15%)	2/42 (5%)	2/28 (7%)
First incidence (days)	589	729 (T)	694	729 (T)
Logistic regression test	P=0.578N	P=0.083	P=0.236	P=0.436

(continued)

TABLE 27
Incidences of Forestomach Lesions in Mice in the 2-Year Gavage Study of Coumarin (continued)

* Significantly different (P≤0.05) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with organ examined microscopically.
[b] Number of animals with lesion.
[c] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 27/902 (3.0% ± 3.4%); range 0%-14%
[d] Number of animals with neoplasm per number of animals necropsied.
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[f] Observed incidence in animals surviving until the end of the study.
[g] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or lower incidence in a dose group is indicated by N.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 4/902 (0.4% ± 0.9%); range 0%-2%
[j] Historical incidence: 31/902 (3.4% ± 3.6%); range 0%-14%
[k] Historical incidence: 27/901 (3.0% ± 2.9%); range 0%-10%
[l] Historical incidence: 3/901 (0.3% ± 1.0%); range 0%-4%
[m] Historical incidence: 30/901 (3.3% ± 3.3%); range 0%-10%

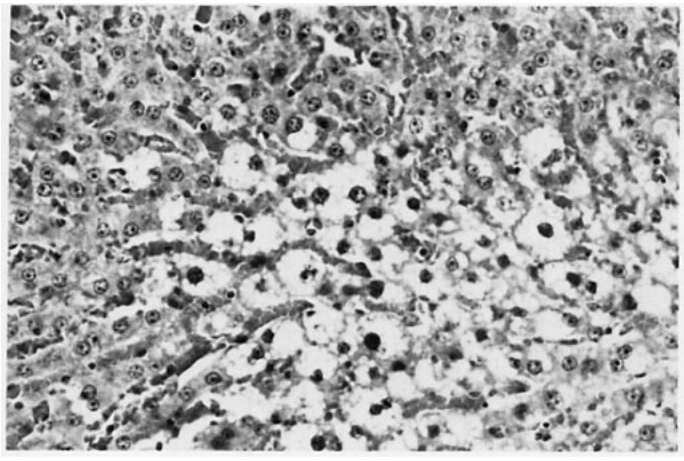


PLATE 1
Centrilobular hepatocellular degeneration of the liver in a male F344/N rat receiving 150 mg/kg coumarin in the 13-week gavage study. Note the clear vacuoles (lipid droplets) within the cytoplasm of the affected cells. H&E, 80X

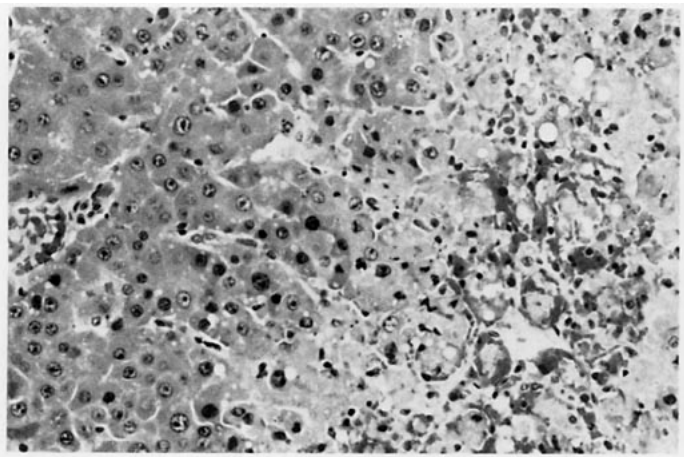


PLATE 2
Centrilobular hepatocellular necrosis of the liver in a male F344/N rat receiving 300 mg/kg coumarin in the 13-week gavage study. Note the necrotic cells with pale cytoplasm and pyknotic or fragmented nuclei surrounding the central venule. H&E, 80X

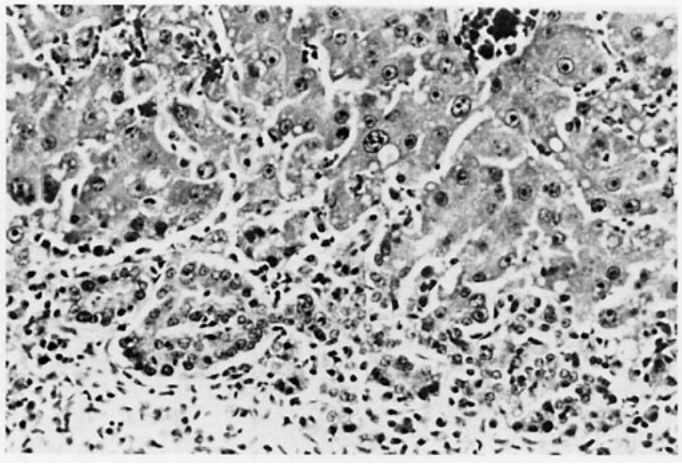


PLATE 3
Bile duct hyperplasia and inflammation of the liver in a male F344/N rat receiving 300 mg/kg coumarin in the 13-week gavage study. The portal area contains branching bile ducts and a mixed leukocyte infiltrate. H&E, 80X

PLATE 4
Moderate coagulative necrosis of the liver in a male F344/N rat receiving 100 mg/kg coumarin in the 2-year gavage study. Note the pale, shrunken hepatocytes with pyknotic or fragmented nuclei. H&E, 50X

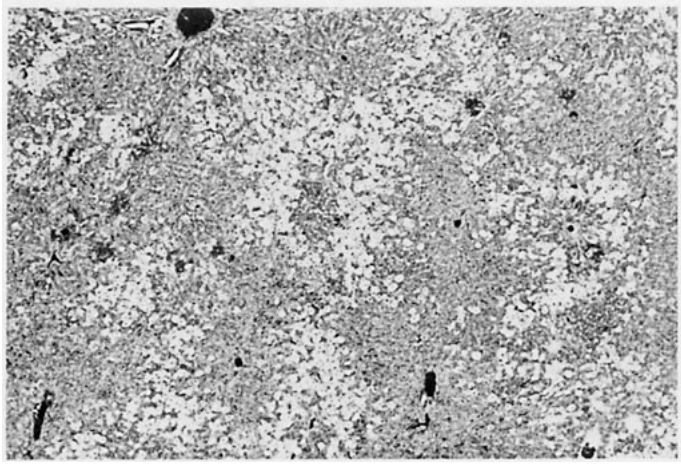


PLATE 5
Hepatocellular granular degeneration of the liver in a female F344/N rat receiving 100 mg/kg coumarin in the 2-year gavage study. Note the hepatocytes with pale cytoplasm which tend to be located in centrilobular or midzonal areas of the hepatic lobules. H&E, 10X

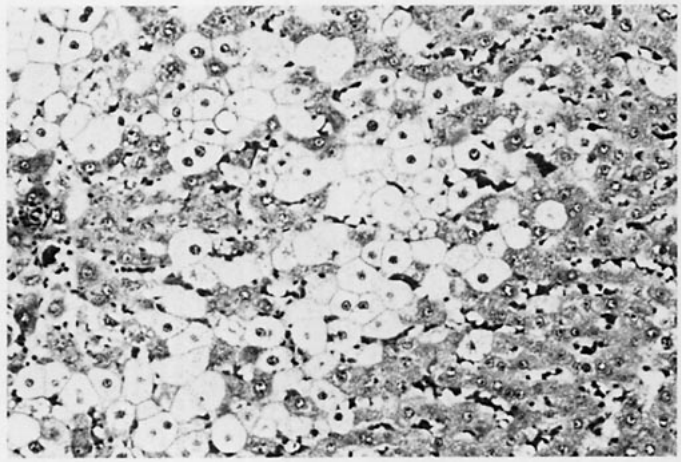


PLATE 6
Higher magnification of the hepatocellular granular degeneration in Plate 5 showing swollen hepatocytes with clear cytoplasm. H&E, 50X

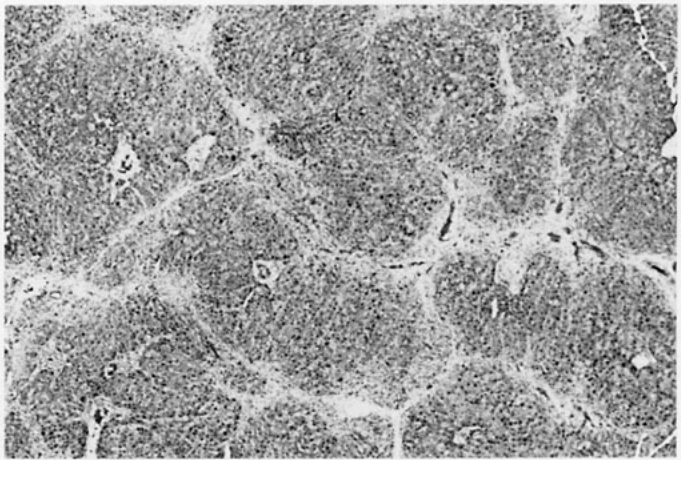


PLATE 7
Moderate fibrosis of the liver in a male F344/N rat receiving 100 mg/kg coumarin in the 2-year gavage study. Bands of collagenous connective tissue extend between hepatic lobules. H&E, 10X

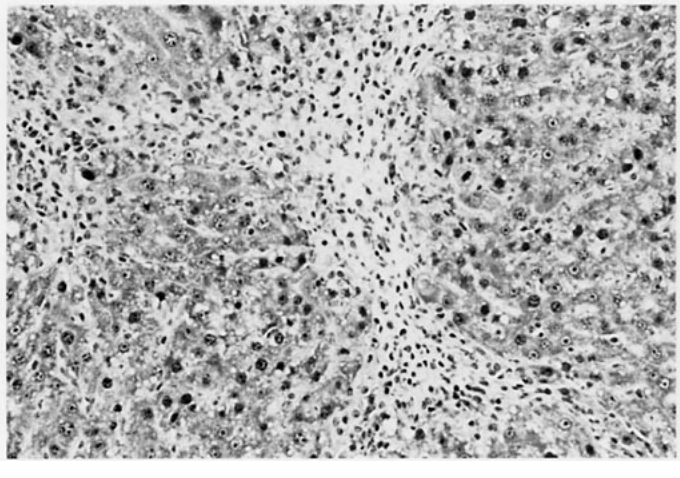


PLATE 8
Higher magnification of the liver fibrosis in Plate 7 showing collapsed stroma and collagenous connective tissue separating hepatic lobules. H&E, 50X

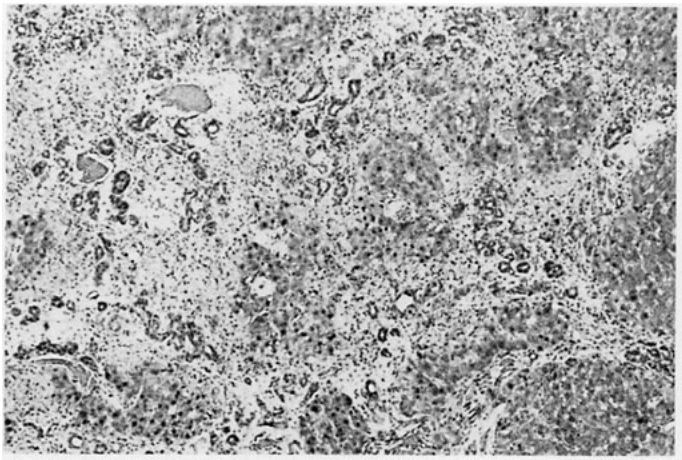


PLATE 9
Fibrosis and moderate bile duct hyperplasia of the liver in a male F344/N rat receiving 100 mg/kg coumarin in the 2-year gavage study. H&E, 20X

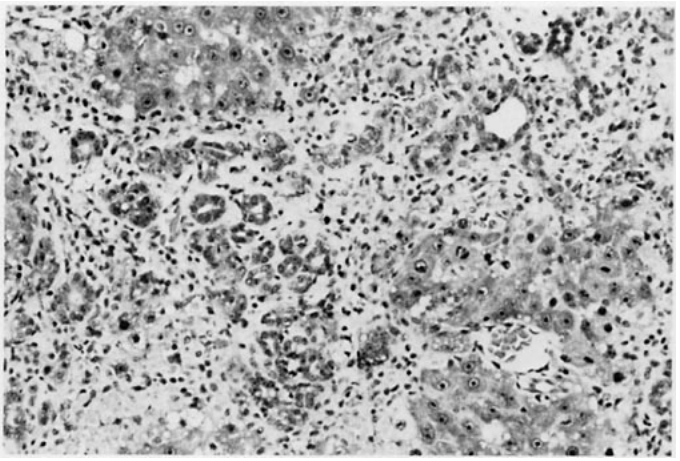


PLATE 10
Higher magnification of the fibrosis and bile duct hyperplasia in Plate 9 showing the increased number of small biliary ducts and ductules. H&E, 50X

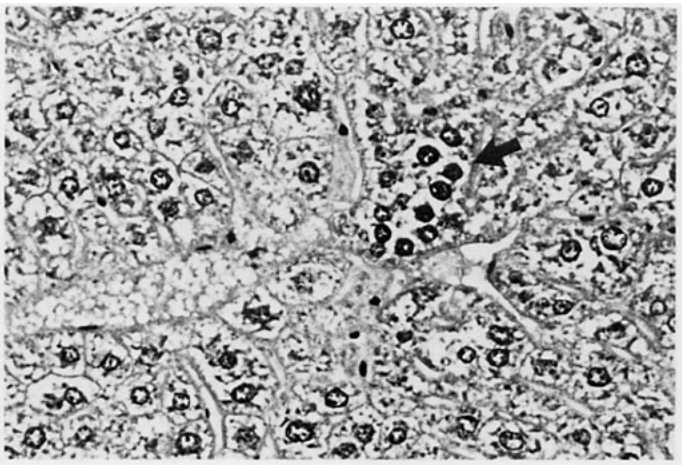


PLATE 11
Syncytial alteration (arrow) of a hepatocyte in the liver of a male $B6C3F_1$ mouse receiving 200 mg/kg coumarin in the 2-year gavage study. H&E, 100X

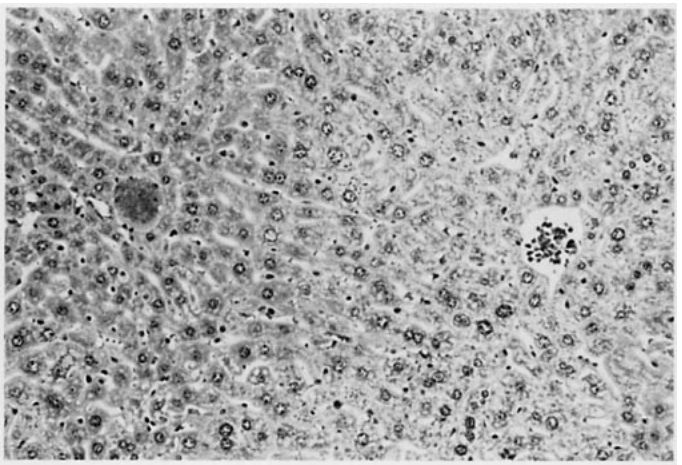


PLATE 12
Centrilobular hepatocellular hypertrophy of the liver in a male $B6C3F_1$ mouse receiving 200 mg/kg coumarin in the 2-year gavage study. Note the pale swollen hepatocytes surrounding the central venule in the right half of the photomicrograph. H&E, 50X

DISCUSSION AND CONCLUSIONS

Coumarin is the basic structure of numerous naturally occurring compounds with important and diverse physiological activities. More than 1,000 coumarin derivatives have been described, varying from simple coumarins, containing alkyl and hydroxyl side chains, to complex coumarins with benzoyl, furanoyl, pyranoyl, or alkylphosphorothionyl substituents. The NTP has previously reported on toxicity and carcinogenicity studies of 8-methoxypsoralen (NTP, 1989a), a furanocoumarin, and ochratoxin A (NTP, 1989b), a dihydroisocoumarin, as well as quercetin (NTP, 1992), a benzo-gamma-pyrone derivative resembling the 1,2-benzopyrone moiety in coumarin.

Coumarin and 3,4-dihydrocoumarin were nominated for study by the Food and Drug Administration and the National Cancer Institute because of the widespread use of coumarin in perfumes, cosmetics, and other products as a fragrance, continued interest in using coumarin compounds as flavor-enhancing agents for foods, and the interest in chemical structure-biological activity relationships of this important group of compounds. This Technical Report describes the findings of the 16-day, 13-week, and 2-year toxicity and carcinogenicity studies of coumarin in F344/N rats and B6C3F$_1$ mice. The results of the NTP toxicity and carcinogenicity studies of 3,4-dihydrocoumarin are reported separately (NTP, 1993).

The principal toxic effects associated with the administration of coumarin occurred in the liver of both rats and mice and in the kidney of rats. Slight, but clinically unimportant, effects also occurred in the blood of both species, and ulcers of the forestomach occurred more frequently in dosed rats than in controls. While the hepatotoxicity of coumarin in several species of experimental animals has previously been described (Hazleton *et al.*, 1956; Hagan *et al.*, 1967; Lake, 1984), the renal effects observed in rats in the NTP studies have not been reported previously.

The hepatic effects observed in rats in the 13-week study occurred primarily in groups receiving 150 or 300 mg/kg and included increased liver weight, accumulation of lipid within hepatocytes, centrilobular hepatocellular degeneration and necrosis, bile duct hyperplasia, and inflammation. Consistent with the histologic observations, there were elevations in activities of several cytoplasmic enzymes found within hepatocytes including alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, and ornithine carbamoyltransferase. These cytoplasmic enzymes are released into the blood following hepatocellular injury and necrosis.

While the hepatic lesions produced in rats by the prolonged administration of coumarin in the 2-year study were similar to those in the 13-week study, there were slight differences possibly due to one or more factors including the lower doses, cumulative toxicity, age of the animals, or the duration or chronicity of the lesions in the 2-year study. In the 2-year study, the degree of inflammation associated with the hepatocellular and biliary lesions was less apparent, and fibrosis, which did not occur in the 13-week study, was seen in dosed rats in the 2-year study. On a body weight basis, male rats were more susceptible than female rats to coumarin. In males, hepatic lesions were seen in groups receiving 25, 50, or 100 mg/kg, while in females they were seen only in groups receiving 50 or 100 mg/kg. Moreover, the various hepatic lesions generally occurred more frequently in males than females at similar dose levels.

While the administration of coumarin to F344/N rats was associated with an increase in the severity of bile duct hyperplasia, the atypical bile duct cells and marked peribiliary fibrosis (cholangiofibrosis) described by Hagan *et al.* (1967) in Osborne-Mendel male rats were not seen in the NTP 2-year study. Further, the induction of bile duct carcinomas as reported by Griepentrog (1973) was also not observed. However, the studies by Hagan *et al.* (1967) and Griepentrog (1973) were conducted by administering coumarin in the diet at levels substantially higher than those received by the rats in the NTP 2-year study. The cholangiofibrosis and bile duct carcinomas were observed in male rats receiving

dietary levels of 5,000 to 6,000 ppm coumarin, which is estimated to deliver 250 to 500 mg/kg, in contrast to the 100 mg/kg given by gavage in the NTP study. Thus, the doses of coumarin used in the NTP study may have been too low to induce these lesions.

The increased liver weights in rats receiving coumarin in the NTP 13-week and 2-year studies is likely related to an increase in hepatocyte endoplasmic reticulum and microsomal protein synthesis or enzyme induction. Grasso *et al.* (1974) have shown by electron microscopy that coumarin administration to rats produces hypertrophy and dilatation of the endoplasmic reticulum. Consistent with the role of the endoplasmic reticulum in protein synthesis, Nievel (1969) demonstrated increased microsomal protein synthesis in the liver of rats given 50 to 450 mg coumarin/kg body weight for 3 to 7 days.

The hepatocyte lipid accumulation observed in the NTP studies may be related to impaired function of the endoplasmic reticulum, the principal site of lipid synthesis and formation of lipoproteins, or to perturbations in glucose metabolism or energy production in hepatocytes. Feuer *et al.* (1965a,b) demonstrated a reduction in glucose-6-phosphatase activity and a concomitant increase in glucose-6-phosphate dehydrogenase activity in the rat liver following oral administration of coumarin. These investigators also showed *o*-hydroxyphenylacetic acid and *o*-hydroxyphenyllactic acid, two metabolites of coumarin in the rat, inhibited glucose-6-phosphatase activity *in vitro*, while coumarin and 3-, 4-, 6-, 7-, and 8-hydroxycoumarin produced no inhibition (Feuer *et al.*, 1966). They concluded that ring opening during the metabolism of coumarin confers inhibitory activity and that the phenolic hydroxyl group in the ortho position of the aromatic acids is important for the inhibitory activity.

While the biochemical mechanisms by which coumarin produces hepatocyte necrosis in rats has not been determined, a reactive intermediate capable of binding to cytoplasmic proteins is generated during the metabolism of coumarin. Coumarin rapidly depletes intracellular glutathione levels both *in vivo* and *in vitro* in rat hepatocyte suspensions or monolayer cultures and enhances urinary mercapturic acid excretion after *in vivo* administration (Lake, 1984; Lake *et al.*, 1989; Peters *et al.*, 1991). Further, sulfhydryl agents inhibit covalent binding to microsomal proteins (den Besten *et al.*, 1990). It has been suggested that coumarin may be converted to a 3,4-epoxide intermediate which may either rearrange to 3-hydroxycoumarin or coumarin 3,4-dihydrodiol, or produce toxicity by covalent binding to cytoplasmic proteins (Lake *et al.*, 1989; Peters *et al.*, 1991). A structurally related compound, precocene I (7-methoxy-2,2-dimethyl-2H-benzo[b]pyran) also produces centrilobular hepatocellular necrosis in the rat and is metabolized by microsomal cytochrome P-450 enzymes to a reactive metabolite which binds covalently to proteins and depletes hepatic glutathione levels (Halpin *et al.*, 1984; Ravindranath *et al.*, 1987).

Although the specific metabolite or metabolites producing the bile duct hyperplasia observed in the NTP study and the cholangiofibrosis observed in male rats by other investigators have not been identified, the biliary lesions are likely related to the excretion of toxic coumarin metabolites in the bile. Williams *et al.* (1965) showed that 50% of an oral or intraperitoneal dose of coumarin was excreted in the bile as unidentified ring-opened compounds.

In contrast to rats, mice did not exhibit lipid accumulation in hepatocytes or centrilobular hepatocellular necrosis in the NTP 13-week and 2-year studies. These differences are likely related to quantitative differences in the coumarin metabolites produced by these species or to differences in the rates of formation and conjugation of the toxic intermediate(s). Coumarin hydroxylase activity has been shown to be highly strain-dependent in mice. In a study of 16 strains of mice for coumarin hydroxylase activity, five strains were shown to have high activity while the other 11 had low activity (Wood and Taylor, 1979). Coumarin hydroxylase activity varied from a low of 32 (units of enzyme activity) to 358 in the strains examined. Endell and Seidel (1978) showed that the LD_{50} in CH3/HeJ mice for orally administered coumarin was approximately half that of DBA/2J mice, and that hepatotoxicity, as measured by elevations in serum enzyme activity, was substantially greater in CH3/HeJ mice than in DBA/2J mice. These observations correlate with the higher hepatic coumarin 7-hydroxylase activity in DBA/2J mice (Wood and Conney, 1974). The metabolism of coumarin in the $B6C3F_1$ mouse has not been studied.

Coumarin likely may not produce hepatoxicity in humans similar to that in rats because of the demonstrated differences in metabolism between

these species. In contrast to rats, the metabolism of coumarin in humans results principally in the hydroxylation at the number 7 position with the formation of 7-hydroxycoumarin and 7-hydroxycoumarin glucuronide (Ritschel *et al.*, 1977). As mentioned above, the higher hepatic coumarin 7-hydroxylase activity in DBA/2J mice is associated with a much higher threshold for hepatotoxicity.

Centrilobular hepatocellular hypertrophy was seen in most male and female mice in the 300 mg/kg dose groups, but not in mice in the lower dose groups in the 13-week study. However, the mean liver weights of the 150 mg/kg groups as well as the 300 mg/kg groups were significantly greater than controls, indicating that hypertrophy was probably also present in mice receiving 150 mg/kg. Centrilobular hypertrophy was also frequently observed in males receiving 100 or 200 mg/kg and in females receiving 200 mg/kg in the 2-year study. The centrilobular hepatocellular hypertrophy in mice was likely related to an increase in endoplasmic reticulum and enzyme induction as reported in rats receiving coumarin (Nievel, 1969; Grasso *et al.*, 1974).

The kidneys of male and female rats, but not mice, also exhibited toxic effects related to the administration of coumarin in the NTP 13-week and 2-year studies. In the 13-week study, the most severe renal lesions were observed in the three male rats receiving 300 mg/kg that died during the study. The lesions in these rats consisted of widespread necrosis of the proximal tubule epithelium, while others exhibited scattered renal tubules with thickened basement membranes and small basophilic cells. While the latter lesion is typical of spontaneous nephropathy occasionally seen in untreated rats, similar lesions were not seen in the concurrent control males. In the 2-year study, nearly all males and most females in each of the groups including the control groups exhibited degenerative renal lesions, but the average severity of the nephropathy increased with dose. The severity of nephropathy in the dosed rats as well as the controls was generally greater in males than in females.

The chemical-related increased severity of nephropathy in dosed males was the principal cause of the decreased survival of the 50 and 100 mg/kg groups. The incidences of parathyroid gland hyperplasia in all groups of dosed males were also higher than controls, consistent with renal secondary hyperparathyroidism. Hyperparathyroidism accompanies severe nephropathy in rats because the progressive loss of renal function disrupts calcium and phosphorus homeostasis, leading to prolonged parathyroid gland stimulation.

Renal toxicity associated with coumarin administration has been reported to occur in dogs given oral doses of 100 mg/kg for 8 consecutive days (Hazleton *et al.*, 1956). These investigators described swelling and granularity of tubule epithelial cells and bile stained hyaline casts in tubule lumens, and suggested that the renal lesions were consistent with "bile nephrosis." Renal toxicity was not described in rats receiving 10,000 ppm in the feed for 8 weeks or in rats receiving 2,500 ppm for 29 weeks (Hazleton *et al.*, 1956). Further, renal toxicity was not reported to occur in a 2-year study in rats given coumarin at dietary levels of 2,500 ppm or 5,000 ppm (Hagan *et al.*, 1967). While it is not clear why renal toxicity was not seen in these studies, the route of administration and the strain of rats used were different from those of the NTP studies.

Increased incidences of neoplasms attributed to the administration of coumarin in the NTP studies were observed in the kidney of male rats, lung of male and female mice, and liver of female mice. Bile duct carcinomas, as reported by Griepentrog (1973) were not seen in dosed F344/N rats, possibly because of differences in route of administration and dose level. There have been no previous long-term studies in mice.

During the initial standard evaluation of single sections of the kidney, renal tubule adenomas were identified in one control, two 25 mg/kg, two 50 mg/kg, and two 100 mg/kg male rats. Moreover, 2 of 20 males receiving 100 mg/kg for 15 months followed by the recovery period also had renal tubule neoplasms, which is substantially greater than the incidence in NTP historical control male rats (8/1,019, 0.8%). In addition, two 100 mg/kg female rats had renal adenomas, which is also much higher than the incidence in historical controls (2/1,018, 0.2%). Although renal neoplasms are relatively uncommon in control rats, the low incidences in rats receiving coumarin were difficult to interpret.

The NTP has found that multiple sectioning of the kidney may enable a more precise evaluation of the

potential chemical-related induction of renal proliferative lesions than observations made from single sections. The majority of renal neoplasms in the 2-year study of coumarin were small and identified only by microscopic examination. Thus, multiple sections might be expected to increase the number of neoplasms observed and allow a more rigorous statistical evaluation. The residual formalin-fixed kidneys from all male and female rats were step sectioned to provide approximately eight additional tissue sections of each kidney for microscopic examination.

As expected, additional renal tubule neoplasms were identified in the step sections, and the majority were seen in dosed males. The overall incidences in rats were as follows: males, control, 1/49; 25 mg/kg, 6/50; 50 mg/kg, 7/50; 100 mg/kg, 5/50; females, 0/49; 0/50; 1/50; 2/50. Moreover, focal hyperplasia was also observed in dosed rats with incidences that generally paralleled the incidences of renal neoplasms. The incidences of focal hyperplasia and of renal tubule adenoma in the low- and mid-dose male rats, but not the high-dose males, were significantly greater than those of the controls. The marginal increased incidence of renal tubule neoplasms was considered chemical related because of the statistical significance and supporting evidence of focal hyperplasia, a lesion considered to be preneoplastic. The lack of statistical significance by pairwise comparison of the high-dose and control incidences and lack of a dose-related trend is likely due to the lower survival of the high-dose group, and perhaps due to the increased severity of nephropathy in the high-dose group. The nephropathy may influence the induction, development, or progression of renal neoplasms in several ways, including a reduction in target cell population from continued degeneration and necrosis, alteration in vascularity as a result of the interstitial fibrosis, or other alterations in microenvironment.

The increased incidences of renal tubule neoplasms in dosed male rats were considered to provide "some" rather than "clear evidence" of carcinogenic activity because a) the increased incidences were marginal and b) the majority of neoplasms were benign. While the evaluation of step sections revealed one additional adenoma in a mid-dose female, the low incidences of renal tubule neoplasms in mid- and high-dose females could not be clearly attributed to coumarin administration.

The incidences of pharyngeal neoplasms, primarily squamous cell papillomas, in mid-dose males, thyroid gland follicular cell neoplasms in low-dose males, and forestomach squamous cell papillomas in low-dose females were notable because they marginally exceeded the incidences of these neoplasms in NTP historical controls. However, they were not attributed to coumarin administration because a) the incidences were not significantly increased relative to concurrent controls, b) there was no apparent dose response, and c) there was no supporting evidence of hyperplasia or other preneoplastic lesions.

The stop-exposure groups of male rats were included in the present NTP studies because of the controversy over the biological potential of coumarin-induced biliary lesions as described by Bär and Griepentrog (1967). These authors reported that diets containing 5,000 ppm or 6,000 ppm coumarin induced bile duct carcinomas in male rats. However, other scientists reviewing these liver lesions considered them to represent a nonneoplastic proliferative lesion sometimes diagnosed as cholangiofibrosis (Cohen, 1979). The intent was to produce the biliary lesions diagnosed as cholangiofibrosis or bile duct carcinoma in rats dosed for 9 or 15 months and to follow their progression or regression during the recovery period. However, the doses administered to male rats in the present study did not produce these lesions. As expected, the degenerative hepatocellular lesions observed in F344/N rats did not progress following cessation of dosing. In contrast to the liver lesions, the renal injury produced by coumarin was not reversible, and the severity of nephropathy in male rats of the two stop-exposure groups was greater than that in the controls. This is not unexpected based on the progressive nature of this spontaneous, age-related disease.

In contrast to rats, the 2-year study of coumarin in mice was associated with chemical-related increased incidences of neoplasms in the lung and liver, but not the kidney. The incidences of alveolar/bronchiolar adenomas in groups of males and females receiving 200 mg/kg were significantly greater than those of the controls. In female mice, the increased incidence of benign pulmonary neoplasms was accompanied by a significant increase in the incidence of malignant neoplasms as well. The incidences of pulmonary neoplasms, benign or malignant combined, in both the high-dose male and female mice were well above the highest incidence observed in groups of NTP

historical controls. The chemical-related increased incidence of benign pulmonary neoplasms in male mice was considered "some evidence" of carcinogenic activity while the increased incidences of benign and malignant pulmonary neoplasms in female mice was considered "clear evidence" of carcinogenic activity.

While nonneoplastic liver lesions related to coumarin administration were observed in both male and female mice, a chemical-related increased incidence of hepatocellular neoplasms was seen only in females receiving 50 or 100 mg/kg. Although only the incidence of hepatocellular adenoma was increased in the 50 and 100 mg/kg females, it was supported by an increased incidence of eosinophilic foci in these dose groups. Eosinophilic foci are morphologically similar to adenomas and are considered preneoplastic in mice. Although it is not known for certain why the incidence of hepatocellular neoplasms in the 200 mg/kg group was not increased relative to controls, the lower body weights of this group may have contributed to the lack of effect. Rao *et al.* (1987) have reported that body weight is positively correlated with the incidence of spontaneous liver neoplasms in mice in 2-year studies.

Squamous cell neoplasms of the forestomach, primarily papillomas, were marginally increased in 50 mg/kg male and female mice. Further, the incidences in the 50 mg/kg groups slightly exceeded the highest incidences observed in groups of historical controls. However, the forestomach neoplasms could not be clearly related to the administration of coumarin because the incidences in the 50 mg/kg groups were not significantly greater than those of the controls and there was no corresponding increase over a fourfold range of doses from 50 to 200 mg/kg.

The results of the *in vitro* genetic toxicity tests are also consistent with the hypothesized metabolism of coumarin to an electrophilic intermediate. Coumarin was mutagenic in *Salmonella typhimurium* strain TA100 only in the presence of liver S9 fraction, indicating that a metabolite, rather than the parent compound, was responsible for the mutagenicity. While it is not clear why coumarin produced a positive response only in strain TA100, this strain has been found to be more sensitive to mutagens. The positive response for mutations in *S. typhimurium* and the increased incidences of neoplasms at several sites in rats and mice administered coumarin is consistent with findings from other studies conducted by the NTP. Of 114 chemicals studied by the NTP, the *S. typhimurium* assay had the highest positive predictivity for carcinogenicity in rodents, with 89% of the mutagenic chemicals also producing increases in neoplasms in rats and/or mice (Tennant *et al.*, 1987; Zeiger *et al.*, 1990).

The toxicity and carcinogenic activity demonstrated by coumarin in the NTP 13-week and 2-year studies contrasts with those of 3,4-dihydrocoumarin (NTP, 1993). While the amount of 3,4-dihydrocoumarin administered to rats was four times that of coumarin in the 13-week studies, hepatocyte lipidosis, degeneration and necrosis, and bile duct hyperplasia were not observed. Partial saturation of the lactone ring by the introduction of a methyl group, as in 6-methylcoumarin, has also been shown to decrease liver toxicity in the rat (Feuer, 1974). Further, 3,4-dihydrocoumarin did not increase the incidence of pulmonary neoplasms in dosed male or female mice in the 2-year study, even though the doses of 3,4-dihydrocoumarin administered to mice were four times greater than those of coumarin. These findings are consistent with the hypothesis that a reactive metabolite generated from oxidation of the coumarin 3,4-double bond, possibly coumarin 3,4-epoxide, is responsible for covalent binding with cytoplasmic constituents and subsequent hepatotoxicity and carcinogenic activity in the lung. 3,4-Dihydrocoumarin, which lacks the double bond, would not be expected to produce the epoxide. Moreover, unlike coumarin, 3,4-dihydrocoumarin was not mutagenic in any of the *S. typhimurium* strains, with or without liver S9 fraction.

Although a reactive intermediate generated at the 3,4-double bond of coumarin may be responsible for the hepatotoxicity in rats and carcinogenic activity in the lung of mice, the renal toxicity in rats and carcinogenic effect in the liver of mice are not so readily explained. The severity of nephropathy was greater in male rats receiving either coumarin or 3,4-dihydrocoumarin, and a marginal increase in the incidence of renal tubule adenomas was also observed in dosed male rats of both studies. The magnitude of these effects was similar despite a sixfold difference in dose, suggesting that there are quantitative differences in the formation of the responsible metabolite.

The mechanism of the development of renal tubule adenomas in male rats receiving coumarin or 3,4-dihydrocoumarin needs to be studied further to

determine the relevance of this effect. While it is possible that an electrophilic metabolite other than a 3,4-epoxide is responsible for induction of renal neoplasms, the potential role of cytotoxicity in the development of these neoplasms should be investigated. DNA damage has been associated with cytotoxicity, but it is clear that the mechanism of cell injury or cell death may determine the type and extent of DNA damage (Stevens and Jones, 1990). Further, injury and necrosis of tubule epithelial cells induces both proliferation and dedifferentiation of regenerating cells. Konishi and Ward (1989) have demonstrated increased ^{3}H-thymidine labeling indices in the tubule epithelium with increasing severity of nephropathy. Cell proliferation is an essential component of the multistage process of carcinogenesis (Cohen and Ellwein, 1990). It is interesting to note that 8-methoxypsoralen (a furanocoumarin), ochratoxin A (a dihydrocoumarin), and quercetin (a benzo-gamma-pyrone derivative resembling the 1,2-benzopyrone moiety in coumarin) were also nephrotoxic and produced renal tubule neoplasms.

Both coumarin and 3,4-dihydrocoumarin also produced an increase in the incidence of hepatocellular neoplasms in female mice. This effect was observed in groups of females receiving 25 to 50 mg/kg coumarin, or 400 or 800 mg/kg 3,4-dihydrocoumarin.

These observations also suggest that the mechanism of induction of liver neoplasms in female mice does not involve an electrophilic metabolite generated from the 3,4-double bond. Unlike the kidney, there was no histologic evidence of liver toxicity to suggest that enhanced cell proliferation secondary to cell injury played a role in the induction of these neoplasms. The possible role of other mechanisms such as alterations in gene expression through changes in DNA methylation cannot be excluded (Goodman *et al.*, 1991).

CONCLUSIONS

Under the conditions of these 2-year gavage studies there was *some evidence of carcinogenic activity** of coumarin in male F344/N rats based on increased incidences of renal tubule adenomas. There was *equivocal evidence of carcinogenic activity* of coumarin in female F344/N rats based on a marginally increased incidence of renal tubule adenomas. There was *some evidence of carcinogenic activity* of coumarin in male B6C3F$_1$ mice based on the increased incidence of alveolar/bronchiolar adenomas. There was *clear evidence of carcinogenic activity* of coumarin in female B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and hepatocellular adenomas. The marginally increased incidences of squamous cell papillomas of the forestomach in male and female mice receiving 50 mg/kg may have been related to coumarin administration.

The administration of coumarin to rats was also associated with an increased severity of nephropathy in the kidney and of bile duct hyperplasia in the liver, increased incidences of ulcers of the forestomach, and necrosis, fibrosis, and cytologic alteration of the liver. Administration of coumarin to mice was also associated with centrilobular hypertrophy, syncytial alteration, and eosinophilic focus in the liver.

---

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

REFERENCES

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Ashby J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* 257, 229-306.

Bär, V.F., and Griepentrog, F. (1967). Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel für Lebensmittel. *Medizin und Ernäehrung* 8, 244-251.

Berkarda, B., Bouffard-Eyüboglu, H., and Derman, U. (1983). The effect of coumarin derivatives on the immunological system of man. *Agents Actions* 13, 50-55.

den Besten, C., Körösi, S.A., Beamand, J.A., Walters, D.G., and Lake, B.G. (1990). Studies on the mechanism of coumarin-induced toxicity in rat hepatocytes. *Toxicol. In Vitro* 4, 518-521.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Code of Federal Regulations (CFR) 21, Part 58.

Cohen, A.J. (1979). Critical review of the toxicology of coumarin with special reference to interspecies differences in metabolism and hepatotoxic response and their significance to man. *Food Cosmet. Toxicol.* 17, 277-289.

Cohen, S.M., and Ellwein, L.B. (1990). Cell proliferation in carcinogenesis. *Science* 249, 1007-1011.

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

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology* (W.G. Flamm and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co., Inc., Princeton, NJ.

D'Amato, F., and D'Amato-Avanzi, M.G. (1954). The chromosome-breaking effect of coumarin derivatives in the *Allium* test. *Caryologia* 6, 134-150.

Dexeus, F.H., Logothetis, C.J., Sella, A., Fitz, K., Amato, R., Reuben, J.M., and Dozier, N. (1990). Phase II study of coumarin and cimetidine in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 8, 325-329.

Dickens, F., and Waynforth, H.B. (1968). Studies on carcinogenesis by lactones and related substances. *Br. Emp. Can. Camp. Res.* 46, 108.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* 6, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* 32, 236-248.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* 6, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* 50, 1096-1121.

Endell, W., and Seidel, G. (1978). Coumarin toxicity in different strains of mice. *Agents Actions* 8, 299-302.

Evans, J.G., Gaunt, I.F., and Lake, B.G. (1979). Two-year toxicity study on coumarin in the baboon. *Food Cosmet. Toxicol.* 17, 187-193.

Evans, J.G., Appleby, E.C., Lake, B.G., and Conning, D.M. (1989). Studies on the induction of cholangiofibrosis by coumarin in the rat. *Toxicology* **55**, 207-224.

Fenaroli's Handbook of Flavor Ingredients (1971). (T.E. Furia and N. Bellanca, Eds.). Chemical Rubber Co., Cleveland, OH.

Feuer, G. (1970a). 3-Hydroxylation of coumarin or 4-methylcoumarin by rat-liver microsomes and its induction by 4-methyl-coumarin given orally. *Chem.-Biol. Interact.* **2**, 203-216.

Feuer, G. (1970b). Induction of drug-metabolizing enzymes of rat liver by derivatives of coumarin. *Can. J. Physiol. Pharmacol.* **48**, 232-240.

Feuer, G. (1974). The metabolism and biological actions of coumarins. In *Progress in Medicinal Chemistry* (G.P. Ellis and G.B. West, Eds.), Vol. 10, pp. 85-158. North-Holland Publishing Co., Amsterdam.

Feuer, G., Golberg, L., and Le Pelley, J.R. (1965a). Liver response tests. II. Effect of coumarin on glucose-6-phosphatase metabolism in rat liver. *Food Cosmet. Toxicol.* **3**, 251.

Feuer, G., Golberg, L., and Le Pelley, J.R. (1965b). Liver response tests. I. Exploratory studies on glucose-6-phosphatase and other liver enzymes. *Food Cosmet. Toxicol.* **3**, 235-250.

Feuer, G., Golberg, L., and Gibson, K.I. (1966). Liver response tests. VII. Coumarin metabolism in relation to the inhibition of rat-liver glucose 6-phosphatase. *Food Cosmet. Toxicol.* **4**, 157-167.

Food and Drug Administration (FDA) (1954). Federal Register, **21**, part 8.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* **10** (Suppl. 10), 1-175.

Gangolli, S.D., Shilling, W.H., Grasso, P., and Gaunt, I.F. (1974). Studies on the metabolism and hepatotoxicity of coumarin in the baboon. *Biochem. Soc. Trans.* **2**, 310-312.

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

Goodman, J.I., Ward, J.M., Popp, J.A., Klaunig, J.E., and Fox, T.R. (1991). Mouse liver carcinogenesis: Mechanisms and relevance. *Fundam. Appl. Toxicol.* **17**, 651-665.

Grasso, P., Wright, M.G., Gangolli, S.D., and Hendy, R.J. (1974). Liver response tests. IX. Cytopathological changes in the enlarged but histologically normal rat liver. *Food Cosmet. Toxicol.* **12**, 341.

Griepentrog, F. (1973). Pathologisch-anatomische Befunde zur karzinogenen Wirkung von Cumarin im Tierversuch. *Toxicology* **1**, 93-102.

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.A., and Brouwer, J.B. (1967). Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Food Cosmet. Toxicol.* **5**, 141-157.

Halpin, R.A., Vyas, K.P., El-Naggar, S.F., and Jerina, D.M. (1984). Metabolism and hepatotoxicity of the naturally occurring benzo[b]pyran precocene I. *Chem.-Biol. Interact.* **48**, 297-315.

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

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

Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *JNCI* **75**, 975-984.

Hawley, G.G. (Ed.) (1977). *The Condensed Chemical Dictionary*, 9th ed., pp. 98, 235, 296. Van Nostrand Reinhold Co., New York.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagen.* 5 (Suppl. 1), 3-142.

Hazleton, L.W., Tusing, T.W., Zeitlin, B.R., Thiessen, R., Jr., and Murer, H.K. (1956). Toxicity of coumarin. *J. Pharmacol. Exp. Ther.* 118, 348-358.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*. John Wiley and Sons, New York.

Ide, F., Ishikawa, T., and Takayama, S. (1981). Detection of chemical carcinogens by assay of unscheduled DNA synthesis in rat tracheal epithelium in short-term organ culture. *J. Cancer Res. Clin. Oncol.* 102, 115-126.

Jonckheere, A. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* 41, 133-145.

Kaighen, M., and Williams, R.T. (1961). The metabolism of [3-^{14}C]coumarin. *J. Med. Pharm. Chem.* 3, 25-43.

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

Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., (1978). Vol. 7, pp. 196-206. John Wiley and Sons, New York.

Konishi, N., and Ward, J.M. (1989). Increased levels of DNA synthesis in hyperplastic renal tubules of aging nephropathy in female F344/NCr rats. *Vet. Pathol.* 26, 6-10.

Lake, B.G. (1984). Investigations into the mechanism of coumarin-induced hepatotoxicity in the rat. *Arch. Toxicol. Suppl.* 7, 16-29.

Lake, B.G., Gray, T.J.B., Evans, J.G., Lewis, D.F.V., Beamand, J.A., and Hue, K.L. (1989). Studies on the mechanism of coumarin-induced toxicity in rat hepatocytes: Comparison with dihydrocoumarin and other coumarin metabolites. *Toxicol. Appl. Pharmacol.* 97, 311-323.

MacGregor, J.T., Wehr, C.M., and Langlois, R.G. (1983). A simple fluorescent staining procedure for micronuclei and RNA in erythrocytes using Hoeschst 33258 and pyronin Y. *Mutat. Res.* 120, 269-275.

MacGregor, J., Wehr, C.M., Henika, P.R., and Shelby, M.D. (1990). The *in vivo* erythrocyte micronucleus test: Measurement at steady state increases assay efficiency and permits integration with toxicity studies. *Fundam. Appl. Toxicol.* 14, 513-522.

Margolin, B., Collings, B., and Mason, J. (1983). Statistical analysis and sample-size determinations for mutagenicity experiments with binomial responses. *Environ. Mutagen.* 5, 705-716.

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

Marshall, M.E., Mendelsohn, L., Butler, K., Cantrell, J., Harvey, J., and Macdonald, J.S. (1987a). Treatment of non-small cell lung cancer with coumarin and cimetidine. *Cancer Treat. Rep.* 71, 91-92.

Marshall, M.E., Mendelsohn, L., Butler, K., Riley, L., Cantrell, J., Wiseman, C., Taylor, R., and Macdonald, J.S. (1987b). Treatment of metastatic renal cell carcinoma with coumarin (1,2-benzopyrone) and cimetidine: A pilot study. *J. Clin. Oncol.* 5, 862-866.

Marshall, M.E., Butler, K., Cantrell, J., Wiseman, C., and Mendelsohn, L. (1989a). Treatment of advanced malignant melanoma with coumarin and cimetidine: A pilot study. *Cancer Chemother. Pharmacol.* 24, 65-66.

Marshall, M.E., Conley, D., Hollingsworth, P., Brown, S., and Thompson, J.S. (1989b). Effects of coumarin (1,2-benzopyrone) on lymphocyte, natural killer cell, and monocyte functions *in vitro*. *J. Biol. Response Mod.* **8**, 70-85.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

Miles, J.S., McLaren, A.W., Forrester, L.M., Glancey, M.J., Lang, M.A., and Wolf, C.R. (1990). Identification of the human liver cytochrome P-450 responsible for coumarin 7-hydroxylase activity. *Biochem. J.* **267**, 365-371.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer*, (H.H. Hiatt, J.D. Watkins, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Murray, R.D.H., Méndez, J., and Brown, S.A. (1982). *The Natural Coumarins: Occurrence, Chemistry and Biochemistry.* John Wiley & Sons, New York.

Nair, R.V., Fisher, E.P., Safe, S.H., Cortez, C., Harvey, R.G., and DiGiovanni, J. (1991). Novel coumarins as potential anticarcinogenic agents. *Carcinogenesis* **12**, 65-69.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. National Institutes of Health, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH) (1990). National Occupation Exposure Survey (NOES) (1981-1983), unpublished provisional data as of July 1, 1990.

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

National Toxicology Program (NTP) (1989a). Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen (CAS No. 298-81-7) in F344/N Rats (Gavage Studies). Technical Report Series No. 359. NIH Publication No. 89-2814. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989b). Toxicology and Carcinogenesis Studies of Ochratoxin A (CAS No. 303-47-9) in F344/N Rats (Gavage Studies). Technical Report Series No. 358. NIH Publication No. 89-2813. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1992). Toxicology and Carcinogenesis Studies of Quercetin (CAS No. 117-39-5) in F344/N Rats (Feed Studies). Technical Report Series No. 409. NIH Publication No. 92-3140. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1993). Toxicology and Carcinogenesis Studies of 3,4-Dihydrocoumarin (CAS No. 119-84-6) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 423. NIH Publication No. 93-3154. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nievel, J.G. (1969). Effect of coumarin, BHT and phenobarbitone on protein synthesis in the rat liver. *Food Cosmet. Toxicol.* **7**, 621.

Norman, R.L., and Wood, A.W. (1981). Assessment of the mutagenic potential of coumarin in histidine-dependent strains of *Salmonella typhimurium*. *Proc. Amer. Assoc. Cancer Res.* **22**, 109. (Abstr.)

Peters, M.M., Walters, D.G., van Ommen, B., van Bladeren, P.J., and Lake, B.G. (1991). Effect of inducers of cytochrome P-450 on the metabolism of [3-^{14}C]coumarin by rat hepatic microsomes. *Xenobiotica* 21, 499-514.

Piller, N.B. (1977). [3-^{14}C]coumarin distribution in rat tissues after the injection of a single dose. *Res. Exp. Med.* 171, 93.

Prival, M.J., Sheldon, A.T., Jr., and Popkin, D. (1982). Evaluation, using *S. typhimurium*, of the mutagenicity of seven chemicals found in cosmetics. *Food Chem. Toxicol.* 20, 427-432.

Rao, G.N., Piegorsch, W.W., and Haseman, J.K. (1987). Influence of body weight on the incidence of spontaneous tumors in rats and mice of long-term studies. *Am. J. Clin. Nutr.* 45, 252-260.

Ravindranath, V., Boyd, M.R., and Jerina, D.M. (1987). Hepatotoxicity of precocene I in rats. Role of metabolic activation *in vivo*. *Biochem. Pharmacol.* 36, 441-446.

Riley, H.P., and Hoff, V.J. (1960). Chromosome breakage in *Tulbaghia violacea* by radiation and chemicals. *Nucleus* 3, 1-18.

Ritschel, W.A., Hoffmann, K.A., Tan, H.S.I., and Sanders, P.R. (1976). Pharmacokinetics of coumarin upon i.v. administration in man. *Arzneimittelforschung* 26, 1382.

Ritschel, W.A., Tan, H.S., Hoffman, K.A., Sanders, P.R., and Schmucker, V.R. (1977). Metabolism of coumarin upon i.v. administration in man. *Drug Dev. Eval.* 22, 190-195.

Roll, R., and Bär, F. (1967). Die Wirkung von Cumarin (*o*-hydroxyzimtsäure-lacton) auf trächtige Mäuseweibchen. *Arzneimittelforschung* 17, 97-100.

Sadtler Standard Spectra. IR No. 1691. Sadtler Research Laboratories, Philadelphia, PA.

Sarma, Y.S.R.K., and Tripathi, S.N. (1976). Effects of chemicals on some members of Indian Charophyta II. *Caryologia* 29, 263-276.

Scheline, R.R. (1968). Studies on the role of the intestinal microflora in the metabolism of coumarin in rats. *Acta Pharmacol. Toxicol.* 26, 325-331.

Schmid, W. (1976). The micronucleus test for cytogenetic analysis. In *Chemical Mutagens: Principles and methods for their detection*, (A. Hollaender, Ed.), Vol. 4, pp. 31-53. Plenum Press, New York.

Schumacher, J.N., Green, C.R., Best, F.W., and Newell, M.P. (1977). Smoke composition. An extensive investigation of the water-soluble portion of cigarette smoke. *J. Agri. Food Chem.* 25, 310-320.

Shilling, W.H., Crampton, R.F., and Longland, R.C. (1969). Metabolism of coumarin in man. *Nature* 221, 664-665.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* 33, 386-389.

Stevens, J.L., and Jones, T.W. (1990). The role of damage and proliferation in renal carcinogenesis. *Toxicol. Lett.* 53, 121-126.

Stoltz, D.R., and Scott, P.M. (1980). Mutagenicity of coumarin and related compounds for *Salmonella typhimurium*. *Can. J. Genet. Cytol.* 22, 679. (Abstr.)

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* 67, 233-241.

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

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* 236, 933-941.

Thornes, R.D. (1983). Coumarins, melanoma and cellular immunity. In *Protective Agents in Cancer*, (D.C.H. McBrien and T.F. Slater, Eds.), pp. 43-56. Academic Press, London.

Thornes, D., Daly, L., Lynch, G., Browne, H., Tanner, A., Keane, F., O'Loughlin, S., Corrigan, T., Daly, P., Edwards, G., Breslin, B., Brown, H., Shine, M., Lennon, F., Hanley, J., McMurray, N., and Gaffrey, E. (1989). Prevention of early recurrence of high risk malignant melanoma by coumarin. *Eur. J. Surg. Oncol.* **15**, 431-435.

Tseng A., Jr. (1991). Chemoprevention of tumors in MTV-H-*ras* transgenic mice with coumarin. *Am. Assoc. Cancer Res. Proc.* **32**, Abstract No. 2257.

Ueno, I., and Hirono, I. (1981). Non-carcinogenic response to coumarin in Syrian golden hamsters. *Food Cosmet. Toxicol.* **19**, 353-355.

Valencia, R., Mason, J.M., and Zimmering, S. (1989). Chemical mutagenesis testing in *Drosophila*. VI. Interlaboratory comparison of mutagenicity tests after treatment of larvae. *Environ. Mol. Mutagen.* **14**, 238-244.

Van Sumere, C.F., and Tuechy, H. (1971). The metabolism of [2-^{14}C]coumarin and [2-^{14}C]-7-hydroxycoumarin in the rat. *Arch. Int. Physiol. Biochim.* **79**, 665-679.

Voogd, C.E., Van der Stel, J.J., and Jacobs, J.J.J.A.A. (1980). On the mutagenic action of some enzyme immunoassay substrates. *J. Immunol. Methods* **36**, 55-61.

Wattenberg, L.W., Lam, L.K.T., and Fladmoe, A.V. (1979). Inhibition of chemical carcinogen-induced neoplasia by coumarins and α-angelicalactone. *Cancer Res.* **39**, 1651-1660.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Williams, R.T., Millburn, P., and Smith, R.L. (1965). The influence of enterohepatic circulation on toxicity of drugs. *Ann. N.Y. Acad. Sci.* **123**, 110.

Wood, A.W., and Conney, A.H. (1974). Genetic variation in coumarin hydroxylase activity in the mouse (*Mus musculus*). *Science* **185**, 612-614.

Wood, A.W., and Taylor, B.A. (1979). Genetic regulation of coumarin hydroxylase activity in mice. *J. Biol. Chem.* **254**, 5647-5651.

Yoon, J.S., Mason, J.M., Valencia, R.C., Woodruff, R.C., and Zimmering, S. (1985). Chemical mutagenesis testing in *Drosophila*. IV. Results of 45 coded compounds tested for the National Toxicology Program. *Environ. Mutagen.* **7**, 349-367.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

Zimmering, S., Mason, J.M., and Valencia, R. (1989). Chemical mutagenesis testing in *Drosophila*. VII. Results of 22 coded compounds tested in larval feeding experiments. *Environ. Mol. Mutagen.* **14**, 245-251.

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

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	10
Early deaths				
Accidental deaths	2	3	2	2
Moribund	14	31	34	31
Natural deaths	6	7	13	17
Survivors				
Terminal sacrifice	28	9	2	
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(10)
Hepatocellular adenoma				1 (10%)
Leukemia mononuclear				1 (10%)
Stomach, forestomach	(10)	(1)		(10)
Papilloma squamous		1 (100%)		1 (10%)
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)		(2)	(10)
Pars distalis, adenoma	1 (10%)		2 (100%)	2 (20%)
General Body System				
None				
Genital System				
Testes	(10)	(9)	(8)	(10)
Interstitial cell, adenoma	8 (80%)	9 (100%)	8 (100%)	8 (80%)
Hematopoietic System				
Lymph node, mandibular	(9)			(10)
Leukemia mononuclear				1 (10%)
Lymph node, mesenteric	(10)			(10)
Leukemia mononuclear				1 (10%)
Spleen	(10)		(1)	(10)
Leukemia mononuclear				1 (10%)
Thymus	(10)			(9)
Leukemia mononuclear				1 (11%)
Integumentary System				
Mammary gland	(9)			(9)
Fibroadenoma	1 (11%)			

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)		(1)	(10)
Alveolar/bronchiolar adenoma			1 (100%)	
Leukemia mononuclear				1 (10%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(9)	(10)
Renal tubule, adenoma			1 (11%)	
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(9)	(10)
Leukemia mononuclear				1 (10%)
2-Year Study				
Alimentary System				
Intestine large, colon	(45)	(48)	(42)	(44)
Adenoma, papillary			1 (2%)	
Intestine small	(45)	(47)	(47)	(44)
Adenocarcinoma			1 (2%)	
Intestine small, duodenum	(46)	(48)	(48)	(46)
Fibrosarcoma, metastatic	1 (2%)			
Intestine small, ileum	(45)	(46)	(43)	(42)
Fibrosarcoma, metastatic	1 (2%)			
Intestine small, jejunum	(45)	(47)	(45)	(44)
Fibrosarcoma, metastatic	1 (2%)			
Liver	(49)	(50)	(51)	(50)
Fibrosarcoma, metastatic	1 (2%)			
Hemangiosarcoma				1 (2%)
Hepatocellular carcinoma	2 (4%)			
Mesentery	(19)	(11)	(15)	(7)
Fibrosarcoma, metastatic	1 (5%)			
Pancreas	(47)	(49)	(50)	(49)
Adenoma	1 (2%)	2 (4%)	3 (6%)	
Fibrosarcoma, metastatic	1 (2%)			
Pharynx	(1)	(1)	(2)	
Carcinoma			1 (50%)	
Papilloma squamous	1 (100%)	1 (100%)	1 (50%)	

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(48)	(50)	(51)	(50)
Papilloma squamous		1 (2%)		1 (2%)
Stomach, glandular	(47)	(48)	(49)	(50)
Fibrosarcoma, metastatic	1 (2%)			
Tooth		(1)		
Cardiovascular System				
Heart	(49)	(49)	(51)	(50)
Endocrine System				
Adrenal gland, cortex	(49)	(50)	(50)	(50)
Adrenal gland, medulla	(49)	(50)	(50)	(50)
Pheochromocytoma benign	9 (18%)	5 (10%)	5 (10%)	
Islets, pancreatic	(47)	(50)	(50)	(49)
Adenoma	4 (9%)	1 (2%)	2 (4%)	
Parathyroid gland	(41)	(47)	(49)	(47)
Adenoma	1 (2%)			
Pituitary gland	(48)	(48)	(49)	(50)
Pars distalis, adenoma	19 (40%)	12 (25%)	16 (33%)	6 (12%)
Thyroid gland	(47)	(49)	(49)	(50)
C-cell, adenoma	1 (2%)	1 (2%)	1 (2%)	
C-cell, carcinoma	1 (2%)			
Follicular cell, adenoma		3 (6%)		
Follicular cell, carcinoma	1 (2%)	1 (2%)		
General Body System				
Tissue NOS	(2)		(1)	(1)
Adenocarcinoma	1 (50%)			
Fibrosarcoma	1 (50%)			
Genital System				
Epididymis	(45)	(50)	(46)	(50)
Preputial gland	(45)	(49)	(50)	(47)
Adenoma	2 (4%)	1 (2%)	1 (2%)	
Carcinoma	1 (2%)	1 (2%)		1 (2%)
Prostate	(45)	(50)	(50)	(49)
Seminal vesicle	(45)	(50)	(50)	(49)
Fibrosarcoma, metastatic	1 (2%)			
Testes	(45)	(49)	(46)	(50)
Interstitial cell, adenoma	38 (84%)	43 (88%)	42 (91%)	46 (92%)

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Hematopoietic System				
Blood	(1)	(1)		
Bone marrow	(48)	(50)	(50)	(50)
Lymph node	(49)	(50)	(49)	(48)
Lymph node, mandibular	(48)	(47)	(48)	(48)
Lymph node, mesenteric	(43)	(50)	(48)	(50)
Spleen	(48)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Thymus	(47)	(48)	(48)	(47)
Sarcoma	1 (2%)			
Integumentary System				
Mammary gland	(45)	(46)	(44)	(45)
Adenoma				1 (2%)
Fibroadenoma	3 (7%)	1 (2%)	2 (5%)	
Skin	(49)	(50)	(51)	(50)
Basal cell adenoma	1 (2%)			
Fibroma			1 (2%)	
Keratoacanthoma		1 (2%)		1 (2%)
Papilloma squamous	1 (2%)	3 (6%)		1 (2%)
Squamous cell carcinoma			1 (2%)	
Face, papilloma squamous		1 (2%)		
Pinna, papilloma squamous		1 (2%)		
Sebaceous gland, adenoma		1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)		1 (2%)	
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Musculoskeletal System				
Bone	(49)	(50)	(51)	(50)
Chordoma	1 (2%)			
Skeletal muscle	(1)		(2)	(1)
Fibrosarcoma, metastatic	1 (100%)			
Nervous System				
Brain	(47)	(50)	(49)	(49)
Respiratory System				
Lung	(49)	(49)	(50)	(50)
Adenocarcinoma, metastatic	1 (2%)			
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)		1 (2%)
Fibrosarcoma	1 (2%)			
Squamous cell carcinoma, metastatic		1 (2%)		

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Special Senses System				
Ear		(3)	(1)	
Fibroma		1 (33%)		
Papilloma squamous		1 (33%)	1 (100%)	
Eye			(3)	(1)
Papilloma squamous			1 (33%)	
Zymbal's gland		(2)	(1)	(1)
Carcinoma		2 (100%)		1 (100%)
Urinary System				
Kidney	(49)	(50)	(51)	(50)
Adenoma		1 (2%)		
Fibrosarcoma, metastatic	1 (2%)			
Renal tubule, adenoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Urethra		(1)		
Urinary bladder	(45)	(49)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(49)	(50)	(51)	(50)
Leukemia mononuclear	8 (16%)	10 (20%)	1 (2%)	
Mesothelioma NOS	1 (2%)		1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	9	9	8	10
2-Year study	46	46	47	47
Total primary neoplasms				
15-Month interim evaluation	10	10	12	13
2-Year study	105	98	85	63
Total animals with benign neoplasms				
15-Month interim evaluation	9	9	8	9
2-Year study	45	46	46	47
Total benign neoplasms				
15-Month interim evaluation	10	10	12	12
2-Year study	85	84	80	58
Total animals with malignant neoplasms				
15-Month interim evaluation				1
2-Year	16	13	4	3
Total malignant neoplasms				
15-Month interim evaluation				1
2-Year study	19	14	4	4
Total animals with metastatic neoplasms				
2-Year study	2	1		
Total metastatic neoplasms				
2-Year study	11	1		
Total animals with uncertain neoplasms benign or malignant				
2-Year study	1		1	1
Total uncertain neoplasms				
2-Year study	3		1	3

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

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

Number of Days on Study	3 3 4 4 4 5 5 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 3 7 0 2 7 1 7 7 8 0 0 1 2 2 6 7 9 9 0 2 2 2 2 2 5 2 8 0 2 3 3 8 6 1 9 1 2 3 0 1 4 9 4 0 8 9 9 9
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 0 1 0 0 1 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 1 0 5 7 2 3 2 3 9 2 6 3 7 3 6 6 8 8 1 1 2 3 4 2 1 5 2 3 1 2 2 5 1 5 2 1 2 4 4 3 4 5 2 3 2
Alimentary System	
Esophagus	+ +
Intestine large	+ + + + + + + M + A + + + M + + + M M + + + + +
Intestine large, cecum	+ + + + + + + M + A + + + M + + + M + + + + + +
Intestine large, colon	+ + + + + + + M + A + + + M + + + M + + + + + +
Intestine large, rectum	+ + + + + + + M + + + + + M + + + M M + + + + +
Intestine small	+ + + + + + + A + + + + + M + + + M M + + + + +
Intestine small, duodenum	+ + + + + + + A + + + + + + + + + M A + + + + +
Fibrosarcoma, metastatic	X
Intestine small, ileum	+ + + + + + + M + + + + + M + + + M M + + + + +
Fibrosarcoma, metastatic	X
Intestine small, jejunum	+ + + + + + + M + + + + + M + + + M A + + + + +
Fibrosarcoma, metastatic	X
Liver	+ +
Fibrosarcoma, metastatic	X
Hepatocellular carcinoma	X
Mesentery	+ + + + + + + + + + + + + + + + + +
Fibrosarcoma, metastatic	X
Pancreas	+ + + + + + + A + + + + + + + + + M + + + + + +
Adenoma	
Fibrosarcoma, metastatic	X
Pharynx	+
Papilloma squamous	X
Salivary glands	+ +
Stomach	+ + + + + + + + + + + + + + + + + M + + + + + +
Stomach, forestomach	+ + + + + + + + + + + + + + + + + M + + + + + +
Stomach, glandular	+ + + + + + + + + + + + + A + + + M + + + + + +
Fibrosarcoma, metastatic	X
Cardiovascular System	
Blood vessel	
Heart	+ +
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adrenal gland, medulla	+ +
Pheochromocytoma benign	X X X X X X X
Islets, pancreatic	+ + + + + + + A + + + + + + + + + M + + + + + +
Adenoma	X
Parathyroid gland	M + + + + + M M + + + + + + + + + + M + + + M +
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 Gavage Study of Coumarin: Vehicle Control
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 2 4	0 0 2 5	0 0 3 3	0 0 4 1	0 0 4 2	0 0 4 5	0 0 5 3	0 0 5 4	0 0 6 5	0 0 7 5	0 0 7 8	0 0 8 1	0 0 8 2	0 0 9 2	0 0 9 4	0 1 1 2	0 1 1 3	0 1 1 5	0 1 2 4	0 2 2 1	0 4 3 3	0 5 1 1	0 6 1 1	0 8 1 3	0 0 4 4	1 1 0 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrosarcoma, metastatic																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibrosarcoma, metastatic																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibrosarcoma, metastatic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
Hepatocellular carcinoma	X																									2
Mesentery	+	+				+			+						+	+	+		+					+		19
Fibrosarcoma, metastatic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma														X												1
Fibrosarcoma, metastatic																										1
Pharynx																										1
Papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma, metastatic																										1
Cardiovascular System																										
Blood vessel											+															1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign		X																	X				X			9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma							X								X		X									4
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Adenoma																										1

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

Number of Days on Study	3 3 4 4 4 5 5 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 3 7 0 2 7 1 7 7 8 0 0 1 2 2 6 7 9 9 0 2 2 2 2 2 5 2 8 0 2 3 3 8 6 1 9 1 2 3 0 1 4 9 4 0 8 9 9 9
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 0 1 0 0 1 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 1 0 1 0 5 7 2 3 2 3 9 2 6 3 7 3 6 6 8 8 1 1 2 3 4 2 1 5 2 3 1 2 2 5 1 5 2 1 2 4 4 3 4 5 2 3 2
Endocrine System (continued)	
Pituitary gland	+ + + M +
Pars distalis, adenoma	X X X X X X
Thyroid gland	+ + + + + + + A + + + + + + + + + + A + + + + +
C-cell, adenoma	X
C-cell, carcinoma	
Follicular cell, carcinoma	
General Body System	
Tissue NOS	+ +
Adenocarcinoma	X
Fibrosarcoma	X
Genital System	
Epididymis	+ + + + + + + M + + + + + M + + + M M + + + + +
Preputial gland	+ + + + + + + M + + + + + M + + + M M + + + + +
Adenoma	
Carcinoma	
Prostate	+ + + + + + + M + + + + + M + + + M M + + + + +
Seminal vesicle	+ + + + + + + M + + + + + M + + + M M + + + + +
Fibrosarcoma, metastatic	X
Testes	+ + + + + + + M + + + + + M + + + M M + + + + +
Interstitial cell, adenoma	X X X X X X X X X X X X
Hematopoietic System	
Blood	
Bone marrow	+ + + + + + + + + + + + + + + + + A + + + + + +
Lymph node	+ +
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ + + + + + + M + + + + + M + + + M + + + + + +
Spleen	+ + + + + + + + + + + + + + + + + M + + + + + +
Thymus	+ + + M + + + + + + + + + + + M + + + + + + + +
Sarcoma	
Integumentary System	
Mammary gland	+ + + M + + + M + + + + + + + + + + M + + + + +
Fibroadenoma	X X X
Skin	+ +
Basal cell adenoma	
Papilloma squamous	X
Subcutaneous tissue, fibroma	X
Subcutaneous tissue, fibrosarcoma	

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 2 4	0 0 2 5	0 0 3 3	0 0 4 1	0 0 4 2	0 0 4 5	0 0 5 3	0 0 5 4	0 0 6 5	0 0 7 5	0 0 8 1	0 0 8 2	0 0 9 2	0 0 9 4	0 1 1 2	0 1 1 3	0 1 1 5	0 1 2 4	0 2 2 1	0 4 3 3	0 5 1 1	0 6 1 3	0 8 3 4	0 0 4 3	1 0 2 3	Total Tissues/ Tumors
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X							X	X	X		X					X			X		X	X		X	19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, adenoma																										1
C-cell, carcinoma			X																							1
Follicular cell, carcinoma													X													1
General Body System																										
Tissue NOS																										2
Adenocarcinoma																										1
Fibrosarcoma																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma							X				X															2
Carcinoma																								X		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibrosarcoma, metastatic																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
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	38
Hematopoietic System																										
Blood											+															1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma				X																						1
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibroadenoma																										3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma					X																					1
Papilloma squamous																										1
Subcutaneous tissue, fibroma								X																		2
Subcutaneous tissue, fibrosarcoma									X																	1

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

Number of Days on Study	3 3 4 4 4 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 3 7 0 2 7 1 7 7 8 0 0 1 2 2 6 7 9 9 0 2 2 2 2 2 5 2 8 0 2 3 3 8 6 1 9 1 2 3 0 1 4 9 4 0 8 9 9 9
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 0 1 0 0 1 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 1 0 1 0 5 7 2 3 2 3 9 2 6 3 7 3 6 6 8 8 1 1 2 3 4 2 1 5 2 3 1 2 2 5 1 5 2 1 2 4 4 3 4 5 2 3 2
Musculoskeletal System	
Bone	+ +
Chordoma	X
Skeletal muscle	+
Fibrosarcoma, metastatic	X
Nervous System	
Brain	+ + + + + + + + + + + + + + + + + A A + + + + +
Respiratory System	
Lung	+ +
Adenocarcinoma, metastatic	X
Alveolar/bronchiolar adenoma	
Fibrosarcoma	X
Nose	+ +
Trachea	+ +
Special Senses System	
None	
Urinary System	
Kidney	+ +
Fibrosarcoma, metastatic	X
Renal tubule, adenoma	X
Urinary bladder	+ + + + + + + M + + + + + M + + + M M + + + + +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X
Mesothelioma NOS	X

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

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1	**Total**
	2	2	3	4	4	4	5	5	6	7	8	8	9	9	1	1	1	2	2	4	5	6	8	0	2	**Tissues/**
	4	5	3	1	2	5	3	4	5	5	1	2	2	4	2	3	5	4	1	3	1	1	3	4	3	**Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chordoma																										1
Skeletal muscle																										1
Fibrosarcoma, metastatic																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																		X								1
Fibrosarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X									X	X														8
Mesothelioma NOS																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	6 5 2	6 5 7	6 6 0	6 6 1	6 6 3	6 6 6	6 7 1	6 7 1	6 7 3	6 7 5	6 7 5	6 8 0	6 9 2	6 9 4	6 9 8	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	0 1 6 2	0 2 0 3	0 2 1 3	0 1 6 3	0 2 4 2	0 2 0 4	0 1 7 1	0 2 4 1	0 1 3 2	0 1 6 4	0 2 0 2	0 2 2 1	0 2 9 1	0 1 2 3	0 2 1 3	0 1 1 5	0 1 1 1	0 1 4 4	0 1 5 2	0 1 7 3	0 1 7 5	0 2 2 5	0 2 3 2	0 2 3 4	0 1 3 3	0 2 2 4	**Total Tissues/ Tumors**
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+		+	+					+							+		+				+					11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										X	2
Pharynx									+																		1
Papilloma squamous									X																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										X	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth															+												1
Cardiovascular System																											
Blood vessel		+																									4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X													X		X				5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X										1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma			X		X			X				X	X				X						X	X			12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																											1
Follicular cell, adenoma			X							X																	3
Follicular cell, carcinoma																X											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	0 9 0	3 4 3	3 5 2	3 7 7	4 8 2	4 9 2	5 0 3	5 1 8	5 1 6	5 6 9	5 7 7	5 8 3	5 9 3	6 0 0	6 0 0	6 1 1	6 1 3	6 1 5	6 2 2	6 2 5	6 2 5	6 3 1	6 3 6	6 4 9	6 4 5
Carcass ID Number	0 2 1 5	0 1 8 4	0 1 8 1	0 2 4 4	0 1 3 1	0 2 0 5	0 1 7 4	0 2 1 4	0 2 2 3	0 1 4 5	0 2 4 3	0 1 4 5	0 1 5 1	0 2 3 1	0 1 5 1	0 1 5 2	0 2 1 1	0 1 4 3	0 1 5 3	0 1 6 1	0 1 2 2	0 2 2 4	0 1 9 5	0 1 3 2	0 1 4 5
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																		X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma					X	X	X	X	X		X		X	X	X			X	X	X	X	X	X	X	X
Hematopoietic System																									
Blood															+										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma					X																				
Papilloma squamous									X																
Face, papilloma squamous																									
Pinna, papilloma squamous																									
Sebaceous gland, adenoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	6 5 2	6 5 7	6 6 0	6 6 1	6 6 3	6 6 6	6 7 1	6 7 1	6 7 3	6 7 5	6 7 5	6 8 0	6 9 2	6 9 4	6 9 8	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	0 1 6 2	0 2 0 3	0 2 1 3	0 1 6 3	0 2 4 2	0 2 0 4	0 1 7 1	0 2 4 1	0 1 3 1	0 1 6 2	0 2 0 4	0 2 0 2	0 2 2 1	0 1 8 1	0 2 3 3	0 1 9 3	0 1 4 5	0 1 5 1	0 1 7 4	0 1 7 2	0 1 7 3	0 2 2 5	0 2 3 2	0 2 3 4	0 1 3 3	0 2 2 4	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X																				1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	43
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Papilloma squamous							X																		X	3
Face, papilloma squamous																						X				1
Pinna, papilloma squamous																						X				1
Sebaceous gland, adenoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	0 9 0	3 4 3	3 5 2	3 7 7	4 8 2	4 9 2	5 0 3	5 1 8	5 1 9	5 6 7	5 7 3	5 8 3	5 9 3	6 0 0	6 0 0	6 1 1	6 1 3	6 1 5	6 2 2	6 2 5	6 2 5	6 3 1	6 3 6	6 3 9	6 4 5	6 4 5
Carcass ID Number	0 2 1 5	0 1 8 4	0 1 8 1	0 2 4 4	0 1 3 1	0 2 0 5	0 1 7 4	0 2 1 4	0 2 2 3	0 1 4 5	0 2 4 3	0 1 4 5	0 1 5 5	0 2 9 1	0 1 3 1	0 1 5 1	0 1 5 2	0 2 1 1	0 1 4 3	0 1 5 3	0 1 6 1	0 2 2 2	0 1 9 4	0 1 3 5	0 1 4 2	0 1 7 5
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Larynx			+																							
Lung	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Squamous cell carcinoma, metastatic																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																	+									
Fibroma																	X									
Papilloma squamous																										
Zymbal's gland					+																					
Carcinoma					X																					
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X															
Renal tubule, adenoma																										
Urethra																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X							X	X	X	X								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	6 5 2	6 5 7	6 6 0	6 6 1	6 6 3	6 6 6	6 7 1	6 7 1	6 7 3	6 7 5	6 7 5	6 8 0	6 9 2	6 9 4	6 9 8	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	0 1 6 2	0 2 0 3	0 2 1 3	0 1 6 3	0 2 4 2	0 2 0 4	0 1 7 1	0 2 4 1	0 1 3 2	0 1 6 4	0 2 0 2	0 2 1 1	0 2 2 1	0 1 8 3	0 2 3 3	0 1 9 5	0 1 4 1	0 1 5 4	0 1 7 2	0 1 7 3	0 2 2 5	0 2 3 2	0 2 3 4	0 1 3 3	0 2 2 4	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X									X																2
Squamous cell carcinoma, metastatic					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear																+	+									3
Fibroma																										1
Papilloma squamous																	X									1
Zymbal's gland					+																					2
Carcinoma					X																					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Renal tubule, adenoma	X																									1
Urethra															+											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X	X					X	X				10

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	5 8 8	5 9 4	5 9 6	5 9 6	6 0 1	6 0 2	6 0 7	6 1 5	6 1 5	6 2 2	6 2 2	6 2 2	6 2 5	6 2 8	6 3 0	6 3 1	6 4 3	6 4 3	6 4 5	6 5 7	6 6 6	6 7 8	6 7 9	6 9 4	7 2 9	7 3 0	
Carcass ID Number	0 2 7 5	0 2 6 5	0 2 5 4	0 2 9 2	0 3 1 5	0 2 7 4	0 3 6 5	0 3 3 5	0 3 4 5	0 2 6 3	0 2 7 1	0 3 1 1	0 2 5 2	0 2 7 2	0 3 5 4	0 2 6 2	0 3 0 3	0 3 2 2	0 3 2 1	0 3 5 2	0 2 8 2	0 2 8 3	0 3 5 1	0 3 2 3	0 3 6 2	0 3 6 4	**Total Tissues/ Tumors**
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+		A	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+		A	+	+	+	+	+	+	+	+	+	42
Adenoma, papillary																		X									1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	43
Intestine small	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																											1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesentery	+		+	+			+	+		+	+			+		+							+			+	15
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X	X																	3
Pharynx																+											2
Carcinoma																											1
Papilloma squamous																X											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Blood vessel													+									+					2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X				X													X					X		5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																						X				2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X			X					X	X		X				X	X						X	X	16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma								X																			1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	0 6 3	4 0 8	4 2 8	4 2 9	4 7 3	4 9 6	4 9 8	5 0 6	5 0 6	5 1 2	5 1 7	5 2 5	5 3 1	5 3 1	5 3 3	5 3 9	5 4 5	5 4 6	5 4 8	5 5 5	5 5 6	5 6 9	5 7 5	5 8 0	5 8 0
Carcass ID Number	0 2 7 3	0 3 1 3	0 2 6 4	0 2 8 5	0 2 5 3	0 2 9 5	0 3 5 5	0 3 2 5	0 3 4 2	0 3 6 1	0 3 1 4	0 3 3 3	0 2 9 1	0 3 5 3	0 3 4 4	0 2 5 5	0 3 2 4	0 2 6 1	0 3 4 1	0 3 0 4	0 3 0 2	0 2 9 3	0 2 8 4	0 2 5 1	0 3 6 3
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Prostate	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M
Interstitial cell, adenoma			X		X	X		X	X	X	X	X			X	X	X		X	X	X	X	X	X	
Hematopoietic System																									
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	M	+	M
Fibroadenoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	5 8 8	5 9 4	5 9 6	5 9 6	6 0 1	6 0 2	6 0 7	6 1 5	6 1 5	6 2 2	6 2 2	6 2 2	6 2 5	6 2 8	6 3 0	6 3 1	6 4 3	6 4 3	6 4 5	6 5 7	6 6 6	6 7 8	6 7 9	6 9 4	7 2 9	7 3 0	
Carcass ID Number	0 2 7 5	0 2 6 5	0 2 5 4	0 2 9 2	0 3 1 5	0 2 7 4	0 3 6 5	0 3 3 5	0 3 4 5	0 2 6 3	0 2 7 1	0 3 1 1	0 2 5 2	0 2 7 2	0 3 5 4	0 2 6 2	0 3 0 3	0 3 3 2	0 3 2 1	0 3 5 2	0 3 8 2	0 2 8 3	0 3 5 1	0 3 2 3	0 3 6 2	0 3 6 4	**Total Tissues/ Tumors**
General Body System																											
Tissue NOS																					+					1	
Genital System																											
Epididymis	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma																										1	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Testes	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
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	42	
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44	
Fibroadenoma															X											2	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Fibroma																								X		1	
Squamous cell carcinoma																								X		1	
Subcutaneous tissue, fibroma																										1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Skeletal muscle							+																			2	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	0 6 3	4 0 8	4 2 8	4 2 9	4 7 3	4 9 6	4 9 8	5 0 6	5 0 6	5 1 2	5 1 7	5 2 5	5 3 1	5 3 1	5 3 3	5 3 9	5 4 5	5 4 6	5 4 8	5 5 5	5 5 6	5 6 9	5 7 5	5 8 0	5 8 0
Carcass ID Number	0 2 7 3	0 3 1 3	0 2 6 4	0 2 8 5	0 2 5 3	0 2 9 5	0 3 5 5	0 3 2 5	0 3 4 2	0 3 6 1	0 3 1 4	0 3 3 3	0 2 9 1	0 3 5 3	0 3 4 4	0 2 5 5	0 3 2 4	0 2 6 1	0 3 4 1	0 3 0 4	0 3 0 2	0 2 9 3	0 2 8 4	0 2 5 1	0 3 6 3
Respiratory System																									
Lung	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Papilloma squamous																									
Eye			+														+			+					
Papilloma squamous																	X								
Zymbal's gland																									+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X	
Mesothelioma NOS																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	5 8 8	5 9 4	5 9 6	5 9 6	6 0 1	6 0 2	6 0 7	6 1 5	6 1 5	6 2 2	6 2 2	6 2 2	6 2 5	6 2 8	6 3 0	6 3 1	6 4 3	6 4 3	6 4 5	6 5 7	6 6 6	6 6 8	6 6 9	6 7 4	7 9 9	7 2 0		
Carcass ID Number	0 2 7 5	0 2 6 5	0 2 5 4	0 2 9 2	0 3 1 5	0 2 7 4	0 3 6 5	0 3 3 5	0 3 4 5	0 2 6 3	0 2 7 1	0 3 1 1	0 2 5 2	0 2 7 2	0 3 5 4	0 2 6 2	0 3 0 3	0 3 3 2	0 3 2 1	0 3 5 2	0 2 8 2	0 2 8 3	0 3 5 1	0 3 2 3	0 3 6 2	0 3 6 4	**Total Tissues/ Tumors**	
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Special Senses System																												
Ear																									+		1	
Papilloma squamous																									X		1	
Eye																											3	
Papilloma squamous																											1	
Zymbal's gland																											1	
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Renal tubule, adenoma						X								X													2	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Leukemia mononuclear																											1	
Mesothelioma NOS										X																	1	

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

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

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

Number of Days on Study	5 6 3	5 6 6	5 6 7	5 7 2	5 8 0	5 8 0	5 8 9	5 9 5	6 0 1	6 0 7	6 1 1	6 1 1	6 1 5	6 1 8	6 1 8	6 3 0	6 3 1	6 3 6	6 3 8	6 4 3	6 4 6	6 5 0	6 5 4	6 6 0	6 9 8	
Carcass ID Number	0 3 7 4	0 4 7 5	0 4 4 4	0 4 3 2	0 4 0 3	0 4 6 2	0 3 7 1	0 3 9 3	0 3 9 4	0 4 2 5	0 4 6 5	0 4 7 2	0 4 1 5	0 3 8 5	0 4 6 3	0 3 8 4	0 3 9 5	0 3 8 1	0 4 8 3	0 4 4 3	0 4 8 4	0 4 8 1	0 4 4 3	0 4 5 2	0 3 7 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	A	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Mesentery	+									+							+							+		7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous						X																				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																				+						1
Cardiovascular System																										
Blood vessel													+													1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma								X		X	X												X			6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS																										1

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

Number of Days on Study	0 1 9	3 0 7	3 8 0	4 2 0	4 2 6	4 5 6	4 7 7	4 8 5	4 9 2	4 9 6	4 9 6	5 0 3	5 1 0	5 1 1	5 1 2	5 1 7	5 1 8	5 1 8	5 2 5	5 3 3	5 3 4	5 5 1	5 5 2	5 5 2	5 6 0
Carcass ID Number	0 3 7 2	0 4 4 2	0 4 2 2	0 4 0 2	0 3 8 3	0 4 1 1	0 4 5 3	0 4 1 3	0 4 5 4	0 3 9 2	0 4 2 1	0 4 1 2	0 3 7 3	0 4 3 4	0 4 5 5	0 4 6 4	0 4 2 3	0 4 7 1	0 4 1 4	0 4 3 3	0 4 2 4	0 4 3 5	0 4 3 1	0 4 7 4	0 4 0 5
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Carcinoma																			X						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma			X																						
Papilloma squamous														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+																					
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	5 6 3	5 6 6	5 6 7	5 7 2	5 8 0	5 8 0	5 8 9	5 9 5	6 0 1	6 0 7	6 1 1	6 1 1	6 1 5	6 1 8	6 1 8	6 3 0	6 3 1	6 3 6	6 3 8	6 4 3	6 4 6	6 5 0	6 5 4	6 6 0	6 9 8	
Carcass ID Number	0 3 7 4	0 4 7 5	0 4 4 4	0 4 3 2	0 4 0 3	0 4 6 2	0 3 7 1	0 3 9 3	0 3 9 4	0 4 2 5	0 4 6 5	0 4 7 2	0 4 1 5	0 3 8 5	0 4 6 3	0 3 8 4	0 3 9 5	0 3 8 1	0 4 8 3	0 4 7 3	0 4 8 4	0 4 8 1	0 4 4 3	0 4 5 2	0 3 7 5	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	46
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Papilloma squamous																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																							+			1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	0	3	3	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
	1	0	8	2	2	5	7	8	9	9	9	0	1	1	1	1	1	1	2	3	3	5	5	5	6	
	9	7	0	0	6	6	7	5	2	6	6	3	0	1	2	7	8	8	5	3	4	1	2	2	0	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	3	4	4	4	3	4	4	4	4	3	4	4	3	4	4	4	4	4	4	4	4	4	4	4	4	
	7	4	2	0	8	1	5	1	5	9	2	1	7	3	5	6	2	7	1	3	2	3	3	7	0	
	2	5	2	2	3	1	3	3	4	2	1	2	3	4	5	4	3	1	4	3	4	5	1	4	5	
Special Senses System																										
Eye																										
Zymbal's gland															+											
Carcinoma															X											
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Renal tubule, adenoma											X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma NOS																										

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

Number of Days on Study	5 6 3	5 6 6	5 6 7	5 7 2	5 8 0	5 8 0	5 8 9	5 9 5	6 0 1	6 0 7	6 1 1	6 1 1	6 1 5	6 1 8	6 1 8	6 3 0	6 3 1	6 3 6	6 3 8	6 4 3	6 4 6	6 5 0	6 5 4	6 6 0	6 9 8	
Carcass ID Number	0 3 7 4	0 4 7 5	0 4 4 4	0 4 3 2	0 4 0 3	0 4 6 2	0 3 7 1	0 3 9 3	0 3 9 4	0 4 2 5	0 4 6 5	0 4 7 2	0 4 1 5	0 3 8 5	0 4 6 3	0 3 8 4	0 3 9 5	0 3 8 1	0 4 8 3	0 4 7 3	0 4 8 4	0 4 8 1	0 4 4 3	0 4 5 2	0 3 7 5	**Total Tissues/ Tumors**
Special Senses System																										
Eye																		+								1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma NOS																							X			1

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	9/49 (18%)	5/50 (10%)	5/50 (10%)	0/50 (0%)
Adjusted rates[b]	27.2%	29.9%	61.1%	0.0%
Terminal rates[c]	5/28 (18%)	2/9 (22%)	1/2 (50%)	0/0 (0%)
First incidence (days)	573	503	506	–[e]
Life table tests[d]	P=0.483	P=0.468	P=0.055	P=0.613N
Logistic regression tests[d]	P=0.038N	P=0.295N	P=0.607N	P=0.078N
Cochran-Armitage test[d]	P=0.002N			
Fisher exact test[d]		P=0.183N	P=0.183N	P=0.001N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rates	1/49 (2%)	2/50 (4%)	2/51 (4%)	1/50 (2%)
Adjusted rates	3.6%	6.4%	12.1%	2.4%
Terminal rates	1/28 (4%)	0/9 (0%)	0/2 (0%)	0/0 (0%)
First incidence (days)	729 (T)	583	602	496
Life table tests	P=0.192	P=0.337	P=0.122	P=0.486
Logistic regression tests	P=0.614	P=0.490	P=0.375	P=0.787
Cochran-Armitage test	P=0.549			
Fisher exact test		P=0.508	P=0.515	P=0.747N
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rates	1/49 (2%)	5/50 (10%)	7/51 (14%)	5/50 (10%)
Adjusted rates	3.6%	22.0%	70.4%	31.8%
Interim rates	0/10 (0%)	0/10 (0%)	1/9 (11%)	0/10 (0%)
First incidence (days)	729 (T)	613	506	426
Life table tests	P<0.001	P=0.024	P<0.001	P=0.003
Logistic regression tests	P=0.059	P=0.078	P=0.009	P=0.119
Cochran-Armitage test	P=0.145			
Fisher exact test		P=0.107	P=0.034	P=0.107
Mammary Gland: Fibroadenoma				
Overall rates	3/49 (6%)	1/50 (2%)	2/51 (4%)	0/50 (0%)
Adjusted rates	8.9%	3.1%	10.8%	0.0%
Terminal rates	1/28 (4%)	0/9 (0%)	0/2 (0%)	0/0 (0%)
First incidence (days)	622	625	533	–
Life table tests	P=0.524N	P=0.463N	P=0.391	P=0.691N
Logistic regression tests	P=0.136N	P=0.317N	P=0.555N	P=0.225N
Cochran-Armitage test	P=0.100N			
Fisher exact test		P=0.301N	P=0.481N	P=0.117N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	3/49 (6%)	1/50 (2%)	2/51 (4%)	1/50 (2%)
Adjusted rates	8.9%	3.1%	10.8%	14.3%
Terminal rates	1/28 (4%)	0/9 (0%)	0/2 (0%)	0/0 (0%)
First incidence (days)	622	625	533	638
Life table tests	P=0.343	P=0.463N	P=0.391	P=0.456
Logistic regression tests	P=0.397N	P=0.317N	P=0.555N	P=0.574N
Cochran-Armitage test	P=0.272N			
Fisher exact test		P=0.301N	P=0.481N	P=0.301N

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Pancreas: Adenoma				
Overall rates	1/47 (2%)	2/49 (4%)	3/50 (6%)	0/49 (0%)
Adjusted rates	3.6%	13.2%	13.5%	0.0%
Terminal rates	1/28 (4%)	1/9 (11%)	0/2 (0%)	0/0 (0%)
First incidence (days)	729 (T)	518	548	–
Life table tests	P=0.376	P=0.255	P=0.060	–[f]
Logistic regression tests	P=0.407N	P=0.493	P=0.279	–
Cochran-Armitage test	P=0.325N			
Fisher exact test		P=0.516	P=0.332	P=0.490N
Pancreatic Islets: Adenoma				
Overall rates	4/47 (9%)	1/50 (2%)	2/50 (4%)	0/49 (0%)
Adjusted rates	13.3%	11.1%	27.9%	0.0%
Terminal rates	3/28 (11%)	1/9 (11%)	0/2 (0%)	0/0 (0%)
First incidence (days)	660	729 (T)	588	–
Life table tests	P=0.468	P=0.554N	P=0.207	P=0.976N
Logistic regression tests	P=0.403N	P=0.399N	P=0.677	P=0.526N
Cochran-Armitage test	P=0.048N			
Fisher exact test		P=0.162N	P=0.310N	P=0.054N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	19/48 (40%)	12/48 (25%)	16/49 (33%)	6/50 (12%)
Adjusted rates	51.2%	56.2%	100.0%	48.1%
Terminal rates	11/28 (39%)	3/9 (33%)	2/2 (100%)	0/0 (0%)
First incidence (days)	472	577	506	485
Life table tests	P=0.005	P=0.296	P<0.001	P=0.130
Logistic regression tests	P=0.072N	P=0.183N	P=0.594	P=0.035N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.095N	P=0.309N	P=0.002N
Preputial Gland: Adenoma or Carcinoma				
Overall rates	3/45 (7%)	2/49 (4%)	1/50 (2%)	1/47 (2%)
Adjusted rates	10.7%	7.8%	3.6%	3.1%
Terminal rates	3/28 (11%)	0/9 (0%)	0/2 (0%)	0/0 (0%)
First incidence (days)	729 (T)	615	580	525
Life table tests	P=0.318	P=0.531	P=0.565	P=0.441
Logistic regression tests	P=0.394N	P=0.602N	P=0.681N	P=0.698N
Cochran-Armitage test	P=0.188N			
Fisher exact test		P=0.459N	P=0.270N	P=0.292N
Skin: Squamous Cell Papilloma				
Overall rates	1/49 (2%)	4/50 (8%)	0/51 (0%)	1/50 (2%)
Adjusted rates	2.6%	28.1%	0.0%	2.7%
Terminal rates	0/28 (0%)	2/9 (22%)	0/2 (0%)	0/0 (0%)
First incidence (days)	609	569	–	511
Life table tests	P=0.284	P=0.053	P=0.643N	P=0.637
Logistic regression tests	P=0.475N	P=0.156	P=0.479N	P=0.708N
Cochran-Armitage test	P=0.330N			
Fisher exact test		P=0.187	P=0.490N	P=0.747N

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rates	1/49 (2%)	4/50 (8%)	1/51 (2%)	1/50 (2%)
Adjusted rates	2.6%	28.1%	50.0%	2.7%
Terminal rates	0/28 (0%)	2/9 (22%)	1/2 (50%)	0/0 (0%)
First incidence (days)	609	569	729 (T)	511
Life table tests	P=0.119	P=0.053	P=0.421	P=0.637
Logistic regression tests	P=0.617	P=0.156	P=0.672	P=0.708N
Cochran-Armitage test	P=0.365N			
Fisher exact test		P=0.187	P=0.742N	P=0.747N
Skin: Basal Cell Adenoma, Keratoacanthoma, Squamous Cell Papilloma, or Squamous Cell Carcinoma				
Overall rates	2/49 (4%)	5/50 (10%)	1/51 (2%)	2/50 (4%)
Adjusted rates	6.0%	29.6%	50.0%	4.7%
Terminal rates	1/28 (4%)	2/9 (22%)	1/2 (50%)	0/0 (0%)
First incidence (days)	609	482	729 (T)	380
Life table tests	P=0.103	P=0.058	P=0.473	P=0.378
Logistic regression tests	P=0.417N	P=0.215	P=0.733	P=0.579N
Cochran-Armitage test	P=0.362N			
Fisher exact test		P=0.226	P=0.485N	P=0.684N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	3/49 (6%)	0/50 (0%)	1/51 (2%)	0/50 (0%)
Adjusted rates	9.5%	0.0%	2.8%	0.0%
Terminal rates	2/28 (7%)	0/9 (0%)	0/2 (0%)	0/0 (0%)
First incidence (days)	609	–	539	–
Life table tests	P=0.418N	P=0.275N	P=0.706	P=0.690N
Logistic regression tests	P=0.132N	P=0.154N	P=0.395N	P=0.348N
Cochran-Armitage test	P=0.083N			
Fisher exact test		P=0.117N	P=0.294N	P=0.117N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	0/49 (0%)	1/50 (2%)	0/51 (0%)	1/50 (2%)
Adjusted rates	0.0%	11.1%	0.0%	4.8%
Terminal rates	0/28 (0%)	1/9 (11%)	0/2 (0%)	0/0 (0%)
First incidence (days)	–	729 (T)	–	580
Life table tests	P=0.060	P=0.275	–	P=0.367
Logistic regression tests	P=219	P=0.275	–	P=0.543
Cochran-Armitage test	P=0.408			
Fisher exact test		P=505	–	P=0.505
Testes: Adenoma				
Overall rates	38/45 (84%)	43/49 (88%)	42/46 (91%)	46/50 (92%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	9/9 (100%)	2/2 (100%)	0/0 (0%)
First incidence (days)	408	482	428	307
Life table tests	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression tests	P=0.002	P=0.167	P=0.018	P=0.005
Cochran-Armitage test	P=0.149			
Fisher exact test		P=0.433	P=0.248	P=0.204

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	0/47 (0%)	3/49 (6%)	0/49 (0%)	0/50 (0%)
Adjusted rates	0.0%	13.6%	0.0%	0.0%
Terminal rates	0/28 (0%)	0/9 (0%)	0/2 (0%)	0/0 (0%)
First incidence (days)	–	645	–	–
Life table tests	P=0.509	P=0.055	–	–
Logistic regression tests	P=0.500N	P=0.110	–	–
Cochran-Armitage test	P=0.299N			
Fisher exact test		P=0.129	–	–
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	1/47 (2%)	4/49 (8%)	0/49 (0%)	0/50 (0%)
Adjusted rates	3.6%	22.3%	0.0%	0.0%
Terminal rates	1/28 (4%)	0/9 (0%)	0/2 (0%)	0/0 (0%)
First incidence (days)	729 (T)	645	–	–
Life table tests	P=0.434	P=0.037	P=0.959N	–
Logistic regression tests	P=0.473N	P=0.118	P=0.959N	–
Cochran-Armitage test	P=0.117N			
Fisher exact test		P=0.194	P=0.490N	P=0.485N
All Organs: Mononuclear Cell Leukemia				
Overall rates	8/49 (16%)	10/50 (20%)	1/51 (2%)	0/50 (0%)
Adjusted rates	22.4%	46.4%	3.6%	0.0%
Terminal rates	3/28 (11%)	2/9 (22%)	0/2 (0%)	0/0 (0%)
First incidence (days)	420	503	580	–
Life table tests	P=0.266N	P=0.058	P=0.390N	P=0.295N
Logistic regression tests	P=0.002N	P=0.385	P=0.022N	P=0.008N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.416	P=0.013N	P=0.003N
All Organs: Benign Neoplasms				
Overall rates	45/49 (92%)	46/50 (92%)	46/51 (90%)	47/50 (94%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	9/9 (100%)	2/2 (100%)	0/0 (0%)
First incidence (days)	408	482	428	307
Life table tests	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression tests	P=0.054	P=0.494	P=0.545	P=0.082
Cochran-Armitage test	P=0.419			
Fisher exact test		P=0.631	P=0.526N	P=0.489
All Organs: Malignant Neoplasms				
Overall rates	17/49 (35%)	13/50 (26%)	4/51 (8%)	3/50 (6%)
Adjusted rates	45.9%	51.5%	53.9%	10.3%
Terminal rates	9/28 (32%)	2/9 (22%)	1/2 (50%)	0/0 (0%)
First incidence (days)	420	482	408	512
Life table tests	P=0.533	P=0.201	P=0.621N	P=0.558
Logistic regression tests	P<0.001N	P=0.302N	P=0.006N	P=0.006N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.235N	P<0.001N	P<0.001N

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rates	46/49 (94%)	46/50 (92%)	47/51 (92%)	47/50 (94%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	9/9 (100%)	2/2 (100%)	0/0 (0%)
First incidence (days)	408	482	408	307
Life table tests	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression tests	P=0.129	P=0.722	P=0.580	P=0.221
Cochran-Armitage test	P=0.527			
Fisher exact test		P=0.511N	P=0.523N	P=0.651

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

TABLE A4a
Historical Incidence of Renal Tubule Neoplasms in Male F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	8/1,019 (0.8%)	2/1,019 (0.2%)	10/1,019 (1.0%)
Standard deviation	1.0%	0.6%	1.2%
Range	0%–2%	0%–2%	0%–4%

[a] Data as of 17 December 1991.

TABLE A4b
Historical Incidence of Oral Cavity Neoplasms in Male F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Overall Historical Incidence			
Total	4/1,020 (0.4%)	1/1,020 (0.1%)	5/1,020 (0.5%)
Standard deviation	0.8%	0.5%	0.9%
Range	0%–2%	0%–2%	0%–2%

[a] Data as of 17 December 1991, includes data for oral mucosa, tongue, pharynx, tooth, and lip.

TABLE A4c
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Male F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	13/1,009 (1.3%)	9/1,009 (0.9%)	22/1,009 (2.2%)
Standard deviation	1.3%	1.2%	1.9%
Range	0%–4%	0%–4%	0%–6%

[a] Data as of 17 December 1991.

TABLE A4d
Historical Incidence of Testicular Neoplasms in Male F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	886/1,012 (87.5%)	0/1,012 (0.0%)	886/1,012 (85.6%)
Standard deviation	5.7%		5.7%
Range	88%–94%		88%–94%

[a] Data as of 17 December 1991.

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	10
Early deaths				
Accidental deaths	2	3	2	2
Moribund	14	31	34	31
Natural deaths	6	7	13	17
Survivors				
Terminal sacrifice	28	9	2	
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(10)
Basophilic focus		1 (10%)		
Fatty change		8 (80%)	8 (89%)	5 (50%)
Inflammation, chronic	1 (10%)			
Necrosis, coagulative				1 (10%)
Bile duct, hyperplasia	6 (60%)	8 (80%)	9 (100%)	9 (90%)
Hepatocyte, degeneration, granular		7 (70%)	8 (89%)	5 (50%)
Mesentery	(2)	(1)	(3)	
Fat, inflammation, suppurative		1 (100%)		
Fat, necrosis, coagulative	2 (100%)	1 (100%)	3 (100%)	
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy	9 (90%)			2 (20%)
Endocrine System				
Thyroid gland	(10)			(10)
C-cell, hyperplasia	1 (10%)			
General Body System				
None				
Genital System				
Preputial gland	(10)			(9)
Inflammation, suppurative	1 (10%)			1 (11%)
Prostate	(10)			(10)
Inflammation, suppurative				1 (10%)
Testes	(10)	(9)	(8)	(10)
Interstitial cell, hyperplasia	3 (30%)			1 (10%)
Seminiferous tubule, atrophy			1 (13%)	
Hematopoietic System				
Spleen	(10)		(1)	(10)
Fibrosis			1 (100%)	

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
15-Month Interim Evaluation (continued)				
Integumentary System				
None				
Musculoskeletal System				
Bone	(10)			(10)
Necrosis	1 (10%)			
Nervous System				
None				
Respiratory System				
Nose	(10)		(1)	(10)
Inflammation, suppurative	2 (20%)		1 (100%)	3 (30%)
Special Senses System				
Eye			(1)	
Pigmentation			1 (100%)	
Urinary System				
Kidney	(10)	(10)	(9)	(10)
Nephropathy	10 (100%)	10 (100%)	9 (100%)	10 (100%)
2-Year Study				
Alimentary System				
Esophagus	(49)	(49)	(51)	(50)
Inflammation, suppurative		1 (2%)		
Periesophageal tissue, hemorrhage		1 (2%)		
Intestine large, colon	(45)	(48)	(42)	(44)
Inflammation, suppurative		1 (2%)		
Intestine small, duodenum	(46)	(48)	(48)	(46)
Ulcer	1 (2%)	1 (2%)	2 (4%)	3 (7%)
Liver	(49)	(50)	(51)	(50)
Basophilic focus	16 (33%)	4 (8%)	2 (4%)	4 (8%)
Clear cell focus	5 (10%)			1 (2%)
Cyst				1 (2%)
Cytologic alterations			28 (55%)	29 (58%)
Developmental malformation	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Eosinophilic focus	5 (10%)	1 (2%)		3 (6%)
Fatty change	4 (8%)	6 (12%)	7 (14%)	1 (2%)
Fibrosis		3 (6%)	41 (80%)	42 (84%)
Hemorrhage				3 (6%)
Hyperplasia	2 (4%)	2 (4%)		2 (4%)
Infiltration cellular, lymphocyte	3 (6%)	1 (2%)		
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		3 (6%)	3 (6%)	2 (4%)

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver (continued)				
Mineralization				2 (4%)
Mixed cell focus	4 (8%)	1 (2%)	1 (2%)	
Necrosis, coagulative	1 (2%)	13 (26%)	38 (75%)	40 (80%)
Bile duct, hyperplasia	41 (84%)	41 (82%)	45 (88%)	47 (94%)
Hepatocyte, degeneration, granular		1 (2%)		1 (2%)
Periductular, fibrosis		1 (2%)		
Mesentery	(19)	(11)	(15)	(7)
Ectopic tissue			1 (7%)	
Fat, hemorrhage	1 (5%)			
Fat, inflammation, chronic	2 (11%)	1 (9%)	1 (7%)	1 (14%)
Fat, inflammation, suppurative		3 (27%)		2 (29%)
Fat, necrosis, coagulative	12 (63%)	7 (64%)	13 (87%)	3 (43%)
Pancreas	(47)	(49)	(50)	(49)
Atrophy	4 (9%)	7 (14%)	2 (4%)	1 (2%)
Fibrosis			2 (4%)	
Infiltration cellular, lymphocyte				1 (2%)
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		1 (2%)		1 (2%)
Acinar cell, hyperplasia	1 (2%)			
Acinus, hyperplasia	2 (4%)	1 (2%)		
Vein, dilatation		1 (2%)		
Salivary glands	(49)	(49)	(49)	(50)
Inflammation, suppurative		1 (2%)		
Necrosis, caseous			1 (2%)	
Stomach, forestomach	(48)	(50)	(51)	(50)
Hyperkeratosis	2 (4%)	3 (6%)	4 (8%)	
Inflammation, chronic		3 (6%)	5 (10%)	4 (8%)
Inflammation, suppurative		3 (6%)	1 (2%)	3 (6%)
Mineralization				1 (2%)
Ulcer	7 (15%)	24 (48%)	35 (69%)	34 (68%)
Stomach, glandular	(47)	(48)	(49)	(50)
Inflammation, chronic		2 (4%)	3 (6%)	1 (2%)
Inflammation, suppurative		1 (2%)		1 (2%)
Mineralization		4 (8%)	5 (10%)	5 (10%)
Ulcer	2 (4%)	5 (10%)	8 (16%)	7 (14%)
Tongue				(1)
Necrosis, Zenker's				1 (100%)
Cardiovascular System				
Blood vessel	(1)	(4)	(2)	(1)
Aorta, mineralization		1 (25%)		1 (100%)
Mesenteric artery, arteriosclerosis		1 (25%)		
Mesenteric artery, polyarteritis			2 (100%)	
Mesenteric artery, thrombus			1 (50%)	
Heart	(49)	(49)	(51)	(50)
Cardiomyopathy	27 (55%)	34 (69%)	25 (49%)	21 (42%)
Inflammation, suppurative			1 (2%)	
Thrombus		1 (2%)		
Atrioventricular valve, inflammation, chronic				1 (2%)

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(49)	(50)	(50)	(50)
Clear cell focus		1 (2%)	1 (2%)	2 (4%)
Cytoplasmic alteration		1 (2%)		
Hypertrophy		1 (2%)		
Adrenal gland, medulla	(49)	(50)	(50)	(50)
Basophilic focus	1 (2%)	1 (2%)		
Congestion	1 (2%)			
Hyperplasia		4 (8%)		
Parathyroid gland	(41)	(47)	(49)	(47)
Hyperplasia	3 (7%)	20 (43%)	31 (63%)	29 (62%)
Pituitary gland	(48)	(48)	(49)	(50)
Pars distalis, cyst	1 (2%)	4 (8%)		3 (6%)
Pars distalis, hypertrophy		1 (2%)		
Pars intermedia, hemorrhage	1 (2%)			
Thyroid gland	(47)	(49)	(49)	(50)
C-cell, hyperplasia	5 (11%)	3 (6%)	1 (2%)	2 (4%)
Follicle, cyst	1 (2%)			
General Body System				
Tissue NOS	(2)		(1)	(1)
Inflammation, chronic				1 (100%)
Genital System				
Preputial gland	(45)	(49)	(50)	(47)
Hyperplasia	1 (2%)			
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)	
Inflammation, suppurative	7 (16%)	6 (12%)	3 (6%)	1 (2%)
Duct, dilatation	3 (7%)		2 (4%)	3 (6%)
Prostate	(45)	(50)	(50)	(49)
Edema			1 (2%)	
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, suppurative	4 (9%)	7 (14%)	6 (12%)	4 (8%)
Testes	(45)	(49)	(46)	(50)
Interstitial cell, hyperplasia		2 (4%)	2 (4%)	1 (2%)
Seminiferous tubule, atrophy	3 (7%)			
Hematopoietic System				
Bone marrow	(48)	(50)	(50)	(50)
Hyperplasia, mononuclear cell	1 (2%)			
Hyperplasia, neutrophil		1 (2%)		
Lymph node	(49)	(50)	(49)	(48)
Lumbar, hemorrhage		1 (2%)	1 (2%)	3 (6%)
Mediastinal, hemorrhage		2 (4%)		1 (2%)
Mediastinal, pigmentation				1 (2%)
Renal, hemorrhage		1 (2%)		

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(47)	(48)	(48)
Congestion	1 (2%)			
Edema				1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	3 (6%)	5 (10%)
Hyperplasia, plasma cell	1 (2%)	2 (4%)		
Infiltration cellular, histiocyte				1 (2%)
Lymph node, mesenteric	(43)	(50)	(48)	(50)
Hyperplasia, lymphoid			1 (2%)	
Infiltration cellular, histiocyte		1 (2%)		
Pigmentation, hemosiderin				1 (2%)
Spleen	(48)	(50)	(50)	(50)
Amyloid deposition				1 (2%)
Congestion	2 (4%)	1 (2%)		1 (2%)
Developmental malformation	2 (4%)			
Hemorrhage		1 (2%)		
Hyperplasia, histiocytic		1 (2%)		
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Hypoplasia	1 (2%)			
Infarct		2 (4%)		
Inflammation, suppurative		2 (4%)	2 (4%)	
Necrosis, coagulative			1 (2%)	
Pigmentation, hemosiderin	1 (2%)		1 (2%)	2 (4%)
Thrombus				1 (2%)
Thymus	(47)	(48)	(48)	(47)
Ectopic tissue			1 (2%)	
Inflammation, suppurative		1 (2%)		1 (2%)
Integumentary System				
Mammary gland	(45)	(46)	(44)	(45)
Galactocele	2 (4%)		2 (5%)	
Skin	(49)	(50)	(51)	(50)
Acanthosis			1 (2%)	
Cyst epithelial inclusion	3 (6%)	1 (2%)	2 (4%)	
Degeneration			1 (2%)	
Hemorrhage	1 (2%)	1 (2%)		
Hyperkeratosis			1 (2%)	
Inflammation, chronic	2 (4%)	3 (6%)		
Inflammation, suppurative		1 (2%)	2 (4%)	
Sebaceous gland, inflammation, chronic		1 (2%)		
Musculoskeletal System				
Bone	(49)	(50)	(51)	(50)
Inflammation, chronic			1 (2%)	
Cranium, proliferation		1 (2%)		
Skeletal muscle	(1)		(2)	(1)
Inflammation, chronic			1 (50%)	
Inflammation, suppurative			1 (50%)	1 (100%)

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Nervous System				
Brain	(47)	(50)	(49)	(49)
Cerebellum, developmental malformation	1 (2%)			
Hypothalamus, compression	1 (2%)			
Meninges, hemorrhage				1 (2%)
Respiratory System				
Larynx		(1)		
Hemorrhage		1 (100%)		
Lung	(49)	(49)	(50)	(50)
Atelectasis			1 (2%)	
Edema			1 (2%)	
Foreign body				1 (2%)
Hemorrhage		1 (2%)		
Hyperplasia, macrophage		2 (4%)		1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)	
Mineralization		1 (2%)		
Alveolar epithelium, hyperplasia	5 (10%)	1 (2%)	1 (2%)	1 (2%)
Nose	(49)	(50)	(51)	(50)
Fungus	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Hemorrhage		1 (2%)		1 (2%)
Inflammation, suppurative	13 (27%)	20 (40%)	27 (53%)	41 (82%)
Metaplasia, squamous		1 (2%)		
Olfactory epithelium, degeneration				1 (2%)
Respiratory epithelium, hyperplasia				1 (2%)
Trachea	(49)	(49)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Special Senses System				
Eye			(3)	(1)
Cataract			1 (33%)	1 (100%)
Cornea, edema			1 (33%)	
Retina, degeneration				1 (100%)
Zymbal's gland		(2)	(1)	(1)
Inflammation, suppurative			1 (100%)	
Urinary System				
Kidney	(49)	(50)	(51)	(50)
Congestion	1 (2%)			
Nephropathy	48 (98%)	48 (96%)	50 (98%)	50 (100%)
Cortex, cyst	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Renal tubule, hyperplasia	1 (2%)	3 (6%)		
Urinary bladder	(45)	(49)	(50)	(49)
Hyperplasia	1 (2%)			
Inflammation, suppurative				1 (2%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

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

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2	1	5	
Moribund	14	7	7	14
Natural deaths	5	4	2	6
Survivors				
Died last week of study			1	
Terminal sacrifice	29	38	35	30
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(9)	(1)		(10)
Pars distalis, adenoma		1 (100%)		
General Body System				
None				
Genital System				
Uterus	(10)	(1)	(3)	(10)
Polyp	1 (10%)	1 (100%)	2 (67%)	2 (20%)
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Intestine large, cecum	(46)	(47)	(49)	(45)
Intestine large, colon	(47)	(48)	(49)	(47)
Intestine large, rectum	(48)	(49)	(48)	(48)
Intestine small, ileum	(46)	(47)	(48)	(46)
Intestine small, jejunum	(46)	(48)	(48)	(46)
Leiomyoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Mesentery	(3)	(6)	(9)	(7)
Sarcoma				1 (14%)
Pancreas	(49)	(49)	(48)	(46)
Pharynx				(2)
Papilloma squamous				2 (100%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(48)	(49)	(50)	(48)
Papilloma squamous	1 (2%)	3 (6%)		1 (2%)
Stomach, glandular	(48)	(49)	(49)	(47)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(48)	(50)
Adenoma	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(48)	(49)
Pheochromocytoma benign	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Islets, pancreatic	(49)	(49)	(48)	(47)
Adenoma	1 (2%)		1 (2%)	2 (4%)
Pituitary gland	(49)	(47)	(48)	(49)
Pars distalis, adenocarcinoma	1 (2%)			
Pars distalis, adenoma	30 (61%)	25 (53%)	23 (48%)	28 (57%)
Thyroid gland	(49)	(50)	(49)	(49)
C-cell, adenoma				1 (2%)
C-cell, carcinoma				1 (2%)
Follicular cell, adenoma				1 (2%)
Follicular cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
General Body System				
Tissue NOS	(2)			(1)
Fibroma	1 (50%)			1 (100%)
Genital System				
Clitoral gland	(48)	(47)	(48)	(49)
Adenoma		6 (13%)		2 (4%)
Carcinoma		1 (2%)	1 (2%)	2 (4%)
Ovary	(50)	(49)	(50)	(49)
Granulosa-theca tumor benign			1 (2%)	
Oviduct			(1)	
Uterus	(50)	(50)	(49)	(49)
Polyp	7 (14%)	13 (26%)	4 (8%)	5 (10%)
Sarcoma				1 (2%)
Vagina	(1)	(1)		(4)
Leiomyoma		1 (100%)		
Leiomyosarcoma				1 (25%)
Sarcoma				1 (25%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(49)
Lymph node	(49)	(50)	(50)	(49)
Lymph node, mandibular	(49)	(47)	(48)	(48)
Lymph node, mesenteric	(47)	(49)	(49)	(49)
Spleen	(49)	(50)	(49)	(49)
Thymus	(48)	(48)	(49)	(47)
Integumentary System				
Mammary gland	(49)	(50)	(50)	(50)
Adenocarcinoma	1 (2%)			1 (2%)
Adenoma	1 (2%)	2 (4%)		
Fibroadenoma	17 (35%)	24 (48%)	22 (44%)	11 (22%)
Fibrosarcoma			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Lipoma			1 (2%)	
Papilloma squamous		1 (2%)		
Squamous cell carcinoma	1 (2%)			1 (2%)
Subcutaneous tissue, fibroma		1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Skeletal muscle			(1)	
Nervous System				
Brain	(50)	(50)	(50)	(49)
Meninges, meningioma NOS			1 (2%)	

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Adenoma		1 (2%)		
Special Senses System				
Ear			(1)	
Papilloma squamous			1 (100%)	
Eye	(1)	(4)	(1)	(1)
Papilloma squamous			1 (100%)	
Zymbal's gland			(1)	
Squamous cell carcinoma			1 (100%)	
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Lipoma		1 (2%)		
Sarcoma				1 (2%)
Renal tubule, adenoma				2 (4%)
Urinary bladder	(50)	(49)	(49)	(47)
Papilloma squamous				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	6 (12%)	5 (10%)	6 (12%)	4 (8%)
Mesothelioma NOS	1 (2%)			
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	2	2	2
2-Year study	41	44	40	43
Total primary neoplasms				
15-Month interim evaluation	1	2	2	2
2-Year study	75	91	71	76
Total animals with benign neoplasms				
15-Month interim evaluation	1	2	2	2
2-Year study	37	43	36	40
Total benign neoplasms				
15-Month interim evaluation	1	2	2	2
2-Year study	64	84	60	61
Total animals with malignant neoplasms				
2-Year study	10	7	10	11
Total malignant neoplasms				
2-Year study	10	7	10	15
Total animals with uncertain neoplasms benign or malignant				
2-Year study	1		1	
Total uncertain neoplasms				
2-Year study	1		1	

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[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 Gavage Study of Coumarin: Vehicle Control

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	0 6 9 1	0 7 1 2	0 7 2 3	0 7 3 5	0 7 4 2	0 7 5 1	0 7 5 3	0 7 8 3	0 7 9 1	0 7 9 4	0 6 9 4	0 7 0 5	0 7 3 1	0 7 6 1	0 7 6 2	0 7 7 1	0 8 0 2	0 7 0 4	0 7 4 1	0 7 4 5	0 7 5 4	0 7 7 2	0 7 9 2	0 8 3 3	0 8 0 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery												+														3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																								X		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X														X			3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenocarcinoma																										1
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X		X			X	X	X	X		X					X		30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma																										1

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

Number of Days on Study	0 9 2	1 8 4	3 5 6	4 3 5	4 9 1	5 5 4	5 8 0	6 0 7	6 1 4	6 2 4	6 4 4	6 5 9	6 6 9	6 6 2	6 6 5	6 9 3	6 9 9	7 0 0	7 0 8	7 1 2	7 1 4	7 1 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 7 0 3	0 7 2 4	0 7 2 5	0 7 2 2	0 7 1 4	0 7 4 4	0 6 9 2	0 7 4 3	0 7 9 3	0 7 2 1	0 8 0 1	0 7 8 1	0 7 8 1	0 6 9 3	0 7 3 3	0 7 6 5	0 7 7 3	0 7 5 5	0 7 1 5	0 7 1 1	0 7 6 4	0 6 9 5	0 7 0 2	0 7 3 2	0 7 8 2	0 7 9 5
General Body System																										
Tissue NOS														+						+						
Fibroma																				X						
Genital System																										
Clitoral gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp																	X					X				
Vagina																										
Hematopoietic System																										
Blood																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Adenoma																							X			
Fibroadenoma					X		X		X		X							X								X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																X										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 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	
Carcass ID Number	0 6 9 1	0 7 1 2	0 7 2 3	0 7 3 5	0 7 4 2	0 7 5 1	0 7 5 3	0 7 8 3	0 7 9 1	0 7 9 4	0 7 9 4	0 6 0 5	0 7 3 1	0 7 6 1	0 7 6 2	0 7 7 1	0 7 8 2	0 7 0 4	0 7 0 4	0 7 4 1	0 7 4 5	0 7 5 4	0 7 7 2	0 7 9 2	0 8 0 3	0 8 0 4	**Total Tissues/ Tumors**
General Body System																											
Tissue NOS																											2
Fibroma																											1
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp	X													X	X			X							X		7
Vagina						+																					1
Hematopoietic System																											
Blood																				+							1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma									X																		1
Adenoma																											1
Fibroadenoma	X	X		X		X	X						X	X		X	X							X	X		17
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	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	0 8 9 5	0 9 0 4	0 9 1 1	0 9 1 4	0 8 1 3	0 8 3 4	0 8 3 5	0 8 5 3	0 8 6 4	0 8 7 5	0 8 8 1	0 8 8 2	0 8 9 2	0 9 0 3	0 9 2 5	0 8 2 2	0 8 2 4	0 8 3 3	0 8 5 2	0 8 6 5	0 9 0 2	0 9 1 2	0 9 1 3	0 9 1 5	0 9 2 3	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																X											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+				+				+						+	+		6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous	X												X														3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign														X													2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+		47
Pars distalis, adenoma	X	X	X	X		X			X	X	X				X	X	X				X	X			X		25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma																		X									1
General Body System																											
None																											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	2 4 5	3 3 4	3 3 4	4 3 9	5 3 1	5 4 7	6 5 4	6 5 9	6 5 9	6 6 2	6 9 3	7 1 3	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 8 8 3	0 8 4 1	0 8 7 1	0 8 4 5	0 8 1 5	0 9 0 5	0 8 9 4	0 8 3 1	0 8 6 1	0 8 7 2	0 8 2 1	0 9 2 2	0 8 2 3	0 8 6 3	0 8 8 4	0 9 0 1	0 8 1 2	0 8 2 5	0 8 3 2	0 8 4 2	0 8 5 4	0 8 6 2	0 8 7 3	0 8 8 5	0 8 9 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X							X										
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp									X					X			X						X	X	
Vagina					+																				
Leiomyoma					X																				
Hematopoietic System																									
Blood				+																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma								X	X	X	X		X		X		X	X					X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibroma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 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	0 8 9 5	0 9 0 4	0 9 1 1	0 9 1 4	0 8 1 3	0 8 3 4	0 8 3 5	0 8 5 3	0 8 6 4	0 8 7 5	0 8 8 1	0 8 8 2	0 8 9 2	0 9 0 3	0 9 2 5	0 8 2 2	0 8 2 4	0 8 3 3	0 8 5 2	0 8 6 5	0 9 0 2	0 9 1 2	0 9 1 3	0 9 2 5	0 9 3 3	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X	X								X							X									6
Carcinoma									X																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp	X									X			X	X	X					X	X			X		13
Vagina																										1
Leiomyoma																										1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X								X													2
Fibroadenoma	X	X	X			X	X	X	X		X	X	X		X			X			X			X		24
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous					X																					1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 25 mg/kg
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 9 3 3	0 9 5 5	0 9 6 2	0 9 6 4	0 9 7 2	0 9 7 4	0 9 9 4	1 0 0 4	1 0 1 1	1 0 1 3	1 0 2 2	1 0 3 2	1 0 3 4	1 0 3 5	0 9 3 1	0 9 4 5	0 9 4 1	1 0 0 5	1 0 1 3	1 0 1 2	1 0 2 5	1 0 2 1	1 0 2 5	1 0 3 1	1 0 3 3	1 0 4 1	1 0 4 2	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+								+						+			+	9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Blood vessel																								+			1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																X									X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X																								1
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X	X	X				X	X	X		X			X			X			X	X			X			X	23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma									X																		1
General Body System																											
None																											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	0 1 3	0 2 1	0 3 4	0 6 7	1 8 9	5 5 4	5 6 5	6 0 1	6 2 2	6 3 5	6 3 7	6 9 1	7 0 5	7 0 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 9 9 3	1 0 1 4	0 9 9 5	0 9 5 2	0 9 7 1	0 9 8 3	0 9 8 1	0 9 7 5	1 0 2 4	0 9 3 4	0 9 7 3	1 0 4 5	1 0 0 5	0 9 4 3	0 9 4 4	0 9 4 2	0 9 8 4	0 9 8 5	1 0 0 1	0 9 5 1	0 9 5 1	0 9 5 3	0 9 4 4	1 0 6 3	1 0 2 3	1 0 3 5
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	
Carcinoma																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granulosa-theca tumor benign																										
Oviduct											+															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Polyp																		X								
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibroadenoma														X	X		X		X	X				X	X	
Fibrosarcoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lipoma																										
Subcutaneous tissue, fibroma																	X									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle													+													
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Meninges, meningioma NOS														X												
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 9 3 3	0 9 5 5	0 9 6 2	0 9 6 4	0 9 7 2	0 9 7 4	0 9 9 4	1 0 0 4	1 0 1 1	1 0 1 3	1 0 2 2	1 0 3 2	1 0 3 4	1 0 3 5	0 9 3 1	0 9 4 5	0 9 4 1	1 0 0 5	1 0 1 3	1 0 2 2	1 0 2 5	1 0 3 1	1 0 3 5	1 0 4 1	1 0 4 3	1 0 4 2	**Total Tissues/ Tumors**
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma															X												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor benign								X																			1
Oviduct																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp			X																			X	X				4
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma		X		X	X		X		X	X	X	X	X	X			X		X			X		X	X		22
Fibrosarcoma												X															1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma						X																					1
Subcutaneous tissue, fibroma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, meningioma NOS																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	0	0	0	0	1	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	1	2	3	6	8	5	6	0	2	3	3	9	0	0	2	2	2	2	2	3	3	3	3	3	3
	3	1	4	7	9	4	5	1	2	5	7	1	5	9	9	9	9	9	9	2	2	2	2	2	2
Carcass ID Number	0	1	0	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	1	0	0	0	0	1	1
	9	0	9	9	9	9	9	9	0	9	9	0	0	9	9	9	9	9	0	9	9	9	9	0	0
	9	1	9	5	7	8	8	7	2	3	7	4	0	4	4	8	8	8	0	5	5	5	6	2	3
	3	4	5	2	1	3	1	5	4	4	3	5	5	3	4	2	4	5	1	1	3	4	3	3	5
Special Senses System																									
Ear																									
Papilloma squamous																									
Eye																									
Papilloma squamous																									
Harderian gland			+																						
Zymbal's gland																									
Squamous cell carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X			X		X				X	X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 9 3 3	0 9 5 5	0 9 6 2	0 9 6 4	0 9 7 2	0 9 7 4	0 9 9 4	0 0 0 4	1 0 1 1	1 0 1 3	1 0 2 2	1 0 3 2	1 0 3 4	1 0 3 5	0 9 4 1	0 9 4 5	0 9 4 3	1 0 1 2	1 0 1 5	1 0 2 5	1 0 2 1	1 0 2 5	1 0 3 1	1 0 3 3	1 0 4 1	1 0 4 2	**Total Tissues/ Tumors**
Special Senses System																										
Ear												+														1
Papilloma squamous												X														1
Eye																							+			1
Papilloma squamous																							X			1
Harderian gland																										1
Zymbal's gland										+																1
Squamous cell carcinoma										X																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 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 4 4	7 4 4	7 4 4	7 4 4		
Carcass ID Number	1 0 6 1	1 0 6 2	1 0 6 4	1 0 7 2	1 0 8 1	1 0 8 4	1 1 0 2	1 1 3 3	1 1 4 1	1 1 5 3	1 0 5 3	1 0 9 3	1 1 2 3	1 1 2 4	1 1 3 4	1 1 4 2	1 1 5 2	1 1 6 5	1 1 8 5	1 0 9 1	1 0 9 5	1 1 0 1	1 1 1 5	1 1 2 2	1 1 5 1	Total Tissues/ Tumors	
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45		
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45		
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46		
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Mesentery						+															+				+	7		
Sarcoma																										1		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46		
Pharynx																+			+							2		
Papilloma squamous																X			X							2		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Papilloma squamous																										1		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Tongue													+													1		
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Pheochromocytoma benign																				X						1		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Adenoma								X																		2		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Pars distalis, adenoma			X	X	X			X	X	X	X	X	X		X		X	X			X			X	X	28		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
C-cell, adenoma																			X							1		
C-cell, carcinoma																										1		
Follicular cell, adenoma																										1		
Follicular cell, carcinoma												X														1		

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

Number of Days on Study	3 7 5	4 6 3	4 9 1	5 4 3	5 5 1	5 8 0	6 1 9	6 2 9	6 4 1	6 4 2	6 5 1	6 5 1	6 5 1	6 5 8	6 6 5	6 7 9	6 7 9	6 8 6	6 9 3	6 9 9	6 9 9	7 2 9	7 2 9	7 2 9	7 3 2
Carcass ID Number	1 0 6 5	1 1 4 3	1 1 3 1	1 1 0 3	1 1 6 4	1 1 1 2	1 1 5 4	1 1 0 4	1 1 4 5	1 1 6 1	1 0 5 5	1 0 5 3	1 1 8 5	1 1 2 3	1 1 1 3	1 0 7 4	1 1 0 5	1 0 8 2	1 0 6 2	1 0 9 2	1 0 9 4	1 0 5 2	1 0 7 5	1 1 5 5	1 1 6 3	1 0 5 4
General Body System																										
Tissue NOS			+																							
Fibroma			X																							
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X							
Carcinoma										X																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp																				X	X					
Sarcoma										X																
Vagina										+						+										
Leiomyosarcoma																										
Sarcoma										X																
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Fibroadenoma					X				X					X	X	X						X			X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																										
Subcutaneous tissue, fibroma																X										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 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	
Carcass ID Number	1 0 6 1	1 0 6 2	1 0 6 4	1 0 7 2	1 0 8 1	1 0 8 4	1 1 0 2	1 1 3 3	1 1 4 1	1 1 5 3	1 0 5 3	1 0 9 3	1 1 2 3	1 1 2 4	1 1 3 4	1 1 4 2	1 1 5 2	1 1 5 5	1 1 6 5	1 0 8 5	1 0 9 1	1 0 9 5	1 1 0 1	1 1 1 5	1 1 2 2	1 1 5 1	Total Tissues/ Tumors
General Body System																											
Tissue NOS																											1
Fibroma																											1
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										X	2
Carcinoma																					X						2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp										X														X		X	5
Sarcoma																											1
Vagina						+											+										4
Leiomyosarcoma						X																					1
Sarcoma																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																X											1
Fibroadenoma						X		X													X			X			11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																	X										1
Subcutaneous tissue, fibroma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	3 7 5	4 6 3	4 9 1	5 4 3	5 5 1	5 8 0	6 1 9	6 2 9	6 4 1	6 4 2	6 5 1	6 5 1	6 5 1	6 5 8	6 6 5	6 7 9	6 7 9	6 8 6	6 9 3	6 9 9	6 9 9	7 2 9	7 2 9	7 2 9	7 3 2
Carcass ID Number	1 0 6 5	1 1 4 3	1 1 3 1	1 1 0 3	1 1 6 4	1 1 1 2	1 1 5 4	1 1 0 4	1 1 4 5	1 1 6 1	1 0 5 5	1 0 8 3	1 1 2 5	1 1 1 3	1 0 7 4	1 1 0 5	1 0 8 2	1 1 6 2	1 0 9 2	1 0 9 2	1 0 9 4	1 0 5 2	1 0 7 5	1 1 5 5	1 1 6 3	1 0 5 4
Nervous System																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord												+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma										X															
Renal tubule, adenoma																				X					
Urinary bladder	A	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X				X																	

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 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	
Carcass ID Number	1 0 6 1	1 0 6 2	1 0 6 4	1 0 7 2	1 0 8 1	1 0 8 4	1 1 0 2	1 1 3 3	1 1 4 1	1 1 5 3	1 0 5 3	1 0 9 3	1 1 2 3	1 1 2 4	1 1 3 4	1 1 4 2	1 1 5 2	1 1 6 5	1 0 8 5	1 0 9 1	1 0 9 5	1 1 0 1	1 1 1 5	1 1 2 2	1 1 5 1	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye								+																		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																										1
Renal tubule, adenoma																					X					2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma squamous											X															1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear														X												4

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	3/50 (6%)	2/50 (4%)	2/48 (4%)	1/49 (2%)
Adjusted rates[b]	9.1%	5.3%	5.7%	3.3%
Terminal rates[c]	2/29 (7%)	2/38 (5%)	2/35 (6%)	1/30 (3%)
First incidence (days)	607	729 (T)	729 (T)	729 (T)
Life table tests[d]	P=0.235N	P=0.401N	P=0.434N	P=0.295N
Logistic regression tests[d]	P=0.235N	P=0.480N	P=0.519N	P=0.300N
Cochran-Armitage test[d]	P=0.241N			
Fisher exact test[d]		P=0.500N	P=0.520N	P=0.316N
Clitoral Gland: Adenoma				
Overall rates	0/48 (0%)	6/47 (13%)	0/48 (0%)	2/49 (4%)
Adjusted rates	0.0%	15.9%	0.0%	6.3%
Terminal rates	0/29 (0%)	5/36 (14%)	0/34 (0%)	1/30 (3%)
First incidence (days)	–[e]	659	–	693
Life table tests	P=0.580	P=0.031	–[f]	P=0.234
Logistic regression tests	P=0.594N	P=0.018	–	P=0.241
Cochran-Armitage test	P=0.584N			
Fisher exact test		P=0.012	–	P=0.253
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	0/48 (0%)	7/47 (15%)	1/48 (2%)	4/49 (8%)
Adjusted rates	0.0%	18.6%	2.9%	11.7%
Terminal rates	0/29 (0%)	6/36 (17%)	1/34 (3%)	2/30 (7%)
First incidence (days)	–	659	729 (T)	642
Life table tests	P=0.252	P=0.018	P=0.532	P=0.066
Logistic regression tests	P=0.280	P=0.010	P=0.532	P=0.067
Cochran-Armitage test	P=0.286			
Fisher exact test		P=0.006	P=0.500	P=0.061
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rates	0/49 (0%)	0/50 (0%)	0/50 (0%)	2/49 (4%)
Adjusted rates	0.0%	0.0%	0.0%	6.4%
Terminal rates	0/29 (0%)	0/38 (0%)	0/36 (0%)	1/30 (3%)
First incidence (days)	–	–	–	699
Life table tests	P=0.037	–	–	P=0.234
Logistic regression tests	P=0.044	–	–	P=0.238
Cochran-Armitage test	P=0.045			
Fisher exact test		–	–	P=0.247
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rates	0/49 (0%)	0/50 (0%)	1/50 (2%)	2/49 (4%)
Adjusted rates	0.0%	0.0%	2.8%	6.4%
Terminal rates	0/29 (0%)	0/38 (0%)	1/36 (3%)	1/30 (3%)
First incidence (days)	–	–	729 (T)	699
Life table tests	P=0.057	–	P=0.543	P=0.234
Logistic regression tests	P=0.065	–	P=0.543	P=0.238
Cochran-Armitage test	P=0.069			
Fisher exact test		–	P=0.505	P=0.247

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Mammary Gland: Fibroadenoma				
Overall rates	17/50 (34%)	24/50 (48%)	22/50 (44%)	11/50 (22%)
Adjusted rates	48.2%	57.0%	59.5%	29.8%
Terminal rates	12/29 (41%)	20/38 (53%)	21/36 (58%)	6/30 (20%)
First incidence (days)	491	659	709	551
Life table tests	P=0.065N	P=0.393	P=0.470	P=0.131N
Logistic regression tests	P=0.045N	P=0.143	P=0.211	P=0.118N
Cochran-Armitage test	P=0.051N			
Fisher exact test		P=0.111	P=0.206	P=0.133N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	18/50 (36%)	25/50 (50%)	22/50 (44%)	11/50 (22%)
Adjusted rates	51.3%	59.4%	59.5%	29.8%
Terminal rates	13/29 (45%)	21/38 (55%)	21/36 (58%)	6/30 (20%)
First incidence (days)	491	659	709	551
Life table tests	P=0.039N	P=0.414	P=0.564	P=0.093N
Logistic regression tests	P=0.026N	P=0.147	P=0.280	P=0.081N
Cochran-Armitage test	P=0.031N			
Fisher exact test		P=0.113	P=0.270	P=0.093N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rates	19/50 (38%)	25/50 (50%)	22/50 (44%)	12/50 (24%)
Adjusted rates	54.3%	59.4%	59.5%	32.7%
Terminal rates	14/29 (48%)	21/38 (55%)	21/36 (58%)	7/30 (23%)
First incidence (days)	491	659	709	551
Life table tests	P=0.044N	P=0.502	P=0.512N	P=0.095N
Logistic regression tests	P=0.030N	P=0.203	P=0.360	P=0.083N
Cochran-Armitage test	P=0.035N			
Fisher exact test		P=0.157	P=0.342	P=0.097N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	30/49 (61%)	25/47 (53%)	23/48 (48%)	28/49 (57%)
Adjusted rates	74.3%	60.7%	60.2%	69.1%
Terminal rates	19/29 (66%)	21/37 (57%)	20/35 (57%)	18/30 (60%)
First incidence (days)	435	547	622	463
Life table tests	P=0.512N	P=0.042N	P=0.033N	P=0.393N
Logistic regression tests	P=0.424N	P=0.211N	P=0.156N	P=0.391N
Cochran-Armitage test	P=0.416N			
Fisher exact test		P=0.278N	P=0.133N	P=0.419N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	31/49 (63%)	25/47 (53%)	23/48 (48%)	28/49 (57%)
Adjusted rates	75.1%	60.7%	60.2%	69.1%
Terminal rates	19/29 (66%)	21/37 (57%)	20/35 (57%)	18/30 (60%)
First incidence (days)	435	547	622	463
Life table tests	P=0.452N	P=0.029N	P=0.023N	P=0.336N
Logistic regression tests	P=0.356N	P=0.155N	P=0.111N	P=0.312N
Cochran-Armitage test	P=0.351N			
Fisher exact test		P=0.214N	P=0.094N	P=0.340N

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	1/50 (2%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rates	3.4%	7.9%	0.0%	2.1%
Terminal rates	1/29 (3%)	3/38 (8%)	0/36 (0%)	0/30 (0%)
First incidence (days)	729 (T)	729 (T)	–	543
Life table tests	P=0.413N	P=0.406	P=0.457N	P=0.752N
Logistic regression tests	P=0.407N	P=0.406	P=0.457N	P=0.749
Cochran-Armitage test	P=0.409N			
Fisher exact test		P=0.309	P=0.500N	P=0.753N
Uterus: Stromal Polyp				
Overall rates	7/50 (14%)	13/50 (26%)	4/50 (8%)	5/50 (10%)
Adjusted rates	22.3%	33.2%	11.1%	15.6%
Terminal rates	5/29 (17%)	12/38 (32%)	4/36 (11%)	3/30 (10%)
First incidence (days)	699	659	729 (T)	699
Life table tests	P=0.128N	P=0.264	P=0.161N	P=0.381N
Logistic regression tests	P=0.127N	P=0.165	P=0.201N	P=0.385N
Cochran-Armitage test	P=0.117N			
Fisher exact test		P=0.105	P=0.262N	P=0.380N
All Organs: Mononuclear Cell Leukemia				
Overall rates	6/50 (12%)	5/50 (10%)	6/50 (12%)	4/50 (8%)
Adjusted rates	15.5%	12.0%	14.4%	9.4%
Terminal rates	1/29 (3%)	3/38 (8%)	2/36 (6%)	1/30 (3%)
First incidence (days)	554	439	554	375
Life table tests	P=0.354N	P=0.401N	P=0.559N	P=0.370N
Logistic regression tests	P=0.223N	P=0.512N	P=0.619	P=0.430N
Cochran-Armitage test	P=0.334N			
Fisher exact test		P=0.500N	P=0.620N	P=0.370N
All Organs: Benign Neoplasms				
Overall rates	37/50 (74%)	43/50 (86%)	36/50 (72%)	40/50 (80%)
Adjusted rates	85.8%	93.5%	90.0%	86.8%
Terminal rates	23/29 (79%)	35/38 (92%)	32/36 (89%)	24/30 (80%)
First incidence (days)	435	531	622	463
Life table tests	P=0.350	P=0.370N	P=0.109N	P=0.415
Logistic regression tests	P=0.547	P=0.126	P=0.540N	P=0.409
Cochran-Armitage test	P=0.454			
Fisher exact test		P=0.105	P=0.500N	P=0.318
All Organs: Malignant Neoplasms				
Overall rates	10/50 (20%)	7/50 (14%)	10/50 (20%)	11/50 (22%)
Adjusted rates	24.9%	17.0%	24.4%	29.9%
Terminal rates	2/29 (7%)	5/38 (13%)	6/36 (17%)	7/30 (23%)
First incidence (days)	554	439	554	375
Life table tests	P=0.311	P=0.202N	P=0.491N	P=0.507
Logistic regression tests	P=0.447	P=0.298N	P=0.588	P=0.487
Cochran-Armitage test	P=0.335			
Fisher exact test		P=0.298N	P=0.598N	P=0.500

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rates	41/50 (82%)	44/50 (88%)	40/50 (80%)	43/50 (86%)
Adjusted rates	89.0%	93.6%	90.9%	89.5%
Terminal rates	24/29 (83%)	35/38 (92%)	32/36 (89%)	25/30 (83%)
First incidence (days)	435	439	554	375
Life table tests	P=0.360	P=0.191N	P=0.127N	P=0.485
Logistic regression tests	P=0.407N	P=0.359	P=0.604	P=0.484
Cochran-Armitage test	P=0.448			
Fisher exact test		P=0.288	P=0.500N	P=0.393

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

TABLE B4a
Historical Incidence of Renal Tubule Neoplasms in Female F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	2/1,018 (0.2%)	0/1,018 (0.0%)	2/1,018 (0.2%)
Standard deviation	0.6%		0.6%
Range	0%–2%		0%–2%

[a] Data as of 17 December 1991.

TABLE B4b
Historical Incidence of Oral Cavity Neoplasms in Female F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Overall Historical Incidence			
Total	4/1,020 (0.4%)	2/1,020 (0.2%)	6/1,020 (0.6%)
Standard deviation	0.8%	0.6%	0.9%
Range	0%–2%	0%–2%	0%–2%

[a] Data as of 17 December 1991, includes data for oral mucosa, tongue, pharynx, tooth, and lip.

TABLE B4c
Historical Incidence of Forestomach Neoplasms in Female F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Overall Historical Incidence			
Total	3/1,020 (0.3%)	0/1,020 (0.0%)	3/1,020 (0.3%)
Standard deviation	0.7%		0.7%
Range	0%–2%		0%–2%

[a] Data as of 17 December 1991.

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths	2	1	5	
Moribund	14	7	7	14
Natural deaths	5	4	2	6
Survivors				
Died last week of study			1	
Terminal sacrifice	29	38	35	30
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(8)	(8)	(10)
Basophilic focus	3 (30%)	1 (13%)		1 (10%)
Developmental malformation		1 (13%)	3 (38%)	2 (20%)
Fatty change			5 (63%)	9 (90%)
Inflammation, chronic	5 (50%)	2 (25%)	3 (38%)	4 (40%)
Necrosis			1 (13%)	
Bile duct, hyperplasia	1 (10%)	3 (38%)	1 (13%)	3 (30%)
Hepatocyte, degeneration, granular			3 (38%)	9 (90%)
Mesentery		(2)	(1)	
Fat, mineralization		2 (100%)	1 (100%)	
Fat, necrosis, coagulative		2 (100%)	1 (100%)	
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy	5 (50%)			2 (20%)
Endocrine System				
Pituitary gland	(9)	(1)		(10)
Pars distalis, cyst				2 (20%)
General Body System				
None				
Genital System				
Clitoral gland	(10)		(1)	(10)
Inflammation, suppurative	1 (10%)		1 (100%)	
Ovary	(10)	(1)		(10)
Follicle, cyst		1 (100%)		
Uterus	(10)	(1)	(3)	(10)
Hydrometra	2 (20%)		1 (33%)	2 (20%)

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mandibular	(10)			(9)
Hyperplasia, lymphoid				1 (11%)
Spleen	(10)	(1)		(10)
Congestion		1 (100%)		
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Nose	(10)			(10)
Inflammation, suppurative				1 (10%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(8)	(10)	(10)
Nephropathy	4 (40%)	8 (100%)	10 (100%)	10 (100%)
2-Year Study				
Alimentary System				
Intestine small, duodenum	(47)	(48)	(48)	(48)
Ulcer				2 (4%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus	36 (72%)	32 (64%)	17 (34%)	20 (40%)
Clear cell focus		1 (2%)		3 (6%)
Cytologic alterations				9 (18%)
Developmental malformation	6 (12%)	3 (6%)	6 (12%)	4 (8%)
Eosinophilic focus		1 (2%)	1 (2%)	2 (4%)
Fatty change	5 (10%)		7 (14%)	8 (16%)
Fibrosis			1 (2%)	12 (24%)
Hematopoietic cell proliferation	1 (2%)			

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver (continued)				
Inflammation, chronic	14 (28%)	22 (44%)	18 (36%)	17 (34%)
Inflammation, suppurative	1 (2%)		1 (2%)	
Mineralization				1 (2%)
Mixed cell focus	6 (12%)		1 (2%)	3 (6%)
Necrosis, coagulative	3 (6%)	3 (6%)	4 (8%)	15 (30%)
Bile duct, cyst			1 (2%)	
Bile duct, hyperplasia	26 (52%)	27 (54%)	29 (58%)	20 (40%)
Hepatocyte, cytologic alterations				1 (2%)
Hepatocyte, degeneration, granular			8 (16%)	30 (60%)
Mesentery	(3)	(6)	(9)	(7)
Fat, cyst		1 (17%)		
Fat, inflammation, chronic		1 (17%)	2 (22%)	2 (29%)
Fat, necrosis, coagulative	3 (100%)	3 (50%)	5 (56%)	2 (29%)
Pancreas	(49)	(49)	(48)	(46)
Infiltration cellular, lymphocyte		1 (2%)		
Acinus, atrophy	6 (12%)	1 (2%)	4 (8%)	4 (9%)
Acinus, hyperplasia				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			
Stomach, forestomach	(48)	(49)	(50)	(48)
Developmental malformation	1 (2%)			
Hyperkeratosis		2 (4%)	1 (2%)	1 (2%)
Hyperplasia, squamous		2 (4%)		
Inflammation, chronic	1 (2%)		1 (2%)	
Inflammation, suppurative		1 (2%)		
Ulcer	1 (2%)	1 (2%)	6 (12%)	9 (19%)
Stomach, glandular	(48)	(49)	(49)	(47)
Mineralization	1 (2%)			
Ulcer	4 (8%)		1 (2%)	7 (15%)
Tongue	(1)			(1)
Hyperkeratosis				1 (100%)
Hyperplasia	1 (100%)			
Inflammation, suppurative	1 (100%)			
Cardiovascular System				
Blood vessel			(1)	
Polyarteritis, chronic			1 (100%)	
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	22 (44%)	20 (40%)	22 (44%)	21 (42%)
Fibrosis	2 (4%)		2 (4%)	1 (2%)
Inflammation, suppurative				1 (2%)
Mineralization	1 (2%)			2 (4%)
Thrombus	2 (4%)		1 (2%)	

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(48)	(50)
Atrophy	1 (2%)			
Clear cell focus	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Hemorrhage	1 (2%)			
Hyperplasia	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(48)	(49)
Basophilic focus	2 (4%)	1 (2%)		
Infiltration cellular, lymphocyte			1 (2%)	
Parathyroid gland	(46)	(47)	(45)	(47)
Hyperplasia			3 (7%)	1 (2%)
Pituitary gland	(49)	(47)	(48)	(49)
Pars distalis, congestion		1 (2%)		
Pars distalis, cyst	5 (10%)	8 (17%)	7 (15%)	4 (8%)
Pars distalis, pigmentation, melanin	1 (2%)			
Pars intermedia, congestion	1 (2%)			
Pars nervosa, cyst multilocular			1 (2%)	
Thyroid gland	(49)	(50)	(49)	(49)
C-cell, hyperplasia	6 (12%)	5 (10%)	6 (12%)	4 (8%)
Follicle, cyst			1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(48)	(47)	(48)	(49)
Inflammation, suppurative	3 (6%)	10 (21%)	6 (13%)	4 (8%)
Duct, dilatation	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Ovary	(50)	(49)	(50)	(49)
Corpus luteum, cyst	2 (4%)		1 (2%)	
Follicle, cyst	4 (8%)	2 (4%)	1 (2%)	2 (4%)
Uterus	(50)	(50)	(49)	(49)
Hydrometra	7 (14%)	5 (10%)	7 (14%)	10 (20%)
Hyperplasia, cystic	3 (6%)	3 (6%)	1 (2%)	1 (2%)
Necrosis, coagulative	1 (2%)			
Cervix, cyst		1 (2%)		
Cervix, inflammation, suppurative	1 (2%)			
Epithelium, cytoplasmic alteration				1 (2%)
Vagina	(1)	(1)		(4)
Cyst	1 (100%)			
Hyperkeratosis				1 (25%)
Inflammation, suppurative		1 (100%)		
Hematopoietic System				
Blood	(1)	(1)		
Anisocytosis		1 (100%)		
Monocytosis		1 (100%)		
Bone marrow	(50)	(50)	(49)	(49)
Hyperplasia, neutrophil			1 (2%)	
Inflammation, chronic	1 (2%)			
Myelofibrosis				1 (2%)

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(49)	(50)	(50)	(49)
Mediastinal, hyperplasia, macrophage				1 (2%)
Pancreatic, hemorrhage, acute			1 (2%)	
Pancreatic, inflammation, suppurative	1 (2%)			
Lymph node, mandibular	(49)	(47)	(48)	(48)
Hyperplasia, lymphoid	1 (2%)			
Hyperplasia, macrophage		1 (2%)		
Hyperplasia, plasma cell			1 (2%)	
Lymph node, mesenteric	(47)	(49)	(49)	(49)
Congestion		2 (4%)		
Hyperplasia, lymphoid	1 (2%)			
Spleen	(49)	(50)	(49)	(49)
Congestion		1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid		2 (4%)	1 (2%)	
Pigmentation, hemosiderin		3 (6%)	1 (2%)	1 (2%)
Sinusoid, dilatation			1 (2%)	
Thymus	(48)	(48)	(49)	(47)
Congestion				1 (2%)
Integumentary System				
Mammary gland	(49)	(50)	(50)	(50)
Galactocele	6 (12%)	4 (8%)	3 (6%)	1 (2%)
Hyperplasia, glandular	1 (2%)			
Inflammation	1 (2%)	1 (2%)		
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		2 (4%)		2 (4%)
Inflammation, suppurative		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture				1 (2%)
Osteopetrosis				1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(49)
Cerebrum, atypical cells	1 (2%)			
Cerebrum, hemorrhage	1 (2%)		1 (2%)	
Cerebrum, mineralization	1 (2%)			
Hypothalamus, compression	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Hypothalamus, developmental malformation	1 (2%)			
Hypothalamus, hemorrhage		2 (4%)		
Meninges, hemorrhage			1 (2%)	

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

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Congestion		2 (4%)	1 (2%)	
Edema	2 (4%)			
Foreign Body			4 (8%)	
Hemorrhage	1 (2%)			
Inflammation	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Alveolus, inflammation, chronic				1 (2%)
Nose	(50)	(50)	(50)	(49)
Congestion			1 (2%)	
Fungus	1 (2%)			1 (2%)
Inflammation, suppurative	4 (8%)	2 (4%)		13 (27%)
Special Senses System				
Eye	(1)	(4)	(1)	(1)
Anterior chamber, edema				1 (100%)
Cornea, edema				1 (100%)
Lens, cataract	1 (100%)	3 (75%)		
Retina, degeneration	1 (100%)			
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Inflammation, suppurative			1 (2%)	
Mineralization	2 (4%)	1 (2%)	1 (2%)	
Nephropathy	34 (69%)	44 (88%)	44 (88%)	49 (100%)
Cortex, cyst			1 (2%)	2 (4%)
Urinary bladder	(50)	(49)	(49)	(47)
Inflammation, suppurative				1 (2%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

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

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	20	20	20	19
Early deaths				
Accidental deaths	1		1	
Moribund	1		6	3
Natural deaths	5	3	1	11
Survivors				
Terminal sacrifice	43	47	42	37
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(4)	(6)	(9)
Hepatocellular adenoma		2 (50%)		3 (33%)
Hepatocellular adenoma, multiple			1 (17%)	
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
None				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(2)	(1)	(9)
Alveolar/bronchiolar adenoma		2 (100%)		3 (33%)
Special Senses System				
Harderian gland				(1)
Adenoma				1 (100%)
Urinary System				
None				
2-Year Study				
Alimentary System				
Gallbladder	(40)	(47)	(47)	(42)
Squamous cell carcinoma, metastatic, stomach			1 (2%)	
Intestine large, cecum	(47)	(47)	(49)	(42)
Intestine small, ileum	(48)	(47)	(48)	(42)
Intestine small, jejunum	(46)	(47)	(49)	(42)
Adenocarcinoma	2 (4%)	1 (2%)		
Adenoma		1 (2%)		
Liver	(50)	(50)	(50)	(51)
Hepatoblastoma			5 (10%)	1 (2%)
Hepatocellular carcinoma	10 (20%)	11 (22%)	5 (10%)	3 (6%)
Hepatocellular carcinoma, multiple	1 (2%)			
Hepatocellular adenoma	15 (30%)	9 (18%)	12 (24%)	13 (25%)
Hepatocellular adenoma, multiple	11 (22%)	20 (40%)	17 (34%)	14 (27%)
Histiocytic sarcoma				1 (2%)
Squamous cell carcinoma, metastatic, stomach			1 (2%)	
Mesentery	(8)	(3)	(3)	(3)
Squamous cell carcinoma, metastatic, stomach			1 (33%)	
Pancreas	(49)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, stomach			1 (2%)	
Stomach, forestomach	(48)	(49)	(49)	(47)
Papilloma squamous	2 (4%)	8 (16%)	2 (4%)	
Squamous cell carcinoma		1 (2%)	2 (4%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Endocrine System				
Adrenal gland, cortex	(49)	(49)	(49)	(51)
Adenoma			1 (2%)	
Adrenal gland, medulla	(49)	(49)	(48)	(50)
Pheochromocytoma benign	1 (2%)			1 (2%)
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma			3 (6%)	2 (4%)
Thyroid gland	(49)	(50)	(50)	(51)
C-cell, adenoma		1 (2%)		
C-cell, carcinoma		1 (2%)		
Follicular cell, adenoma				2 (4%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
General Body System				
None				
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Preputial gland	(16)	(18)	(13)	(9)
Prostate	(49)	(50)	(50)	(51)
Seminal vesicle	(49)	(50)	(50)	(51)
Squamous cell carcinoma, metastatic, stomach			1 (2%)	
Testes	(49)	(50)	(50)	(50)
Interstitial cell, adenoma	3 (6%)			
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Lymph node	(49)	(50)	(49)	(51)
Histiocytic sarcoma				1 (2%)
Lymph node, mandibular	(48)	(48)	(48)	(46)
Lymph node, mesenteric	(49)	(49)	(47)	(48)
Spleen	(49)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Thymus	(47)	(45)	(44)	(41)
Integumentary System				
Skin	(49)	(50)	(50)	(51)
Basal cell adenoma		1 (2%)		
Tail, neurofibroma		1 (2%)		
Musculoskeletal System				
Bone	(49)	(50)	(50)	(51)
Skeletal muscle			(1)	
Diaphragm, squamous cell carcinoma, metastatic, stomach			1 (100%)	
Nervous System				
Brain	(49)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Alveolar/bronchiolar adenoma	12 (24%)	8 (16%)	12 (24%)	19 (37%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)		2 (4%)	5 (10%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Carcinoma, metastatic	1 (2%)			
Hepatocellular carcinoma, metastatic	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)	1 (2%)	
Hepatocellular carcinoma, metastatic				1 (2%)
Nose	(49)	(50)	(50)	(51)

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Special Senses System				
Harderian gland	(3)	(1)	(1)	
Adenoma	3 (100%)	1 (100%)	1 (100%)	
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Squamous cell carcinoma, metastatic, stomach			1 (2%)	
Renal tubule, adenoma	1 (2%)			
Urinary bladder	(49)	(50)	(50)	(48)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(51)
Histiocytic sarcoma				1 (2%)
Lymphoma malignant			2 (4%)	1 (2%)
Lymphoma malignant histiocytic				2 (4%)
Lymphoma malignant lymphocytic		3 (6%)	1 (2%)	
Lymphoma malignant mixed			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation		3	1	6
2-Year study	42	40	42	39
Total primary neoplasms				
15-Month interim evaluation		4	1	7
2-Year study	64	68	68	65
Total animals with benign neoplasms				
15-Month interim evaluation		3	1	6
2-Year study	38	35	36	38
Total benign neoplasms				
15-Month interim evaluation		4	1	7
2-Year study	50	50	50	56
Total animals with malignant neoplasms				
2-Year study	14	14	16	8
Total malignant neoplasms				
2-Year study	14	18	18	9
Total animals with metastatic neoplasms				
2-Year study	2	1	2	1
Total metastatic neoplasms				
2-Year study	2	1	8	1

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Of the animals designated for the 15-month interim evaluation, only 5-10 per dose group were examined microscopically.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

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

Number of Days on Study	456	541	653	670	680	716	726	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730
Carcass ID Number	0691	0591	0171	0681	0341	0031	0301	0011	0161	0181	0211	0231	0311	0321	0331	0361	0391	0401	0471	0481	0491	0621	0021	0041	0061
Alimentary System																									
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	M	A	+	A	+	+	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+
Intestine large	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	I	I	+	+	+	+
Intestine small	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X	X	X				X												X					X
Hepatocellular carcinoma, multiple													X												
Hepatocellular adenoma					X		X		X					X	X		X					X			
Hepatocellular adenoma, multiple						X				X								X	X		X				X
Mesentery											+	+								+	+				+
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X												
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	I	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Pituitary gland	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

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

Number of Days on Study	7 3 0	7 3 0	7 3 0	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	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 8 1	0 6 1 1	0 6 6 1	0 0 9 1	0 1 2 1	0 1 5 1	0 1 9 1	0 2 4 1	0 2 5 1	0 2 9 1	0 6 3 1	0 0 5 1	0 1 0 1	0 1 1 1	0 1 3 1	0 1 4 1	0 2 2 1	0 3 8 1	0 5 0 1	0 5 1 1	0 5 3 1	0 5 4 1	0 5 6 1	0 6 0 1	0 6 7 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma					X				X																	2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X	X					X							X											10
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X			X				X			X	X				X						X			X	15
Hepatocellular adenoma, multiple					X		X						X					X					X			11
Mesentery															+	+		+								8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																		X						X		2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	M	+	M	+	+	+	+	38
Pituitary gland	+	+	M	M	+	I	+	+	+	+	+	+	+	+	I	M	+	+	M	+	+	+	+	+	+	42
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

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

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

Number of Days on Study	7 3 0	7 3 0	7 3 0	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	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 8 1	0 6 1 1	0 6 6 1	0 0 9 1	0 1 2 1	0 1 5 1	0 1 9 1	0 2 4 1	0 2 5 1	0 2 9 1	0 6 3 1	0 0 5 1	0 1 0 1	0 1 1 1	0 1 3 1	0 1 4 1	0 2 2 1	0 3 8 1	0 5 0 1	0 5 1 1	0 5 3 1	0 5 4 1	0 5 6 1	0 6 0 1	0 6 7 1	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland								+			+				+	+		+			+	+	+	+	+	16
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma														X								X				3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X				X					X						X				X			X	12
Alveolar/bronchiolar adenoma, multiple																								X		2
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

Number of Days on Study	4	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	5	4	5	7	8	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3
	6	1	3	0	0	6	6	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	5	1	6	3	0	3	0	1	1	2	2	3	3	3	3	3	4	4	4	4	6	0	0	0
	9	9	7	8	4	3	0	1	6	8	1	3	1	2	3	6	9	0	7	8	9	2	2	4	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Special Senses System																									
Eye					+			+																	
Harderian gland					+			+																	
Adenoma					X			X																	
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma													X												
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 0	7 3 0	7 3 0	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	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 8 1	0 6 1 1	0 6 6 1	0 0 9 1	0 1 2 1	0 1 5 1	0 1 9 1	0 2 4 1	0 2 5 1	0 2 9 1	0 6 3 1	0 0 5 1	0 1 0 1	0 1 1 1	0 1 3 1	0 1 4 1	0 2 2 1	0 3 8 1	0 5 0 1	0 5 1 1	0 5 3 1	0 5 4 1	0 5 6 1	0 6 0 1	0 6 7 1	**Total Tissues/ Tumors**
Special Senses System																										
Eye																										2
Harderian gland						+																				3
Adenoma						X																				3
Lacrimal gland						M																				
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 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	
Carcass ID Number	0 8 9 1	1 1 8 1	1 2 1 1	1 2 7 1	1 2 8 1	1 3 5 1	0 7 9 1	0 8 5 1	1 0 2 1	1 1 0 1	1 1 4 1	1 5 5 1	1 6 6 1	1 2 0 1	1 2 3 1	1 3 0 1	1 3 1 1	0 7 7 1	0 8 6 1	0 9 4 1	1 0 4 1	1 1 2 1	1 3 7 1	1 3 8 1	1 3 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma	X																									1
Adenoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X		X													X	X		X				X			11
Hepatocellular adenoma							X			X				X			X		X							9
Hepatocellular adenoma, multiple	X	X		X		X					X				X			X			X		X		X	20
Mesentery																+			+							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous					X				X							X						X				8
Squamous cell carcinoma																								X		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	41
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
C-cell, carcinoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	5	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3
	2	7	1	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0
	8	9	7	7	7	8	8	8	9	9	9	9	0	0	0	0	0	1	2	2	2	2	7	7	8
	4	8	2	1	3	0	3	8	1	2	7	9	0	1	3	8	9	3	2	5	6	9	5	8	7
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+				+			+			+		+								+	+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	I	+	+	+	+	+	+	+	+	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Tail, neurofibroma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X					X		X						
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 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	
Carcass ID Number	0 8 9 1	1 1 8 1	1 2 1 1	1 2 7 1	1 2 8 1	1 3 5 1	0 7 9 1	0 8 5 1	1 0 2 1	1 1 0 1	1 1 4 1	1 1 5 1	1 1 6 1	1 2 0 1	1 2 3 1	1 2 3 1	1 3 0 1	1 3 1 1	0 7 7 1	0 8 6 1	0 9 4 1	1 0 4 1	1 1 2 1	1 3 7 1	1 3 8 1	1 3 9 1	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland		+				+				+	+		+						+	+	+	+			+	+	18
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma						X																					1
Tail, neurofibroma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X	X				X									X							X	8
Alveolar/bronchiolar carcinoma	X																										1
Hepatocellular carcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

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

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

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

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

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	0	0	0	0	0	0	0	0	0	0	0	3	3	3	3	3	3	3	3	3	4	4	4	4	
Carcass ID Number	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	2	2	**Total**
	0	4	5	6	7	7	7	8	8	8	8	9	4	5	6	6	6	7	7	8	0	9	9	0	0	**Tissues/**
	8	8	0	0	3	4	7	1	3	7	8	1	3	5	3	5	8	0	8	4	6	5	8	4	7	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, stomach																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma									X		X															5
Hepatocellular carcinoma				X					X						X										X	5
Hepatocellular adenoma				X								X		X					X			X	X			12
Hepatocellular adenoma, multiple	X	X					X	X	X	X	X				X		X	X			X			X		17
Squamous cell carcinoma, metastatic, stomach																										1
Mesentery																										3
Squamous cell carcinoma, metastatic, stomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																		X								2
Squamous cell carcinoma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																					X		3
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Pituitary gland	+	+	+	+	M	+	M	+	M	+	+	+	+	I	+	M	+	M	+	+	+	+	+	+	+	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	0	0	4	5	5	5	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	6	1	2	6	6	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	4	9	5	7	7	6	3	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	1	1	2	1	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	
	4	9	1	9	8	0	7	0	4	4	4	5	5	5	5	5	6	7	8	8	8	9	9	0	0		
	1	7	0	2	5	0	6	9	2	5	7	1	2	3	8	9	7	5	0	6	9	4	6	1	3		
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Preputial gland							+	+					+	+						+				+			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Squamous cell carcinoma, metastatic, stomach						X																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node, mandibular	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node, mesenteric	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Thymus	I	+	+	+	+	+	I	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Skeletal muscle						+																					
Diaphragm, squamous cell carcinoma, metastatic, stomach						X																					

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

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	0	0	0	0	0	0	0	0	0	0	0	3	3	3	3	3	3	3	3	3	4	4	4	4	
Carcass ID Number	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	2	2	Total
	0	4	5	6	7	7	7	8	8	8	8	9	4	5	6	6	6	7	7	8	0	9	9	0	0	Tissues/
	8	8	0	0	3	4	7	1	3	7	8	1	3	5	3	5	8	0	8	4	6	5	8	4	7	Tumors
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland		+					+	+		+				+								+			+	13
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	44
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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, squamous cell carcinoma, metastatic, stomach																										1

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

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

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

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	733	733	733	733	733	733	733	733	733	734	734	734	734	
Carcass ID Number	2081	1481	1501	1601	1731	1741	1771	1811	1831	1871	1881	1911	1431	1531	1631	1651	1681	1701	1781	1841	2061	1951	1981	2041	2071	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X									X			X			X		X								12
Alveolar/bronchiolar adenoma, multiple							X													X						2
Alveolar/bronchiolar carcinoma						X												X								2
Hepatocellular carcinoma, metastatic, liver															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										2
Lymphoma malignant lymphocytic																			X							1
Lymphoma malignant mixed																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg

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

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	3	3	3	3	3	3	4	4	4	4	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	6	6	7	7	7	7	7	1	1	3	3	4	4	5	5	5	2	2	2	3	4	6	2	3	4	8	**Total**
	6	8	2	5	6	7	8	5	6	2	4	1	5	7	8	9	0	5	6	1	0	9	1	0	3	0	**Tissues/**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**Tumors**
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	39
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatoblastoma																											1
Hepatocellular carcinoma																							X				3
Hepatocellular adenoma						X		X					X		X				X				X	X	X		13
Hepatocellular adenoma, multiple		X		X					X	X	X	X									X						14
Histiocytic sarcoma																										X	1
Mesentery		+																									3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X																			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X		X												2
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	I	+	+	+	M	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	M	I	+	+	+	I	+	+	M	M	+	+	+	M	+	+	+	39
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma																										X	2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	1 7 7	3 2 3	4 1 2	4 7 6	4 9 8	5 4 1	5 5 8	6 0 8	6 5 9	6 6 1	6 7 4	6 8 7	6 9 2	7 1 2	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 4 4 1	2 5 1 1	2 6 3 1	2 5 4 1	2 2 7 1	2 7 4 1	2 5 0 1	2 5 3 1	2 1 4 1	2 5 2 1	2 1 1 1	2 6 0 1	2 7 3 1	2 2 4 1	2 1 7 1	2 1 8 1	2 2 2 1	2 2 3 1	2 2 8 1	2 3 9 1	3 3 3 1	3 3 5 1	3 6 8 1	3 6 2 1	3 6 5 1
General Body System																									
Tissue NOS					+																				
Genital System																									
Epididymis	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+																+	+						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mandibular	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	M	+	M	+	I	M	+	+	+	A	+	I	+	+	I	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																									
Hepatocellular carcinoma, metastatic, metastatic							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 3 4	
Carcass ID Number	2 6 6 1	2 6 8 1	2 7 2 1	2 7 5 1	2 7 6 1	2 7 7 1	2 7 8 1	2 1 5 1	2 1 6 1	2 3 2 1	2 3 4 1	2 4 1 1	2 4 5 1	2 5 7 1	2 5 8 1	2 5 9 1	2 2 0 1	2 2 5 1	2 2 6 1	2 3 1 1	2 4 0 1	2 6 9 1	2 2 1 1	2 3 0 1	2 4 3 1	2 8 0 1	Total Tissues/ Tumors
General Body System																											
Tissue NOS																											1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+							+		+			+									+		+			9
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										X	1
Lymph node, mandibular	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										X	1
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma					X						X		X			X			X	X			X		X	X	19
Alveolar/bronchiolar adenoma, multiple		X												X				X									5
Alveolar/bronchiolar carcinoma																					X						1
Hepatocellular carcinoma, metastatic, metastatic																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	1	3	4	4	4	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	2	1	7	9	4	5	0	5	6	7	8	9	1	2	2	2	2	2	2	2	2	2	2	2	2
	7	3	2	6	8	1	8	8	9	1	4	7	2	2	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	4	5	6	5	2	7	5	5	1	5	1	6	7	2	1	1	2	2	2	2	3	3	3	6	6	
	4	1	3	4	7	4	0	3	4	2	1	0	3	4	7	8	2	3	8	9	3	5	8	2	5	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urethra								+																		
Urinary bladder	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																										
Lymphoma malignant																	X									
Lymphoma malignant histiocytic														X												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	733	733	733	733	733	733	734	734	734	734	
Carcass ID Number	2661	2681	2721	2751	2761	2771	2781	2151	2161	2321	2341	2411	2451	2571	2581	2591	2201	2251	2261	2311	2401	2691	2211	2301	2431	2801	**Total Tissues/ Tumors**
Special Senses System																											
None																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urethra																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										X	1
Lymphoma malignant																											1
Lymphoma malignant histiocytic		X																									2

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Harderian Gland: Adenoma				
Overall rates[a]	3/50 (6%)	1/50 (2%)	1/50 (2%)	0/51 (0%)
Adjusted rates[b]	6.7%	2.1%	2.3%	0.0%
Terminal rates[c]	2/43 (5%)	1/47 (2%)	0/42 (0%)	0/37 (0%)
First incidence (days)	680	729 (T)	723	–[e]
Life table tests[d]	P=0.091N	P=0.280N	P=0.320N	P=0.150N
Logistic regression tests[d]	P=0.071N	P=0.305N	P=0.305N	P=0.117N
Cochran-Armitage test[d]	P=0.071N			
Fisher exact test[d]		P=0.309N	P=0.309N	P=0.118N
Liver: Hepatocellular Adenoma				
Overall rates	26/50 (52%)	29/50 (58%)	29/50 (58%)	27/51 (53%)
Adjusted rates	56.5%	59.2%	67.4%	64.0%
Terminal rates	23/43 (53%)	27/47 (57%)	28/42 (67%)	22/37 (59%)
First incidence (days)	680	607	567	476
Life table tests	P=0.155	P=0.526	P=0.293	P=0.231
Logistic regression tests	P=0.519N	P=0.344	P=0.344	P=0.542
Cochran-Armitage test	P=0.519N			
Fisher exact test		P=0.344	P=0.344	P=0.542
Liver: Hepatocellular Carcinoma				
Overall rates	11/50 (22%)	11/50 (22%)	5/50 (10%)	3/51 (6%)
Adjusted rates	23.6%	22.0%	11.6%	7.5%
Terminal rates	8/43 (19%)	8/47 (17%)	4/42 (10%)	2/37 (5%)
First incidence (days)	541	532	636	558
Life table tests	P=0.018N	P=0.520N	P=0.109N	P=0.045N
Logistic regression tests	P=0.003N	P=0.505	P=0.099N	P=0.011N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.595N	P=0.086N	P=0.019N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	35/50 (70%)	34/50 (68%)	31/50 (62%)	29/51 (57%)
Adjusted rates	71.4%	68.0%	70.4%	67.2%
Terminal rates	29/43 (67%)	31/47 (66%)	29/42 (69%)	23/37 (62%)
First incidence (days)	541	532	567	476
Life table tests	P=0.483N	P=0.302N	P=0.346N	P=0.470N
Logistic regression tests	P=0.080N	P=0.500N	P=0.263N	P=0.122N
Cochran-Armitage test	P=0.080N			
Fisher exact test		P=0.500N	P=0.263N	P=0.122N
Liver: Hepatoblastoma				
Overall rates	0/50 (0%)	0/50 (0%)	5/50 (10%)	1/51 (2%)
Adjusted rates	0.0%	0.0%	11.3%	2.7%
Terminal rates	0/43 (0%)	0/47 (0%)	4/42 (10%)	1/37 (3%)
First incidence (days)	–	–	1	729 (T)
Life table tests	P=0.196	–[f]	P=0.033	P=0.470
Logistic regression tests	P=0.299	–	P=0.060	P=0.470
Cochran-Armitage test	P=0.248			
Fisher exact test		–	P=0.028	P=0.505

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rates	11/50 (22%)	11/50 (22%)	9/50 (18%)	3/51 (6%)
Adjusted rates	23.6%	22.0%	20.2%	7.5%
Terminal rates	8/43 (19%)	8/47 (17%)	7/42 (17%)	2/37 (5%)
First incidence (days)	541	532	1	558
Life table tests	P=0.034N	P=0.520N	P=0.438N	P=0.045N
Logistic regression tests	P=0.004N	P=0.505	P=0.347N	P=0.011N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.595N	P=0.402N	P=0.019N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	14/50 (28%)	8/50 (16%)	14/50 (28%)	24/51 (47%)
Adjusted rates	29.7%	17.0%	33.3%	58.3%
Terminal rates	10/43 (23%)	8/47 (17%)	14/42 (33%)	20/37 (54%)
First incidence (days)	653	729 (T)	729 (T)	558
Life table tests	P<0.001	P=0.087N	P=0.549	P=0.012
Logistic regression tests	P=0.004	P=0.114N	P=0.588N	P=0.038
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.114N	P=0.588N	P=0.038
Lung Alveolar/bronchiolar Carcinoma				
Overall rates	1/50 (2%)	1/50 (2%)	2/50 (4%)	1/51 (2%)
Adjusted rates	2.2%	2.1%	4.8%	2.7%
Terminal rates	0/43 (0%)	1/47 (2%)	2/42 (5%)	1/37 (3%)
First incidence (days)	716	729(T)	729(T)	729(T)
Life table tests	P=0.530	P=0.746N	P=0.489	P=0.722
Logistic regression tests	P=0.579	P=0.619	P=0.332	P=0.758N
Cochran-Armitage test	P=0.597			
Fisher exact test		P=0.753N	P=0.500	P=0.748N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	14/50 (28%)	9/50 (18%)	15/50 (30%)	25/51 (49%)
Adjusted rates	29.7%	19.1%	35.7%	60.8%
Terminal rates	10/43 (23%)	9/47 (19%)	15/42 (36%)	21/37 (57%)
First incidence (days)	653	729 (T)	729 (T)	558
Life table tests	P<0.001	P=0.131N	P=0.463	P=0.007
Logistic regression tests	P=0.003	P=0.171N	P=0.500N	P=0.025
Cochran-Armitage test	P=0.003			
Fisher exact test		P=0.171N	P=0.500	P=0.024
Pancreatic Islets: Adenoma				
Overall rates	0/49 (0%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rates	0.0%	0.0%	7.1%	5.4%
Terminal rates	0/43 (0%)	0/47 (0%)	3/42 (7%)	2/37 (5%)
First incidence (days)	–	–	729 (T)	729 (T)
Life table tests	P=0.067	–	P=0.117	P=0.206
Logistic regression tests	P=0.067	–	P=0.117	P=0.206
Cochran-Armitage test	P=0.099			
Fisher exact test		–	P=0.125	P=0.253

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	2/50 (4%)	8/50 (16%)	2/50 (4%)	0/51 (0%)
Adjusted rates	4.7%	17.0%	4.8%	0.0%
Terminal rates	2/43 (5%)	8/47 (17%)	2/42 (5%)	0/37 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	–
Life table tests	P=0.078N	P=0.064	P=0.686	P=0.272N
Logistic regression tests	P=0.051N	P=0.048	P=0.695	P=0.233N
Cochran-Armitage test	P=0.051N			
Fisher exact test		P=0.046	P=0.691N	P=0.243N
Stomach (Forestomach): Squamous Cell Carcinoma				
Overall rates	0/50 (0%)	1/50 (2%)	2/50 (4%)	0/51 (0%)
Adjusted rates	0.0%	2.1%	4.1%	0.0%
Terminal rates	0/43 (0%)	1/47 (2%)	0/42 (0%)	0/37 (0%)
First incidence (days)	–	729(T)	1	–
Life table tests	P=0.638N	P=0.518	P=0.235	–
Logistic regression tests	P=0.289N	P=0.518	–	–
Cochran-Armitage test	P=0.611N			
Fisher exact test		P=0.500	P=0.247	–
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rates	2/50 (4%)	9/50 (18%)	4/50 (8%)	0/51 (0%)
Adjusted rates	4.7%	19.1%	8.7%	0.0%
Terminal rates	2/43 (5%)	9/47 (19%)	2/42 (5%)	0/37 (0%)
First incidence (days)	729 (T)	729 (T)	1	–
Life table tests	P=0.100N	P=0.039	P=0.329	P=0.272N
Logistic regression tests	P=0.042N	P=0.039	P=0.686	P=0.272N
Cochran-Armitage test	P=0.064N			
Fisher exact test		P=0.026	P=0.339	P=0.243N
Testes: Adenoma				
Overall rates	3/49 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rates	7.0%	0.0%	0.0%	0.0%
Terminal rates	3/43 (7%)	0/47 (0%)	0/42 (0%)	0/37 (0%)
First incidence (days)	729 (T)	–	–	–
Life table tests	P=0.054N	P=0.106N	P=0.125N	P=0.149N
Logistic regression tests	P=0.046N	P=0.117N	P=0.117N	P=0.117N
Cochran-Armitage test	P=0.046N			
Fisher exact test		P=0.117N	P=0.117N	P=0.117N
All Organs: Malignant Lymphoma and Histiocytic Sarcoma				
Overall rates	0/50 (0%)	3/50 (6%)	4/50 (8%)	4/51 (8%)
Adjusted rates	0.0%	6.4%	9.2%	10.5%
Terminal rates	0/43 (0%)	3/47 (6%)	3/42 (7%)	3/37 (8%)
First incidence (days)	–	729 (T)	567	712
Life table tests	P=0.047	P=0.138	P=0.062	P=0.047
Logistic regression tests	P=0.083	P=0.121	P=0.063	P=0.066
Cochran-Armitage test	P=0.083			
Fisher exact test		P=0.121	P=0.059	P=0.061

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or NOS)				
Overall rates	0/50 (0%)	3/50 (6%)	4/50 (8%)	3/51 (6%)
Adjusted rates	0.0%	6.4%	9.2%	7.9%
Terminal rates	0/43 (0%)	3/47 (6%)	3/42 (7%)	2/37 (5%)
First incidence (days)	–	729 (T)	567	712
Life table tests	P=0.111	P=0.138	P=0.062	P=0.097
Logistic regression tests	P=0.175	P=0.138	P=0.117	P=0.116
Cochran-Armitage test	P=0.169			
Fisher exact test		P=0.121	P=0.059	P=0.125
All Organs: Benign Neoplasms				
Overall rates	38/50 (76%)	38/50 (76%)	36/50 (72%)	39/51 (76%)
Adjusted rates	79.2%	77.6%	81.8%	86.6%
Terminal rates	33/43 (77%)	36/47 (77%)	34/42 (81%)	31/37 (84%)
First incidence (days)	653	607	567	476
Life table tests	P=0.056	P=0.324N	P=0.500N	P=0.137
Logistic regression tests	P=0.208	P=0.592N	P=0.418	P=0.285
Cochran-Armitage test	P=0.541			
Fisher exact test		P=0.592N	P=0.410N	P=0.570
All Organs: Malignant Neoplasms				
Overall rates	15/50 (30%)	14/50 (28%)	16/50 (32%)	8/51 (16%)
Adjusted rates	31.1%	28.0%	34.6%	20.2%
Terminal rates	10/43 (23%)	11/47 (23%)	12/42 (29%)	6/37 (16%)
First incidence (days)	541	532	1	558
Life table tests	P=0.174N	P=0.416N	P=0.458	P=0.164N
Logistic regression tests	P=0.061N	P=0.500N	P=0.500N	P=0.070N
Cochran-Armitage test	P=0.061N			
Fisher exact test		P=0.500N	P=0.500	P=0.069N
All Organs: Benign or Malignant Neoplasms				
Overall rates	42/50 (84%)	42/50 (84%)	42/50 (84%)	40/51 (78%)
Adjusted rates	85.7%	84.0%	89.3%	88.8%
Terminal rates	36/43 (84%)	39/47 (83%)	37/42 (88%)	32/37 (86%)
First incidence (days)	541	532	1	476
Life table tests	P=0.140	P=0.297N	P=0.486	P=0.278
Logistic regression tests	P=0.474N	P=0.572	P=0.517	P=0.589
Cochran-Armitage test	P=0.251N			
Fisher exact test		P=0.607N	P=0.607N	P=0.323N

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

TABLE C4a
Historical Incidence of Alveolar/Bronchiolar Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	141/900 (15.7%)	34/900 (3.8%)	166/900 (18.4%)
Standard deviation	5.7%	3.6%	5.9%
Range	4%–28%	0%–12%	6%–28%

[a] Data as of 17 December 1991.

TABLE C4b
Historical Incidence of Liver Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls			
	Hepatoblastoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Overall Historical Incidence				
Total	2/901 (0.2%)	249/901 (27.6%)	155/901 (17.2%)	370/901 (41.1%)
Standard deviation	0.7%	15.0%	5.8%	15.5%
Range	0%–2%	4%–58%	8%–32%	14%–72%

[a] Data as of 17 December 1991.

TABLE C4c
Historical Incidence of Forestomach Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Overall Historical Incidence			
Total	27/902 (3.0%)	4/902 (0.4%)	31/902 (3.4%)
Standard deviation	3.4%	0.9%	3.6%
Range	0%–14%	0%–2%	0%–14%

[a] Data as of 17 December 1991.

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	20	20	20	19
Early deaths				
Accidental deaths	1		1	
Moribund	1		6	3
Natural deaths	5	3	1	11
Survivors				
Terminal sacrifice	43	47	42	37
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine small, ileum	(10)		(1)	(9)
Lymphoid tissue, inflammation, suppurative	1 (10%)			
Intestine small, jejunum	(10)		(1)	(9)
Lymphoid tissue, hyperplasia, lymphoid			1 (100%)	
Liver	(10)	(4)	(6)	(9)
Clear cell focus				2 (22%)
Fatty change	1 (10%)			
Syncytial alteration		1 (25%)	4 (67%)	9 (100%)
Vacuolization cytoplasmic	9 (90%)	1 (25%)	3 (50%)	1 (11%)
Centrilobular, hypertrophy				8 (89%)
Salivary glands	(10)			(9)
Infiltration cellular, lymphocyte	3 (30%)			4 (44%)
Stomach, glandular	(10)		(1)	(9)
Infiltration cellular, lymphocyte			1 (100%)	
Mineralization				1 (11%)
Cardiovascular System				
None				
Endocrine System				
Adrenal gland	(10)			(8)
Spindle cell, hyperplasia	3 (30%)			1 (13%)
General Body System				
None				
Genital System				
Epididymis	(10)			(9)
Infiltration cellular, lymphocyte	1 (10%)			
Preputial gland		(3)		
Duct, dilatation		3 (100%)		
Prostate	(10)			(9)
Infiltration cellular, lymphocyte	2 (20%)			1 (11%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
15-Month Interim Evaluation (continued)				
Hematopoietic System				
None				
Integumentary System				
Skin	(10)	(1)	(1)	(9)
Alopecia	2 (20%)	1 (100%)	1 (100%)	
Hemorrhage				1 (11%)
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(2)	(1)	(9)
Bronchiole, dilatation, focal			1 (100%)	
Special Senses System				
Eye	(1)			(1)
Inflammation, diffuse, chronic				1 (100%)
Retrobulbar, infiltration cellular, lymphocyte, focal	1 (100%)			
Urinary System				
Kidney	(10)			(9)
Nephropathy				1 (11%)
Pelvis, infiltration cellular, lymphocyte	5 (50%)			2 (22%)
Urinary bladder	(10)			(9)
Infiltration cellular, lymphocyte	2 (20%)			4 (44%)
2-Year Study				
Alimentary System				
Esophagus	(49)	(49)	(49)	(51)
Periesophageal tissue, edema			1 (2%)	
Intestine large, cecum	(47)	(47)	(49)	(42)
Hyperplasia, lymphoid	3 (6%)		5 (10%)	
Inflammation, chronic				1 (2%)
Necrosis, coagulative				1 (2%)
Intestine large, colon	(46)	(50)	(49)	(43)
Inflammation, chronic			1 (2%)	
Intestine small, ileum	(48)	(47)	(48)	(42)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	1 (2%)			1 (2%)
Lymphoid tissue, inflammation, suppurative				1 (2%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(51)
Angiectasis				2 (4%)
Basophilic focus	1 (2%)	4 (8%)	2 (4%)	3 (6%)
Clear cell focus	4 (8%)	7 (14%)	8 (16%)	9 (18%)
Congestion	1 (2%)		1 (2%)	7 (14%)
Developmental malformation				1 (2%)
Eosinophilic focus	6 (12%)	15 (30%)	13 (26%)	15 (29%)
Fatty change				1 (2%)
Inflammation, suppurative			1 (2%)	
Mixed cell focus	4 (8%)	3 (6%)	4 (8%)	1 (2%)
Necrosis, coagulative	3 (6%)	1 (2%)		8 (16%)
Syncytial alteration		6 (12%)	35 (70%)	47 (92%)
Vacuolization cytoplasmic	4 (8%)		8 (16%)	5 (10%)
Centrilobular, hypertrophy	1 (2%)	2 (4%)	23 (46%)	44 (86%)
Mesentery	(8)	(3)	(3)	(3)
Inflammation, granulomatous	1 (13%)			
Fat, hemorrhage				1 (33%)
Fat, inflammation, chronic	2 (25%)			1 (33%)
Fat, inflammation, suppurative	1 (13%)			
Fat, necrosis, coagulative	4 (50%)	2 (67%)	1 (33%)	2 (67%)
Fat, necrosis, liquifactive	2 (25%)			
Pancreas	(49)	(50)	(50)	(50)
Atrophy		3 (6%)	1 (2%)	1 (2%)
Degeneration			1 (2%)	
Infiltration cellular, lymphocyte		1 (2%)	3 (6%)	4 (8%)
Inflammation, granulomatous	1 (2%)			
Necrosis, coagulative		1 (2%)		
Polyarteritis		1 (2%)		
Salivary glands	(49)	(50)	(50)	(51)
Infiltration cellular, lymphocyte	13 (27%)	19 (38%)	14 (28%)	17 (33%)
Stomach, forestomach	(48)	(49)	(49)	(47)
Hemorrhage	1 (2%)			
Hyperkeratosis	2 (4%)	2 (4%)		
Hyperplasia, squamous	1 (2%)	3 (6%)	3 (6%)	
Ulcer	1 (2%)		1 (2%)	
Stomach, glandular	(46)	(48)	(49)	(44)
Infiltration cellular, lymphocyte				1 (2%)
Ulcer	1 (2%)		1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Infiltration cellular, lymphocyte	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic				1 (2%)
Inflammation, chronic active		1 (2%)		
Mineralization				4 (8%)
Endocrine System				
Adrenal gland	(49)	(49)	(49)	(51)
Spindle cell, hyperplasia	9 (18%)	12 (24%)	6 (12%)	9 (18%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal gland, cortex	(49)	(49)	(49)	(51)
Basophilic focus				1 (2%)
Clear cell focus	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Cyst			1 (2%)	
Cytomegaly	1 (2%)			
Cytoplasmic alteration		1 (2%)	1 (2%)	
Hypertrophy	1 (2%)	1 (2%)		
Islets, pancreatic	(49)	(50)	(50)	(50)
Hyperplasia	1 (2%)	3 (6%)	1 (2%)	
Pituitary gland	(42)	(46)	(40)	(39)
Fibrosis		1 (2%)		
Pars distalis, cyst	1 (2%)	1 (2%)		
Thyroid gland	(49)	(50)	(50)	(51)
Infiltration cellular, lymphocyte		1 (2%)	1 (2%)	
Follicular cell, cyst	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Follicular cell, hyperplasia	2 (4%)	6 (12%)	3 (6%)	2 (4%)
Follicular cell, hyperplasia, papillary				1 (2%)
General Body System				
Tissue NOS	(1)			(1)
Mediastinum, inflammation, suppurative	1 (100%)			
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Granuloma		1 (2%)		
Infiltration cellular, lymphocyte		1 (2%)		1 (2%)
Inflammation, chronic				1 (2%)
Preputial gland	(16)	(18)	(13)	(9)
Hyperplasia	1 (6%)			
Inflammation, suppurative	1 (6%)	1 (6%)	1 (8%)	
Duct, dilatation	14 (88%)	16 (89%)	12 (92%)	7 (78%)
Prostate	(49)	(50)	(50)	(51)
Infiltration cellular, lymphocyte			1 (2%)	2 (4%)
Inflammation, suppurative				1 (2%)
Seminal vesicle	(49)	(50)	(50)	(51)
Dilatation	1 (2%)		1 (2%)	
Fibrosis	1 (2%)			
Inflammation, chronic	1 (2%)			
Testes	(49)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hyperplasia, neutrophil			1 (2%)	
Lymph node	(49)	(50)	(49)	(51)
Deep cervical, hyperplasia, plasma cell	1 (2%)			
Mediastinal, hyperplasia, lymphoid	1 (2%)			
Lymph node, mandibular	(48)	(48)	(48)	(46)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(49)	(49)	(47)	(48)
Congestion	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	5 (10%)		2 (4%)	2 (4%)
Inflammation, granulomatous	1 (2%)			
Inflammation, suppurative	2 (4%)			
Spleen	(49)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Angiectasis	1 (2%)			
Congestion	1 (2%)	1 (2%)		
Developmental malformation	1 (2%)			
Hematopoietic cell proliferation erythrocytic	4 (8%)	1 (2%)		
Hyperplasia, lymphoid	4 (8%)	1 (2%)	3 (6%)	2 (4%)
Lymphocyte, atrophy		1 (2%)		
Thymus	(47)	(45)	(44)	(41)
Inflammation, suppurative	1 (2%)			
Integumentary System				
Skin	(49)	(50)	(50)	(51)
Alopecia	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)			1 (2%)
Ulcer				1 (2%)
Musculoskeletal System				
Bone	(49)	(50)	(50)	(51)
Metacarpal, inflammation, chronic	1 (2%)			
Nervous System				
Brain	(49)	(50)	(50)	(50)
Meninges, fibrosis		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Congestion				2 (4%)
Inflammation, suppurative	1 (2%)		1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	1 (2%)	4 (8%)	5 (10%)
Alveolus, hemorrhage			2 (4%)	
Bronchiole, epithelium, hyperplasia		2 (4%)		1 (2%)
Bronchiole, epithelium, necrosis				2 (4%)
Pleura, inflammation, suppurative			1 (2%)	
Nose	(49)	(50)	(50)	(51)
Fungus				1 (2%)
Inflammation, suppurative				1 (2%)
Lumen, inflammation, suppurative				4 (8%)
Special Senses System				
None				

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Ectopic tissue	1 (2%)			
Fibrosis				1 (2%)
Glomerulosclerosis	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, lymphocyte	5 (10%)	4 (8%)	4 (8%)	5 (10%)
Nephropathy	8 (16%)	12 (24%)	8 (16%)	2 (4%)
Collecting tubule, necrosis, coagulative			1 (2%)	1 (2%)
Cortex, cyst	1 (2%)		4 (8%)	
Cortex, cyst multilocular	1 (2%)	1 (2%)	1 (2%)	
Glomerulus, inflammation, chronic				1 (2%)
Renal tubule, mineralization	1 (2%)			
Renal tubule, necrosis, coagulative	1 (2%)	2 (4%)	3 (6%)	
Renal tubule, pigmentation, hemosiderin		1 (2%)		
Urethra				(1)
Inflammation, chronic active				1 (100%)
Urinary bladder	(49)	(50)	(50)	(48)
Hemorrhage			1 (2%)	
Infiltration cellular, lymphocyte	2 (4%)	2 (4%)	4 (8%)	5 (10%)
Inflammation, chronic	1 (2%)			

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Of the animals designated for the 15-month interim evaluation, only 5-10 per dose group were examined microscopically.

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

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	18	20	19	19
Early deaths				
Accidental deaths	4		1	2
Moribund	8	6	5	8
Natural deaths	7	5	3	13
Survivors				
Terminal sacrifice	33	39	42	28
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(8)	(1)	(2)	(9)
Hepatocellular adenoma	1 (13%)			
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
None				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(8)	(1)	(1)	(9)
Alveolar/bronchiolar adenoma			1 (100%)	2 (22%)
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Gallbladder	(41)	(44)	(47)	(39)
Intestine large, cecum	(42)	(46)	(48)	(41)
Intestine small	(44)	(46)	(48)	(41)
Intestine small, ileum	(41)	(46)	(48)	(39)
Intestine small, jejunum	(41)	(46)	(48)	(41)
Sarcoma				1 (2%)
Liver	(50)	(49)	(51)	(50)
Alveolar/bronchiolar carcinoma, metastatic				1 (2%)
Hemangiosarcoma		1 (2%)		
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma		3 (6%)	3 (6%)	1 (2%)
Hepatocellular adenoma	8 (16%)	18 (37%)	20 (39%)	10 (20%)
Hepatocellular adenoma, multiple		8 (16%)	9 (18%)	2 (4%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Mesentery	(7)	(6)	(3)	(4)
Histiocytic sarcoma		1 (17%)		
Squamous cell carcinoma, metastatic, stomach			1 (33%)	
Pancreas	(48)	(48)	(48)	(45)
Salivary glands	(51)	(50)	(51)	(51)
Leiomyosarcoma, metastatic	1 (2%)			
Stomach, forestomach	(48)	(49)	(49)	(46)
Papilloma squamous	1 (2%)	5 (10%)	2 (4%)	2 (4%)
Squamous cell carcinoma		1 (2%)	1 (2%)	
Cardiovascular System				
Heart	(51)	(50)	(51)	(51)
Endocrine System				
Adrenal gland	(49)	(47)	(48)	(51)
Spindle cell, adenoma				1 (2%)
Adrenal gland, cortex	(49)	(47)	(47)	(51)
Alveolar/bronchiolar carcinoma, metastatic				1 (2%)
Spindle cell, adenoma		1 (2%)		
Adrenal gland, medulla	(49)	(47)	(48)	(50)
Pheochromocytoma benign	2 (4%)			

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Islets, pancreatic	(49)	(48)	(48)	(47)
Adenoma	1 (2%)	2 (4%)	1 (2%)	
Carcinoma		1 (2%)		
Pituitary gland	(45)	(45)	(45)	(48)
Neoplasm NOS			1 (2%)	
Pars distalis, adenoma	4 (9%)	3 (7%)	4 (9%)	
Thyroid gland	(47)	(49)	(50)	(47)
Bilateral, follicular cell, carcinoma	1 (2%)			
Follicular cell, adenoma			1 (2%)	1 (2%)
General Body System				
Tissue NOS		(2)	(1)	
Posterior, fibrosarcoma			1 (100%)	
Genital System				
Ovary	(51)	(49)	(50)	(51)
Cystadenoma	2 (4%)	3 (6%)	4 (8%)	2 (4%)
Histiocytic sarcoma		1 (2%)		
Uterus	(50)	(49)	(49)	(51)
Hemangioma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Leiomyosarcoma	1 (2%)			
Polyp		1 (2%)		
Sarcoma			1 (2%)	
Sarcoma stromal				2 (4%)
Hematopoietic System				
Bone marrow	(51)	(48)	(49)	(51)
Lymph node	(49)	(49)	(49)	(50)
Mediastinal, histiocytic sarcoma		1 (2%)		
Lymph node, mandibular	(47)	(47)	(49)	(48)
Lymph node, mesenteric	(45)	(45)	(48)	(47)
Squamous cell carcinoma, metastatic, stomach			1 (2%)	
Spleen	(50)	(48)	(48)	(48)
Thymus	(43)	(44)	(49)	(42)
Alveolar/bronchiolar carcinoma, metastatic				1 (2%)
Integumentary System				
Skin	(51)	(49)	(51)	(51)
Fibroma	1 (2%)			
Fibrosarcoma	1 (2%)	1 (2%)		
Hemangioma			1 (2%)	
Subcutaneous tissue, leiomyosarcoma	1 (2%)			
Musculoskeletal System				
Bone	(52)	(50)	(51)	(51)
Vertebra, osteosarcoma		1 (2%)		
Skeletal muscle	(2)		(1)	
Leiomyosarcoma, metastatic	1 (50%)			

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Nervous System				
Brain	(49)	(49)	(50)	(49)
Meningioma malignant		1 (2%)		
Respiratory System				
Lung	(51)	(49)	(49)	(51)
Alveolar/bronchiolar adenoma	2 (4%)	5 (10%)	7 (14%)	15 (29%)
Alveolar/bronchiolar adenoma, multiple				5 (10%)
Alveolar/bronchiolar carcinoma				7 (14%)
Nose	(50)	(50)	(51)	(50)
Special Senses System				
Harderian gland	(1)	(1)	(1)	(1)
Adenoma	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(47)	(49)	(49)
Urinary bladder	(45)	(47)	(48)	(47)
Systemic Lesions				
Multiple organs[c]	(52)	(50)	(51)	(51)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Lymphoma malignant	4 (8%)	2 (4%)	1 (2%)	
Lymphoma malignant histiocytic	1 (2%)			1 (2%)
Lymphoma malignant lymphocytic		6 (12%)	6 (12%)	4 (8%)
Lymphoma malignant mixed		3 (6%)	1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	1		1	2
2-Year study	25	41	36	34
Total primary neoplasms				
15-Month interim evaluation	1		1	2
2-Year study	33	69	65	56
Total animals with benign neoplasms				
15-Month interim evaluation	1		1	2
2-Year study	20	33	33	26
Total benign neoplasms				
15-Month interim evaluation	1		1	2
2-Year study	23	47	50	39
Total animals with malignant neoplasms				
2-Year study	8	19	13	14
Total malignant neoplasms				
2-Year study	10	22	14	17

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Neoplasm Summary (continued)				
Total animals with metastatic neoplasms				
2-Year study	1		1	1
Total metastatic neoplasms				
2-Year study	2		2	3
Total animals with uncertain neoplasms benign or malignant				
2-Year study			1	
Total uncertain neoplasms				
2-Year study			1	

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Of the animals designated for the 15-month interim evaluation, only 5-10 per dose group were examined microscopically.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

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

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 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	3 1 1 1	3 1 9 1	3 2 6 1	3 3 5 1	3 4 0 1	3 4 3 1	3 4 6 1	3 4 9 1	3 5 0 1	3 8 9 1	2 9 3 1	3 0 9 1	3 1 8 1	3 2 0 1	2 8 1 1	2 8 2 1	2 8 7 1	2 9 0 1	2 9 2 1	2 9 6 1	3 0 2 1	3 0 4 1	3 2 1 1	3 3 2 1	3 4 7 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	50
Gallbladder	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, jejunum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																X	X						X			8
Histiocytic sarcoma																										1
Mesentery		+																+	+		+					7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leiomyosarcoma, metastatic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																		X				X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	I	+	M	+	+	+	+	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Pars distalis, adenoma																				X						4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	47
Bilateral, follicular cell, carcinoma																										1

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

Number of Days on Study	0 0 0 0 0 1 3 4 5 5 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 0 0 0 0 1 5 6 7 5 5 8 8 2 7 8 8 9 0 1 2 2 2 2 2 2 3 2 2 4 4 2 9 7 4 0 7 9 9 3 3 3 3 4 8 4 9 9 9 9 9 9 2
Carcass ID Number	3 3 3 3 3 3 2 3 3 2 2 3 3 2 3 3 2 2 2 3 3 3 3 3 3 3 3 0 4 1 4 3 1 8 1 0 9 8 2 2 8 3 4 8 9 9 0 1 3 3 3 3 4 0 7 2 5 5 7 6 4 0 3 7 3 2 5 8 4 4 5 5 4 1 2 1 3 8 9 1 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
General Body System	
None	
Genital System	
Ovary	+ + + + + + + + + + + + + + A + + + + + + + + + + +
Cystadenoma	X
Uterus	+ + + + A + + + + + + + + + A + + + + + + + + + + +
Hemangioma	
Leiomyosarcoma	X
Vagina	+
Hematopoietic System	
Bone marrow	+ + + + + + + + + + + + + + A + + + + + + + + + + +
Lymph node	+ + + A + + + + + + + + + + M A + + + + + + + + + +
Lymph node, mandibular	M + + M + M + + + + + + + + M A + + + + + + + + + +
Lymph node, mesenteric	+ + + A + + M M M + + + + + M A + A + + + + + + + +
Spleen	+ + A + + + + + + + + + + + A + + + + + + + + + + +
Thymus	+ + + A + + + + + + + I + + A A M + + + + + M + + + +
Integumentary System	
Mammary gland	+ M M + + + + + + + M + + + A + + + + + M + + + + + +
Skin	+ + + + + + + + + + + + + + A + + + + + + + + + + +
Fibroma	X
Fibrosarcoma	X
Subcutaneous tissue, leiomyosarcoma	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Leiomyosarcoma, metastatic	X
Nervous System	
Brain	+ + + + + + + + A + + + + + A + + A + + + + + + + +
Respiratory System	
Lung	+ + + + + + + + + + + + + + A + + + + + + + + + + +
Alveolar/bronchiolar adenoma	X
Nose	A + + + + + + + + + + + + + + A + + + + + + + + + + +
Trachea	+ + + + + + + + A + + + + + A + + + + + + + + + + +

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 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	3 1 1	3 1 9	3 2 6	3 3 5	3 4 0	3 4 3	3 4 6	3 4 9	3 5 0	3 8 9	2 9 3	2 0 9	3 1 9	3 2 8	3 8 0	2 8 1	2 8 2	2 8 7	2 9 0	2 9 2	2 9 6	3 0 2	3 0 4	3 2 1	3 3 2	3 4 7	Total Tissues/ Tumors
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																											
None																											
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cystadenoma																										X	2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma			X																								1
Leiomyosarcoma																											1
Vagina																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	43
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibroma																											1
Fibrosarcoma																											1
Subcutaneous tissue, leiomyosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Skeletal muscle																				+							2
Leiomyosarcoma, metastatic																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma							X																				2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 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	3 1 1 1	3 1 9 1	3 2 6 1	3 3 5 1	3 4 0 1	3 4 3 1	3 4 6 1	3 4 9 1	3 5 0 1	2 8 9 1	2 9 3 1	3 0 9 1	3 1 8 1	3 2 0 1	2 8 1 1	2 8 2 1	2 8 7 1	2 9 0 1	2 9 2 1	2 9 6 1	3 0 2 1	3 0 4 1	3 2 1 1	3 3 2 1	3 4 7 1	Total Tissues/ Tumors
Special Senses System																										
Eye																	+								1
Harderian gland																	+								1
Adenoma																	X								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	A	+	A	A	+	+	+	+	A	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																										1
Lymphoma malignant																										4
Lymphoma malignant histiocytic							X																			1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	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 0 8 1	4 1 4 1	3 5 3 1	3 5 4 1	3 6 4 1	3 6 9 1	3 8 1 1	3 9 0 1	3 9 5 1	3 9 8 1	3 9 9 1	4 0 3 1	4 0 6 1	4 1 1 1	4 1 3 1	4 2 0 1	3 5 2 1	3 6 8 1	3 7 2 1	3 7 7 1	3 8 2 1	4 0 5 1	4 0 7 1	4 0 9 1	4 1 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma			X																							1
Hepatoblastoma							X																			1
Hepatocellular carcinoma																		X								3
Hepatocellular adenoma		X			X			X	X	X		X	X			X		X	X		X					18
Hepatocellular adenoma, multiple			X				X				X				X										X	8
Histiocytic sarcoma																										1
Mesentery					+								+						+			+				6
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous		X					X																X	X		5
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spindle cell, adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										2
Carcinoma																										1
Parathyroid gland	M	+	+	+	+	M	+	+	+	+	+	M	M	+	+	M	+	+	M	M	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Pars distalis, adenoma												X							X							3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	4 5 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	9 9 2 3 3 7 7 8 1 2 2 2 2 2 2 2 2 2 2 2 2 3 3 3 3
	5 3 2 5 5 0 3 3 5 2 9 9 9 9 9 9 9 9 9 9 9 0 2 2 2
Carcass ID Number	3 3 3 3 4 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4 3 3 3 3
	9 6 8 8 0 6 7 7 5 5 6 6 7 7 8 8 9 9 9 0 1 5 6 7 9
	1 6 0 9 0 7 4 9 1 7 3 5 0 1 3 4 2 6 7 1 2 5 0 8 4
	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
General Body System	
Tissue NOS	+ +
Genital System	
Ovary	+ + + + + + + A + + + + + + + + + + + + + + + + +
Cystadenoma	X
Histiocytic sarcoma	X
Uterus	+ + + + + + + A + + + + + + + + + + + + + + + + +
Histiocytic sarcoma	X
Polyp	
Hematopoietic System	
Bone marrow	A + + + + + + A + + + + + + + + + + + + + + + + +
Lymph node	+ + + + + + + M + + + + + + + + + + + + + + + + +
Mediastinal, histiocytic sarcoma	X
Lymph node, mandibular	+ + + + + + + M + + + + + + + + + + + + + + + M +
Lymph node, mesenteric	M + M + + A + M + + + + I + + + + + + + + + + + +
Spleen	+ + A + + + + A + + + + + + + + + + + + + + + + +
Thymus	+ + M + I A + A M + + + + + + + + + + + + + + + +
Integumentary System	
Mammary gland	+ + M + M +
Skin	+ + A +
Fibrosarcoma	X
Musculoskeletal System	
Bone	+ +
Vertebra, osteosarcoma	
Nervous System	
Brain	+ + + + + + + A + + + + + + + + + + + + + + + + +
Meningioma malignant	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 0 8 1	4 1 4 1	3 5 3 1	3 5 4 1	3 6 4 1	3 6 9 1	3 8 1 1	3 9 0 1	3 9 5 1	3 9 8 1	3 9 9 1	4 0 3 1	4 0 6 1	4 1 1 1	4 1 3 1	4 2 0 1	3 5 2 1	3 6 8 1	3 7 2 1	3 7 7 1	3 8 2 1	4 0 5 1	4 0 7 1	4 0 9 1	4 1 0 1	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										2
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma									X													X				3
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Polyp																X										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma			X																							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Meningioma malignant																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 50 mg/kg
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	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 0 8 1	4 1 4 1	3 5 3 1	3 5 4 1	3 6 4 1	3 6 9 1	3 8 1 1	3 9 0 1	3 9 5 1	3 9 8 1	3 9 9 1	4 0 3 1	4 0 6 1	4 1 1 1	4 1 3 1	4 2 0 1	4 5 2 1	3 6 8 1	3 7 2 1	3 7 7 1	3 8 2 1	4 0 5 1	4 0 7 1	4 0 9 1	4 1 0 1	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma									X									X								5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye						+																				1
Harderian gland						+																				1
Adenoma						X																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																									X	2
Lymphoma malignant lymphocytic				X															X	X		X				6
Lymphoma malignant mixed							X																			3

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 8 5 1	4 8 8 1	4 9 0 1	4 2 5 1	4 2 6 1	4 3 3 1	4 3 6 1	4 4 0 1	4 4 5 1	4 5 4 1	4 6 5 1	4 6 9 1	4 7 6 1	4 7 8 1	4 7 9 1	4 8 9 1	4 8 9 1	4 3 0 1	4 3 4 1	4 5 3 1	4 5 8 1	4 5 9 1	4 6 2 1	4 6 4 1	4 7 2 1	4 7 4 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma			X																								3
Hepatocellular adenoma	X	X		X	X			X			X					X	X	X		X	X			X			20
Hepatocellular adenoma, multiple						X				X		X													X		9
Mesentery			+							+																	3
Squamous cell carcinoma, metastatic, stomach																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																	X					X					2
Squamous cell carcinoma																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																				X							1
Parathyroid gland	+	+	+	M	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	I	+	+	M	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Neoplasm NOS																											1
Pars distalis, adenoma	X														X										X		4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																											1

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

Number of Days on Study	0	0	0	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	7	6	8	7	7	8	9	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	
	3	4	0	4	6	2	9	9	4	9	9	9	9	9	9	9	9	9	9	9	9	2	2	2	2	2	
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	5	4	8	6	5	4	2	6	5	2	3	3	4	4	5	6	6	7	8	8	8	2	3	4	5	7	
	0	9	4	3	5	6	9	1	1	3	5	7	1	2	6	6	7	7	1	6	7	7	9	7	2	1	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																											
Tissue NOS																											
Posterior, fibrosarcoma																											
Genital System																											
Ovary	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma											X																
Uterus	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																											
Hematopoietic System																											
Bone marrow	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach									X																		
Spleen	+	M	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																											
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																											
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																											
Nervous System																											
Brain	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																											
Lung	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X											X				X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	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 8 5 1	4 8 8 1	4 8 0 1	4 2 5 1	4 2 6 1	4 3 3 1	4 3 6 1	4 4 0 1	4 4 5 1	4 5 4 1	4 6 5 1	4 6 9 1	4 7 6 1	4 7 8 1	4 7 9 1	4 8 9 1	4 8 9 1	4 3 0 1	4 3 4 1	4 5 3 1	4 5 8 1	4 5 9 1	4 6 2 1	4 6 4 1	4 7 2 1	4 7 4 1	Total Tissues/ Tumors
General Body System																											
Tissue NOS																		+								1
Posterior, fibrosarcoma																		X								1
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma						X						X					X										4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																								X			1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic, stomach																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangioma								X																			1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle			+																								1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma										X									X						X	X	7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	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 8 5 1	4 8 8 1	4 9 0 1	4 2 5 1	4 2 6 1	4 3 3 1	4 3 6 1	4 4 0 1	4 4 5 1	4 5 4 1	4 6 5 1	4 6 9 1	4 7 6 1	4 7 8 1	4 7 9 1	4 8 9 1	4 3 0 1	4 3 4 1	4 5 3 1	4 5 8 1	4 5 9 1	4 6 2 1	4 6 4 1	4 7 2 1	4 7 4 1	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland																										1
Adenoma																										1
Zymbal's gland																+										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant								X																		1
Lymphoma malignant lymphocytic	X					X											X							X		6
Lymphoma malignant mixed																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 3 4	
Carcass ID Number	5 4 9 1	5 6 0 1	4 9 1 1	5 0 0 1	5 0 3 1	5 0 1 1	5 2 2 1	5 2 4 1	5 3 3 1	5 3 4 1	5 4 0 1	5 5 5 1	5 5 6 1	5 5 7 1	5 5 0 1	5 6 1 1	5 6 6 1	5 7 5 1	5 7 7 1	5 8 8 1	5 8 9 1	5 8 2 1	5 9 8 1	6 1 3 1	6 1 8 1	6 2 5 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, rectum	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic																										1
Hepatocellular carcinoma																										1
Hepatocellular adenoma		X		X				X		X					X		X	X						X	X	10
Hepatocellular adenoma, multiple						X																				2
Mesentery		+		+								+														4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	45
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Papilloma squamous		X																				X				2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spindle cell, adenoma						X																				1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar carcinoma, metastatic																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell, adenoma						X																				1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	0 4 8	1 3 9	2 2 5	2 5 3	2 5 7	2 6 0	2 8 8	3 5 8	4 2 6	4 9 6	5 0 8	6 1 1	6 1 5	6 1 5	6 3 7	6 5 5	6 7 8	6 8 4	6 8 4	7 0 0	7 0 0	7 1 6	7 1 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 2 7 1	5 5 0 1	5 0 9 1	4 9 4 1	5 3 1 1	5 4 1 1	5 3 6 1	5 1 7 1	5 3 0 1	5 4 4 1	5 0 1 1	5 5 1 1	5 0 8 1	5 4 8 1	5 3 2 1	5 2 8 1	5 1 2 1	4 9 5 1	5 1 5 1	4 9 5 1	5 5 8 1	5 2 2 1	5 4 6 1	5 0 7 1	5 2 1 1	5 4 3 1
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma															X									X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal													X													
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	M	+	A	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	I	+	+	+	M	+
Alveolar/bronchiolar carcinoma, metastatic														X												
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X	X				X		X	
Alveolar/bronchiolar adenoma, multiple																	X							X		
Alveolar/bronchiolar carcinoma														X		X										
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	
Carcass ID Number	5 4 9 1	5 6 0 1	4 9 1 1	5 0 1 1	5 0 3 1	5 0 3 1	5 2 2 1	5 2 2 1	5 2 4 1	5 3 3 1	5 3 4 1	5 4 0 1	5 5 5 1	5 5 6 1	5 5 7 1	5 0 6 1	5 1 6 1	5 3 5 1	5 3 7 1	5 3 8 1	5 3 9 1	5 4 2 1	5 5 8 1	5 1 3 1	5 1 8 1	5 2 5 1	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cystadenoma																											2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma stromal																							X				2
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	M	+	+	+	M	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	I	+	+	+	+	42
Alveolar/bronchiolar carcinoma, metastatic																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma						X			X			X	X	X				X	X	X		X		X	X		15
Alveolar/bronchiolar adenoma, multiple		X								X													X				5
Alveolar/bronchiolar carcinoma				X			X				X					X					X						7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Coumarin: 200 mg/kg
(continued)

Number of Days on Study	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	
Carcass ID Number	5 4 9 1	5 6 0 1	4 9 1 1	5 0 0 1	5 0 3 1	5 2 0 1	5 2 2 1	5 2 4 1	5 3 3 1	5 3 4 1	5 4 0 1	5 5 5 1	5 5 6 1	5 5 7 1	5 5 6 1	5 0 1 1	5 1 6 1	5 3 6 1	5 3 5 1	5 3 7 1	5 3 8 1	5 3 9 1	5 4 2 1	5 5 8 1	5 1 3 1	5 1 8 1	5 2 5 1	Total Tissues/ Tumors
Special Senses System																											
Harderian gland																											1
Adenoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant histiocytic																X											1
Lymphoma malignant lymphocytic						X					X						X								X		4
Lymphoma malignant mixed																	X										1

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Liver: Hepatocellular Adenoma				
Overall rates[a]	8/50 (16%)	26/49 (53%)	29/51 (57%)	12/50 (24%)
Adjusted rates[b]	23.4%	63.4%	62.9%	39.7%
Terminal rates[c]	7/33 (21%)	25/40 (63%)	25/42 (60%)	10/28 (36%)
First incidence (days)	694	722	564	684
Life table tests[d]	P=0.222	P=0.001	P<0.001	P=0.124
Logistic regression tests[d]	P=0.525	P<0.001	P<0.001	P=0.227
Cochran-Armitage test[d]	P=0.525			
Fisher exact test[d]		P<0.001	P<0.001	P=0.227
Liver: Hepatocellular Carcinoma				
Overall rates	0/50 (0%)	3/49 (6%)	3/51 (6%)	1/50 (2%)
Adjusted rates	0.0%	7.3%	6.7%	2.8%
Terminal rates	0/33 (0%)	2/40 (5%)	1/42 (2%)	0/28 (0%)
First incidence (days)	–[e]	715	672	655
Life table tests	P=0.465	P=0.162	P=0.162	P=0.484
Logistic regression tests	P=0.570N	P=0.132	P=0.101	P=0.594
Cochran-Armitage test	P=0.530			
Fisher exact test		P=0.117	P=0.125	P=0.500
Liver Hepatoblastoma				
Overall rates	0/50 (0%)	1/49 (2%)	0/51 (0%)	0/50 (0%)
Adjusted rates	0.0%	2.5%	0.0%	0.0%
Terminal rates	0/33 (0%)	1/40 (3%)	0/42 (0%)	0/28 (0%)
First incidence (days)	–	729(T)	–	–
Life table tests	P=0.601N	P=0.538	–[f]	–
Logistic regression tests	P=0.601N	P=0.538	–	–
Cochran-Armitage test	P=0.566N			
Fisher exact test		P=0.495	–	–
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rates	0/50 (0%)	4/49 (8%)	3/51 (6%)	1/50 (2%)
Adjusted rates	0.0%	9.7%	6.7%	2.8%
Terminal rates	0/33 (0%)	3/40 (8%)	1/42 (2%)	0/28 (0%)
First incidence (days)	–	715	672	655
Life table tests	P=0.533	P=0.094	P=0.162	P=0.484
Logistic regression tests	P=0.502N	P=0.076	P=0.101	P=0.594
Cochran-Armitage test	P=0.593N			
Fisher exact test		P=0.056	P=0.125	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	8/50 (16%)	27/49 (55%)	31/51 (61%)	13/50 (26%)
Adjusted rates	23.4%	64.3%	65.9%	41.4%
Terminal rates	7/33 (21%)	25/40 (63%)	26/42 (62%)	10/28 (36%)
First incidence (days)	694	715	564	655
Life table tests	P=0.162	P<0.001	P<0.001	P=0.084
Logistic regression tests	P=0.447	P<0.001	P<0.001	P=0.163
Cochran-Armitage test	P=0.447			
Fisher exact test		P<0.001	P<0.001	P=0.163

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	2/51 (4%)	5/49 (10%)	7/49 (14%)	20/51 (39%)
Adjusted rates	5.8%	11.8%	16.3%	64.2%
Terminal rates	1/33 (3%)	3/40 (8%)	6/42 (14%)	17/28 (61%)
First incidence (days)	708	673	694	684
Life table tests	P<0.001	P=0.301	P=0.151	P<0.001
Logistic regression tests	P<0.001	P=0.201	P=0.072	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.202	P=0.071	P<0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	0/51 (0%)	0/49 (0%)	0/49 (0%)	7/51 (14%)
Adjusted rates	0.0%	0.0%	0.0%	22.3%
Terminal rates	0/33 (0%)	0/40 (0%)	0/42 (0%)	5/28 (18%)
First incidence (days)	–	–	–	615
Life table tests	P<0.001	–	–	P=0.006
Logistic regression tests	P<0.001	–	–	P=0.007
Cochran-Armitage test	P<0.001			
Fisher exact test		–	–	P=0.006
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	2/51 (4%)	5/49 (10%)	7/49 (14%)	27/51 (53%)
Adjusted rates	5.8%	11.8%	16.3%	81.5%
Terminal rates	1/33 (3%)	3/40 (8%)	6/42 (14%)	22/28 (79%)
First incidence (days)	708	673	694	615
Life table tests	P<0.001	P=0.301	P=0.151	P<0.001
Logistic regression tests	P<0.001	P=0.201	P=0.072	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.202	P=0.071	P<0.001
Ovary: Cystadenoma				
Overall rates	2/51 (4%)	3/49 (6%)	4/50 (8%)	2/51 (4%)
Adjusted rates	6.1%	7.5%	9.5%	6.2%
Terminal rates	2/33 (6%)	3/40 (8%)	4/42 (10%)	1/28 (4%)
First incidence (days)	729 (T)	729 (T)	729 (T)	637
Life table tests	P=0.519	P=0.588	P=0.453	P=0.644
Logistic regression tests	P=0.507	P=0.588	P=0.453	P=0.628
Cochran-Armitage test	P=0.556N			
Fisher exact test		P=0.481	P=0.329	P=0.691N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	1/49 (2%)	3/48 (6%)	1/48 (2%)	0/47 (0%)
Adjusted rates	3.0%	7.0%	2.4%	0.0%
Terminal rates	1/33 (3%)	2/40 (5%)	1/42 (2%)	0/28 (0%)
First incidence (days)	729 (T)	635	729 (T)	–
Life table tests	P=0.225N	P=0.377	P=0.707N	P=0.533N
Logistic regression tests	P=0.208N	P=0.298	P=0.758	P=0.508N
Cochran-Armitage test	P=0.208N			
Fisher exact test		P=0.301	P=0.747	P=0.510N

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	4/45 (9%)	3/45 (7%)	4/45 (9%)	0/48 (0%)
Adjusted rates	11.0%	7.7%	10.8%	0.0%
Terminal rates	2/30 (7%)	3/39 (8%)	4/37 (11%)	0/26 (0%)
First incidence (days)	367	729 (T)	729 (T)	–
Life table tests	P=0.082N	P=0.382N	P=0.541N	P=0.081N
Logistic regression tests	P=0.056N	P=0.500	P=0.645N	P=0.055N
Cochran-Armitage test	P=0.056N			
Fisher exact test		P=0.500N	P=0.643N	P=0.051N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	1/52 (2%)	5/50 (10%)	2/51 (4%)	2/51 (4%)
Adjusted rates	2.4%	12.5%	4.8%	7.1%
Terminal rates	0/33 (0%)	5/40 (13%)	2/42 (5%)	2/28 (7%)
First incidence (days)	589	729 (T)	729 (T)	729 (T)
Life table tests	P=0.552	P=0.152	P=0.566	P=0.456
Logistic regression tests	P=0.548N	P=0.095	P=0.493	P=0.493
Cochran-Armitage test	P=0.548N			
Fisher exact test		P=0.094	P=0.493	P=0.493
Stomach (Forestomach): Squamous Cell Carcinoma				
Overall rates	0/52 (0%)	1/50 (2%)	1/51 (2%)	0/51 (0%)
Adjusted rats	0.0%	2.5%	2.3%	0.0%
Terminal rates	0/33 (0%)	1/40 (3%)	0/42 (0%)	0/28 (0%)
First incidence (days)	–	729(T)	694	–
Life table tests	P=0.636N	P=0.538	P=0.535	–
Logistic regression tests	P=0.573N	P=0.538	P=0.419	–
Cochran-Armitage test	P=0.596N			
Fisher exact test		P=0.490	P=0.495	–
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rates	1/52 (2%)	6/50 (12%)	3/51 (6%)	2/51 (4%)
Adjusted rates	2.4%	15.0%	7.0%	7.1%
Terminal rates	0/33 (0%)	6/40 (15%)	2/42 (5%)	2/28 (7%)
First incidence (days)	589	729 (T)	694	729 (T)
Life table tests	P=0.575	P=0.095	P=0.376	P=0.456
Logistic regression tests	P=0.578N	P=0.083	P=0.236	P=0.436
Cochran-Armitage test	P=0.505N			
Fisher exact test		P=0.050	P=0.301	P=0.493
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rates	6/52 (12%)	12/50 (24%)	8/51 (16%)	5/51 (10%)
Adjusted rates	15.6%	26.8%	18.5%	17.9%
Terminal rates	3/33 (9%)	8/40 (20%)	7/42 (17%)	5/28 (18%)
First incidence (days)	550	495	672	729 (T)
Life table tests	P=0.367N	P=0.200	P=0.550	P=0.598N
Logistic regression tests	P=0.251N	P=0.082	P=0.372	P=0.514N
Cochran-Armitage test	P=0.251N			
Fisher exact test		P=0.082	P=0.372	P=0.514N

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or NOS)				
Overall rates	5/52 (10%)	11/50 (22%)	8/51 (16%)	5/51 (10%)
Adjusted rates	13.3%	25.3%	18.5%	17.9%
Terminal rates	3/33 (9%)	8/40 (20%)	7/42 (17%)	5/28 (18%)
First incidence (days)	550	635	672	729 (T)
Life table tests	P=0.496N	P=0.176	P=0.427	P=0.536
Logistic regression tests	P=0.465N	P=0.111	P=0.288	P=0.516
Cochran-Armitage test	P=0.362N			
Fisher exact test		P=0.073	P=0.265	P=0.617
All Organs: Benign Neoplasms				
Overall rates	20/52 (38%)	33/50 (66%)	34/51 (67%)	26/51 (51%)
Adjusted rates	50.9%	76.7%	72.3%	78.6%
Terminal rates	14/33 (42%)	30/40 (75%)	29/42 (69%)	21/28 (75%)
First incidence (days)	367	673	564	637
Life table tests	P=0.044	P=0.086	P=0.096	P=0.051
Logistic regression tests	P=0.079	P=0.032	P=0.007	P=0.067
Cochran-Armitage test	P=0.259			
Fisher exact test		P=0.005	P=0.004	P=0.140
All Organs: Malignant Neoplasms				
Overall rates	8/52 (15%)	19/50 (38%)	13/51 (25%)	14/51 (27%)
Adjusted rates	19.5%	40.2%	28.9%	42.4%
Terminal rates	3/33 (9%)	12/40 (30%)	10/42 (24%)	10/28 (36%)
First incidence (days)	474	495	672	615
Life table tests	P=0.138	P=0.059	P=0.330	P=0.073
Logistic regression tests	P=0.269	P=0.009	P=0.152	P=0.105
Cochran-Armitage test	P=0.269			
Fisher exact test		P=0.009	P=0.152	P=0.105
All Organs: Benign or Malignant Neoplasms				
Overall rates	25/52 (48%)	41/50 (82%)	37/51 (73%)	34/51 (67%)
Adjusted rates	56.5%	87.2%	77.1%	91.8%
Terminal rates	14/33 (42%)	34/40 (85%)	31/42 (74%)	25/28 (89%)
First incidence (days)	367	495	564	615
Life table tests	P=0.019	P=0.062	P=0.226	P=0.020
Logistic regression tests	P=0.025	P=0.002	P=0.004	P=0.012
Cochran-Armitage test	P=0.136			
Fisher exact test		P<0.001	P=0.009	P=0.044

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

TABLE D4a
Historical Incidence of Alveolar/Bronchiolar Neoplasms in Female B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	40/899 (4.4%)	19/899 (2.1%)	58/899 (6.5%)
Standard deviation	2.4%	2.0%	3.7%
Range	0%–10%	0%–6%	0%–14%

[a] Data as of 17 December 1991.

TABLE D4b
Historical Incidence of Liver Neoplasms in Female B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Overall Historical Incidence			
Total	94/898 (10.5%)	41/898 (4.6%)	129/898 (14.4%)
Standard deviation	7.2%	3.6%	8.1%
Range	2%–26%	0%–14%	2%–34%

[a] Data as of 17 December 1991.

TABLE D4c
Historical Incidence of Forestomach Neoplasms in Female B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Overall Historical Incidence			
Total	27/901 (3.0%)	3/901 (0.3%)	30/901 (3.3%)
Standard deviation	2.9%	1.0%	3.3%
Range	0%–10%	0%–4%	0%–10%

[a] Data as of 17 December 1991.

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	18	20	19	19
Early deaths				
Accidental deaths	4		1	2
Moribund	8	6	5	8
Natural deaths	7	5	3	13
Survivors				
Terminal sacrifice	33	39	42	28
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(8)	(1)	(2)	(9)
Eosinophilic focus		1 (100%)	2 (100%)	
Infiltration cellular, lymphocyte	2 (25%)			2 (22%)
Necrosis, coagulative	1 (13%)			
Syncytial alteration				4 (44%)
Vacuolization cytoplasmic				3 (33%)
Centrilobular, hypertrophy				8 (89%)
Pancreas	(8)			(9)
Fibrosis	1 (13%)			
Infiltration cellular, lymphocyte				3 (33%)
Necrosis, coagulative	1 (13%)			
Salivary glands	(8)			(9)
Infiltration cellular, lymphocyte	3 (38%)			4 (44%)
Cardiovascular System				
None				
Endocrine System				
Adrenal gland	(8)			(9)
Spindle cell, hyperplasia	8 (100%)			9 (100%)
Pituitary gland	(8)			(9)
Pars distalis, cyst	1 (13%)			
General Body System				
None				
Genital System				
Ovary	(8)	(3)	(2)	(9)
Inflammation, suppurative	1 (13%)	1 (33%)		
Capsule, inflammation, chronic		1 (33%)		
Follicle, cyst		2 (67%)	2 (100%)	
Uterus	(8)	(6)	(2)	(9)
Hydrometra		1 (17%)		1 (11%)
Hyperplasia, cystic	6 (75%)	3 (50%)	2 (100%)	7 (78%)
Inflammation, suppurative	1 (13%)	1 (17%)		1 (11%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node	(8)			(9)
Pancreatic, inflammation, chronic active				1 (11%)
Lymph node, mesenteric	(8)			(9)
Amyloid deposition				1 (11%)
Hyperplasia, lymphoid				1 (11%)
Integumentary System				
Skin	(8)	(2)	(5)	(9)
Alopecia	2 (25%)	2 (100%)	3 (60%)	4 (44%)
Hyperkeratosis	1 (13%)			
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(8)	(1)	(1)	(9)
Alveolar epithelium, hyperplasia		1 (100%)		
Special Senses System				
None				
Urinary System				
Kidney	(8)			(9)
Pelvis, infiltration cellular, lymphocyte	4 (50%)			7 (78%)
Urinary bladder	(8)			(9)
Infiltration cellular, lymphocyte	4 (50%)			4 (44%)
2-Year Study				
Alimentary System				
Intestine large, cecum	(42)	(46)	(48)	(41)
Hyperplasia, lymphoid				1 (2%)
Intestine small, jejunum	(41)	(46)	(48)	(41)
Hyperplasia, lymphoid			1 (2%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(49)	(51)	(50)
Angiectasis	1 (2%)		1 (2%)	
Basophilic focus	2 (4%)	1 (2%)		4 (8%)
Clear cell focus			1 (2%)	2 (4%)
Congestion				3 (6%)
Cytoplasmic alteration	1 (2%)			
Developmental malformation	1 (2%)			
Eosinophilic focus	4 (8%)	20 (41%)	20 (39%)	9 (18%)
Fatty change		1 (2%)		1 (2%)
Hemorrhage	1 (2%)			
Infarct			1 (2%)	
Infiltration cellular, plasma cell	1 (2%)			
Infiltration cellular, lymphocyte	6 (12%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)	1 (2%)
Inflammation, necrotizing		1 (2%)		
Inflammation, suppurative		2 (4%)	2 (4%)	1 (2%)
Mineralization				3 (6%)
Mixed cell focus		1 (2%)	1 (2%)	
Necrosis, coagulative	2 (4%)	2 (4%)	2 (4%)	11 (22%)
Pigmentation	1 (2%)			
Syncytial alteration			2 (4%)	19 (38%)
Bile duct, cyst			1 (2%)	
Centrilobular, hypertrophy				17 (34%)
Centrilobular, necrosis	1 (2%)			
Hepatocyte, hyperplasia			1 (2%)	
Mesentery	(7)	(6)	(3)	(4)
Cyst	1 (14%)			
Fat, necrosis, coagulative	5 (71%)	3 (50%)	2 (67%)	4 (100%)
Pancreas	(48)	(48)	(48)	(45)
Atrophy	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Hyperplasia			1 (2%)	
Infiltration cellular, lymphocyte	10 (21%)	4 (8%)	9 (19%)	7 (16%)
Inflammation, suppurative				1 (2%)
Necrosis, coagulative			1 (2%)	
Pharynx		(1)		
Cyst		1 (100%)		
Salivary glands	(51)	(50)	(51)	(51)
Infiltration cellular, lymphocyte	19 (37%)	14 (28%)	16 (31%)	21 (41%)
Stomach, forestomach	(48)	(49)	(49)	(46)
Hyperkeratosis		4 (8%)	1 (2%)	
Hyperplasia, squamous		2 (4%)	5 (10%)	
Inflammation, suppurative		2 (4%)		
Stomach, glandular	(46)	(48)	(49)	(41)
Dilatation				1 (2%)
Infiltration cellular, lymphocyte	1 (2%)			1 (2%)
Ulcer		1 (2%)		

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Cardiovascular System				
Heart	(51)	(50)	(51)	(51)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active			1 (2%)	
Mineralization	1 (2%)	1 (2%)		2 (4%)
Necrosis, zenkers				1 (2%)
Nuclear alteration			1 (2%)	
Artery, inflammation, chronic active			1 (2%)	
Artery, mineralization				1 (2%)
Perivascular, inflammation, chronic		1 (2%)		
Endocrine System				
Adrenal gland	(49)	(47)	(48)	(51)
Corticomedullary junction, hemorrhage		1 (2%)	1 (2%)	
Corticomedullary junction, necrosis, coagulative		1 (2%)		
Spindle cell, hyperplasia	34 (69%)	13 (28%)	23 (48%)	15 (29%)
Adrenal gland, cortex	(49)	(47)	(47)	(51)
Clear cell focus			1 (2%)	
Cytoplasmic alteration			1 (2%)	
Hyperplasia			2 (4%)	1 (2%)
Necrosis, coagulative		1 (2%)		
Vacuolization cytoplasmic	1 (2%)			1 (2%)
Corticomedullary junction, necrosis, coagulative		1 (2%)		
Adrenal gland, medulla	(49)	(47)	(48)	(50)
Hyperplasia		1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(49)	(48)	(48)	(47)
Atrophy		1 (2%)		
Parathyroid gland	(35)	(38)	(40)	(41)
Ectopic thymus				1 (2%)
Hyperplasia	1 (3%)			
Pituitary gland	(45)	(45)	(45)	(48)
Pars distalis, cyst	1 (2%)			1 (2%)
Pars distalis, hyperplasia		1 (2%)	1 (2%)	2 (4%)
Thyroid gland	(47)	(49)	(50)	(47)
Inflammation, suppurative		1 (2%)	1 (2%)	
C-cell, hyperplasia		2 (4%)	1 (2%)	
Follicle, cyst		1 (2%)	1 (2%)	1 (2%)
Follicle, dilatation		1 (2%)	1 (2%)	
Follicular cell, hyperplasia	2 (4%)	4 (8%)	6 (12%)	4 (9%)
General Body System				
Tissue NOS		(2)	(1)	
Hemorrhage		1 (50%)		
Abdominal, necrosis, coagulative		1 (50%)		
Posterior, abscess			1 (100%)	

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Genital System				
Ovary	(51)	(49)	(50)	(51)
Hematocyst	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Pigmentation, ceroid			1 (2%)	
Bilateral, corpus luteum, cyst				1 (2%)
Follicle, cyst	13 (25%)	14 (29%)	13 (26%)	6 (12%)
Follicle, hematocyst				1 (2%)
Uterus	(50)	(49)	(49)	(51)
Hydrometra	10 (20%)	9 (18%)	6 (12%)	11 (22%)
Hyperplasia, cystic	25 (50%)	23 (47%)	33 (67%)	22 (43%)
Inflammation, suppurative	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Endometrium, hyperplasia, cystic				1 (2%)
Vagina	(1)			
Hyperkeratosis	1 (100%)			
Inflammation, suppurative	1 (100%)			
Hematopoietic System				
Bone marrow	(51)	(48)	(49)	(51)
Hyperplasia, neutrophil			1 (2%)	
Myelofibrosis			2 (4%)	
Lymph node	(49)	(49)	(49)	(50)
Mediastinal, hyperplasia, lymphoid	1 (2%)			
Lymph node, mandibular	(47)	(47)	(49)	(48)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, plasma cell		1 (2%)		
Lymph node, mesenteric	(45)	(45)	(48)	(47)
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid	1 (2%)	4 (9%)	7 (15%)	1 (2%)
Hyperplasia, macrophage	1 (2%)			
Hyperplasia, plasma cell		1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)		
Necrosis			1 (2%)	
Spleen	(50)	(48)	(48)	(48)
Angiectasis	1 (2%)			
Atrophy	1 (2%)			
Congestion	1 (2%)			
Developmental malformation		2 (4%)	1 (2%)	
Hematopoietic cell proliferation erythrocytic		2 (4%)	1 (2%)	
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid	4 (8%)	5 (10%)	6 (13%)	1 (2%)
Hyperplasia, plasma cell		1 (2%)		
Inflammation, suppurative	2 (4%)	1 (2%)		
Thymus	(43)	(44)	(49)	(42)
Atrophy	1 (2%)		1 (2%)	3 (7%)
Hyperplasia, lymphoid		2 (5%)		1 (2%)
Inflammation, suppurative		1 (2%)		
Necrosis, coagulative				2 (5%)

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Integumentary System				
Mammary gland	(47)	(48)	(50)	(50)
Inflammation, necrotizing				1 (2%)
Duct, dilatation		1 (2%)		
Duct, hyperplasia		1 (2%)		
Skin	(51)	(49)	(51)	(51)
Alopecia	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Foot, inflammation, suppurative	1 (2%)			
Subcutaneous tissue, inflammation, chronic active		1 (2%)	1 (2%)	
Musculoskeletal System				
Skeletal muscle	(2)		(1)	
Inflammation, chronic active			1 (100%)	
Nervous System				
Brain	(49)	(49)	(50)	(49)
Hypothalamus, compression	1 (2%)			
Meninges, infiltration cellular, lymphocyte				2 (4%)
Thalamus, compression	1 (2%)			
Respiratory System				
Lung	(51)	(49)	(49)	(51)
Congestion	2 (4%)			1 (2%)
Foreign body	3 (6%)			
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	3 (6%)	2 (4%)	2 (4%)	
Infiltration cellular, lymphocyte	1 (2%)			
Inflammation, suppurative	1 (2%)		1 (2%)	
Alveolar epithelium, hyperplasia		3 (6%)	4 (8%)	4 (8%)
Alveolus, hemorrhage	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Alveolus, infiltration cellular, lymphocyte			1 (2%)	
Alveolus, inflammation, chronic			1 (2%)	
Bronchiole, inflammation, suppurative				1 (2%)
Bronchiole, epithelium, hyperplasia		1 (2%)		4 (8%)
Bronchiole, epithelium, necrosis				3 (6%)
Mediastinum, foreign body	1 (2%)			
Peribronchial, inflammation, suppurative				1 (2%)
Peribronchiolar, hemorrhage	1 (2%)			
Pleura, inflammation, suppurative	1 (2%)		1 (2%)	1 (2%)
Subpleura, mineralization			1 (2%)	
Nose	(50)	(50)	(51)	(50)
Lumen, inflammation, suppurative			2 (4%)	5 (10%)
Special Senses System				
Eye	(1)	(1)	(1)	
Cataract	1 (100%)			

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

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(47)	(49)	(49)
Glomerulosclerosis	2 (4%)	1 (2%)		
Infiltration cellular, lymphocyte	8 (16%)	5 (11%)	8 (16%)	6 (12%)
Nephropathy				1 (2%)
Artery, necrosis, fibrinoid	1 (2%)			
Collecting tubule, mineralization				1 (2%)
Collecting tubule, necrosis, coagulative				1 (2%)
Collecting tubule, pigmentation, hemoglobin	1 (2%)			
Cortex, cyst multilocular				1 (2%)
Cortex, pigmentation, bile		1 (2%)		
Pelvis, infiltration cellular, lymphocyte				2 (4%)
Renal tubule, degeneration		1 (2%)	1 (2%)	
Urinary bladder	(45)	(47)	(48)	(47)
Infiltration cellular, lymphocyte	23 (51%)	14 (30%)	23 (48%)	16 (34%)
Inflammation, suppurative		1 (2%)		

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Of the animals designated for the 15-month interim evaluation, only 5-10 per dose group were examined microscopically.

APPENDIX E
SUMMARY OF LESIONS IN MALE RATS IN THE STOP-EXPOSURE GAVAGE STUDY OF COUMARIN

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin[a]

	Vehicle Control[b]	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Disposition Summary			
Animals initially in study	80	40	30
9-Month interim evaluation	20	20	
15-Month interim evaluation	10		10
Early deaths			
Accidental deaths	2	1	3
Moribund	14	6	13
Natural deaths	6	4	2
Survivors			
Died last week of study		1	
Terminal sacrifice	28	8	2
Animals examined microscopically	80	40	30
9-Month Interim Evaluation			
Alimentary System			
None			
Cardiovascular System			
None			
Endocrine System			
Thyroid gland	(17)	(18)	
Follicular cell, adenoma	1 (6%)		
General Body System			
None			
Genital System			
Testes	(17)	(18)	
Interstitial cell, adenoma		1 (6%)	
Hematopoietic System			
None			
Integumentary System			
None			
Musculoskeletal System			
None			

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
9-Month Interim Evaluation (continued)			
Nervous System			
None			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
None			
15-Month Interim Evaluation			
Alimentary System			
None			
Cardiovascular System			
None			
Endocrine System			
Pituitary gland	(7)		(10)
Pars distalis, adenoma			2 (20%)
General Body System			
None			
Genital System			
Testes	(7)		(10)
Interstitial cell, adenoma	7 (100%)		10 (100%)
Hematopoietic System			
None			
Integumentary System			
None			
Musculoskeletal System			
None			

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
15-Month Interim Evaluation (continued)			
Nervous System			
None			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
None			
2-Year Study			
Alimentary System			
Intestine large, cecum	(45)	(17)	(20)
Intestine large, colon	(45)	(18)	(20)
Intestine large, rectum	(45)	(18)	(20)
Intestine small, duodenum	(46)	(18)	(20)
Fibrosarcoma, metastatic	1 (2%)		
Intestine small, ileum	(45)	(17)	(20)
Fibrosarcoma, metastatic	1 (2%)		
Intestine small, jejunum	(45)	(17)	(20)
Fibrosarcoma, metastatic	1 (2%)		
Liver	(49)	(20)	(20)
Fibrosarcoma, metastatic	1 (2%)		
Hepatocellular carcinoma	2 (4%)		
Hepatocellular adenoma			1 (5%)
Mesentery	(19)	(7)	(4)
Fibrosarcoma, metastatic	1 (5%)		
Pancreas	(47)	(19)	(20)
Adenoma	1 (2%)	1 (5%)	
Fibrosarcoma, metastatic	1 (2%)		
Pharynx	(1)		
Squamous cell papilloma	1 (100%)		
Stomach, forestomach	(48)	(19)	(19)
Stomach, glandular	(47)	(18)	(20)
Fibrosarcoma, metastatic	1 (2%)		
Tongue		(1)	
Squamous cell papilloma		1 (100%)	
Cardiovascular System			
Heart	(49)	(20)	(20)
Fibrosarcoma		1 (5%)	

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
2-Year Study (continued)			
Endocrine System			
Adrenal gland, cortex	(49)	(20)	(20)
Adrenal gland, medulla	(49)	(20)	(20)
Pheochromocytoma benign	9 (18%)	4 (20%)	1 (5%)
Islets, pancreatic	(47)	(19)	(20)
Adenoma	4 (9%)	1 (5%)	
Parathyroid gland	(41)	(19)	(18)
Adenoma	1 (2%)	1 (5%)	
Pituitary gland	(48)	(20)	(20)
Pars distalis, adenoma	19 (40%)	4 (20%)	5 (25%)
Thyroid gland	(47)	(20)	(20)
C-cell, adenoma	1 (2%)		
C-cell, carcinoma	1 (2%)		
Follicular cell, carcinoma	1 (2%)		1 (5%)
General Body System			
Tissue NOS	(2)	(1)	
Adenocarcinoma	1 (50%)		
Fibrosarcoma	1 (50%)		
Genital System			
Epididymis	(45)	(20)	(20)
Preputial gland	(45)	(19)	(20)
Adenoma	2 (4%)	1 (5%)	
Carcinoma	1 (2%)	1 (5%)	
Seminal vesicle	(45)	(20)	(20)
Fibrosarcoma, metastatic	1 (2%)		
Testes	(45)	(20)	(20)
Interstitial cell, adenoma	38 (84%)	18 (90%)	15 (75%)
Hematopoietic System			
Bone marrow	(48)	(19)	(20)
Lymph node	(49)	(20)	(20)
Lymph node, mandibular	(48)	(20)	(20)
Lymph node, mesenteric	(43)	(20)	(20)
Spleen	(48)	(19)	(20)
Thymus	(47)	(20)	(19)
Sarcoma	1 (2%)		
Integumentary System			
Mammary gland	(45)	(20)	(16)
Fibroadenoma	3 (7%)	2 (10%)	
Skin	(49)	(20)	(20)
Basal cell adenoma	1 (2%)		
Squamous cell papilloma	1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)		

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
2-Year Study (continued)			
Musculoskeletal System			
Bone	(49)	(20)	(20)
Chordoma	1 (2%)		
Lumbar, vertebra, sarcoma			1 (5%)
Skeletal muscle	(1)		(1)
Fibrosarcoma, metastatic	1 (100%)		
Back, sarcoma			1 (100%)
Nervous System			
Brain	(47)	(19)	(20)
Squamous cell carcinoma, metastatic			1 (5%)
Spinal cord			(1)
Meninges, sarcoma			1 (100%)
Respiratory System			
Lung	(49)	(20)	(20)
Adenocarcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	1 (2%)		
Fibrosarcoma	1 (2%)		
Squamous cell carcinoma		1 (5%)	
Nose	(49)	(20)	(20)
Polyp			1 (5%)
Special Senses System			
Ear			(1)
Basal cell adenoma			1 (100%)
Zymbal's gland			(1)
Squamous cell carcinoma			1 (100%)
Urinary System			
Kidney	(49)	(20)	(20)
Fibrosarcoma, metastatic	1 (2%)		
Renal tubule, adenoma	1 (2%)	1 (5%)	2 (10%)
Renal tubule, oncocytoma benign			2 (10%)
Urinary bladder	(45)	(20)	(20)
Systemic Lesions			
Multiple organs[c]	(49)	(20)	(20)
Leukemia mononuclear	8 (16%)	5 (25%)	4 (20%)
Mesothelioma NOS	1 (2%)	1 (5%)	

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Neoplasm Summary			
Total animals with primary neoplasms[d]			
9-Month interim evaluation	1	1	
15-Month interim evaluation	7		10
2-Year study	46	18	17
Total primary neoplasms			
9-Month interim evaluation	1	1	
15-Month interim evaluation	7		12
2-Year study	105	43	37
Total animals with benign neoplasms			
9-Month interim evaluation	1	1	
15-Month interim evaluation	7		10
2-Year study	45	18	16
Total benign neoplasms			
9-Month interim evaluation	1	1	
15-Month interim evaluation	7		12
2-Year study	85	34	28
Total animals with malignant neoplasms			
2-Year study	16	8	7
Total malignant neoplasms			
2-Year study	19	8	9
Total animals with metastatic neoplasms			
2-Year study	2		1
Total metastatic neoplasms			
2-Year study	11		1
Total animals with uncertain neoplasms benign or malignant			
2-Year study	1	1	
Total uncertain neoplasms			
2-Year study	3	3	

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Includes the 50 vehicle control animals from the 2-year core study.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E2a
Individual Animal Tumor Pathology of Male Rats in the 9-Month Stop-Exposure Gavage Study of Coumarin: 100 mg/kg

Number of Days on Study	0 4 9	3 0 7	5 2 0	5 8 3	5 8 8	6 1 8	6 1 9	6 8 0	6 8 0	6 8 0	6 8 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	0 5 9 4	0 5 8 5	0 5 8 2	0 5 8 1	0 5 9 3	0 5 7 2	0 5 9 1	0 5 8 4	0 5 9 5	0 6 0 3	0 5 9 2	0 5 7 1	0 5 7 3	0 5 7 4	0 6 0 1	0 6 0 2	0 6 0 4	0 6 0 5	0 5 7 5	0 5 8 3	**Total Tissues/ Tumors**
Alimentary System																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	17
Intestine large, cecum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	17
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	18
Intestine large, rectum	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18
Intestine small	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	18
Intestine small, duodenum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18
Intestine small, ileum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	17
Intestine small, jejunum	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	17
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Mesentery				+			+				+	+	+						+	+	7
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Adenoma														X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Stomach, glandular	+	A	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	18
Tongue														+							1
Squamous cell papilloma														X							1
Cardiovascular System																					
Blood vessel									+												1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Fibrosarcoma																X					1
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pheochromocytoma benign										X					X	X			X		4
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Adenoma					X																1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	19
Adenoma									X												1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pars distalis, adenoma												X	X	X					X		4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
General Body System																					
Tissue NOS				+																	1

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

TABLE E2a
Individual Animal Tumor Pathology of Male Rats in the 9-Month Stop-Exposure Gavage Study of Coumarin: 100 mg/kg (continued)

Number of Days on Study	0 4 9	3 0 7	5 2 0	5 8 3	5 8 8	6 1 8	6 1 9	6 8 0	6 8 0	6 8 0	6 8 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	0 5 9 4	0 5 8 5	0 5 8 2	0 5 8 1	0 5 9 3	0 5 7 2	0 5 9 1	0 5 8 4	0 5 9 5	0 6 0 3	0 5 9 2	0 5 7 1	0 5 7 3	0 5 7 4	0 6 0 1	0 6 0 2	0 6 0 4	0 6 0 5	0 5 7 5	0 5 8 3	Total Tissues/ Tumors
Genital System																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Preputial gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Adenoma																X					1
Carcinoma																	X				1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Interstitial cell, adenoma			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	18
Hematopoietic System																					
Blood									+												1
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Integumentary System																					
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Fibroadenoma														X					X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Nervous System																					
Brain	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Respiratory System																					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Squamous cell carcinoma												X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Special Senses System																					
Eye						+															1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Renal tubule, adenoma																X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Leukemia mononuclear							X	X			X			X	X						5
Mesothelioma NOS				X																	1

TABLE E2b
Individual Animal Tumor Pathology of Male Rats in the 15-Month Stop-Exposure Gavage Study of Coumarin: 100 mg/kg

Number of Days on Study	0 4 0	0 4 0	0 7 0	2 5 3	4 9 6	4 9 9	5 6 5	5 6 6	5 8 5	5 8 8	5 9 3	6 0 9	6 1 8	6 1 8	6 2 3	6 3 9	6 3 9	7 2 6	7 2 9	7 2 9	
Carcass ID Number	0 6 5 4	0 6 8 4	0 6 8 1	0 6 8 5	0 6 7 3	0 6 7 4	0 6 5 1	0 6 5 5	0 6 8 2	0 6 8 3	0 6 7 2	0 6 6 5	0 6 7 1	0 6 7 5	0 6 6 3	0 6 5 3	0 6 6 2	0 6 6 1	0 6 5 2	0 6 6 4	**Total Tissues/ Tumors**
Alimentary System																					
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Hepatocellular adenoma														X							1
Mesentery													+	+				+		+	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	19
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Cardiovascular System																					
Blood vessel																		+			1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pheochromocytoma benign																			X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	18
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pars distalis, adenoma							X			X	X	X			X						5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Follicular cell, carcinoma										X											1
General Body System																					
None																					
Genital System																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Interstitial cell, adenoma					X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	15

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

TABLE E2b
Individual Animal Tumor Pathology of Male Rats in the 15-Month Stop-Exposure Gavage Study of Coumarin: 100 mg/kg (continued)

Number of Days on Study	0 4 0	0 4 0	0 7 0	2 5 3	4 9 6	4 9 9	5 6 5	5 6 6	5 8 5	5 8 8	5 9 3	6 0 9	6 1 8	6 1 8	6 2 3	6 3 9	6 3 9	7 2 6	7 2 9	7 2 9	
Carcass ID Number	0 6 5 4	0 6 4 4	0 6 8 1	0 6 8 5	0 6 7 3	0 6 7 4	0 6 5 1	0 6 5 5	0 6 8 2	0 6 8 3	0 6 7 2	0 6 6 5	0 6 7 1	0 6 7 5	0 6 6 3	0 6 5 3	0 6 6 2	0 6 6 1	0 6 5 2	0 6 6 4	Total Tissues/ Tumors
Hematopoietic System																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Integumentary System																					
Mammary gland	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	16
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lumbar, vertebra, sarcoma				X																	1
Skeletal muscle				+																	1
Back, sarcoma				X																	1
Nervous System																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Squamous cell carcinoma, metastatic								X													1
Spinal cord				+																	1
Meninges, sarcoma				X																	1
Respiratory System																					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Polyp																		X			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Special Senses System																					
Ear												+									1
Basal cell adenoma												X									1
Eye								+													1
Zymbal's gland								+													1
Squamous cell carcinoma								X													1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Renal tubule, adenoma					X															X	2
Renal tubule, oncocytoma benign							X				X										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Leukemia mononuclear						X			X							X			X		4

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Coumarin: 2-Year Vehicle Control versus Stop-Exposure 100 mg/kg Groups

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	9/49 (18%)	4/20 (20%)	1/20 (5%)
Adjusted rates[b]	27.2%	38.5%	50.0%
Terminal rates[c]	5/28 (18%)	3/9 (33%)	1/2 (50%)
First incidence (days)	573	680	729 (T)
Life table tests[d]	P=0.405	P=0.431	P=0.663
Logistic regression tests[d]	P=0.509N	P=0.499	P=0.465N
Cochran-Armitage test[d]	P=0.148N		
Fisher exact test[d]		P=0.560	P=0.145N
Kidney (Renal Tubule): Adenoma (Single Sections)			
Overall rates	1/49 (2%)	1/20 (5%)	2/20 (10%)
Adjusted rates	3.6%	11.1%	53.1%
Terminal rates	1/28 (4%)	1/9 (11%)	1/2 (50%)
First incidence (days)	729 (T)	729 (T)	496
Life table tests	P=0.011	P=0.491	P=0.025
Logistic regression tests	P=0.064	P=0.491	P=0.137
Cochran-Armitage test	P=0.130		
Fisher exact test		P=0.499	P=0.199
Kidney (Renal Tubule): Adenoma (Single and Step Sections)			
Overall rates	1/49 (2%)	4/20 (20%)	2/20 (10%)
Adjusted rates	3.6%	38.1%	53.1%
Terminal rates	1/28 (4%)	3/9 (33%)	1/2 (50%)
First incidence (days)	729 (T)	619	496
Life table tests	P=0.001	P=0.008	P=0.025
Logistic regression tests	P=0.019	P=0.011	P=0.137
Cochran-Armitage test	P=0.069		
Fisher exact test		P=0.023	P=0.199
Kidney (Renal Tubule): Benign Oncocytoma			
Overall rates	0/49 (0%)	0/20 (0%)	2/20 (10%)
Adjusted rates	0.0%	0.0%	16.4%
Terminal rates	0/28 (0%)	0/9 (0%)	0/2 (0%)
First incidence (days)	–[e]	–	565
Life table tests	P=0.015	–[f]	P=0.036
Logistic regression tests	P=0.031	–	P=0.076
Cochran-Armitage test	P=0.030		
Fisher exact test		–	P=0.081
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	2/49 (4%)	0/20 (0%)	1/20 (5%)
Adjusted rates	6.8%	0.0%	12.5%
Terminal rates	1/28 (4%)	0/9 (0%)	0/2 (0%)
First incidence (days)	720	–	618
Life table tests	P=0.395	P=0.517N	P=0.380
Logistic regression tests	P=0.531	P=0.506N	P=0.551
Cochran-Armitage test	P=0.634N		
Fisher exact test		P=0.501N	P=0.648

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Coumarin: 2-Year Vehicle Control versus Stop-Exposure 100 mg/kg Groups (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Mammary Gland: Fibroadenoma			
Overall rates	3/49 (6%)	2/20 (10%)	0/20 (0%)
Adjusted rates	8.9%	22.2%	0.0%
Terminal rates	1/28 (4%)	2/9 (22%)	0/2 (0%)
First incidence (days)	622	729 (T)	–
Life table tests	P=0.596	P=0.401	P=0.665N
Logistic regression tests	P=0.479N	P=0.447	P=0.395N
Cochran-Armitage test	P=0.312N		
Fisher exact test		P=0.453	P=0.352N
Pancreatic Islets: Adenoma			
Overall rates	4/47 (9%)	1/19 (5%)	0/20 (0%)
Adjusted rates	13.3%	6.3%	0.0%
Terminal rates	3/28 (11%)	0/9 (0%)	0/2 (0%)
First incidence (days)	660	588	–
Life table tests	P=0.373N	P=0.588N	P=0.672N
Logistic regression tests	P=0.207N	P=0.538N	P=0.455N
Cochran-Armitage test	P=0.140N		
Fisher exact test		P=0.551N	P=0.233N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	19/48 (40%)	4/20 (20%)	5/20 (25%)
Adjusted rates	51.2%	44.4%	43.7%
Terminal rates	11/28 (39%)	4/9 (44%)	0/2 (0%)
First incidence (days)	472	729 (T)	565
Life table tests	P=0.271	P=0.245N	P=0.176
Logistic regression tests	P=0.269N	P=0.131N	P=0.404N
Cochran-Armitage test	P=0.100N		
Fisher exact test		P=0.100N	P=0.194N
Preputial Gland: Adenoma			
Overall rates	2/45 (4%)	1/19 (5%)	0/20 (0%)
Adjusted rates	7.1%	11.1%	0.0%
Terminal rates	2/28 (7%)	1/9 (11%)	0/2 (0%)
First incidence (days)	729 (T)	729 (T)	–
Life table tests	P=0.699	P=0.625	P=0.855N
Logistic regression tests	P=0.699	P=0.625	P=0.855N
Cochran-Armitage test	P=0.333N		
Fisher exact test		P=0.659	P=0.476N
Preputial Gland: Adenoma or Carcinoma			
Overall rates	3/45 (7%)	2/19 (11%)	0/20 (0%)
Adjusted rates	10.7%	22.2%	0.0%
Terminal rates	3/28 (11%)	2/9 (22%)	0/2 (0%)
First incidence (days)	729 (T)	729 (T)	–
Life table tests	P=0.555	P=0.377	P=0.764N
Logistic regression tests	P=0.555	P=0.377	P=0.764N
Cochran-Armitage test	P=0.286N		
Fisher exact test		P=0.468	P=0.325N

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Coumarin: 2-Year Vehicle Control versus Stop-Exposure 100 mg/kg Groups (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	3/49 (6%)	0/20 (0%)	0/20 (0%)
Adjusted rates	9.5%	0.0%	0.0%
Terminal rates	2/28 (7%)	0/9 (0%)	0/2 (0%)
First incidence (days)	609	–	–
Life table tests	P=0.261N	P=0.362N	P=0.634N
Logistic regression tests	P=0.181N	P=0.332N	P=0.449N
Cochran-Armitage test	P=0.137N		
Fisher exact test		P=0.352N	P=0.352N
Testes: Adenoma			
Overall rates	38/45 (84%)	18/20 (90%)	15/20 (75%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	9/9 (100%)	2/2 (100%)
First incidence (days)	408	520	496
Life table tests	P<0.001	P=0.040	P<0.001
Logistic regression tests	P=0.112	P=0.220	P=0.201
Cochran-Armitage test	P=0.283N		
Fisher exact test		P=0.432	P=0.282N
All Organs: Mononuclear Cell Leukemia			
Overall rates	8/49 (16%)	5/20 (25%)	4/20 (20%)
Adjusted rates	22.4%	40.0%	65.8%
Terminal rates	3/28 (11%)	2/9 (22%)	1/2 (50%)
First incidence (days)	420	619	499
Life table tests	P=0.019	P=0.215	P=0.048
Logistic regression tests	P=0.222	P=0.287	P=0.392
Cochran-Armitage test	P=0.366		
Fisher exact test		P=0.302	P=0.481
All Organs: Benign Neoplasms			
Overall rates	45/49 (92%)	18/20 (90%)	16/20 (80%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	9/9 (100%)	2/2 (100%)
First incidence (days)	408	520	496
Life table tests	P<0.001	P=0.251	P<0.001
Logistic regression tests	P=0.268	P=0.659	P=0.413
Cochran-Armitage test	P=0.129N		
Fisher exact test		P=0.565N	P=0.163N
All Organs: Malignant Neoplasms			
Overall rates	17/49 (35%)	8/20 (40%)	7/20 (35%)
Adjusted rates	45.9%	65.7%	73.0%
Terminal rates	9/28 (32%)	5/9 (56%)	1/2 (50%)
First incidence (days)	420	619	253
Life table tests	P=0.007	P=0.264	P=0.015
Logistic regression tests	P=0.272	P=0.370	P=0.452
Cochran-Armitage test	P=0.508		
Fisher exact test		P=0.440	P=0.596

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Coumarin: 2-Year Vehicle Control versus Stop-Exposure 100 mg/kg Groups (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
All Organs: Benign or Malignant Neoplasms			
Overall rates	46/49 (94%)	18/20 (90%)	17/20 (85%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	9/9 (100%)	2/2 (100%)
First incidence (days)	408	520	253
Life table tests	P<0.001	P=0.296	P<0.001
Logistic regression tests	P=0.102	P=0.761	P=0.200
Cochran-Armitage test	P=0.170N		
Fisher exact test		P=0.453N	P=0.229N

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

TABLE E3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Coumarin: 2-Year 100 mg/kg Group versus Stop-Exposure 100 mg/kg Groups

	100 mg/kg (24-month exposure)	100 mg/kg (15-month exposure)	100 mg/kg (9-month exposure)
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	0/50 (0%)	1/20 (5%)	4/20 (20%)
Adjusted rates[b]	0.0%	50.0%	38.5%
Terminal rates[c]	0/0 (0%)	1/2 (50%)	3/9 (33%)
First incidence (days)	–[e]	729 (T)	680
Life table tests[d]	P=0.711	–	P=0.952
Logistic regression tests[d]	P=0.379	–[f]	P=0.579
Cochran-Armitage test[d]	P=0.002		
Fisher exact test[d]		P=0.286	P=0.005
Kidney (Renal Tubule): Adenoma (Single Sections)			
Overall rates	1/50 (2%)	2/20 (10%)	1/20 (5%)
Adjusted rates	2.4%	53.1%	11.1%
Terminal rates	0/0 (0%)	1/2 (50%)	1/9 (11%)
First incidence (days)	496	496	729 (T)
Life table tests	P=0.341N	P=0.539	P=0.664N
Logistic regression tests	P=0.404	P=0.199	P=0.657
Cochran-Armitage test	P=0.301		
Fisher exact test		P=0.194	P=0.493
Kidney (Renal Tubule): Adenoma (Single and Step Sections)			
Overall rates	5/50 (10%)	2/20 (10%)	4/20 (20%)
Adjusted rates	31.8%	53.1%	38.1%
Terminal rates	0/0 (0%)	1/2 (50%)	3/9 (33%)
First incidence (days)	426	496	619
Life table tests	P=0.086N	P=0.378N	P=0.121N
Logistic regression tests	P=0.419	P=0.669	P=0.479
Cochran-Armitage test	P=0.224		
Fisher exact test		P=0.684N	P=0.226
Kidney (Renal Tubule): Benign Oncocytoma			
Overall rates	0/50 (0%)	2/20 (10%)	0/20 (0%)
Adjusted rates	0.0%	16.4%	0.0%
Terminal rates	0/0 (0%)	0/2 (0%)	0/9 (0%)
First incidence (days)	–	565	–
Life table tests	P=0.598	P=0.127	–
Logistic regression tests	P=0.461	P=0.070	–
Cochran-Armitage test	P=0.442		
Fisher exact test		P=0.079	–
Mammary Gland: Fibroadenoma			
Overall rates	0/50 (0%)	0/20 (0%)	2/20 (10%)
Adjusted rates	0.0%	0.0%	22.2%
Terminal rates	0/0 (0%)	0/2 (0%)	2/9 (22%)
First incidence (days)	–	–	729 (T)
Life table tests	P=0.604	–	–
Logistic regression tests	P=0.604	–	–
Cochran-Armitage test	P=0.029		
Fisher exact test		–	P=0.079

TABLE E3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Coumarin: 2-Year 100 mg/kg Group versus Stop-Exposure 100 mg/kg Groups (continued)

	100 mg/kg	100 mg/kg (15-month exposure)	100 mg/kg (9-month exposure)
Mammary Gland: Fibroadenoma or Adenoma			
Overall rates	1/50 (2%)	0/20 (0%)	2/20 (10%)
Adjusted rates	14.3%	0.0%	22.2%
Terminal rates	0/0 (0%)	0/2 (0%)	2/9 (22%)
First incidence (days)	638	–	729 (T)
Life table tests	P=0.354N	P=0.567N	P=0.377N
Logistic regression tests	P=0.600N	P=0.579N	P=0.667N
Cochran-Armitage test	P=0.140		
Fisher exact test		P=0.714N	P=0.194
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	6/50 (12%)	5/20 (25%)	4/20 (20%)
Adjusted rates	48.1%	43.7%	44.4%
Terminal rates	0/0 (0%)	0/2 (0%)	4/9 (44%)
First incidence (days)	485	565	729 (T)
Life table tests	P=0.060N	P=0.373	P=0.018N
Logistic regression tests	P=0.514	P=0.173	P=0.461N
Cochran-Armitage test	P=0.193		
Fisher exact test		P=0.161	P=0.304
Preputial Gland: Adenoma or Carcinoma			
Overall rates	1/47 (2%)	0/20 (0%)	2/19 (11%)
Adjusted rates	3.1%	0.0%	22.2%
Terminal rates	0/0 (0%)	0/2 (0%)	2/9 (22%)
First incidence (days)	525	–	729 (T)
Life table tests	P=0.541N	P=0.665N	P=0.626N
Logistic regression tests	P=0.403	P=0.669N	P=0.595
Cochran-Armitage test	P=0.143		
Fisher exact test		P=0.701N	P=0.197
Testes: Adenoma			
Overall rates	46/50 (92%)	15/20 (75%)	18/20 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	0/0 (0%)	2/2 (100%)	9/9 (100%)
First incidence (days)	307	496	520
Life table tests	P<0.001N	P=0.013N	P<0.001N
Logistic regression tests	P=0.352N	P=0.321N	P=0.633N
Cochran-Armitage test	P=0.323N		
Fisher exact test		P=0.068N	P=0.556N
All Organs: Mononuclear Cell Leukemia			
Overall rates	0/50 (0%)	4/20 (20%)	5/20 (25%)
Adjusted rates	0.0%	65.8%	40.0%
Terminal rates	0/0 (0%)	1/2 (50%)	2/9 (22%)
First incidence (days)	–	499	619
Life table tests	P=0.377	P=0.048	P=0.450
Logistic regression tests	P=0.013	P=0.006	P=0.062
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.005	P=0.001

TABLE E3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Coumarin: 2-Year 100 mg/kg Group versus Stop-Exposure 100 mg/kg Groups (continued)

	100 mg/kg	100 mg/kg (15-month exposure)	100 mg/kg (9-month exposure)
All Organs: Benign Neoplasms			
Overall rates	47/50 (94%)	16/20 (80%)	18/20 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	0/0 (0%)	2/2 (100%)	9/9 (100%)
First incidence (days)	307	496	520
Life table tests	P<0.001N	P=0.018N	P<0.001N
Logistic regression tests	P=0.469N	P=0.754N	P=0.610N
Cochran-Armitage test	P=0.259N		
Fisher exact test		P=0.097N	P=0.444N
All Organs: Malignant Neoplasms			
Overall rates	5/50 (10%)	7/20 (35%)	8/20 (40%)
Adjusted rates	43.3%	73.0%	65.7%
Terminal rates	0/0 (0%)	1/2 (50%)	5/9 (56%)
First incidence (days)	512	253	619
Life table tests	P=0.248N	P=0.152	P=0.143N
Logistic regression tests	P=0.011	P=0.014	P=0.200
Cochran-Armitage test	P=0.002		
Fisher exact test		P=0.018	P=0.007
All Organs: Benign or Malignant Neoplasms			
Overall rates	47/50 (94%)	17/20 (85%)	18/20 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	0/0 (0%)	2/2 (100%)	9/9 (100%)
First incidence (days)	307	253	520
Life table tests	P<0.001N	P=0.030N	P<0.001N
Logistic regression tests	P=0.558N	P=0.540	P=0.610N
Cochran-Armitage test	P=0.298N		
Fisher exact test		P=0.222N	P=0.444N

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

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin[a]

	Vehicle Control[b]	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
Disposition Summary			
Animals initially in study	80	40	30
9-Month interim evaluation	20	20	
15-month interim evaluation	10		10
Early deaths			
Accidental deaths	2	1	3
Moribund	14	6	13
Natural deaths	6	4	2
Survivors			
Died last week of study		1	
Terminal sacrifice	28	8	2
Animals examined microscopically	80	40	30
9-Month Interim Evaluation			
Alimentary System			
Liver	(17)	(18)	
Clear cell focus	1 (6%)	2 (11%)	
Fatty change	4 (24%)		
Inflammation, focal, chronic		1 (6%)	
Necrosis, coagulative		11 (61%)	
Necrosis, multifocal		6 (33%)	
Bile duct, hyperplasia	7 (41%)	17 (94%)	
Mesentery	(1)	(1)	
Fat, inflammation, chronic	1 (100%)		
Fat, necrosis, coagulative		1 (100%)	
Cardiovascular System			
Heart	(17)	(18)	
Cardiomyopathy	10 (59%)	9 (50%)	
Endocrine System			
Pituitary gland	(17)	(18)	
Pars distalis, hyperplasia	1 (6%)		
General Body System			
None			
Genital System			
Seminal vesicle	(17)	(18)	
Atrophy	1 (6%)		
Testes	(17)	(18)	
Interstitial cell, hyperplasia	9 (53%)	14 (78%)	
Seminiferous tubule, atrophy	1 (6%)		

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
9-Month Interim Evaluation (continued)			
Hematopoietic System			
None			
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung	(17)	(18)	
Hemorrhage		1 (6%)	
Inflammation, granulomatous	2 (12%)		
Special Senses System			
None			
Urinary System			
Kidney	(17)	(18)	
Nephropathy	17 (100%)	18 (100%)	
Urinary bladder	(17)	(18)	
Calculus gross observation		2 (11%)	
15-Month Interim Evaluation			
Alimentary System			
Liver	(7)		(10)
Basophilic focus	1 (14%)		
Clear cell focus	1 (14%)		
Fatty change	1 (14%)		9 (90%)
Inflammation, chronic	1 (14%)		
Necrosis, coagulative			2 (20%)
Bile duct, hyperplasia	5 (71%)		10 (100%)
Hepatocyte, degeneration, granular			8 (80%)
Mesentery	(3)		(1)
Fat, inflammation, chronic	1 (33%)		
Fat, necrosis, coagulative	2 (67%)		1 (100%)
Pancreas	(7)		(10)
Inflammation, chronic			1 (10%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats
in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
15-Month Interim Evaluation (continued)			
Cardiovascular System			
Heart	(7)		(10)
Cardiomyopathy	6 (86%)		4 (40%)
Endocrine System			
Pituitary gland	(7)		(10)
Pars distalis, hyperplasia	1 (14%)		
Pars distalis, hypertrophy	1 (14%)		
General Body System			
None			
Genital System			
Preputial gland	(7)		(10)
Inflammation, suppurative	1 (14%)		
Testes	(7)		(10)
Atrophy			1 (10%)
Hematopoietic System			
Spleen	(7)		(10)
Ectopic tissue	1 (14%)		
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Nose	(7)		(10)
Inflammation, suppurative			1 (10%)
Special Senses System			
None			

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
15-Month Interim Evaluation (continued)			
Urinary System			
Kidney	(7)		(10)
Hydronephrosis			1 (10%)
Nephropathy	7 (100%)		10 (100%)
2-Year Study[b]			
Alimentary System			
Intestine large, rectum	(45)	(18)	(20)
Inflammation, suppurative			1 (5%)
Intestine small, duodenum	(46)	(18)	(20)
Ulcer	1 (2%)		
Intestine small, jejunum	(45)	(17)	(20)
Necrosis, coagulative			1 (5%)
Liver	(49)	(20)	(20)
Basophilic focus	16 (33%)	2 (10%)	1 (5%)
Clear cell focus	5 (10%)		
Developmental malformation	2 (4%)	2 (10%)	
Eosinophilic focus	5 (10%)		
Fatty change	4 (8%)	2 (10%)	3 (15%)
Fibrosis			2 (10%)
Hyperplasia	2 (4%)	1 (5%)	
Infiltration cellular, lymphocyte	3 (6%)		
Inflammation, chronic		1 (5%)	
Mixed cell focus	4 (8%)		1 (5%)
Necrosis, coagulative	1 (2%)	2 (10%)	3 (15%)
Bile duct, hyperplasia	41 (84%)	17 (85%)	14 (70%)
Hepatocyte, degeneration, granular			1 (5%)
Periductular, fibrosis			1 (5%)
Mesentery	(19)	(7)	(4)
Fat, hemorrhage	1 (5%)		
Fat, inflammation, chronic	2 (11%)	2 (29%)	
Fat, inflammation, suppurative			1 (25%)
Fat, necrosis, coagulative	12 (63%)	2 (29%)	3 (75%)
Pancreas	(47)	(19)	(20)
Atrophy	4 (9%)	1 (5%)	2 (10%)
Hyperplasia		1 (5%)	
Acinar cell, hyperplasia	1 (2%)		
Acinus, hyperplasia	2 (4%)		
Stomach, forestomach	(48)	(19)	(19)
Cyst epithelial inclusion		1 (5%)	
Hyperkeratosis	2 (4%)	2 (11%)	
Hyperplasia		1 (5%)	1 (5%)
Inflammation, chronic		3 (16%)	3 (16%)
Inflammation, suppurative		1 (5%)	1 (5%)
Ulcer	7 (15%)	3 (16%)	5 (26%)
Stomach, glandular	(47)	(18)	(20)
Dilatation			1 (5%)
Inflammation, chronic		1 (6%)	
Mineralization		1 (6%)	2 (10%)
Ulcer	2 (4%)		2 (10%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
2-Year Study (continued)			
Cardiovascular System			
Blood vessel	(1)	(1)	(1)
Aorta, mineralization		1 (100%)	1 (100%)
Mesenteric artery, mineralization		1 (100%)	
Heart	(49)	(20)	(20)
Cardiomyopathy	27 (55%)	11 (55%)	10 (50%)
Fibrosis		1 (5%)	
Thrombosis		1 (5%)	
Endocrine System			
Adrenal gland, cortex	(49)	(20)	(20)
Congestion		1 (5%)	
Adrenal gland, medulla	(49)	(20)	(20)
Basophilic focus	1 (2%)		
Congestion	1 (2%)		
Parathyroid gland	(41)	(19)	(18)
Hyperplasia	3 (7%)	4 (21%)	8 (44%)
Pituitary gland	(48)	(20)	(20)
Pars distalis, congestion		1 (5%)	
Pars distalis, cyst	1 (2%)	1 (5%)	
Pars distalis, hyperplasia		1 (5%)	
Pars intermedia, hemorrhage	1 (2%)		
Thyroid gland	(47)	(20)	(20)
C-cell, hyperplasia	5 (11%)		
Follicle, cyst	1 (2%)		
Follicular cell, cyst		1 (5%)	
General Body System			
None			
Genital System			
Preputial gland	(45)	(19)	(20)
Dilatation			1 (5%)
Hemorrhage		1 (5%)	
Hyperplasia	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, suppurative	7 (16%)	1 (5%)	2 (10%)
Duct, dilatation	3 (7%)		
Prostate	(45)	(20)	(20)
Hemorrhage			1 (5%)
Hyperplasia	1 (2%)	2 (10%)	1 (5%)
Inflammation, chronic			1 (5%)
Inflammation, suppurative	4 (9%)		
Testes	(45)	(20)	(20)
Atrophy		1 (5%)	1 (5%)
Infarct			1 (5%)
Seminiferous tubule, atrophy	3 (7%)		

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
2-Year Study (continued)			
Hematopoietic System			
Bone marrow	(48)	(19)	(20)
Hyperplasia, mononuclear cell	1 (2%)	1 (5%)	
Lymph node, mandibular	(48)	(20)	(20)
Congestion	1 (2%)	1 (5%)	
Hyperplasia, lymphoid	1 (2%)		1 (5%)
Hyperplasia, plasma cell	1 (2%)		
Lymph node, mesenteric	(43)	(20)	(20)
Congestion		1 (5%)	
Spleen	(48)	(19)	(20)
Congestion	2 (4%)		
Developmental malformation	2 (4%)	1 (5%)	
Fibrosis			1 (5%)
Hypoplasia	1 (2%)		
Necrosis			1 (5%)
Pigmentation, hemosiderin	1 (2%)		
Integumentary System			
Mammary gland	(45)	(20)	(16)
Galactocele	2 (4%)		
Skin	(49)	(20)	(20)
Cyst epithelial inclusion	3 (6%)		1 (5%)
Hemorrhage	1 (2%)		
Inflammation, chronic	2 (4%)		
Musculoskeletal System			
None			
Nervous System			
Brain	(47)	(19)	(20)
Cerebellum, developmental malformation	1 (2%)		
Cerebellum, hemorrhage			1 (5%)
Cerebrum, hemorrhage			1 (5%)
Cerebrum, infarct			1 (5%)
Hypothalamus, compression	1 (2%)		
Respiratory System			
Lung	(49)	(20)	(20)
Emphysema		1 (5%)	
Fibrosis		1 (5%)	
Foreign body			3 (15%)
Hemorrhage			1 (5%)
Inflammation, suppurative	1 (2%)		1 (5%)
Alveolar epithelium, hyperplasia	5 (10%)	3 (15%)	1 (5%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Study of Coumarin (continued)

	Vehicle Control	100 mg/kg (9-month exposure)	100 mg/kg (15-month exposure)
2-Year Study (continued)			
Respiratory System (continued)			
Nose	(49)	(20)	(20)
Fungus	4 (8%)	1 (5%)	2 (10%)
Inflammation, suppurative	13 (27%)	3 (15%)	3 (15%)
Metaplasia, squamous			1 (5%)
Necrosis, coagulative			1 (5%)
Trachea	(49)	(20)	(20)
Metaplasia, squamous			1 (5%)
Special Senses System			
Eye		(1)	(1)
Inflammation, suppurative		1 (100%)	
Posterior chamber, hemorrhage			1 (100%)
Urinary System			
Kidney	(49)	(20)	(20)
Congestion	1 (2%)		
Nephropathy	48 (98%)	20 (100%)	20 (100%)
Cortex, cyst	1 (2%)		1 (5%)
Renal tubule, hyperplasia	1 (2%)		3 (15%)
Urinary bladder	(45)	(20)	(20)
Hyperplasia	1 (2%)		
Inflammation, suppurative		1 (5%)	
Lumen, hemorrhage			1 (5%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Includes the 50 vehicle control animals from the 2-year core study.

APPENDIX F
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). Coumarin 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 at least five doses of coumarin. The high dose was limited by toxicity. All positive trials were repeated under the conditions that elicited the positive response.

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, nor is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to the judged positive (+) or weakly positive (+w).

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Coumarin was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of coumarin; the high dose was limited by toxicity. 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 coumarin 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 coumarin 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 coumarin, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no coumarin 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. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

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 (+w); increases at two or more doses resulted in a determination that the trial was positive (+). A statistically significant trend ($P \leq 0.05$) 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 coumarin for 12 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 coumarin and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 12 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: if cell cycle delay was anticipated, the incubation period was extended.

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. One 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. Statistical 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 (+w); significant differences for two or more doses indicate the trial is positive (+). A positive trend test in the absence of a statistically significant increase at any one dose results in an equivocal call (Galloway *et al.*, 1987).

Drosophila melanogaster Test Protocol

The assays for induction of sex-linked recessive lethal (SLRL) mutations were performed with adult flies as described by Valencia *et al.* (1989) and with larvae as described by Zimmering *et al.* (1989). Coumarin was supplied as a coded aliquot by Radian Corporation. It was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, coumarin was retested by injection into adult males.

To administer a chemical by injection, a glass Pasteur pipette is drawn out in a flame to a microfine filament, and the tip is broken off to allow delivery of the test solution. Injection is performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 μL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector which automatically delivers a calibrated volume. Flies are anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, is performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of coumarin at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males to feed for 72 hours on a solution of coumarin in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of coumarin dissolved in 0.7% saline or peanut oil and allowed to recover for 24 hours. A concurrent saline or peanut oil control group was also included. For the larval feeding experiment, Canton-S females and males were mated and eggs were exposed in vials with standard cornmeal food containing coumarin in solvent (5% ethanol) or solvent alone (Valencia *et al.*, 1989). Adult emergent males were mated at approximately 24 hours of age with two successive harems of three to five *Basc* females to establish two single-day broods. In the adult

exposures, treated males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier post-meiotic stages). F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male results from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls, using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result is considered positive if the P value is less than 0.01 and the mutation frequency in the tested group is greater than 0.10%, or if the P value is less than 0.05 and the frequency in the treatment group is greater than 0.15%. A test is considered to be inconclusive if (a) the P value is between 0.05 and 0.01 but the frequency in the treatment group is between 0.10% and 0.15% or (b) the P value is between 0.10 and 0.05 but the frequency in the treatment group is greater than 0.10%. A test is considered negative if the P value is greater than 0.10 or if the frequency in the treatment group is less than 0.10%.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay can be found in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the termination of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol, stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in each animal per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 510 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell.

Log transformation of the NCE data, and testing for normality by the Shapiro-Wilk test, and for heterogeneity of variance by Cochran's test, were performed before statistical analyses. The frequencies of micronucleated cells among NCEs were analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group was compared with the concurrent solvent control using Student's t-test.

RESULTS

Positive results were obtained with *in vitro* mutagenicity tests with coumarin, but no mutagenic responses were observed *in vivo*. Coumarin (33 to 3,333 μg/plate) was tested for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat and Syrian hamster liver S9; a positive response was obtained only in TA100 with S9 (Table F1; Haworth *et al.*, 1983).

In Chinese hamster ovary cells, coumarin induced sister chromatid exchanges in the absence, but not the presence, of Aroclor 1254-induced male Sprague-Dawley rat liver S9; the lowest effective dose was 100 μg/mL (Table F2; Galloway *et al.*, 1987). In both SCE trials without S9, the increases in sister chromatid exchanges were significant, but did not correlate with dose. Coumarin was also tested for induction of chromosomal aberrations in Chinese hamster ovary cells with and without S9. A dose-related positive response was also observed, but only in the presence of S9 (Table F3;

Galloway *et al.*, 1987). A significant increase in chromosomal aberrations was seen at the highest dose tested (1,600 μg/mL) with S9; at this dose, 37% of cells showed chromosomal damage.

Coumarin did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* exposed either as adults, by feeding (70 ppm) or by injection (500 ppm), or as larvae, treated by feeding (194 and 200 ppm) (Table F4; Yoon *et al.*, 1985; Valencia *et al.*, 1989).

Peripheral blood erythrocytes of male and female mice administered coumarin at doses up to 300 mg/kg, for 13 weeks by gavage were examined for frequencies of micronuclei; no increases in micronucleated normochromatic erythrocytes were observed (Table F5).

TABLE F1
Mutagenicity of Coumarin 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	112 ± 9.1	108 ± 9.1	84 ± 1.2	114 ± 6.9	121 ± 12.7	106 ± 5.5
	33	112 ± 7.4		104 ± 3.5		138 ± 2.3	
	100	130 ± 11.0	115 ± 10.7	116 ± 9.8	120 ± 11.6	152 ± 7.0	123 ± 5.4
	333	107 ± 9.2	111 ± 8.2	143 ± 7.3		150 ± 4.1	
	1,000	125 ± 3.8	111 ± 7.3	196 ± 10.1	287 ± 20.8	186 ± 3.2	176 ± 3.8
	2,000		118 ± 1.2		379 ± 18.6		198 ± 9.1
	2,150	122 ± 11.1					
	2,500		62 ± 5.3[c]		364 ± 12.7		196 ± 4.9
	3.000				286 ± 16.5[c]		133 ± 1.5[c]
	3,333			188 ± 24.0[c]		Toxic	
Trial summary		Negative	Negative	Positive	Positive	Equivocal	Positive
Positive control[d]		1,890 ± 51.6	1,371 ± 29.9	2,384 ± 120.0	3,128 ± 44.7	859 ± 51.2	1,547 ± 31.0

Strain	Dose (μg/plate)	Revertants/plate -S9	+10% hamster S9	+10% rat S9
TA1535	0	17 ± 1.2	11 ± 2.0	11 ± 0.7
	33	21 ± 5.2	13 ± 1.0	10 ± 1.2
	100	18 ± 2.5	8 ± 0.7	11 ± 1.0
	333	23 ± 3.2	9 ± 1.8	5 ± 0.3
	1,000	24 ± 5.0	9 ± 1.5	8 ± 1.2
	2,150	23 ± 4.3		
	3,333		11 ± 2.8	10 ± 0.6[c]
Trial summary		Negative	Negative	Negative
Positive control		1,212 ± 35.3	145 ± 4.8	51 ± 5.0
TA1537	0	5 ± 1.3	11 ± 1.2	9 ± 3.2
	33	6 ± 1.2	11 ± 3.9	10 ± 2.2
	100	6 ± 0.7	9 ± 2.3	8 ± 2.3
	333	7 ± 0.9	7 ± 2.6	8 ± 0.9
	1,000	6 ± 0.9	9 ± 0.9	9 ± 1.8
	2,150	3 ± 0.6[c]		
	3,333		6 ± 1.5[c]	9 ± 2.5[c]
Trial summary		Negative	Negative	Negative
Positive control		69 ± 12.3	207 ± 16.8	57 ± 6.0

TABLE F1
Mutagenicity of Coumarin in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9	Revertants/plate +10% hamster S9	Revertants/plate +10% rat S9
TA98	0	14 ± 2.5	22 ± 2.9	30 ± 2.7
	33	12 ± 0.3	27 ± 0.9	34 ± 8.5
	100	15 ± 1.2	27 ± 2.6	30 ± 3.8
	333	16 ± 2.3	36 ± 0.7	27 ± 2.9
	1,000	12 ± 3.5	23 ± 1.8	24 ± 1.5
	2,150	15 ± 1.9		
	3,333		11 ± 1.2[c]	17 ± 3.2[c]
Trial summary		Negative	Negative	Negative
Positive control		1,433 ± 23.6	1,754 ± 118.2	477 ± 29.1

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

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

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,044	465	0.44	9.3	26.0	
Mitomycin-C	0.005	25	524	603	1.15	24.1	26.0	158.37
Coumarin	50	50	1,047	549	0.52	11.0	26.0	17.73
	160	50	1,044	580	0.55	11.6	26.0	24.73*
	500	50	1,047	526	0.50	10.5	26.0	12.79
								P=0.020[c]
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,043	426	0.40	8.5	26.0	
Mitomycin-C	0.005	25	523	732	1.39	29.3	26.0	242.68
Coumarin	100	50	1,048	589	0.56	11.8	26.0	37.60*
	200	50	1,047	683	0.65	13.7	26.0	59.72*
	300	50	1,038	582	0.56	11.6	26.0	37.28*
								P<0.001
+S9								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		100	2,094	1,029	0.49	10.3	26.0	
Cyclophosphamide	1.0	100	2,094	1,714	0.81	17.1	26.0	66.57
Coumarin	160	50	1,044	580	0.55	11.6	26.0	13.05
	500	50	1,039	581	0.55	11.6	26.0	13.80
	1,600	50	1,043	503	0.48	10.1	26.0	-1.86
								P=0.336

* Positive (>20% increase over solvent control)
a Study performed at Columbia University. SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.
b SCEs/chromosome of culture exposed to coumarin relative to those of culture exposed to solvent
c Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

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

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 – Harvest time: 14.0 hours Summary: Negative					Trial 1 – Harvest time: 14.0 hours Summary: Weak positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	4	0.04	4.0		100	5	0.05	5.0
Mitomycin-C					Cyclophosphamide				
0.15	100	41	0.41	27.0	15	100	30	0.30	26.0
Coumarin					Coumarin				
50.00	100	8	0.08	8.0	160	100	11	0.11	10.0
160.00	100	6	0.06	6.0	500	100	14	0.14	12.0
500.00	100	8	0.08	7.0	1,600	100	51	0.51	37.0*
				P=0.259[b]					P<0.001

* Positive (P≤0.05)
[a] Study performed at Columbia University. Abs = aberrations.
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

TABLE F4
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Coumarin[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Feeding	70	11	0	2/3,114	2/3,073	0/2,909	4/9,096 (0.04%)
	0			1/3,280	1/3,240	1/2,996	3/9,516 (0.03%)
Injection	500	0	0	2/2,115	2/2,015	2/1,853	6/5,983 (0.10%)
	0			0/1,895	3/1,844	0/1,623	3/5,362 (0.06%)
Larval feeding	200	51	2	6/3,532	1/3,349	0/000	7/6,881 (0.10%)
	0			3/3,437	1/2,345	0/000	4/5,782 (0.07%)
Larval feeding	194	44	0	1/2,593	0/2,548	0/000	1/5,141 (0.02%)
	0			2/2,660	5/2,659	0/000	7/5,319 (0.13%)

[a] The adult treatments and the 200 ppm larval feeding studies were performed at University of Wisconsin, Madison. The 194 ppm larval feeding study was performed at Brown University. Detailed protocols and these data are presented in Yoon *et al.* (1985) and Valencia *et al.* (1989). Results were not significant at the 5% level (Margolin *et al.*, 1983).
[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE F5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice in the 13-Week Gavage Study of Coumarin[a]

	Dose (mg/kg)	Mean Frequency of Micronuclei per 1,000 Erythrocytes[b]	Number of Mice Scored
Males			
	0	0.78 ± 0.12	9
	75	0.83 ± 0.13	9
	150	0.74 ± 0.08	10
	300	0.67 ± 0.09	7
Females			
	0	0.66 ± 0.11	10
	75	0.59 ± 0.07	9
	150	0.60 ± 0.09	10
	300	0.65 ± 0.09	9

[a] 10,000 normochromatic erythrocytes scored per animal. Smears were prepared from peripheral blood samples obtained by cardiac puncture of dosed and control animals at the termination of the 13-week study.
[b] Values are mean ± standard error of the mean. Micronucleus frequency of each treated group compared to the concurrent control by Student's t-test. None of the dosed groups differed significantly from the control values.

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

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of Coumarin[a]

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male						
n	10	10	10	10	10	7
Necropsy body wt	318 ± 8	321 ± 5	316 ± 7	299 ± 6*	280 ± 5**	242 ± 4**
Brain						
Absolute	1.75 ± 0.06	1.82 ± 0.03	1.80 ± 0.03	1.76 ± 0.03	1.77 ± 0.02	1.71 ± 0.02
Relative	5.51 ± 0.21	5.66 ± 0.08	5.70 ± 0.10	5.91 ± 0.12*	6.33 ± 0.12**	7.08 ± 0.07**
Heart						
Absolute	1.018 ± 0.034	1.052 ± 0.042	1.060 ± 0.029	1.037 ± 0.036	1.024 ± 0.031[b]	0.912 ± 0.021
Relative	3.20 ± 0.07	3.27 ± 0.11	3.36 ± 0.10	3.47 ± 0.12	3.63 ± 0.09**[b]	3.77 ± 0.07**
R. Kidney						
Absolute	1.10 ± 0.04[b]	1.10 ± 0.04	1.14 ± 0.03	1.14 ± 0.04	1.21 ± 0.03	1.19 ± 0.03
Relative	3.43 ± 0.06[b]	3.41 ± 0.07	3.60 ± 0.07	3.79 ± 0.08**	4.30 ± 0.09**	4.92 ± 0.15**
Liver						
Absolute	10.55 ± 0.40	11.16 ± 0.31	11.00 ± 0.36	11.16 ± 0.27	11.96 ± 0.35**	11.86 ± 0.22*
Relative	33.2 ± 1.0	34.8 ± 0.8	34.8 ± 0.7	37.3 ± 0.8**	42.6 ± 0.9**	49.0 ± 0.8**
Lungs						
Absolute	1.32 ± 0.03	1.36 ± 0.04	1.33 ± 0.05	1.29 ± 0.03	1.25 ± 0.03	1.25 ± 0.03
Relative	4.17 ± 0.10	4.24 ± 0.12	4.22 ± 0.13	4.31 ± 0.11	4.46 ± 0.08	5.18 ± 0.11**
R. Testis						
Absolute	1.40 ± 0.03	1.44 ± 0.02	1.45 ± 0.02	1.43 ± 0.03	1.41 ± 0.03[b]	1.29 ± 0.05*
Relative	4.40 ± 0.06	4.50 ± 0.05	4.59 ± 0.06	4.79 ± 0.10**	5.01 ± 0.12**[b]	5.34 ± 0.16**
Thymus						
Absolute	0.251 ± 0.017	0.287 ± 0.023	0.261 ± 0.018	0.232 ± 0.013	0.211 ± 0.013[b]	0.127 ± 0.011**
Relative	0.787 ± 0.042	0.892 ± 0.062	0.826 ± 0.056	0.777 ± 0.044	0.759 ± 0.044[b]	0.526 ± 0.047**
Female						
n	10	10	10	10	10	6
Necropsy body wt	191 ± 2	190 ± 3	186 ± 3	182 ± 3	183 ± 2	164 ± 5**
Brain						
Absolute	1.74 ± 0.02	1.72 ± 0.02	1.72 ± 0.03	1.72 ± 0.02	1.69 ± 0.02	1.64 ± 0.02*
Relative	9.14 ± 0.19	9.08 ± 0.13	9.26 ± 0.13	9.47 ± 0.17	9.23 ± 0.10	9.87 ± 0.18**
Heart						
Absolute	0.701 ± 0.019	0.708 ± 0.022	0.695 ± 0.021	0.734 ± 0.021	0.722 ± 0.023	0.673 ± 0.028
Relative	3.68 ± 0.10	3.73 ± 0.08	3.74 ± 0.08	4.06 ± 0.15*	3.93 ± 0.10*	4.04 ± 0.13*
R. Kidney						
Absolute	0.673 ± 0.013	0.668 ± 0.015	0.674 ± 0.022	0.719 ± 0.037	0.732 ± 0.012	0.812 ± 0.031**
Relative	3.53 ± 0.07	3.53 ± 0.08	3.62 ± 0.08	3.98 ± 0.24*	3.99 ± 0.05**	4.87 ± 0.09**
Liver						
Absolute	6.09 ± 0.18	5.61 ± 0.17	5.81 ± 0.19	6.18 ± 0.13	7.23 ± 0.16**	8.55 ± 0.45**
Relative	32.0 ± 0.9	29.6 ± 0.8	31.2 ± 0.6	34.1 ± 0.8	39.5 ± 0.8**	51.2 ± 1.8**
Lungs						
Absolute	1.068 ± 0.019	1.008 ± 0.022	0.989 ± 0.044	1.039 ± 0.027	1.049 ± 0.021	1.000 ± 0.035
Relative	5.61 ± 0.13	5.31 ± 0.06	5.31 ± 0.18	5.74 ± 0.18	5.71 ± 0.11	6.02 ± 0.21
Thymus						
Absolute	0.245 ± 0.012	0.231 ± 0.008	0.235 ± 0.013	0.243 ± 0.028	0.219 ± 0.008	0.121 ± 0.012**
Relative	1.28 ± 0.06	1.22 ± 0.03	1.27 ± 0.07	1.35 ± 0.17	1.20 ± 0.05	0.73 ± 0.08**

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤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 G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Gavage Study of Coumarin[a]

	Vehicle Control	100 mg/kg
n	17	18
Necropsy body wt	460 ± 7	396 ± 8°°
Brain		
Absolute	2.194 ± 0.022	2.111 ± 0.029°
Relative	4.79 ± 0.08	5.37 ± 0.15°°
L. Kidney		
Absolute	1.524 ± 0.022	1.533 ± 0.029
Relative	3.33 ± 0.06	3.88 ± 0.06°°
R. Kidney		
Absolute	1.453 ± 0.024	1.483 ± 0.025
Relative	3.17 ± 0.07	3.75 ± 0.05°°
Liver		
Absolute	16.841 ± 0.364	17.100 ± 0.392
Relative	36.71 ± 0.80	43.16 ± 0.53°°

°° Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[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 G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Gavage Study of Coumarin[a]

	Vehicle Control	100 mg/kg
n	7	10
Necropsy body wt	529 ± 3	462 ± 9**
Brain		
Absolute	2.086 ± 0.026	2.090 ± 0.023
Relative	3.94 ± 0.05	4.54 ± 0.09**
L. Kidney		
Absolute	1.786 ± 0.040	1.900 ± 0.065
Relative	3.37 ± 0.08	4.11 ± 0.09**
R. Kidney		
Absolute	1.714 ± 0.034	1.860 ± 0.076
Relative	3.24 ± 0.07	4.02 ± 0.12**
Liver		
Absolute	17.686 ± 0.434	19.278 ± 0.772[b]
Relative	33.41 ± 0.81	42.19 ± 1.13**[b]

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[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 G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Male				
n	10	10	9	10
Necropsy body wt	527 ± 15	523 ± 11	482 ± 11*	454 ± 13**
Brain				
Absolute	2.100 ± 0.037	2.030 ± 0.045	2.067 ± 0.033[b]	2.100 ± 0.037
Relative	4.01 ± 0.14	3.90 ± 0.13	4.29 ± 0.12[b]	4.64 ± 0.10**
L. Kidney				
Absolute	1.700 ± 0.037	1.900 ± 0.056	1.733 ± 0.055	1.860 ± 0.106
Relative	3.24 ± 0.08	3.63 ± 0.08*	3.59 ± 0.05*	4.08 ± 0.16**
R. Kidney				
Absolute	1.700 ± 0.030	1.910 ± 0.050*	1.767 ± 0.044	1.860 ± 0.112
Relative	3.25 ± 0.10	3.65 ± 0.07*	3.67 ± 0.05*	4.11 ± 0.18**
Liver				
Absolute	17.010 ± 0.536	18.840 ± 0.570	18.022 ± 0.485	20.230 ± 1.587*
Relative	32.28 ± 0.61	36.01 ± 0.71	37.42 ± 0.44*	44.10 ± 2.42**
Female				
n	10	10	10	10
Necropsy body wt	302 ± 3	314 ± 9	304 ± 7	285 ± 9
Brain				
Absolute	1.900 ± 0.033	1.890 ± 0.028	1.950 ± 0.022	1.900 ± 0.033
Relative	6.31 ± 0.12	6.07 ± 0.19	6.44 ± 0.17	6.72 ± 0.18
L. Kidney				
Absolute	0.970 ± 0.021	1.040 ± 0.034	1.060 ± 0.031	1.020 ± 0.036
Relative	3.22 ± 0.07	3.32 ± 0.09	3.49 ± 0.08*	3.59 ± 0.11**
R. Kidney				
Absolute	0.930 ± 0.030	1.000 ± 0.033	0.980 ± 0.020	1.020 ± 0.044
Relative	3.08 ± 0.09	3.20 ± 0.11	3.23 ± 0.07	3.58 ± 0.10**
Liver				
Absolute	8.670 ± 0.236	9.860 ± 0.286*	10.410 ± 0.361**	11.810 ± 0.563**
Relative	28.76 ± 0.75	31.61 ± 1.11*	34.19 ± 0.75**	41.33 ± 0.89**

* 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=8

TABLE G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of Coumarin[a]

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male						
n	10	10	10	10	10	8
Necropsy body wt	29.7 ± 0.8	28.8 ± 0.8	29.6 ± 0.7	29.0 ± 0.7	28.5 ± 0.5	25.9 ± 0.6**
Brain						
Absolute	0.430 ± 0.005	0.432 ± 0.008	0.431 ± 0.006	0.431 ± 0.005	0.429 ± 0.002	0.440 ± 0.009
Relative	14.5 ± 0.3	15.1 ± 0.5	14.6 ± 0.2	14.9 ± 0.3	15.1 ± 0.2	17.1 ± 0.5**
Heart						
Absolute	0.155 ± 0.005	0.168 ± 0.007	0.165 ± 0.007	0.161 ± 0.007	0.168 ± 0.012	0.145 ± 0.007
Relative	5.23 ± 0.14	5.83 ± 0.23	5.56 ± 0.17	5.54 ± 0.17	5.87 ± 0.35	5.61 ± 0.25
R. Kidney						
Absolute	0.244 ± 0.005	0.250 ± 0.011	0.245 ± 0.008[b]	0.245 ± 0.006	0.246 ± 0.006	0.217 ± 0.008*
Relative	8.24 ± 0.12	8.63 ± 0.17	8.34 ± 0.15[b]	8.46 ± 0.09	8.61 ± 0.13	8.37 ± 0.23
Liver[c]						
Absolute	1.08 ± 0.03	1.14 ± 0.05	1.17 ± 0.03	1.21 ± 0.04	1.24 ± 0.04*	1.31 ± 0.07**
Relative	36.5 ± 0.83	39.3 ± 0.89	39.6 ± 0.85*	41.7 ± 0.66**	43.5 ± 0.76**	50.6 ± 2.05**
Lungs						
Absolute	0.208 ± 0.004	0.210 ± 0.008	0.194 ± 0.006	0.195 ± 0.009	0.210 ± 0.009	0.202 ± 0.009
Relative	7.05 ± 0.20	7.30 ± 0.25	6.56 ± 0.17	6.75 ± 0.33	7.38 ± 0.33	7.82 ± 0.35
R. Testis						
Absolute	0.120 ± 0.004	0.120 ± 0.003	0.114 ± 0.006	0.118 ± 0.002	0.117 ± 0.003	0.118 ± 0.004
Relative	4.05 ± 0.16	4.18 ± 0.13	3.87 ± 0.21	4.09 ± 0.10	4.10 ± 0.10	4.56 ± 0.15*
Thymus						
Absolute	0.034 ± 0.002	0.036 ± 0.001	0.034 ± 0.002	0.035 ± 0.002	0.031 ± 0.002	0.032 ± 0.002
Relative	1.15 ± 0.07	1.26 ± 0.04	1.15 ± 0.06	1.21 ± 0.07	1.10 ± 0.08	1.22 ± 0.09
Female						
n	10	9	10	9	10	10
Necropsy body wt	22.4 ± 0.6	22.4 ± 0.6	22.4 ± 0.6	23.4 ± 0.8	22.6 ± 0.7	23.3 ± 0.8
Brain						
Absolute	0.445 ± 0.007	0.454 ± 0.005	0.445 ± 0.007	0.445 ± 0.007	0.444 ± 0.008	0.436 ± 0.008
Relative	20.00 ± 0.79	20.3 ± 0.51	20.00 ± 0.52	19.1 ± 0.48	19.8 ± 0.54	18.8 ± 0.48
Heart						
Absolute	0.122 ± 0.004	0.132 ± 0.008	0.126 ± 0.004	0.138 ± 0.010	0.124 ± 0.008	0.117 ± 0.004
Relative	5.52 ± 0.29	5.89 ± 0.30	5.65 ± 0.20	5.86 ± 0.30	5.47 ± 0.29	5.02 ± 0.13
R. Kidney						
Absolute	0.156 ± 0.003[b]	0.165 ± 0.005	0.161 ± 0.006	0.169 ± 0.003	0.155 ± 0.005	0.160 ± 0.005
Relative	7.08 ± 0.22[b]	7.38 ± 0.26	7.23 ± 0.28	7.26 ± 0.21	6.88 ± 0.18	6.87 ± 0.08
Liver[c]						
Absolute	0.884 ± 0.022	0.940 ± 0.031	0.919 ± 0.026	0.978 ± 0.027	1.003 ± 0.034*	1.210 ± 0.070**
Relative	39.6 ± 1.0	41.9 ± 0.9	41.1 ± 0.7	41.8 ± 0.8	44.4 ± 0.9**	51.8 ± 2.3**
Lungs						
Absolute	0.181 ± 0.006	0.193 ± 0.009	0.187 ± 0.008	0.197 ± 0.008	0.176 ± 0.009	0.182 ± 0.006
Relative	8.11 ± 0.29	8.63 ± 0.37	8.36 ± 0.33	8.47 ± 0.44	7.79 ± 0.33	7.84 ± 0.23
Thymus						
Absolute	0.040 ± 0.002	0.042 ± 0.003	0.044 ± 0.003	0.040 ± 0.002[d]	0.041 ± 0.002[b]	0.040 ± 0.003
Relative	1.77 ± 0.10	1.87 ± 0.12	1.96 ± 0.10	1.68 ± 0.06[d]	1.84 ± 0.05[b]	1.68 ± 0.10

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights are given in milligrams unless otherwise noted 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] Liver weight is given in grams.
[d] n=8

TABLE G6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Male				
n	10	10	10	9
Necropsy body wt	53.6 ± 0.8	50.6 ± 1.2	51.1 ± 1.8	47.2 ± 1.6**
Brain				
Absolute	0.500 ± 0.000	0.500 ± 0.015	0.500 ± 0.000	0.489 ± 0.011
Relative	9.35 ± 0.14	9.94 ± 0.40	9.90 ± 0.40	10.50 ± 0.51*
L. Kidney				
Absolute	0.430 ± 0.021	0.400 ± 0.015	0.390 ± 0.010	0.389 ± 0.020
Relative	8.01 ± 0.37	7.93 ± 0.30	7.71 ± 0.35	8.35 ± 0.56
R. Kidney				
Absolute	0.400 ± 0.015	0.420 ± 0.013	0.420 ± 0.020	0.400 ± 0.017[b]
Relative	7.45 ± 0.22	8.33 ± 0.27	8.20 ± 0.23	8.74 ± 0.51**[b]
Liver				
Absolute	2.420 ± 0.101	2.280 ± 0.101	2.380 ± 0.190	2.444 ± 0.153[b]
Relative	45.08 ± 1.59	44.97 ± 1.34	46.23 ± 2.73	54.23 ± 3.76*[b]
Female				
n	8	10	10	9
Necropsy body wt	49.9 ± 1.7	44.3 ± 1.4*	45.9 ± 1.4*	41.2 ± 1.4**
Brain				
Absolute	0.488 ± 0.013	0.480 ± 0.013	0.480 ± 0.013	0.500 ± 0.000
Relative	9.86 ± 0.46	10.98 ± 0.55	10.54 ± 0.39	12.23 ± 0.42**
L. Kidney				
Absolute	0.288 ± 0.030	0.250 ± 0.017	0.260 ± 0.016	0.256 ± 0.018
Relative	5.78 ± 0.57	5.67 ± 0.40	5.68 ± 0.33	6.29 ± 0.55
R. Kidney				
Absolute	0.250 ± 0.019	0.250 ± 0.017	0.290 ± 0.023	0.278 ± 0.015
Relative	5.04 ± 0.40	5.68 ± 0.40	6.33 ± 0.51	6.78 ± 0.40*
Liver				
Absolute	1.688 ± 0.069	1.660 ± 0.060	1.720 ± 0.055	1.756 ± 0.044
Relative	33.88 ± 1.14	37.49 ± 0.80*	37.59 ± 0.88*	42.80 ± 1.31**

* 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=8

APPENDIX H
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE H1
Hematology Data for Rats in the 16-Day Gavage Study of Coumarin[a]

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Male						
n	5	5	4	5	5	1
Platelets ($10^3/\mu L$)	612.2 ± 43.2	676.5 ± 26.7[b]	544.3 ± 81.8	677.2 ± 35.9	774.6 ± 21.7**	916.0[c]
Capillary clotting (min)	2.20 ± 0.37	1.85 ± 0.28	1.63 ± 0.07	1.55 ± 0.25	1.60 ± 0.13	1.50[c]
Fibrinogen (mg/dL)	170 ± 5	158 ± 6[b]	154 ± 2*	150 ± 6*	151 ± 6*	119[c]
Prothrombin (sec)	12.3 ± 0.1[b]	12.1 ± 0.1[b]	14.5 ± 1.9[d]	12.4 ± 0.3	12.8 ± 0.4	14.2[c]
Activated partial thromboplastin time (sec)	26.8 ± 3.4	23.8 ± 2.0	28.2 ± 2.5	23.7 ± 2.7	23.1 ± 1.3	26.5[c]
Female						
n	5	5	5	5	5	0[e]
Platelets ($10^3/\mu L$)	594.4 ± 83.0	521.6 ± 62.6	622.0 ± 25.2	520.8 ± 83.7	592.4 ± 87.9	
Capillary clotting (min)	1.75 ± 0.19	1.15 ± 0.20	1.70 ± 0.38	1.40 ± 0.17	1.70 ± 0.17	
Fibrinogen (mg/dL)	136 ± 5	141 ± 4	139 ± 8	130 ± 13[b]	135 ± 7	
Prothrombin (sec)	12.3 ± 0.1[b]	12.2 ± 0.2[b]	12.3 ± 0.2[b]	12.1 ± 0.2[b]	12.8 ± 0.5[b]	
Activated partial thromboplastin time (sec)	33.8 ± 7.5	27.3 ± 2.1	24.7 ± 1.3	26.9 ± 2.2	21.4 ± 3.4*	

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=4
[c] No standard error calculated due to high mortality
[d] n=3
[e] No data measurements due to 100% mortality

TABLE H2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Gavage Study of Coumarin[a]

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male						
Hematology						
n	5	10	10	10	10	7
Hematocrit (%)	47.0 ± 0.7	48.3 ± 0.7	47.3 ± 0.5	46.7 ± 0.4	46.3 ± 0.7	46.6 ± 0.9
Hemoglobin (g/dL)	17.9 ± 0.4	18.0 ± 0.2	17.8 ± 0.2	17.6 ± 0.2	17.7 ± 0.2	18.1 ± 0.5
Erythrocytes ($10^6/\mu L$)	8.66 ± 0.16	8.95 ± 0.10	8.92 ± 0.08	9.16 ± 0.07*	9.46 ± 0.13**	9.97 ± 0.21**
Mean cell volume (fL)	54.2 ± 0.4	54.1 ± 0.3	52.9 ± 0.3*	51.0 ± 0.2**	48.6 ± 0.2**	45.3 ± 0.4**
Mean cell hemoglobin (pg)	20.6 ± 0.1	20.1 ± 0.1*	19.9 ± 0.1**	19.2 ± 0.1**	18.4 ± 0.2**	17.8 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	38.0 ± 0.4	37.2 ± 0.4	37.6 ± 0.2	37.7 ± 0.1	38.2 ± 0.2	39.2 ± 0.3
Platelets ($10^3/\mu L$)	612.8 ± 14.7	564.3 ± 12.0	553.9 ± 18.4	616.0 ± 12.8	622.1 ± 19.2	917.0 ± 19.7*
Leukocytes ($10^3/\mu L$)	6.64 ± 0.63	6.29 ± 0.28	6.31 ± 0.22	5.81 ± 0.19	6.27 ± 0.26	8.34 ± 0.51
Segmented neutrophils ($10^3/\mu L$)	1.69 ± 0.06	1.87 ± 0.20	1.52 ± 0.12	1.50 ± 0.13	1.47 ± 0.09	3.06 ± 0.52
Lymphocytes ($10^3/\mu L$)	4.76 ± 0.53	4.33 ± 0.21	4.64 ± 0.19	4.13 ± 0.18	4.68 ± 0.27	5.05 ± 0.28
Monocytes ($10^3/\mu L$)	0.10 ± 0.03	0.07 ± 0.02	0.10 ± 0.02	0.14 ± 0.03	0.05 ± 0.02	0.12 ± 0.04
Eosinophils ($10^3/\mu L$)	0.07 ± 0.03	0.01 ± 0.01	0.05 ± 0.03	0.02 ± 0.01	0.06 ± 0.02	0.09 ± 0.03
Activated partial thromboplastin time (sec)	11.8 ± 0.2	11.8 ± 0.2	11.3 ± 0.2	11.3 ± 0.2	11.1 ± 0.2	13.3 ± 0.8
Clinical Chemistry						
n	5	10	10	10	10	7
Urea nitrogen (mg/dL)	8.8 ± 0.6	8.9 ± 0.3	9.2 ± 0.4	8.5 ± 0.3	7.1 ± 0.5	8.9 ± 0.5
Creatinine (mg/dL)	0.86 ± 0.04	0.74 ± 0.03	0.68 ± 0.02**	0.74 ± 0.03	0.72 ± 0.02	0.73 ± 0.03
Sodium (mEq/L)	145 ± 1	146 ± 1	144 ± 1	145 ± 1	145 ± 1	142 ± 1
Potassium (mEq/L)	5.9 ± 0.2	5.9 ± 0.2	5.6 ± 0.2	5.7 ± 0.1	5.9 ± 0.1	5.5 ± 0.2
Chloride (mEq/L)	105 ± 1	106 ± 1	105 ± 0	105 ± 1	105 ± 0	105 ± 1
Calcium (mg/dL)	10.56 ± 0.12	10.72 ± 0.17	10.52 ± 0.12	10.71 ± 0.13	10.60 ± 0.06	10.54 ± 0.14
Phosphorus (mg/dL)	6.4 ± 0.2	6.2 ± 0.1	6.2 ± 0.1	6.3 ± 0.1	6.2 ± 0.1	6.4 ± 0.1
Total protein (g/dL)	6.5 ± 0.1	6.7 ± 0.1	6.5 ± 0.1	6.6 ± 0.1	6.4 ± 0.1	6.1 ± 0.1

TABLE H2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Gavage Study of Coumarin (continued)

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male (continued)						
Clinical Chemistry (continued)						
n	5	10	10	10	10	7
Albumin (g/dL)	3.5 ± 0.0	3.6 ± 0.0	3.5 ± 0.0	3.6 ± 0.0	3.6 ± 0.1	3.2 ± 0.1
A/G ratio	1.1 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0
Total bilirubin (mg/dL)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0**	1.3 ± 0.4**
Alanine aminotransferase (IU/L)	42 ± 3[b]	43 ± 2	51 ± 6	48 ± 3	123 ± 24**	2,209 ± 750**
Aspartate aminotransferase (IU/L)	67 ± 7	55 ± 1	57 ± 3	56 ± 2	80 ± 9	985 ± 357*
Lactate dehydrogenase (IU/L)	452 ± 54	371 ± 25	417 ± 32	391 ± 27	357 ± 25	443 ± 47
Ornithine carbamoyltransferase (IU/L)	8 ± 3	4 ± 1	7 ± 2	4 ± 1	4 ± 1[c]	104 ± 35*
Sorbitol dehydrogenase (IU/L)	8 ± 1	8 ± 1	11 ± 2	8 ± 1	27 ± 6**	370 ± 116**
Cholinesterase (IU/L)	933 ± 20	845 ± 20*	763 ± 15**	723 ± 17**	683 ± 13**	853 ± 30**
Urinalysis						
n	5	10	10	10	10	7
Specific gravity	1.034 ± 0.006	1.041 ± 0.002	1.045 ± 0.000	1.044 ± 0.001	1.029 ± 0.003	1.029 ± 0.006
Female						
Hematology						
n	5	10	10	9	10	7
Hematocrit (%)	46.2 ± 0.3	47.8 ± 0.3	48.0 ± 0.3*	47.7 ± 0.6	47.1 ± 0.2	46.0 ± 0.9
Hemoglobin (g/dL)	17.3 ± 0.2	17.6 ± 0.1	17.7 ± 0.2	17.5 ± 0.2	17.6 ± 0.2	17.7 ± 0.5
Erythrocytes ($10^6/\mu L$)	7.87 ± 0.04	8.11 ± 0.07*	8.20 ± 0.06**	8.28 ± 0.09**	8.70 ± 0.06**	9.25 ± 0.17**
Mean cell volume (fL)	58.6 ± 0.2	58.9 ± 0.3	58.6 ± 0.2	57.7 ± 0.2	54.1 ± 0.2**	49.1 ± 0.4**
Mean cell hemoglobin (pg)	22.0 ± 0.1	21.7 ± 0.1	21.6 ± 0.1**	21.2 ± 0.2**	20.3 ± 0.1**	18.9 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	37.5 ± 0.4	36.9 ± 0.2	36.8 ± 0.2	36.8 ± 0.2	37.4 ± 0.2	38.4 ± 0.4
Platelets ($10^3/\mu L$)	638.4 ± 26.2	583.9 ± 17.0	550.5 ± 15.7**	536.4 ± 20.9**	566.4 ± 24.5*	476.7 ± 80.4
Leukocytes ($10^3/\mu L$)	5.08 ± 0.50	4.15 ± 0.21	3.81 ± 0.19	4.29 ± 0.19	5.66 ± 0.34	5.50 ± 0.38

TABLE H2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Gavage Study of Coumarin (continued)

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Female (continued)						
Hematology (continued)						
n	5	10	10	9	10	7
Segmented neutrophils ($10^3/\mu L$)	1.01 ± 0.15	0.94 ± 0.10	0.77 ± 0.07	0.78 ± 0.13	1.16 ± 0.13	1.44 ± 0.22
Lymphocytes ($10^3/\mu L$)	3.93 ± 0.45	3.10 ± 0.17	2.96 ± 0.15	3.37 ± 0.17	4.30 ± 0.23	3.91 ± 0.28
Monocytes ($10^3/\mu L$)	0.09 ± 0.05	0.07 ± 0.02	0.06 ± 0.01	0.07 ± 0.02	0.11 ± 0.03	0.11 ± 0.05
Eosinophils ($10^3/\mu L$)	0.05 ± 0.03	0.03 ± 0.01	0.02 ± 0.01	0.05 ± 0.01	0.09 ± 0.02	0.02 ± 0.01
Activated partial thromboplastin time (sec)	11.6 ± 0.2	10.9 ± 0.4[d]	11.0 ± 0.3[c]	11.2 ± 0.2	11.1 ± 0.4[c]	12.0 ± 0.4[e]
Clinical Chemistry						
n	5	10	9	10	10	7
Urea nitrogen (mg/dL)	8.3 ± 1.0	8.4 ± 0.5	8.0 ± 0.3	8.0 ± 0.5	6.8 ± 0.4	7.7 ± 1.0
Creatinine (mg/dL)	0.72 ± 0.04	0.76 ± 0.04	0.76 ± 0.03	0.69 ± 0.02	0.72 ± 0.02	0.81 ± 0.05
Sodium (mEq/L)	144 ± 1	144 ± 1	144 ± 1	144 ± 1	143 ± 1	142 ± 1
Potassium (mEq/L)	5.5 ± 0.2	5.6 ± 0.2	5.6 ± 0.1	5.7 ± 0.1	5.6 ± 0.1	5.5 ± 0.2
Chloride (mEq/L)	107 ± 1	107 ± 1	106 ± 1	106 ± 1	104 ± 0**	103 ± 1**
Calcium (mg/dL)	10.42 ± 0.18	10.38 ± 0.08	10.38 ± 0.09	10.53 ± 0.13	10.74 ± 0.09	11.03 ± 0.12*
Phosphorus (mg/dL)	5.7 ± 0.3	5.6 ± 0.1	5.7 ± 0.3	5.9 ± 0.1	6.1 ± 0.1	6.5 ± 0.1*
Total protein (g/dL)	6.3 ± 0.1	6.5 ± 0.1	6.5 ± 0.1	6.7 ± 0.1	6.8 ± 0.1**	6.6 ± 0.1*
Albumin (g/dL)	3.5 ± 0.0	3.5 ± 0.0	3.6 ± 0.1	3.6 ± 0.1	3.8 ± 0.1**	3.6 ± 0.1
A/G ratio	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0
Total bilirubin (mg/dL)	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.0**	1.1 ± 0.5**
Alanine aminotransferase (IU/L)	59 ± 10	40 ± 3	37 ± 2	39 ± 3	50 ± 5[c]	1,672 ± 923
Aspartate aminotransferase (IU/L)	67 ± 4	63 ± 3	59 ± 2	61 ± 5	72 ± 10	360 ± 169[e]
Lactate dehydrogenase (IU/L)	371 ± 26	337 ± 26	344 ± 23	328 ± 26	295 ± 24	328 ± 53[e]
Ornithine carbamoyltransferase (IU/L)	7 ± 3	4 ± 1	5 ± 1[d]	4 ± 1[c]	4 ± 1	78 ± 36
Sorbitol dehydrogenase (IU/L)	9 ± 1	8 ± 1	7 ± 0	8 ± 1	12 ± 2[c]	104 ± 36*[e]
Cholinesterase (IU/L)	2,652 ± 127	2,178 ± 108*	1,795 ± 71**	1,415 ± 42**	1,137 ± 20**	1,044 ± 37**

TABLE H2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Gavage Study of Coumarin (continued)

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Female (continued)						
Urinalysis						
n	5	10	10	10	10	7
Specific gravity	1.024 ± 0.006	1.028 ± 0.004	1.014 ± 0.003	1.025 ± 0.004	1.020 ± 0.003	1.023 ± 0.004

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; A/G ratio = albumin/globulin ratio
[b] n=4
[c] n=9
[d] n=8
[e] n=6

TABLE H3
Hematology and Clinical Chemistry Data for Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Gavage Study of Coumarin[a]

	Vehicle Control	100 mg/kg
Hematology		
n	17	18
Hematocrit (%)	38.4 ± 0.4	35.3 ± 0.4**
Hemoglobin (g/dL)	14.4 ± 0.1	13.2 ± 0.1**
Erythrocytes (10^6/μL)	8.14 ± 0.09	8.28 ± 0.10
Mean cell volume (fL)	47.2 ± 0.2	42.7 ± 0.2**
Mean cell hemoglobin (pg)	17.7 ± 0.1	15.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	37.4 ± 0.2	37.3 ± 0.2
Platelets (10^3/μL)	555.1 ± 18.3	620.1 ± 14.3**
Reticulocytes (10^6/μL)	0.17 ± 0.01	0.26 ± 0.01**
Leukocytes (10^3/μL)	3.81 ± 0.31	4.03 ± 0.21
Segmented neutrophils (10^3/μL)	1.03 ± 0.09	1.07 ± 0.08
Lymphocytes (10^3/μL)	2.62 ± 0.22	2.66 ± 0.18
Atypical lymphocytes (10^3/μL)	0.05 ± 0.01	0.15 ± 0.04
Monocytes (10^3/μL)	0.01 ± 0.01	0.00 ± 0.00
Eosinophils (10^3/μL)	0.05 ± 0.01	0.08 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.02 ± 0.01	0.03 ± 0.01
Activated partial thromboplastin time (sec)	19 ± 1	18 ± 1
Thromboplastin time (sec)	13 ± 0	13 ± 0
Clinical Chemistry		
n	16	18
Calcium (mg/dL)	11.44 ± 0.13	11.83 ± 0.09*
Alkaline phosphatase (IU/L)	205 ± 4	337 ± 10**
Alanine aminotransferase (IU/L)	81 ± 9	406 ± 51**
Sorbitol dehydrogenase (IU/L)	20 ± 2[b]	30 ± 2**
Gamma-glutamyltransferase (IU/L)	0 ± 0	1 ± 1**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=17

TABLE H4
Hematology and Clinical Chemistry Data for Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Gavage Study of Coumarin[a]

	Vehicle Control	100 mg/kg
n	7	9
Hematology		
Hematocrit (%)	41.2 ± 0.9	37.6 ± 0.9*
Hemoglobin (g/dL)	14.6 ± 0.3	13.2 ± 0.2**
Erythrocytes (10^6/μL)	8.54 ± 0.19	8.54 ± 0.27
Mean cell volume (fL)	48.6 ± 0.3	44.1 ± 0.6**
Mean cell hemoglobin (pg)	17.1 ± 0.2	15.6 ± 0.5*
Mean cell hemoglobin concentration (g/dL)	35.4 ± 0.3	35.3 ± 0.8
Platelets (10^3/μL)	561.9 ± 26.8	873.4 ± 31.3**
Reticulocytes (10^6/μL)	0.21 ± 0.03	0.25 ± 0.02
Leukocytes (10^3/μL)	3.40 ± 0.66	3.42 ± 0.33
Segmented neutrophils (10^3/μL)	1.30 ± 0.39	1.38 ± 0.19
Lymphocytes (10^3/μL)	1.79 ± 0.15	1.80 ± 0.23
Atypical lymphocytes (10^3/μL)	0.09 ± 0.03	0.11 ± 0.04
Monocytes (10^3/μL)	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/μL)	0.04 ± 0.02	0.05 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.06 ± 0.04	0.03 ± 0.01
Activated partial thromboplastin time (sec)	20.4 ± 0.9	18.1 ± 0.6
Thromboplastin time (sec)	14.1 ± 0.2	13.3 ± 0.2*
Clinical Chemistry		
Calcium (mg/dL)	11.29 ± 0.18	11.22 ± 0.15
Alkaline phosphatase (IU/L)	165 ± 20	246 ± 17*
Alanine aminotransferase (IU/L)	56 ± 4	105 ± 19**
Sorbitol dehydrogenase (IU/L)	18 ± 1	31 ± 2**
Gamma-glutamyltransferase (IU/L)	0 ± 0	4 ± 1**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error

TABLE H5
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Male				
Hematology				
n	10	10	8	10
Hematocrit (%)	40.5 ± 1.6	40.0 ± 0.5	39.7 ± 0.7	37.1 ± 0.8**
Hemoglobin (g/dL)	14.4 ± 0.6	14.3 ± 0.1	14.1 ± 0.4*	13.3 ± 0.2**
Erythrocytes (10^6/μL)	8.16 ± 0.37	8.27 ± 0.13	8.62 ± 0.20	8.27 ± 0.33
Mean cell volume (fL)	49.9 ± 0.7	48.3 ± 0.3	46.3 ± 0.4**	45.4 ± 1.7**
Mean cell hemoglobin (pg)	17.7 ± 0.2	17.4 ± 0.2	16.3 ± 0.2**	16.3 ± 0.7**
Mean cell hemoglobin concentration (g/dL)	35.5 ± 0.3	35.9 ± 0.4	35.4 ± 0.4	36.1 ± 1.0
Platelets (10^3/μL)	503.7 ± 24.4[b]	559.3 ± 26.5	671.3 ± 26.6**	712.3 ± 81.4**
Reticulocytes (10^6/μL)	0.19 ± 0.02[b]	0.20 ± 0.01	0.19 ± 0.02	0.24 ± 0.03
Leukocytes (10^3/μL)	3.07 ± 0.34	3.02 ± 0.09	3.64 ± 0.35	3.48 ± 0.30[b]
Segmented neutrophils (10^3/μL)	0.94 ± 0.09	0.87 ± 0.08	1.61 ± 0.23*	2.12 ± 0.60*
Lymphocytes (10^3/μL)	1.86 ± 0.28	1.95 ± 0.12	1.71 ± 0.16	1.86 ± 0.19
Atypical lymphocytes (10^3/μL)	0.09 ± 0.04	0.08 ± 0.02	0.19 ± 0.05	0.45 ± 0.34
Monocytes (10^3/μL)	0.00 ± 0.00	0.03 ± 0.01	0.04 ± 0.02	0.02 ± 0.01[b]
Eosinophils (10^3/μL)	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.08 ± 0.05	0.02 ± 0.01	0.04 ± 0.01	0.05 ± 0.01[b]
Activated partial thromboplastin time (sec)	20.8 ± 0.4	19.8 ± 0.6	18.7 ± 0.4**	18.8 ± 0.6**
Thromboplastin time (sec)	14.2 ± 0.3	13.9 ± 0.2	13.5 ± 0.3	13.6 ± 0.3
Clinical Chemistry				
n	10	10	10	8
Calcium (mg/dL)	11.10 ± 0.18	11.20 ± 0.20	11.60 ± 0.16	11.63 ± 0.18
Alkaline phosphatase (IU/L)	165 ± 11	152 ± 8	247 ± 19*	175 ± 21
Alanine aminotransferase (IU/L)	62 ± 10	81 ± 11	131 ± 20**	75 ± 11*
Sorbitol dehydrogenase (IU/L)	23 ± 2	26 ± 2	31 ± 2**	26 ± 3
Gamma-glutamyltransferase (IU/L)	0 ± 0	0 ± 0	6 ± 1**	1 ± 1**

TABLE H5
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Coumarin (continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Female				
n	9	10	10	10
Hematology				
Hematocrit (%)	38.7 ± 1.2	39.6 ± 0.6	38.8 ± 0.5	38.7 ± 0.6
Hemoglobin (g/dL)	13.8 ± 0.5	14.0 ± 0.2	13.8 ± 0.3	13.6 ± 0.2*
Erythrocytes (10^6/μL)	6.98 ± 0.33	7.34 ± 0.16	7.58 ± 0.10	7.82 ± 0.16**
Mean cell volume (fL)	56.2 ± 1.5	54.1 ± 0.6*	51.2 ± 0.5**	49.6 ± 0.5**
Mean cell hemoglobin (pg)	19.9 ± 0.4	19.1 ± 0.3	18.2 ± 0.3**	17.3 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	35.6 ± 0.4	35.3 ± 0.4	35.6 ± 0.4	35.0 ± 0.2
Platelets (10^3/μL)	523.3 ± 24.2	445.3 ± 14.1*	528.4 ± 30.9	564.0 ± 35.3
Reticulocytes (10^6/μL)	0.20 ± 0.02[c]	0.21 ± 0.02	0.18 ± 0.01	0.18 ± 0.02
Leukocytes (10^3/μL)	1.43 ± 0.09[c]	1.65 ± 0.16	1.91 ± 0.22	1.75 ± 0.11*
Segmented neutrophils (10^3/μL)	0.80 ± 0.46	0.45 ± 0.06	0.73 ± 0.20	0.59 ± 0.08
Lymphocytes (10^3/μL)	2.14 ± 1.13	1.09 ± 0.10	1.08 ± 0.07	1.08 ± 0.07
Atypical lymphocytes (10^3/μL)	0.09 ± 0.06	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01
Monocytes (10^3/μL)	0.02 ± 0.02	0.01 ± 0.01	0.01 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.09 ± 0.08	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.01 ± 0.00[c]	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.00
Activated partial thromboplastin time (sec)	17.0 ± 0.4	16.4 ± 0.1	16.6 ± 0.4	16.3 ± 0.3
Thromboplastin time (sec)	13.6 ± 0.1	13.4 ± 0.2	13.6 ± 0.2	13.3 ± 0.1
Clinical Chemistry				
Calcium (mg/dL)	10.89 ± 0.20	10.60 ± 0.16	11.00 ± 0.00	10.60 ± 0.31
Alkaline phosphatase (IU/L)	230 ± 9	257 ± 13	287 ± 38	264 ± 13
Alanine aminotransferase (IU/L)	47 ± 3	48 ± 2	47 ± 2[b]	62 ± 4**
Sorbitol dehydrogenase (IU/L)	16 ± 1	16 ± 1	16 ± 1	21 ± 2*
Gamma-glutamyltransferase (IU/L)	0 ± 0[c]	2 ± 1	1 ± 0[b]	6 ± 1**

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

TABLE H6
Hematology Data for Mice in the 16-Day Gavage Study of Coumarin[a]

	Vehicle Control	40 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg
Male						
n	5	5	4	5	4	0[b]
Platelets ($10^3/\mu L$)	278.0 ± 115.0[c]	242.0 ± 104.0[c]	191.3 ± 103.0[d]	247.4 ± 45.5	289.8 ± 53.7	
Capillary clotting (min)	1.6 ± 0.3	1.8 ± 0.3	2.0 ± 0.2	1.4 ± 0.3	2.2 ± 0.5	
Female						
n	5	5	5	5	4	0[b]
Platelets ($10^3/\mu L$)	255.0 ± 74.3[c]	233.8 ± 69.2	289.5 ± 53.8[c]	310.5 ± 42.8[c]	306.3 ± 64.5	
Capillary clotting (min)	1.9 ± 0.4	2.1 ± 0.4	2.5 ± 0.4	1.8 ± 0.2	2.1 ± 0.3	

[a] Mean ± standard error
[b] No data measurements due to 100% mortality
[c] n=4
[d] n=3

TABLE H7
Hematology Data for Mice in the 13-Week Gavage Study of Coumarin[a]

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male						
n	10	10	10	10	10	8
Hematocrit (%)	32.4 ± 1.0	32.7 ± 0.9	31.4 ± 0.7	30.6 ± 0.5	29.1 ± 1.0*	28.7 ± 0.9**
Hemoglobin (g/dL)	12.6 ± 0.4	12.8 ± 0.3	12.3 ± 0.3	12.1 ± 0.2	11.2 ± 0.5*	11.3 ± 0.4*
Erythrocytes ($10^6/\mu L$)	6.15 ± 0.19	6.26 ± 0.16	6.07 ± 0.15	6.08 ± 0.11[b]	5.86 ± 0.20	5.97 ± 0.20
Mean cell volume (fL)	52.7 ± 0.2	52.1 ± 0.2	51.6 ± 0.3**	50.6 ± 0.4**	49.6 ± 0.3**	47.9 ± 0.3**
Mean cell hemoglobin (pg)	20.5 ± 0.1	20.4 ± 0.1	20.3 ± 0.1	19.9 ± 0.2*	19.1 ± 0.4**	19.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	39.0 ± 0.2	39.1 ± 0.4	39.3 ± 0.2	39.4 ± 0.2	38.5 ± 0.8	39.4 ± 0.3
Platelets ($10^3/\mu L$)	417.7 ± 60.8	477.3 ± 63.8	478.3 ± 70.2	468.0 ± 62.9	499.0 ± 80.7	576.1 ± 90.5
Leukocytes ($10^3/\mu L$)	3.83 ± 0.57	3.22 ± 0.30	4.00 ± 0.37	3.62 ± 0.33[b]	4.16 ± 0.55	3.59 ± 0.55
Segmented neutrophils ($10^3/\mu L$)	0.50 ± 0.09	0.58 ± 0.10	0.68 ± 0.14	0.58 ± 0.08[b]	0.73 ± 0.20	0.79 ± 0.19
Lymphocytes ($10^3/\mu L$)	3.25 ± 0.50	2.51 ± 0.23	3.15 ± 0.23	2.96 ± 0.25[b]	3.24 ± 0.34	2.66 ± 0.41
Monocytes ($10^3/\mu L$)	0.05 ± 0.01	0.07 ± 0.02	0.07 ± 0.02	0.03 ± 0.01[b]	0.08 ± 0.04	0.05 ± 0.01
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.06 ± 0.01*	0.05 ± 0.02[b]	0.05 ± 0.02[b]	0.10 ± 0.05	0.09 ± 0.02*
Activated partial thromboplastin time (sec)	8.4 ± 1.7[c]	9.7 ± 0.2[b]	9.0 ± 1.1[b]	8.9 ± 1.2[b]	8.8 ± 1.2[b]	9.8 ± 0.2

TABLE H7
Hematology Data for Mice in the 13-Week Gavage Study of Coumarin (continued)

	Vehicle Control	19 mg/kg	38 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Female						
n	10	9	10	9	10	10
Hematocrit (%)	32.3 ± 0.9	32.2 ± 0.9	30.5 ± 0.8	31.0 ± 1.0	32.6 ± 0.4[b]	29.2 ± 1.2
Hemoglobin (g/dL)	12.5 ± 0.3	12.5 ± 0.4	11.9 ± 0.3	12.0 ± 0.4	12.8 ± 0.2[b]	11.1 ± 0.5
Erythrocytes ($10^6/\mu L$)	6.08 ± 0.15	6.08 ± 0.18	5.85 ± 0.15	6.02 ± 0.20	6.40 ± 0.08[b]	5.71 ± 0.28
Mean cell volume (fL)	53.2 ± 0.3	53.0 ± 0.3	52.2 ± 0.4	51.6 ± 0.3**	50.8 ± 0.4**	49.3 ± 0.4**
Mean cell hemoglobin (pg)	20.6 ± 0.2	20.5 ± 0.2	20.3 ± 0.1	20.0 ± 0.1*	20.0 ± 0.1*	19.5 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	38.8 ± 0.3	38.7 ± 0.5	39.0 ± 0.3	38.7 ± 0.2	39.5 ± 0.3	39.5 ± 0.3*
Platelets ($10^3/\mu L$)	400.9 ± 56.3	419.9 ± 65.7	394.4 ± 32.7	389.8 ± 74.2	489.5 ± 81.2	523.5 ± 98.5
Leukocytes ($10^3/\mu L$)	3.19 ± 0.39	3.77 ± 0.41	3.40 ± 0.49	2.91 ± 0.33	3.39 ± 0.36	2.87 ± 0.46
Segmented neutrophils ($10^3/\mu L$)	0.50 ± 0.10	0.74 ± 0.09	0.40 ± 0.07	0.43 ± 0.06	0.52 ± 0.06	0.43 ± 0.09
Lymphocytes ($10^3/\mu L$)	2.55 ± 0.30	2.92 ± 0.33	2.86 ± 0.40	2.41 ± 0.28	2.75 ± 0.33	2.32 ± 0.36
Monocytes ($10^3/\mu L$)	0.07 ± 0.01	0.07 ± 0.02	0.10 ± 0.03	0.03 ± 0.01*	0.03 ± 0.01	0.04 ± 0.01*
Eosinophils ($10^3/\mu L$)	0.06 ± 0.01	0.02 ± 0.01	0.05 ± 0.02	0.04 ± 0.01	0.08 ± 0.03	0.05 ± 0.01
Activated partial thromboplastin time (sec)	9.5 ± 1.1	10.2 ± 0.2	9.3 ± 1.2[b]	10.2 ± 0.3[d]	9.4 ± 1.2[b]	10.2 ± 0.1[b]

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

TABLE H8
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Coumarin[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Male				
Hematology				
n	5	5	5	4
Hematocrit (%)	40.9 ± 0.3	38.6 ± 1.5	39.6 ± 0.3	37.3 ± 1.4**
Hemoglobin (g/dL)	13.9 ± 0.1	13.1 ± 0.4	13.6 ± 0.2	12.8 ± 0.5*
Erythrocytes ($10^6/\mu L$)	8.73 ± 0.07	8.38 ± 0.46	8.84 ± 0.08	8.58 ± 0.34
Mean cell volume (fL)	47.0 ± 0.3	46.2 ± 1.0	44.8 ± 0.4*	43.5 ± 0.3**
Mean cell hemoglobin (pg)	16.0 ± 0.2	15.7 ± 0.4	15.4 ± 0.1*	15.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.1 ± 0.3	33.8 ± 0.3	34.3 ± 0.5	34.4 ± 0.2
Platelets ($10^3/\mu L$)	842.8 ± 9.9	901.4 ± 33.6	885.0 ± 40.0	1,188.0 ± 53.6**
Leukocytes ($10^3/\mu L$)	1.72 ± 0.35	1.36 ± 0.19	1.18 ± 0.16	1.45 ± 0.38
Reticulocytes ($10^6/\mu L$)	0.18 ± 0.03	0.24 ± 0.05	0.15 ± 0.04	0.24 ± 0.05
Segmented neutrophils ($10^3/\mu L$)	0.38 ± 0.07	0.31 ± 0.05	0.27 ± 0.05	0.39 ± 0.12
Lymphocytes ($10^3/\mu L$)	1.29 ± 0.28	1.02 ± 0.14	0.90 ± 0.11	1.03 ± 0.25
Atypical lymphocytes ($10^3/\mu L$)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.00	0.03 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Clinical Chemistry				
n	8	9	10	9
Alkaline phosphatase (IU/L)	48 ± 3	42 ± 1	45 ± 1	39 ± 2**
Alanine aminotransferase (IU/L)	49 ± 5	50 ± 8	68 ± 17	83 ± 22
Sorbitol dehydrogenase (IU/L)	40 ± 1	40 ± 1	39 ± 3	37 ± 4
Gamma-glutamyltransferase (IU/L)	0 ± 0	0 ± 0	0 ± 0	1 ± 1

TABLE H8
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Coumarin (continued)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Female				
n	8	10	10	9
Hematology				
Hematocrit (%)	39.3 ± 0.7	37.8 ± 0.3	38.6 ± 0.5	38.1 ± 0.5
Hemoglobin (g/dL)	13.8 ± 0.2	13.4 ± 0.1	13.6 ± 0.1	13.6 ± 0.1
Erythrocytes (10^6/μL)	8.62 ± 0.16	8.39 ± 0.06	8.60 ± 0.10	8.62 ± 0.12
Mean cell volume (fL)	45.8 ± 0.3	45.1 ± 0.4	45.0 ± 0.2	44.1 ± 0.2**
Mean cell hemoglobin (pg)	16.0 ± 0.2	16.0 ± 0.1	15.8 ± 0.1	15.8 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.1 ± 0.3	35.5 ± 0.2	35.2 ± 0.3	35.6 ± 0.3
Platelets (10^3/μL)	723.1 ± 16.1	792.1 ± 29.7	790.3 ± 39.9*	859.0 ± 28.6**
Reticulocytes (10^6/μL)	0.19 ± 0.02	0.18 ± 0.02	0.21 ± 0.02[b]	0.17 ± 0.01
Leukocytes (10^3/μL)	0.93 ± 0.15	1.13 ± 0.15	1.17 ± 0.17[b]	0.88 ± 0.12
Segmented neutrophils (10^3/μL)	0.21 ± 0.07	0.34 ± 0.06	0.30 ± 0.05[b]	0.22 ± 0.05
Lymphocytes (10^3/μL)	0.71 ± 0.10	0.77 ± 0.10	0.85 ± 0.13[b]	0.64 ± 0.07
Atypical lymphocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[b]	0.01 ± 0.00
Monocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00
Eosinophils (10^3/μL)	0.00 ± 0.00	0.01 ± 0.00	0.01 ± 0.00[b]	0.00 ± 0.00
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00
Clinical Chemistry				
Alkaline phosphatase (IU/L)	110 ± 10	118 ± 10	102 ± 6	100 ± 6[c]
Alanine aminotransferase (IU/L)	31 ± 3	35 ± 5	41 ± 7	44 ± 9[c]
Sorbitol dehydrogenase (IU/L)	37 ± 2	37 ± 2	38 ± 1	39 ± 1
Gamma-glutamyltransferase (IU/L)	1 ± 0	1 ± 1	0 ± 0	0 ± 0[c]

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

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

PROCUREMENT AND CHARACTERIZATION OF COUMARIN

Coumarin was obtained from Rhone Poulenc, Incorporated (Monmouth Junction, NJ) in two lots (lot 7971 and lot 5H2003). Lot 7971 was used throughout the 16-day and 13-week studies in rats and mice and lot 5H2003 was used throughout the 2-year studies in rats and mice. 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 coumarin studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a white crystalline powder, were identified as coumarin by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra of coumarin (*Sadtler Standard Spectra*), as shown in Figures I1 and I2.

The purity of both lots was determined by elemental analyses, Karl Fischer water analysis, titration of free acid, lactone hydrolysis and back titration, thin-layer chromatography (TLC), and gas chromatography. Titration of free acid was performed by dissolving a 5 g sample in methanol and titrating with standardized 0.1 N aqueous sodium hydroxide to the phenolphthalein endpoint. Lactone hydrolysis was performed with alcoholic potassium hydroxide and back-titration with sulfuric acid. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) toluene:acetone (90:10) and 2) petroleum ether:ethyl acetate (55:45). Plates were examined under shortwave (254 nm) and longwave (366 nm) ultraviolet light and a spray of 0.5% (w/v) potassium permanganate dissolved in 1 N sodium hydroxide. Gas chromatographic analysis was performed with a flame ionization detector (FID) with a nitrogen gas carrier at a flow rate of 70 cc/minute. Two systems were used for each lot:

A) 1% SP-1000 on 100/120 Supelcoport, with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute
B) 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, with an oven temperature program of 50° C for 5 minutes, then 50° to 170° C at 10° C per minute.

Elemental analyses of both lots for carbon and hydrogen were in agreement with the theoretical values for coumarin. Karl Fischer water analysis of lot 7971 indicated 0.020 ± 0.003% water and 0.15 ± 0.01% water for lot 5H2003. For lot 7971 titration of the free acid indicated 0.298 ± 0.014 mEq of acid per g of sample. For lot 5H2003 free acid titration indicated 0.008 ± 0.001 mEq of acid per g of sample. Lactone hydrolysis for lot 7971 indicated a purity of 100.1 ± 0.3%, and a purity of 97.2 ± 0.4% for lot 5H2003. Thin-layer chromatography for both lots indicated only a major spot in each system. Gas chromatography of both lots indicated only a major peak and no impurities with a total area of ≥0.1% relative to the major peak area. The overall purity of lot 7971 was determined to be greater than 99%, and the overall purity of lot 5H2003 was determined to be 97%.

Stability studies were performed by the analytical chemistry laboratory. Gas chromatography was performed using System A described above except with an oven temperature of 170° C and 0.5% docosane added as an internal standard. These studies indicated the coumarin was stable as a bulk chemical for at least 2 weeks when stored at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically at the study laboratory with gas chromatography and free acid titration methods similar to those described above. No degradation of the bulk chemical was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulation suspensions were prepared by mixing coumarin in Mazola® corn oil to give the required concentrations (Table I1). The dose formulations were stored in the dark at room temperature. Dose formulations were prepared once for the 16-day studies, and every 2 weeks for the 13-week and 2-year studies. Formulations were discarded 21 days after the date of preparation.

Dose formulation stability analyses at the 5 mg/mL concentration were performed by the analytical chemistry laboratory. Aliquots were extracted with methanol, then decyl alcohol (1.9 mg/mL in methylene chloride) was added as an internal standard. After dilution with methylene chloride, gas chromatographic analysis was performed using System B described above, except with a carrier gas flow rate of 30 mL/minute and an oven temperature of 160° C. The stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored in the dark, as well as for at least 3 hours when exposed to air and light. The study laboratory also conducted and confirmed the stability of dose formulations.

Periodic analyses of the dose formulations of coumarin were conducted at the study laboratory and analytical chemistry laboratory using ultraviolet spectroscopy. In this procedure the samples were extracted with methanol; then after centrifugation the extracts were diluted with methanol, and the absorbance determined at 274 nm. During the 16-day studies all formulations were analyzed (Table I2). During the 13-week studies, the dose formulations were analyzed every 6 weeks (Table I3). During the 2-year studies, the dose formulations were analyzed every 6 to 10 weeks (Table I4). In the 2-year studies all dose formulations (154/154) were within 10% of the target concentrations. Periodic peroxide analyses of the corn oil vehicle by the study laboratory indicated that peroxide levels were within the acceptable limit of 10 mEq/kg. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table I5).

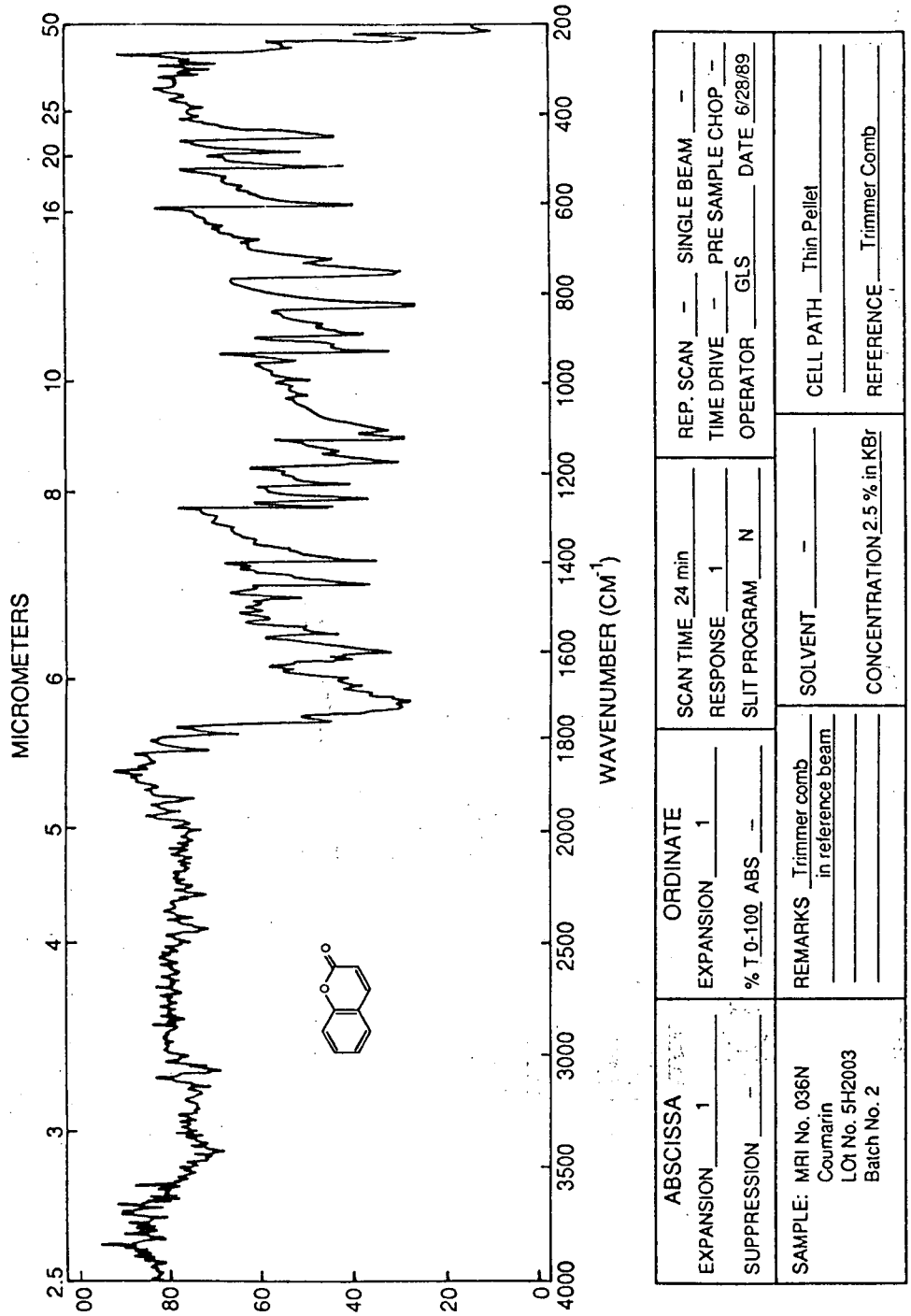


FIGURE I1
Infrared Absorption Spectrum of Coumarin

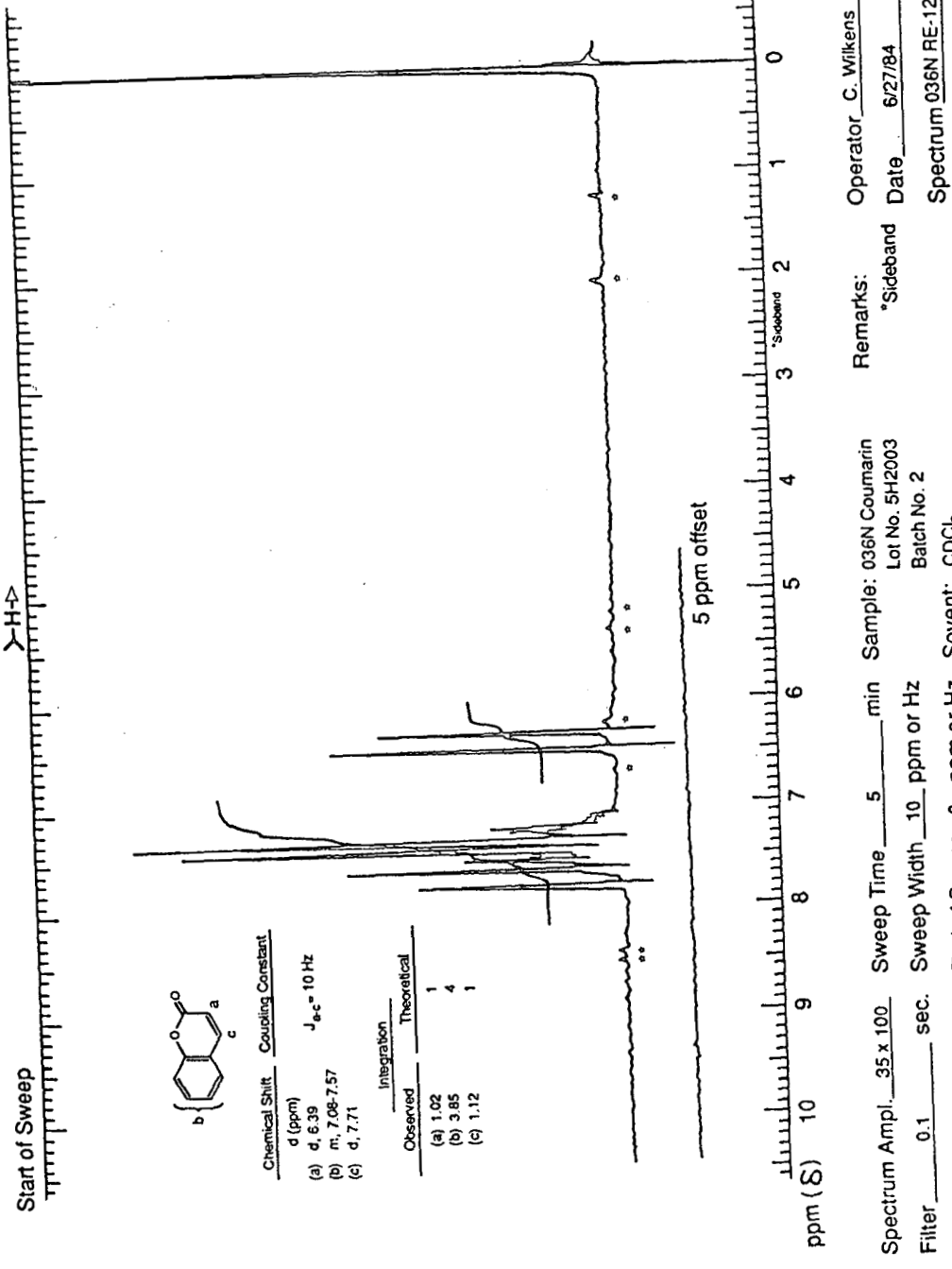


FIGURE I2
Nuclear Magnetic Resonance Spectrum of Coumarin

TABLE I1
Preparation and Storage of Dose Formulations in the Gavage Studies of Coumarin

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Coumarin was mixed with corn oil while stirring.	Coumarin was mixed with corn oil while stirring; homogeneity was maintained with a magnetic stir plate on day 1 and a Polytron homogenizer for the remainder of the studies.	Coumarin was mixed with corn oil using a magnetic stir bar and stirrer; all doses were homogenized for 30 to 60 seconds before stirring with an homogenizer.
Chemical Lot Number		
7971	7971	5H2003
Maximum Storage Time		
14 days	Same as 16-day studies	21 days
Storage Conditions		
Stored at room temperature in the dark.	Same as 16-day studies	Stored at room temperature in teflon sealed, amber serum bottles.
Study Laboratory		
International Research and Development Corporation, Mattawan, MI	Same as 16-day studies	American Biogenics Corporation, Woburn, MA
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 16-day studies	Same as 16-day studies

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of Coumarin

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
Rats[b]				
5 January 1981	19 January 1981	2.5	2.40	–4
		5.0	5.09	+2
		10.0	11.4	+14
		20.0	20.0	0
		40.0	43.0	+8
Mice[c]				
5 January 1981	29 January 1981	4.0	4.05	+1
		7.5	7.55	+1
		15.0	15.0	0
		30.0	32.5	+8
		60.0	57.4	–4

[a] Results of duplicate analyses
[b] Rats: 2.5 mg/mL = 25 mg/kg, 5.0 mg/mL = 50 mg/kg, 10.0 mg/mL = 100 mg/kg, 20.0 mg/mL = 200 mg/kg, and 40.0 mg/mL = 400 mg/kg; dosing volume = 10 mL/kg.
[c] Mice: 4.0 mg/mL = 40 mg/kg, 7.5 mg/mL = 75 mg/kg, 15.0 mg/mL = 150 mg/kg, 30.0 mg/mL = 300 mg/kg, and 60.0 mg/mL = 600 mg/kg; dosing volume = 10 mL/kg.

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Coumarin

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	% Difference from Target
Rats				
3 April 1981	6 April 1981	1.9	1.93	+2
		3.8	3.87	+2
		7.5	7.61	+1
		15.0	15.1	+1
		30.0	30.4	+1
15 May 1981	22 May 1981	1.9	1.91	+1
		3.8	3.89	+2
		7.5	7.68	+2
		15.0	15.6	+4
		30.0	29.2	–3
Mice				
6 April 1981	7 April 1981	1.9	1.84	–3
		3.8	3.65	–4
		7.5	7.65	+2
		15.0	15.2	+1
		30.0	29.7	–1
18 May 1981	22 May 1981	1.9	1.95	+3
		3.8	3.83	+1
		7.5	7.76	+3
		15.0	15.1	+1
		30.0	29.7	–1

[a] Mg/mL values: 1.9 mg/mL = 19 mg/kg, 3.8 mg/mL = 38 mg/kg, 7.5 mg/mL = 75 mg/kg, 15.0 mg/mL = 150 mg/kg, and 30.0 mg/mL = 300 mg/kg; dosing volume = 10 mL/kg.
[b] Results of duplicate analyses

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Coumarin

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
Rats[b]				
4 September 1984	5 September 1984	5	5.16	+3
		10	10.7	+7
		20	19.9	–1
	14 September 1984[c]	20	19.6	–2
	17 September 1984[c]	5	5.14	+3
		10	9.94	–1
22 October 1984	24 October 1984	5	5.14	+3
		10	10.1	+1
		20	19.3	–4
17 December 1984	18, 19 December 1984	5	5.22	+4
		5	5.32	+6
	20, 21 December 1984	10	9.99	0
		10	9.78	–2
		20	20.4	+2
		20	20.9	+5
11 February 1985	12, 13 February 1985	5	5.04	+1
		5	4.94	–1
		10	10.1	+1
		10	10.1	+1
		20	19.6	–2
		20	19.8	–1
	28 February 1985[c]	5	4.85	–3
		10	9.77	–2
		20	19.8	–1
8 April 1985	9 April 1985	5	4.88	–2
		5	4.87	–3
		10	10.0	0
		10	10.0	0
		20	19.8	–1
		20	19.6	–2
	25 April 1985[c]	5	5.33	+7
		10	10.9	+9
		20	21.4	+7
3 June 1985	4 June 1985	5	5.00	0
		5	5.00	0
		10	10.0	0
		10	10.2	+2
		20	19.9	–1
		20	19.8	–1

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Coumarin (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats (continued)				
29 July 1985	30 July 1985	5	4.90	–2
		5	4.89	–2
		10	10.0	0
		10	9.88	–1
		20	19.4	–3
		20	19.5	–3
	16 August 1985[c]	5	5.07	+1
		10	10.3	+3
		20	21.3	+7
7 October 1985	8 October 1985	5	5.02	0
		5	5.03	+1
		10	9.99	0
		10	9.92	–1
		20	19.9	–1
		20	19.8	–1
2 December 1985	3 December 1985	5	4.75	–5
		5	4.79	–4
		5	4.71	–6
		10	9.52	–5
		10	9.49	–5
		20	19.6	–2
		20	19.0	–5
	19 December 1985[c]	5	5.09	+2
		10	9.63	–4
		20	19.2	–4
27 January 1986	28 January 1986	5	4.78	–4
		5	4.98	0
		10	9.39	–6
		10	9.16	–8
		20	20.0	0
		20	19.9	–1
31 March 1986	1 April 1986	5	4.56	–9
		5	4.72	–6
		10	9.72	–3
		10	9.80	–2
		20	19.0	–5
		20	19.4	–3
	17 April 1986[c]	5	4.81	–4
		10	9.43	–6
		20	19.5	–3

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Coumarin (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats (continued)				
12 May 1986	13 May 1986	5	5.13	+3
		5	5.14	+3
		10	10.0	0
		10	9.87	–1
		20	19.2	–4
		20	19.7	–2
7 July 1986	8 July 1986	5	4.94	–1
		5	4.96	–1
		10	10.0	0
		10	10.1	+1
		20	20.8	+4
		20	20.8	+4
18 August 1986	19 August 1986	5	5.02	0
		5	5.06	+1
		10	9.48	–5
		20	19.3	–4
Mice[d]				
5 November 1984	7 November 1984	5	5.06	+1
		10	10.1	+1
	15 November 1984[c]	5	4.91	–2
		10	10.2	+2
		20	19.5	–3
6 November 1984	7 November 1984	20	20.0	0
17 December 1984	18, 19 December 1984	5	5.22	+4
		5	5.32	+6
	20, 21 December 1984	10	9.99	0
		10	9.78	–2
		20	20.4	+2
		20	20.9	+5
11 February 1985	12, 13 February 1985	5	5.04	+1
		5	4.94	–1
		10	10.1	+1
		10	10.1	+1
		20	19.6	–2
		20	19.8	–1
	28 February 1985[c]	5	4.85	–3
		10	9.77	–2
		20	19.8	–1

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Coumarin (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Mice (continued)				
8 April 1985	9 April 1985	5	4.88	–2
		5	4.87	–3
		10	10.0	0
		10	10.0	0
		20	19.8	–1
		20	19.6	–2
	25 April 1985[c]	5	5.33	+7
		10	10.9	+9
		20	21.4	+7
3 June 1985	4 June 1985	5	5.00	0
		5	5.00	0
		10	10.0	0
		10	10.2	+2
		20	19.9	–1
		20	19.8	–1
29 July 1985	30 July 1985	5	4.90	–2
		5	4.89	–2
		10	10.0	0
		10	9.88	–1
		20	19.4	–3
		20	19.5	–3
	16 August 1985[c]	5	5.07	+1
		10	10.3	+3
		20	21.3	+7
7 October 1985	8 October 1985	5	5.02	0
		5	5.03	+1
		10	9.99	0
		10	9.92	–1
		20	19.9	–1
		20	19.8	–1
	24 October 1985[c]	5	4.87	–3
		10	9.81	–2
		20	20.0	0
2 December 1985	3 December 1985	5	4.75	–5
		5	4.79	–4
		10	9.52	–5
		10	9.49	–5
		20	19.6	–2
		20	19.0	–5

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Coumarin (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Mice (continued)				
27 January 1986	28 January 1986	5	4.78	–4
		5	4.98	0
		10	9.39	–6
		10	9.16	–8
		20	20.0	0
		20	19.9	–1
31 March 1986	1 April 1986	5	4.56	–9
		5	4.72	–6
		10	9.72	–3
		10	9.80	–2
		20	19.0	–5
		20	19.4	–3
	17 April 1986[c]	5	4.74	–5
		10	9.50	–5
		20	19.3	–4
12 May 1986	13 May 1986	5	5.13	+3
		5	5.14	+3
		10	10.0	0
		10	9.87	–1
		20	19.2	–4
		20	19.7	–2
7 July 1986	8 July 1986	5	4.94	–1
		5	4.96	–1
		10	10.0	0
		10	10.1	+1
		20	20.8	+4
		20	20.8	+4
18 August 1986	19 August 1986	5	5.02	0
		5	5.06	+1
		10	9.48	–5
		20	19.3	–4
14 October 1986	15 October 1986	5	5.09	+2
		10	10.2	+2
		20	19.9	–1
	30 October 1986[c]	5	5.09	+2
		10	9.81	–2
		20	18.8	–6

[a] Mean of duplicate analyses
[b] Rats: 5 mg/mL = 25 mg/kg, 10 mg/mL = 50 mg/kg, and 20 mg/mL = 100 mg/kg; dosing volume = 5 mL/kg.
[c] Animal room samples
[d] Mice: 5 mg/mL= 50 mg/kg, 10 mg/mL = 100 mg/kg, and 20 mg/mL = 200 mg/kg; dosing volume = 10 mL/kg.

TABLE I5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Coumarin

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
4 September 1984	20	19.9	19.9
8 April 1985	10	10.0	9.96
7 October 1985	5	5.03	5.26
31 March 1986	10	9.72	10.2
18 August 1986	5	5.02	4.97

[a] Results of duplicate analyses
[b] Results of triplicate analyses

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

TABLE J1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

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

TABLE J2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.11 ± 0.49	21.1 – 23.1	23
Crude fat (% by weight)	5.58 ± 0.48	4.7 – 6.5	23
Crude fiber (% by weight)	3.46 ± 0.48	2.7 – 5.4	23
Ash (% by weight)	6.45 ± 0.25	6.1 – 6.8	23
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)	9,091 ± 2,401	5,600 – 15,000	23
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.41	22.5 – 48.9	8
Thiamine (ppm)	20.30 ± 1.58	17.0 – 23.0	23
Riboflavin (ppm)	7.92 ± 0.87	6.10 – 9.00	8
Niacin (ppm)	103.4 ± 26.59	65.0 – 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0 – 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60 – 14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80 – 3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19 – 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 – 65.0	8
Choline (ppm)	3,089 ± 328.69	2,400 – 3,430	8
Minerals			
Calcium (%)	1.14 ± 0.10	0.95 – 1.41	23
Phosphorus (%)	0.92 ± 0.05	0.73 – 0.99	23
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)	360.5 ± 100	255.0 – 523.0	8
Manganese (ppm)	92.0 ± 6.01	81.70 – 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10 – 64.50	8
Copper (ppm)	11.06 ± 2.50	8.090 – 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52 – 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04 – 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490 – 0.780	4

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.76 ± 0.17	0.32 – 1.07	23
Cadmium (ppm)	<0.1		23
Lead (ppm)	0.53 ± 0.26	0.05 – 1.32	23
Mercury (ppm)	<0.05		23
Selenium (ppm)	0.35 ± 0.09	0.17 – 0.48	23
Aflatoxins (ppb)	<5.0		23
Nitrate nitrogen (ppm)[b]	14.96 ± 4.73	2.80 – 22.0	23
Nitrite nitrogen (ppm)[bc]	0.29 ± 0.58	<0.10 – 2.60	23
BHA (ppm)[d]	2.61 ± 1.08	<2.00 – 5.00	23
BHT (ppm)[d]	1.91 ± 1.08	<1.00 – 4.00	23
Aerobic plate count (CFU/g)[e]	38,337 ± 42,308	7,770 – 130,000	23
Coliform (MPN/g)[f]	16.22 ± 49.50	<3.00 – 240	23
E. coli (MPN/g)[g]	6.04 ± 8.57	<3.00 – 43.0	23
E. coli (MPN/g)[h]	3.04 ± 0.21	<3.00 – 4.00	23
Total nitrosoamines (ppb)[i]	7.47 ± 3.14	3.80 – 16.0	23
N-Nitrosodimethylamine (ppb)[i]	6.31 ± 2.93	2.80 – 15.0	23
N–Nitrosopyrrolidine (ppb)[i]	1.16 ± 0.56	<1.00 – 3.40	23
Pesticides			
α–BHC[j]	<0.01		23
ß–BHC	<0.02		23
γ–BHC	<0.01		23
δ–BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.1		23
Estimated PCB's	<0.2		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.1		23
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion[k]	0.24 ± 0.66	0.05 – 3.20	23
Endosulfan 1	<0.01		23
Endosulfan 2	<0.01		23
Endosulfan sulfate	<0.03		23

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Includes one large value of 7.20 ppm obtained from the lot milled on 17 August 1983.
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony forming unit
[f] MNP = most probable number
[g] Excludes one high value of 240 MPN/g obtained from the lot milled on 14 September 1984.
[h] Includes one value of 4.0 MPN/g obtained from the lot milled on 17 October 1984.
[i] All values were corrected for percent recovery.
[j] BHC = hexachlorocyclohexane or benzene hexachloride
[k] Nine lots contained more than 0.05 ppm, including one lot milled on 7 May 1985 that contained 3.20 ppm.

APPENDIX K
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 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.

Rats

During the 2-year study, 15 F344/N rats of each sex were maintained with the study animals to serve as sentinel animals. At 6, 12, and 18 months into the study, blood was drawn from five rats of each sex. Additional analyses were conducted at the final sacrifice (24 months) on samples collected from vehicle control animals. Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
KRV (Kilham rat virus)	6, 12, 18, and 24 months
H-1 (Toolan's H-1 virus)	6, 12, 18, and 24 months
ELISA	
Mycoplasma arthritidis	6, 12, and 18 months
Mycoplasma pulmonis	6, 12, 18, and 24 months
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	6, 12, and 18 months
RCV (rat coronavirus)	24 months
CARB (cilia-associated respiratory bacillus)	24 months

Mice

During the 2-year study, 15 F344/N rats of each sex were maintained with the study animals to serve as sentinel animals. At 6, 12, and 18 months into the study, blood was drawn from five rats of each sex. Additional analyses were conducted at the final sacrifice (24 months) on samples collected from vehicle control animals. Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
K (papovirus)	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	6, 12, 18 months

Mice (continued)

Method of Analysis	Time of Analysis
ELISA	
M. arthritidis	6, 12, 18, and 24 months
M. pulmonis	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
Ectromelia virus	6, 12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
Immunofluorescent Assay	
EDIM (Epizootic diarrhea of infant mice)	6, 12, 18, and 24 months
LCM	24 months

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Gavage Studies of Coumarin

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats	6 months	10/10	PVM
		1/10	Possible *M. arthritidis*
	12 months	10/10	PVM
	18 months	10/10	PVM
		1/10	KRV
	24 months	8/9	PVM
Mice	6 months	0/10	None positive
	12 months	0/10	None positive
	18 months	0/8	None positive
	24 months	0/10	None positive

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF SEPTEMBER 1993

TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4′-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

☆ U.S. GOVERNMENT PRINTING OFFICE: 1993 300-970/00001

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF SEPTEMBER 1993 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Rotenone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Hellow 4
427	Turmeric Oleoresin
434	1,3-Butadiene
443	Oxazepam

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD A0-01
Research Triangle Park, NC 27709

Official Business
Penalty for Private Use - $300

NIH Publication No. 93-3153
September 1993