NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 423

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 3,4-DIHYDROCOUMARIN

(CAS NO. 119-84-6)

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.

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NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
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CONTENTS

ABSTRACT 5

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 10

TECHNICAL REPORTS REVIEW SUBCOMMITTEE 11

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS 12

INTRODUCTION 13

MATERIALS AND METHODS 19

RESULTS 31

DISCUSSION AND CONCLUSIONS 65

REFERENCES 69

APPENDIX A Summary of Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 75

APPENDIX B Summary of Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 121

APPENDIX C Summary of Lesions in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 165

APPENDIX D Summary of Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 209

APPENDIX E Summary of Lesions in Male Rats in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin 251

APPENDIX F Genetic Toxicology 281

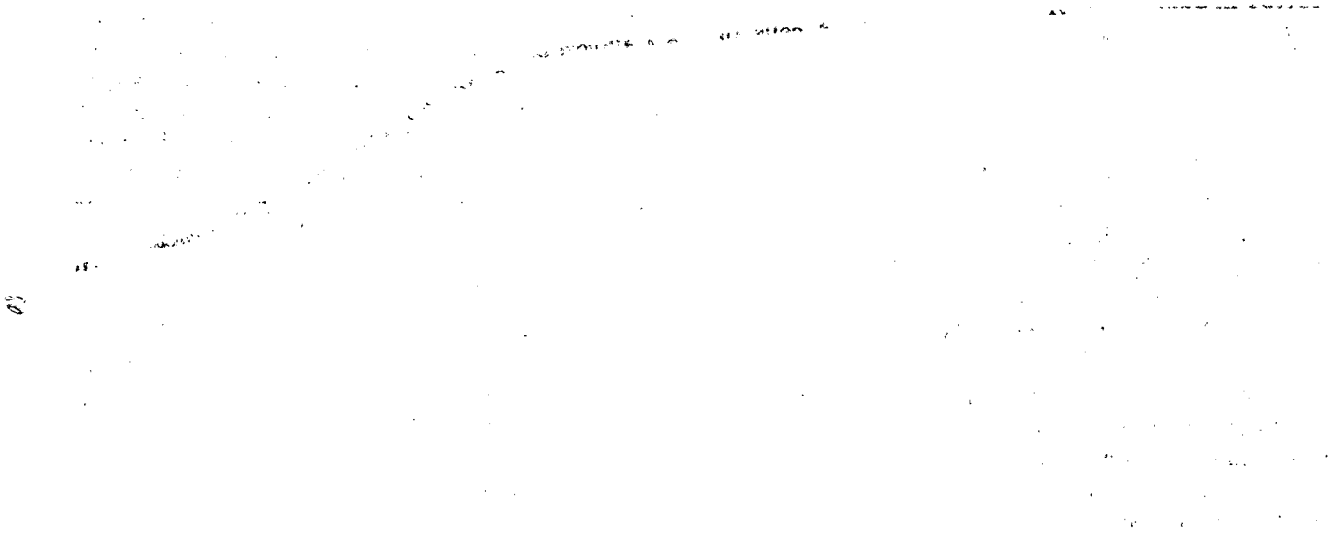
APPENDIX G Organ Weights and Organ-Weight-to-Body-Weight Ratios 291

APPENDIX H Hematology and Clinical Chemistry Results 301

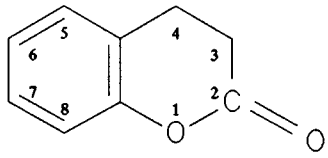
APPENDIX I Chemical Characterization and Dose Formulation Studies 317

APPENDIX J Ingredients, Nutrient Composition, and Contaminant Levels in NIH-07 Rat and Mouse Ration 331

APPENDIX K Sentinel Animal Program 337



ABSTRACT



3,4-DIHYDROCOUMARIN

CAS No. 119-84-6

Chemical Formula: $C_9H_8O_2$ Molecular Weight: 148.17

Synonyms: 1,2-benzodihydropyrone, 2H-1-benzopyran-2-one, 2-chromanone, 3,4-dihydro-2H-1-benzopyran-2-one, dihydrocoumarin, hydrocoumarin, *o*-hydroxycinnamic acid, delta-lactone-hydrocinnamic acid, melilotin, melilotine, melilotol, 2-oxochroman

3,4-Dihydrocoumarin was nominated by the Food and Drug Administration and the National Cancer Institute for study because of its widespread use as a flavoring agent in beverages, gelatins, puddings, candy, and other food items; as a fragrance in perfumes, creams, and cosmetics; and because of interest in the structure-activity relationships of the coumarin derivatives.

Toxicity and carcinogenicity studies were conducted by administering 3,4-dihydrocoumarin (99% 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, and peripheral blood cells of mice.

16-Day Study in Rats

Groups of five male and five female rats received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 190, 375, 750, 1,500, or 3,000 mg/kg body weight 5 days per week for a total of 12 doses in a 16-day period. All male and female rats given 3,000 mg/kg, and four male rats and five female rats given 1,500 mg/kg died. Body weight gains and final mean body weights of rats receiving 190, 375, or 750 mg/kg were similar to those of the controls. There were no clinical findings of organ-specific toxicity or evidence of impaired blood coagulation.

16-Day Study in Mice

Groups of five male and five female mice received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 140, 280, 560, 1,125, or 2,250 mg/kg body weight 5 days per week for a total of 12 doses in a 16-day period. All mice given 2,250 mg/kg died. Body weight gains and final mean body weights of mice receiving 140, 280, 560, and 1,125 mg/kg were similar to those of the controls. There were no clinical findings of organ-specific toxicity or evidence of impaired blood coagulation.

13-Week Study in Rats

Groups of 10 male and 10 female rats received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 75, 150, 300, 600, or 1,200 mg/kg body weight 5 days per week for 13 weeks. Two male rats and five female rats given 1,200 mg/kg died. The body weight gain and final mean body weight of male rats that received 1,200 mg/kg were significantly lower than those of the controls, but the final mean body weights of other dosed groups of male rats and all dosed groups of female rats were similar to or slightly greater than those of the controls. Platelet counts were significantly lower in males and females receiving 600 and 1,200 mg/kg and in females receiving 300 mg/kg. Hemoglobin and hematocrit values and erythrocyte counts were significantly lower in males that received 300 mg/kg or more. The absolute and relative liver and kidney weights of males and females

receiving 600 and 1,200 mg/kg were significantly greater than those of the controls. Hepatocellular hypertrophy was observed in rats given 300, 600, and 1,200 mg/kg. The high dose selected for the 2-year study was 600 mg/kg, which was below the level at which mortality, lower final mean body weights, and treatment-related liver lesions were observed.

13-Week Study in Mice

Groups of 10 male and 10 female mice received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 100, 200, 400, 800, or 1,600 mg/kg body weight 5 days per week for 13 weeks. Eight male and five female mice receiving 1,600 mg/kg died. Deaths in other groups were attributed to dosing accidents. Final mean body weights of dosed male and female mice were similar to those of the controls, and there were no treatment-related changes in any hematologic parameters. The absolute and relative liver weights of males and females that received 1,600 mg/kg and the relative kidney weight of males that received 1,600 mg/kg were significantly greater than those of the controls. No treatment-related lesions were noted. The high dose selected for the 2-year study was 600 mg/kg, which was below the level at which mortality, lower final mean body weights, and treatment-related liver lesions were observed.

2-Year Study in Rats

Groups of 60 male and 60 female rats received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 150, 300, or 600 mg/kg body weight. After 15 months, up to 10 animals from each group were evaluated.

Survival, Body Weights, and Clinical Findings

Survival rates of dosed male rats were lower than that of the controls (0 mg/kg, 28/51; 150 mg/kg, 12/50; 300 mg/kg, 8/50; 600 mg/kg, 2/50) but survival rates of dosed female rats were similar to that of the controls (31/50, 21/51, 26/50, 23/51). The decreased survival in dosed male rats was attributed to a chemical-related increase in the severity of nephropathy. The final mean body weight of male rats receiving 600 mg/kg was lower than that of the controls, but the final mean body weights of other dosed groups of male rats and all dosed groups of female rats were similar to those of the controls. No clinical findings related to chemical administration were observed.

Hematology and Clinical Chemistry

At the 15-month interim evaluation, the hemoglobin concentrations, mean erythrocyte volumes, or mean erythrocyte hemoglobin concentrations in the 300 and 600 mg/kg female rats were slightly, but significantly, lower than those of the controls. In males, only the hemoglobin concentration in the 600 mg/kg group was significantly lower. Serum levels of alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, or γ-glutamyltransferase in the 300 and 600 mg/kg male rats were significantly higher than those in the controls. In females, alkaline phosphatase and γ-glutamyltransferase levels were significantly higher in the 600 mg/kg group.

Pathology Findings

The principal lesions associated with the administration of 3,4-dihydrocoumarin to rats occurred in the kidney and forestomach. There was a chemical-related increase in the severity of nephropathy in all dosed male rats and in 300 and 600 mg/kg female rats. There was a corresponding increased incidence of parathyroid gland hyperplasia, probably as a result of compromised renal function. In the standard evaluation of single kidney sections, renal tubule adenomas were observed in one 150 and two 600 mg/kg males and one each in the control, 150, and 300 mg/kg females. Transitional cell carcinomas were also observed in two 600 mg/kg male rats. However, an extended evaluation of step sections identified significantly higher incidences of focal hyperplasia and adenoma in the 600 mg/kg males than in controls (hyperplasia: 0/50, 5/48, 6/47, 8/50; adenoma: 1/50, 1/48, 3/47, 6/50).

The incidence of forestomach ulcers in all groups of dosed male rats was significantly greater than that of the controls (4/47, 14/48, 20/50, 16/46).

Stop-Exposure Evaluation

A group of 40 male rats received 600 mg/kg 3,4-dihydrocoumarin 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 until the end of the study. Similarly, a group of 30 male rats received 600 mg/kg 3,4-dihydrocoumarin 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 was necropsied

at 9 months, and another 10 vehicle control male rats were necropsied at 15 months.

The severity of nephropathy in male rats of the stop-exposure groups was significantly greater than that of males examined at the 9- and 15-month interim evaluations. This was expected because nephropathy is a progressive degenerative disease that naturally increases in severity with age.

2-Year Study in Mice

Groups of 70 male and 70 female mice received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 200, 400, or 800 mg/kg body weight. After 15 months, five to 10 animals from each group were evaluated. Additional groups of 8 to 10 animals were evaluated for clinical pathology after 15 months.

Survival, Body Weights, and Clinical Findings

Survival rates of dosed male and female mice were similar to those of the controls (males: 0 mg/kg, 42/50; 200 mg/kg, 39/51; 400 mg/kg, 34/51; 800 mg/kg, 38/50; females: 36/51, 39/50, 41/50, 28/52). Final mean body weights of dosed male and female mice were similar to those of the controls. No clinical findings were noted that were related to chemical administration.

Hematology and Clinical Chemistry

There were no differences in hematology or clinical chemistry parameters that were considered to be chemical related.

Pathology Findings

The principal neoplasms associated with the administration of 3,4-dihydrocoumarin to mice occurred in the liver. There were significantly increased incidences of hepatocellular adenomas in all groups of dosed female mice. Further, the incidences of multiple hepatocellular adenomas in dosed female mice were greater than that of the controls (control, 0/51; 200 mg/kg, 6/50; 400 mg/kg, 9/50; 800 mg/kg, 9/52). However, there was no corresponding increased incidence of hepatocellular carcinoma in dosed female mice (3/51, 2/50, 4/50, 6/52), and the incidences of hepatocellular adenoma or carcinoma were similar between dosed and control male groups (adenoma: 29/50, 23/51, 36/51, 31/50; carcinoma: 11/50, 11/51, 11/51, 6/50).

The incidence of alveolar/bronchiolar adenoma in the 200 and 400 mg/kg male mice was marginally greater than that of the controls (8/50, 15/50, 15/51, 10/50). However, these neoplasms were not considered chemical related because the increased incidence was slight and there was no corresponding increased incidence in the 800 mg/kg group. The incidence of alveolar/bronchiolar neoplasms in female mice was similar between the dosed and control groups (adenoma: 2/51, 5/50, 1/48, 3/51; carcinoma: 0/51, 1/50, 0/48, 0/51).

In the standard evaluation of single sections of kidney, focal hyperplasia and adenoma or carcinoma of the renal tubule were identified in several dosed male mice, but not in controls [adenoma or carcinoma (combined): 0/50, 1/51, 2/51, 1/49; hyperplasia: 2/50, 2/51, 5/51, 2/49]. In an extended evaluation of step sections, a few additional males with focal hyperplasia or renal tubule adenomas were identified in the dosed groups. However, the incidences of these lesions in dosed groups of male mice were not significantly greater than those of the controls, and did not increase with dose (hyperplasia: 0/50, 1/51, 3/51, 1/49; renal tubule adenoma: 0/50, 0/51, 2/51, 1/49). Therefore, the low number of renal tubule neoplasms in male mice was not considered to be chemical related.

Genetic Toxicology

3,4-Dihydrocoumarin did not induce gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without exogenous metabolic activation (S9). It induced sister chromatid exchanges but not chromosomal aberrations in cultured Chinese hamster ovary cells, with and without S9. No induction of micronuclei was noted in peripheral blood erythrocyte samples obtained from male and female B6C3F$_1$ mice at the end of the 13-week toxicology study.

Conclusions

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of 3,4-dihydrocoumarin in male F344/N rats based on increased incidences of renal tubule adenomas and focal hyperplasia. The transitional cell carcinomas in two 600 mg/kg males may also have been chemical

related. There was *no evidence of carcinogenic activity* of 3,4-dihydrocoumarin in female F344/N rats receiving 150, 300, or 600 mg/kg. There was *no evidence of carcinogenic activity* of 3,4-dihydrocoumarin in male B6C3F$_1$ mice receiving 200, 400, or 800 mg/kg. There was *some evidence of carcinogenic activity* in female B6C3F$_1$ mice based on increased incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined).

3,4-Dihydrocoumarin caused ulcers, hyperplasia, and inflammation of the forestomach, parathyroid gland hyperplasia, and increased severity of nephropathy in male rats.

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

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 3,4-Dihydrocoumarin

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses			
0, 150, 300, or 600 mg/kg in corn oil by gavage	0, 150, 300, or 600 mg/kg in corn oil by gavage	0, 200, 400, or 800 mg/kg in corn oil by gavage	0, 200, 400, or 800 mg/kg in corn oil by gavage
Body weights			
High-dose group lower than controls	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls
2-Year survival rates			
28/51, 12/50, 8/50, 2/50	31/50, 21/51, 26/50, 23/51	42/50, 39/51, 34/51, 38/50	36/51, 39/50, 41/50, 28/52
Nonneoplastic effects			
Forestomach: ulcer (4/47, 14/48, 20/50, 16/46); hyperplasia (3/47, 11/48, 14/50, 11/46); inflammation (3/47, 8/48, 15/50, 8/46) Parathyroid gland: hyperplasia (0/47, 15/41, 26/48, 19/41) Kidney: renal tubule hyperplasia - single sections (0/50, 3/48, 0/47, 3/50); step sections (0/50, 3/48, 6/47, 6/50); nephropathy severity grades (2.2, 2.9, 3.2, 3.2)	None	None	None
Neoplastic effects			
Kidney: renal tubule adenoma - single sections (0/50, 1/48, 0/47, 2/50); step sections (1/50, 0/48, 3/47, 5/50)	None	None	Liver: hepatocellular adenoma (10/51, 20/50, 22/50, 20/52); hepatocellular adenoma or carcinoma (combined) (13/51, 21/50, 25/50, 24/52)
Uncertain findings			
Kidney: transitional cell carcinoma (0/50, 0/48, 0/47, 2/50)	None	None	None
Level of evidence of carcinogenic activity			
Some evidence	No evidence	No evidence	Some evidence
Genetic toxicology			
Salmonella typhimurium gene mutation:		Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537	
Sister chromatid exchanges Chinese hamster ovary cells *in vitro*:		Positive without S9; weakly positive with S9	
Chromosomal aberrations Chinese hamster ovary cells *in vitro*:		Negative with and without S9	
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 lesions 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 3,4-dihydrocoumarin 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.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 23, 1992, the draft Technical Report on the toxicology and carcinogenesis studies of 3,4-dihydrocoumarin 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 3,4-dihydrocoumarin by discussing the uses and rationale for the study, describing the experimental design including the additional 2-year stop-exposure evaluation in rats, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in rats and mice. She noted that additional step-sections of the kidney of male and female rats and male mice were examined.

The proposed conclusions were *some evidence of carcinogenic activity* of 3,4-dihydrocoumarin in male F344/N rats, *no evidence of carcinogenic activity* in female F344/N rats, *no evidence of carcinogenic activity* in male B6C3F_1 mice, and *some evidence of carcinogenic activity* in female B6C3F_1 mice.

Dr. Dunnick presented a brief comparison of the toxic effects of coumarin and 3,4-dihydrocoumarin in 2-year studies. She noted that: (1) coumarin and 3,4-dihydrocoumarin caused increases in nephropathy and kidney neoplasms in male rats; (2) coumarin, but not 3,4-dihydrocoumarin, caused liver toxicity in rats and mice; (3) coumarin and 3,4-dihydrocoumarin caused treatment-related hepatocellular neoplasms in female mice; and (4) significant treatment-related lung lesions were observed after coumarin treatment, but not after treatment with 3,4-dihydrocoumarin.

Dr. Davidson, a principal reviewer, agreed with the proposed conclusions. She asked about the apportionment of the additional controls used for the stop-exposure evaluation. (All additional controls were sacrificed at the 9- and 15-month evaluations.)

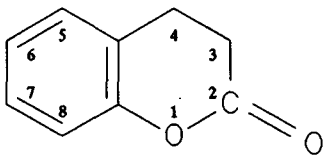
Dr. Hayden, the second principal reviewer, agreed with the proposed conclusions. He thought the mice might have been able to tolerate higher doses. He asked if there was an explanation for the significant reduction in cholinesterase values in male and female rats. Dr. Dunnick said there was not an apparent biological explanation for these reductions.

Dr. Bailey, the third principal reviewer, agreed with the proposed conclusions. He also thought that male and female mice might have tolerated higher doses. Dr. Dunnick said there was treatment-related mortality at 1,600 mg/kg in the 13-week study mice but not at 800 mg/kg, which was the rationale for selecting the high dose.

Dr. Zeise noted the occurrence of rare neoplasms, hepatoblastomas, in male mice, and asked for comment. Dr. S.L. Eustis, NIEHS, explained that hepatoblastomas are hepatocellular carcinomas with a clonal proliferation of cells which are similar to embryonic hepatoblasts and should not be considered separately from carcinomas.

Dr. Hayden moved that the Technical Report on 3,4-dihydrocoumarin be accepted with the revisions discussed and with the conclusions as written for male rats and female mice, *some evidence of carcinogenic activity*, and for female rats and male mice, *no evidence of carcinogenic activity*. Dr. Bailey seconded the motion, which was accepted unanimously with eight votes.

INTRODUCTION



3,4-DIHYDROCOUMARIN

CAS No. 119-84-6

Chemical Formula: $C_9H_8O_2$ Molecular Weight: 148.17

Synonyms: 1,2-benzodihydropyrone, 2H-1-benzopyran-2-one, 2-chromanone, 3,4-dihydro-2H-1-benzopyran-2-one, dihydrocoumarin, hydrocoumarin, *o*-hydroxycinnamic acid, delta-lactone-hydrocinnamic acid, melilotin, melilotine, melilotol, 2-oxochroman

CHEMICAL AND PHYSICAL PROPERTIES

3,4-Dihydrocoumarin is a colorless liquid with a sweet odor. It is insoluble in water, but soluble in alcohol, chloroform, and ether. The melting point of 3,4-dihydrocoumarin is 25° C and the boiling point is 272° C. 3,4-Dihydrocoumarin has an odor similar to coumarin and is synthesized by the reduction of coumarin under pressure in the presence of nickel at 150° to 200° C (Hawley, 1977; *Kirk-Othmer*, 1978).

USE AND HUMAN EXPOSURE

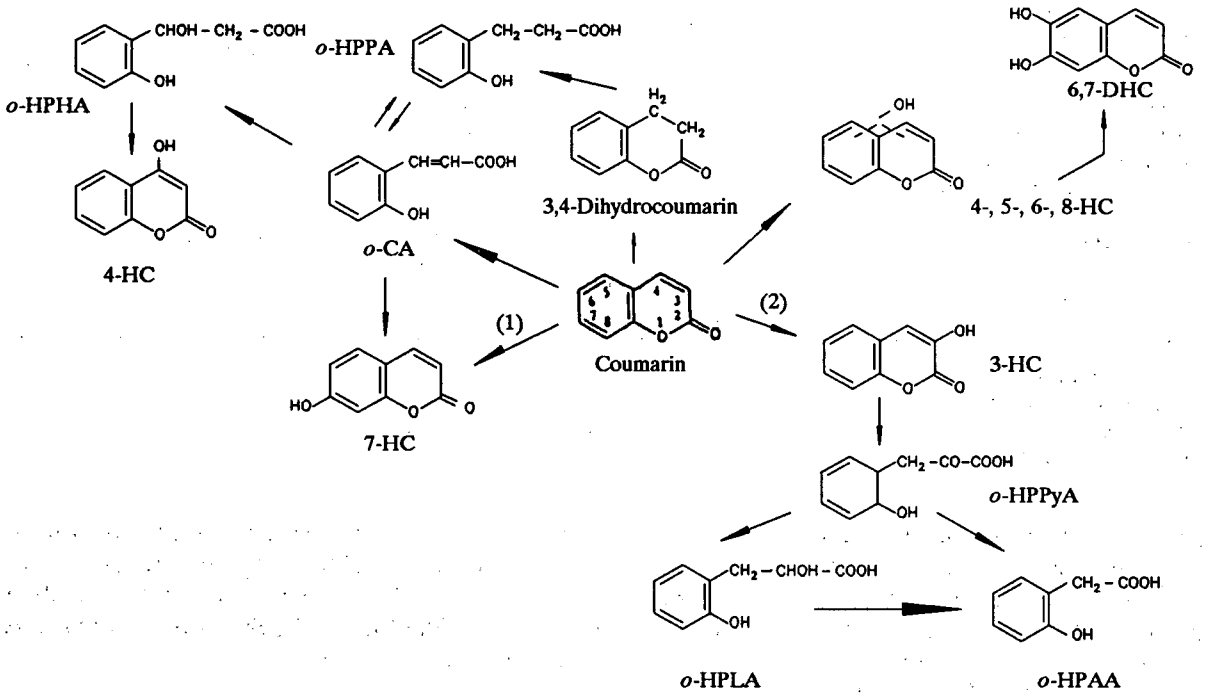
3,4-Dihydrocoumarin is not on the Food and Drug Administration lists of synthetic or natural food flavoring substances that are generally recognized as safe, nor is it regulated as a food additive. However, it is generally recognized as safe by the Flavor and Extract Manufacturers' Association for use as a synthetic flavoring ingredient in food, and it has been used as a component of artificial flavors in food; the FDA has no objection to such use now. 3,4-Dihydrocoumarin is used as a flavoring agent to give a sweet caramel-like taste to beverages (7.8 ppm), frozen desserts (21 ppm), baked goods (28 ppm), gelatins and puddings (10 ppm), candy (44 ppm), and chewing gum (78 ppm). It is also used as a fragrance in perfumes, creams, lotions, soaps, and detergents (*Fenaroli's*, 1971; Opdyke, 1974). The United States annual production of 3,4-dihydrocoumarin is estimated to be 14 metric tons (*Kirk-Othmer*, 1978).

The National Institute for Occupational Safety and Health estimated that approximately 2,054 workers are potentially exposed to 3,4-dihydrocoumarin (NIOSH, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Although studies on the metabolism of 3,4-dihydrocoumarin have not been reported in the literature, the metabolism and excretion of coumarin have been studied in several different species including humans. As a basis for comparison, the probable pathways for the metabolism of coumarin are shown in Figure 1, and the metabolites identified and the percentages of dose excreted in the urine and feces for the rat, rabbit, and human are shown in Table 1.



(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)

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

	Rabbit[b]	Rat[b]	Man[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 percent of dose administered
[b] From Kaighen and Williams (1961)
[c] From Shilling *et al.* (1969)
[d] Metabolite not measured for this species.

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 orally, 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). Over 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 tissues following oral administration to rats (Kaighen and Williams, 1961; Feuer *et al.*, 1966) or rabbits (Kaighen and Williams, 1961), or following intraperitoneal administration to rats (van Sumere and Teuchy, 1971). Following the administration of a single intraperitoneal dose of [3-^{14}C]-coumarin, ^{14}C was detected in various organs, particularly the liver and kidneys, at levels much higher than that in the blood at any given period (Piller, 1977). The blood and tissue levels declined steadily over a post-administration period of 100 hours with a half-life of approximately 43 hours. Ritschel *et al.* (1977) 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.

Coumarin is metabolized primarily in the liver by microsomal enzymes associated with the endoplasmic reticulum (Feuer *et al.*, 1966; Feuer, 1974; Peters *et al.*, 1991). Coumarin is first metabolized by cytochrome P-450 enzymes resulting in hydroxylation prior to conjugation with glucuronide. Hydroxylation occurs primarily at positions 3 and 7 to yield 3-hydroxycoumarin and 7-hydroxycoumarin, respectively. 3-Hydroxycoumarin can be further metabolized by nonenzymatic ring opening to form *o*-hydroxyphenylacetic acid and *o*-hydroxyphenyllactic acid. 3,4-Dihydrocoumarin may also undergo ring opening to form *o*-hydroxyphenyllactic acid as shown in Figure 1.

There are substantial qualitative differences in the metabolism of coumarin among various species. Studies with rat hepatic microsomes have found that coumarin is metabolized by isoenzymes of the cytochrome P-450 IA and IIB subfamilies, resulting in hydroxylation primarily at position 3 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 of coumarin apparently also occurs at other ring positions, the extent of activity at positions 4, 5, 6, 7, or 8 is low in rats.

In contrast to rats, metabolism of coumarin in humans results primarily in hydroxylation at the 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, 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 are largely reflected by the quantitative differences in hydroxylation at the 3 and 7 positions. Gangolli *et al.* (1974) found that the fraction of coumarin found as 7-hydroxycoumarin in the urine of various species 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.

Humans

No information on the absorption, distribution, metabolism, or excretion of 3,4-dihydrocoumarin in humans has been reported.

TOXICITY

Experimental Animals

The oral LD_{50} for 3,4-dihydrocoumarin in rats was reported as 1,460 mg/kg (Jenner *et al.*, 1964). The LD_{50} value for the structurally related chemical, coumarin, in rats was reported as 292 mg/kg to 680 mg/kg (Hazleton *et al.*, 1956). The oral LD_{50} for coumarin was reported as 420 mg/kg in C3H/HeJ mice and 780 mg/kg in DBA/2J mice (Endell and Seidel, 1978).

There is little published information on the toxicity of 3,4-dihydrocoumarin. Most of the studies in the literature deal with the toxicity of coumarin where liver is reported as the primary target organ in animals.

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 coumarin at a level of 10,000 ppm 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 one 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

No information concerning the toxic effects of 3,4-dihydrocoumarin in humans is available.

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 observed at all levels (Roll and Bär, 1967). The purity of the coumarin used in these studies was not given.

Humans

No information on reproductive or developmental toxicity in humans has been reported.

Carcinogenicity

Experimental Animals

No neoplasms were found 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. Only a few animals were included in each treatment group (Dickens and Waynforth, 1968). In addition, no neoplasms 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).

Coumarin administered at a dietary 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 neoplasms. 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 fed diets which delivered 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 neoplasms. 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 after long-term administration of coumarin as bile duct carcinomas. 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 observed 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 carcinomas 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.

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

Humans

No published information is available on the carcinogenicity of 3,4-dihydrocoumarin in humans.

Genetic Toxicology

Published genotoxicity data for 3,4-dihydrocoumarin are limited to two *Salmonella typhimurium* gene mutation tests conducted with and without S9. Results from both studies were negative (Prival *et al.*, 1982; Haworth *et al.*, 1983).

The structural analogue and metabolic precursor, coumarin, induced gene mutations in *Salmonella*

typhimurium strain TA100 with S9; no mutagenic activity was noted in any other tester strains with or without S9 (Stoltz and Scott, 1980; Norman and Wood, 1981; Haworth *et al.*, 1983; NTP, 1993). Coumarin did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Yoon *et al.*, 1985; Valencia *et al.*, 1989; NTP, 1993), and no increase in unscheduled DNA synthesis was reported in rat tracheal epithelium cultures treated with coumarin in the absence of S9 (Ide *et al.*, 1981). Chromosomal effects (breakage, sister chromatid exchanges, mitotic inhibition) have been reported in mammalian cells (Galloway *et al.*, 1987; NTP, 1993) and plants (D'Amato and D'Amato-Avanzi, 1954; Riley and Hoff, 1960; Sarma and Tripathi, 1976) following treatment with coumarin. No increases in micronucleated normochromatic erythrocytes were observed in a study of mice administered coumarin by gavage for 13 weeks (NTP, 1993).

STUDY RATIONALE

3,4-Dihydrocoumarin was nominated by the FDA and NCI for toxicity and carcinogenicity studies because it is widely distributed in perfumes, soaps, other common household products, and foods. The oral route of exposure was used to mimic exposure in foods. Because of minimal solubility in water and unpalatability in feed, the chemical was administered by oral gavage in corn oil.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 3,4-DIHYDROCOUMARIN

3,4-Dihydrocoumarin was obtained from Givaudan Corporation (Clifton, NJ) in two lots (lot 57599 and lot 44981). Lot 57599 was used throughout the 16-day and 13-week studies and lot 44981 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).

Both lots of the chemical, a colorless liquid, were identified as 3,4-dihydrocoumarin by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of both lots was approximately 99% as determined by elemental analyses, Karl Fischer water analysis, lactone titration, thin-layer chromatography, and gas chromatography. The purity of lot 44981 was also evaluated for free acid content. For both lots, elemental analyses for carbon and hydrogen were in agreement with the theoretical values for 3,4-dihydrocoumarin. Karl Fischer water analysis indicated less than 0.05% water. The purity by lactone titration was approximately 100%. Thin-layer chromatography indicated two trace impurities. Gas chromatography analyses indicated a major peak and seven impurities totaling 0.8% in lot 57599 and two impurities totaling 0.5% in lot 44981. The free acid content was low (0.04 mEq/g).

Stability studies were performed at the analytical chemistry laboratory utilizing gas chromatography. These studies indicated that 3,4-dihydrocoumarin was stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. Throughout the studies the bulk chemical was stored protected from light at room temperature. The stability of the bulk chemical was monitored periodically at the study laboratory with infrared spectroscopy, gas chromatography, and free acid titration methods. No degradation of the chemical was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulation solutions were prepared by mixing 3,4-dihydrocoumarin and corn oil (Table I1). Stability studies conducted by the analytical chemistry laboratory using gas chromatography confirmed that the solutions were stable for at least 3 weeks at room temperature. During the studies the formulations were prepared once for the 16-day studies, every 2 weeks during the 13-week studies, and weekly then every 2 weeks for the 2-year studies. Formulations were discarded 21 days after the date of preparation.

To verify dose concentration, the formulations were periodically analyzed by the study laboratory prior to administration and from animal room samples after dose administration. The concentrations of 3,4-dihydrocoumarin were determined using an ultraviolet spectrophotometric method (Tables I2, I3, and I4). During the 2-year studies, all dose formulations were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table I5). Monthly peroxide analyses of the corn oil vehicle by the study laboratory indicated that the peroxide levels were within the limit set for the studies (< 10 mEq/kg).

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA); at receipt, the rats were 29 days old and mice were 28 days old. The animals were quarantined for 16 days before dosing began. During this time, five male and five female rats and mice were randomly selected for necropsy. All organs appeared normal and there was no evidence of disease.

Groups of five male and five female rats received 3,4-dihydrocoumarin in corn oil by gavage at doses of

0, 190, 375, 750, 1,500, or 3,000 mg/kg body weight. Groups of five male and five female mice received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 140, 280, 560, 1,125, or 2,250 mg/kg body weight. All doses were given daily 5 days per week for 12 dose days, not including weekends. Animals were housed five per cage; water and feed were available *ad libitum*. Clinical findings were recorded daily and the health status of the animals was observed on days 6, 10, and 14. The animals were weighed at the beginning of the study, on days 7 and 14, and at the end of the study. 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 sinuses of all animals for clinical pathology analyses; the clinical pathology parameters measured are listed in Table 2. A necropsy was performed on all animals.

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 3,4-dihydrocoumarin and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats (6 to 7 weeks old) and B6C3F$_1$ mice (7 to 8 weeks old) were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA). The animals were quarantined for 15 or 16 days before dosing began. One day prior to the beginning of the studies, five male and five female rats and mice were randomly selected and examined by a pathologist for disease and parasites. Gross necropsies were performed and special attention was given to the liver, lungs, kidneys, and the entire intestinal tract. These animals were found to be disease- and parasite-free.

Groups of 10 male and 10 female rats received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 75, 150, 300, 600, or 1,200 mg/kg body weight 5 days a week for 13 weeks. Groups of 10 male and 10 female mice received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 100, 200, 400, 800, or 1,600 mg/kg body weight 5 days a week for 13 weeks. Animals were housed five per cage; water and feed were available *ad libitum*. The health status of the animals was monitored on 13 occasions (at least once per week) after the studies began. Individual animal weights were recorded at the beginning of the studies, at the first of each week, and at the end of the study. Further details of study design and animal maintenance are summarized in Table 2.

At the end of the studies, blood samples were collected from the orbital sinuses of all surviving animals for clinical pathology analyses. The clinical pathology parameters measured are listed in Table 2. Necropsies were performed on all animals. The brain, lungs, heart, thymus, liver, right kidney, and right testis of all animals were weighed. Additionally, the epididymis of rats was weighed. The tissues and organs listed in Table 2 were examined *in situ*, then removed from the carcass, reexamined, and fixed in 10% buffered formalin. Formalin-fixed, hematoxylin-eosin stained sections of tissues of all animals which died or were killed moribund during the studies, all rats receiving 1,200 mg/kg, and all mice receiving 1,600 mg/kg were examined microscopically. In addition, the livers of all rats were examined.

2-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 150, 300, or 600 mg/kg body weight for 103 weeks. Ten rats per dose group were designated for an interim evaluation after 15 months of chemical administration. Groups of 70 male and 70 female mice received 3,4-dihydrocoumarin in corn oil by gavage at doses of 0, 200, 400, or 800 mg/kg body weight for 103 weeks. Ten mice per dose group were designated for an interim evaluation after 15 months. In addition, up to 10 mice per group were selected for clinical pathology evaluation at 15 months.

Stop-Exposure Evaluation

Groups of male rats receiving 600 mg/kg 3,4-dihydrocoumarin for 9 or 15 months followed by a recovery period were evaluated to assess the potential for 3,4-dihydrocoumarin-induced lesions to progress or regress following cessation of exposure.

A group of 40 male rats received 600 mg/kg 3,4-dihydrocoumarin 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 until the end of the study. Similarly, a group of 30 male rats received 600 mg/kg 3,4-dihydrocoumarin 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 stop-exposure rats. The incidences of lesions in male rats receiving 3,4-dihydrocoumarin and evaluated at 9 or 15 months were compared with those in male rats receiving 3,4-dihydrocoumarin 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). The animals were quarantined for 13 to 15 days before the beginning of the studies. Five male and female rats and mice were selected for necropsy. All organs appeared normal and there was no evidence of disease. The animals were 42 or 43 days old when the studies began. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Feed and water were available *ad libitum*. 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 weighed and observed for clinical signs of toxicity weekly for the first 13 weeks and monthly thereafter. Blood was collected by cardiac puncture from all rats at the 9- and 15-month interim evaluations to determine hematology and clinical chemistry parameters. An additional 8 to 10 mice per group were examined at 15 months for clinical pathology. The hematology and clinical chemistry parameters measured are listed in Table 2. The brain, kidney, and liver of all animals scheduled for 9- or 15-month interim evaluations were weighed at necropsy.

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 Archive 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 following organs for accuracy and consistency of lesion diagnoses: the kidney, stomach, and parathyroid gland of male and female rats; the lung, liver, forestomach, and kidney of male mice; and the liver, forestomach, lung, and pituitary gland of female mice.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. The PWG reviewed kidneys of male and female rats and mice, stomachs of male rats, adrenal glands of female rats, livers of male and female mice, and lungs, small and large intestines, forestomachs, and glandular stomachs of male mice. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, 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 the 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; 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 analysis 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 lesion incidence. Consequently, lesion incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for lesions 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 have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). 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 16-day, 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 all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of 3,4-dihydrocoumarin was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, chromosome damage in cultured 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 3,4-dihydrocoumarin 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 chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the 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 3,4-Dihydrocoumarin

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., Wilmington, MA	Charles River Breeding Laboratories, Inc., Wilmington, MA	Frederick Cancer Research Center, Frederick, MD	Frederick Cancer Research Center, Frederick, MD
Time Held Before Studies			
16 days	Rats: 15 days Mice: 16 days	13-15 days	13-15 days
Average Age When Studies Began			
Rats: 44-51 days Mice: 51-58 days	Rats: 43-50 days Mice: 51-58 days	42 days	Rats: 42-43 days Mice: 42-43 days
Date of First Dose			
7 January 1981	Rats: 22 April 1981 Mice: 23 April 1981	9 October 1984	Rats: 2 October 1984 (males) 3 October 1984 (females) Mice: 18 December 1984 (males) 19 December 1984 (females)
Duration of Dosing			
16 days	Rats: 14 weeks Mice: 13 weeks	9-month stop-exposure group: 9 months followed by corn oil gavage for remainder of study 15-month stop-exposure group: 15 months followed by corn oil gavage for remainder of study	103 weeks
Date of Last Dose			
23 January 1981	Rats: 23 July 1981 Mice: 27 July 1981	29 September 1986	Rats: 22 September 1986 (males) 23 September 1986 (females) Mice: 8 December 1986 (males) 9 December 1986 (females)

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of 3,4-Dihydrocoumarin (continued)

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Necropsy Dates			
23 January 1981	Rats: 23 July 1981 Mice: 27 July 1981	9-month stop-exposure: Interim: 9-11 July 1985 15-month stop-exposure: Interim: 8 January 1986 Terminal: 7 October 1986	Rats: 15-month interim – 2-3 January 1986 (males) 6-7 January 1986 (females) Terminal – 30 September-1 October 1986 (males) 1-7 October 1986 (females) Mice: 15-month interim – 17-20 March 1986 (males) 18-21 March 1986 (females) Terminal – 16-17 December 1986 (males) 17-19 December 1986 (females)
Average Age at Necropsy			
Rats: 60-67 days Mice: 67-74 days	Rats: 134-141 days Mice: 142-149 days	9-month interim: 46 weeks 15-month interim: 72 weeks Terminal: 111 weeks	15-month interim: 71-72 weeks 2-year study: 111-112 weeks
Size of Study Groups			
5 males and 5 females	10 males and 10 females	9-month stop-exposure: 20 dose and 20 controls evaluated at 9 months; 20 dose evaluated after recovery period of up to 15 months. 15-month stop-exposure: 10 dose and 10 controls evaluated at 15 months; 20 dose evaluated after recovery period of up to 9 months	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			
Ear tag	Toe clip	Toe clip	Toe clip

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of 3,4-Dihydrocoumarin
(continued)

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Diet			
NIH-07 open formula mash diet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as 16-day studies	NIH-07 pelleted diet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as stop-exposure evaluation
Maximum Storage Time for Feed			
120 days from 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			
Polycarbonate, changed twice weekly	Same as 16-day studies	Polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice weekly	Same as stop-exposure evaluation
Bedding			
Beta-Chip® hardwood laboratory bedding (Northeastern Products Corporation, 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	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Racks			
Stainless steel, changed every other week	Same as 16-day studies	Same as 16-day studies	Same as 16-day studies
Animal Room Environment			
Temperature: 22.1° C Relative humidity: 36.6% Fluorescent light: 12 hours/day Room air changes: not available	Temperature: Rats – 22.8° C Mice – 23.0° C Relative humidity: Rats – 53.2% Mice – 53.1% Fluorescent light: 12 hours/day Room air changes: not available	Temperature: 23.1° C ± 1.1° C Relative humidity: 55.1% ± 7.4% Fluorescent light: 12 hours/day Room air changes (average number changes/hour): 13.7	Temperature: Rats – 23.1° C ± 1.1° C Mice – 21.7° C ± 0.8° C Relative humidity: Rats – 55.1% ± 7.4% Mice – 55.9% ± 7.8% Fluorescent light: 12 hours/day Room air changes (average number changes/hour): Rats – 13.7 Mice – 13.5

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of 3,4-Dihydrocoumarin (continued)

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Doses			
Rats: 0, 190, 375, 750, 1,500 or 3,000 mg/kg 3,4-dihydrocoumarin in corn oil by gavage; once daily, 5 days per week Mice: 0, 140, 280, 560, 1,125, or 2,250 mg/kg 3,4-dihydrocoumarin in corn oil by gavage; once daily, 5 days per week	Rats: 0, 75, 150, 300, 600 or 1,200 mg/kg 3,4-dihydrocoumarin in corn oil by gavage; once daily, 5 days per week Mice: 0, 100, 200, 400, 800, or 1,600 mg/kg 3,4-dihydrocoumarin in corn oil by gavage; once daily, 5 days per week	0 or 600 mg/kg 3,4-dihydrocoumarin in corn oil by gavage; once daily, 5 days per week for 9 or 15 months	Rats: 0, 150, 300, or 600 mg/kg 3,4-dihydrocoumarin in corn oil by gavage; once daily, 5 days per week Mice: 0, 200, 400, or 800 mg/kg 3,4-dihydrocoumarin in corn oil by gavage; once daily, 5 days per week
Type and Frequency of Observation			
Animals observed twice daily for mortality and daily for pharmacotoxic signs; animals weighed initially, weekly, and at the end of the studies; health status observed on days 6, 10, and 14.	All animals were palpitated once weekly for masses. Animals observed for mortality twice daily; health status of the animals was monitored on 13 occasions (at least once per week) after study initiation; animals weighed initially, weekly, and at the end of the study; clinical observations recorded weekly at the following intervals: pre-dose, 30-60 minutes post-dose, and 2 hours post-dosing.	Animals observed for mortality and morbidity twice daily; animal weights and clinical findings recorded weekly for the first 13 weeks, and monthly thereafter.	Same as stop-exposure evaluation
Method of Sacrifice			
Carbon dioxide asphyxiation	Same as 16-day studies	9- and 15-Month interims: anesthetized with an overdose of methoxyflurane followed by exsanguination Terminal: carbon dioxide asphyxiation	15-Month interim: anesthetized with an overdose of methoxyflurane followed by exsanguination Terminal sacrifice animals: carbon dioxide asphyxiation
Necropsy			
Necropsy performed on all animals	Necropsy performed on all animals; organs weighed included: brain, lung, heart, thymus, liver, right kidney, and right testis. The epididymis (tunica vaginalis of the testis and scrotal sac) was weighed for rats only.	Necropsy performed on all animals; organs weighed at the 9- and 15-month interim evaluations included: brain, kidney, and liver.	Necropsy performed on all animals; organs weighed at the 15-month interim evaluations included: brain, kidney, and liver.

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of 3,4-Dihydrocoumarin
(continued)

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Clinical Pathology			
Blood samples were collected from the orbital sinuses of all surviving animals at necropsy ***Hematology:*** clotting time, fibrinogen (rats), activated partial thromboplastin time (rats), prothrombin time (rats), platelet count	Blood was collected from the orbital sinus of all surviving animals ***Hematology:*** hemoglobin, hematocrit, erythrocytes, leukocyte count and differential, platelet count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, prothrombin time (mice only), capillary clotting time (mice only) ***Clinical Chemistry:*** Rats only: sodium, potassium, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, total protein, albumin, cholinesterase, ornithine carbamyl transferase, sorbitol dehydrogenase	Blood samples were collected by cardiac puncture from all surviving animals at the 9- and 15-month interim evaluations ***Hematology:*** hemoglobin, hematocrit, mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, erythrocytes, nucleated erythrocytes, platelets, leukocyte count and differential, activated partial thromboplastin time, thromboplastin time ***Clinical Chemistry:*** alkaline phosphatase, alanine aminotransferase, calcium, sorbitol dehydrogenase, γ-glutamyltransferase	Blood samples were collected by cardiac puncture from all surviving core study rats and mice at the 15-month interim evaluation and from the additional groups of mice slated for clinical pathology analyses only ***Hematology:*** hematocrit, hemoglobin, mean cell hemoglobin, mean cell volume, mean cell hemoglobin concentration, erythrocytes, nucleated erythrocytes, platelets, reticulocytes, atypical lymphocytes, leukocyte count and differential, activated partial thromboplastin time (rats only) ***Clinical Chemistry:*** alkaline phosphatase, alanine aminotransferase, γ-glutamyltransferase, sorbitol dehydrogenase, calcium (rats only)
Histopathology			
None	Complete histopathologic examinations were performed on all controls, rats receiving 1,200 mg/kg, mice receiving 1,600 mg/kg, and all animals that died before the end of the studies. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, kidney, large intestine (colon, cecum, (continued)	Complete histopathologic examinations were performed on all animals. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, epididymis, esophagus, femur (including marrow), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, (continued)	Complete histopathologic examinations were performed on all animals. 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 and mesenteric lymph nodes, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, (continued)

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of 3,4-Dihydrocoumarin (continued)

16-Day Studies	13-Week Studies	Stop-Exposure Evaluation	2-Year Studies
Histopathology (continued)			
	rectum), liver, lung, mammary gland, mesenteric lymph node, nose, ovary, pancreas, parathyroid gland (rats), pituitary gland, preputial gland (rats) prostate gland, salivary gland, small intestine (duodenum, jejunum, ileum), spleen, sternum (including marrow), stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the liver of all rats was examined.	prostate gland, salivary glands, seminal vesicle, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis, thymus, thyroid gland, trachea, and urinary bladder.	prostate gland, salivary glands, seminal vesicle, 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 male and female rats receiving 3,000 mg/kg died within the first two days of dosing, and four male rats and all female rats receiving 1,500 mg/kg died within in the first four days of dosing (Table 3). The death of one male rat administered 375 mg/kg was considered to be a gavage accident. The body weight gains and final mean body weights of male and female rats that received 190, 375, and 750 mg/kg were similar to those of the controls. There were no treatment-related lesions noted at necropsy, no changes in any hematologic parameters (Table H1), and no treatment-related clinical findings of toxicity. The high dose selected for the 13-week study was 1,200 mg/kg, which was just below the dose where mortality was observed in the 16-day study.

TABLE 3
Survival and Mean Body Weights of Rats in the 16-Day Gavage Study of 3,4-Dihydrocoumarin

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	153 ± 8	196 ± 8	43 ± 3	
190	5/5	148 ± 7	202 ± 7	54 ± 3	103
375	4/5[c]	158 ± 10	207 ± 9	50 ± 4	106
750	5/5	154 ± 12	205 ± 9	51 ± 3	105
1,500	1/5[d]	154 ± 9	167	37	85
3,000	0/5[e]	151 ± 7	–	–	–
Female					
0	5/5	117 ± 2	141 ± 4	24 ± 1	
190	5/5	112 ± 5	140 ± 6	27 ± 1	99
375	5/5	115 ± 3	141 ± 2	26 ± 2	100
750	5/5	116 ± 2	142 ± 2	26 ± 1	99
1,500	0/5[e]	116 ± 3	–	–	–
3,000	0/5[f]	115 ± 4	–	–	–

[a] Number of rats surviving at 16 days/number initially in group
[b] Weights given as mean ± standard error. Subsequent calculations are based on rats surviving to the end of the study. Differences from the control group are not significant by Dunnett's test.
[c] Death attributed to gavage accident
[d] Day of death: 2, 3, 4, 4
[e] Day of death: 1, 2, 2, 2, 2
[f] Day of death: 1, 1, 2, 2, 2

13-WEEK STUDY

Two males and four females receiving 1,200 mg/kg died during the first week of treatment and one female receiving 1,200 mg/kg died during week 12 (Table 4). The death of one control male rat was due to a gavage accident. The final mean body weight and body weight gain of males that received 1,200 mg/kg were significantly lower than those of the controls, but the final mean body weights of other dosed groups of male rats and all dosed groups of female rats were similar to or slightly greater than those of the controls. No treatment-related clinical findings of toxicity were noted.

The platelet counts of male rats receiving 600 and 1,200 mg/kg and the hematocrit, erythrocyte counts, and hemoglobin concentrations of males receiving 300 to 1,200 mg/kg were significantly lower than those of the controls (Table H2). While not clinically important, these findings are consistent with blood loss and platelet consumption associated with an anticoagulant effect of 3,4-dihydrocoumarin. The platelet counts of females that received 300 to 1,200 mg/kg were also significantly lower than those of controls, but the percent hematocrit, erythrocyte counts, and hemoglobin concentrations were not significantly different from those of the controls.

The partial thromboplastin time in males receiving 300, 600, and 1,200 mg/kg and in females receiving 600 and 1,200 mg/kg were significantly lower than those of controls. The reason for this difference is unknown. Partial thromboplastin time is usually normal with acute hemorrhage or prolonged with hypoprothrombinemia or hemophilia.

TABLE 4
Survival and Mean Body Weights of Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	9/10[c]	143 ± 5	331 ± 8	190 ± 4	
75	10/10	145 ± 4	338 ± 2	193 ± 4	102
150	10/10	144 ± 5	334 ± 6	190 ± 5	101
300	10/10	144 ± 4	335 ± 9	191 ± 5	101
600	10/10	144 ± 4	325 ± 6	181 ± 5	98
1,200	8/10[d]	145 ± 4	282 ± 7**	140 ± 6**	85
Female					
0	10/10	111 ± 2	196 ± 2	85 ± 2	
75	10/10	111 ± 3	202 ± 4	91 ± 2	103
150	10/10	115 ± 2	209 ± 2*	93 ± 2*	106
300	10/10	111 ± 2	203 ± 3*	92 ± 2*	103
600	10/10	110 ± 2	203 ± 3*	93 ± 3*	104
1,200	5/10[e]	113 ± 3	205 ± 4	95 ± 5*	104

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

A number of constituents of the blood plasma were significantly elevated or decreased in dosed male or female rats; the cause and biological significance of these effects are uncertain. The blood urea nitrogen concentration in males that received 1,200 mg/kg was significantly greater than controls, while the creatinine concentration was significantly lower. Since there was no histologic evidence of renal disease, the slight increase in urea nitrogen is prerenal in origin and possibly related to dehydration or increased muscle catabolism that occurs with a negative nitrogen balance. Serum levels of creatinine, the end product of muscle metabolism, are related to total muscle mass and muscular conditioning. Thus, the slightly lower creatinine concentration may be related to the significantly lower mean body weight gain of this dose group.

The albumin levels in male rats that received 600 and 1,200 mg/kg and in all dosed groups of females were significantly greater than those of the controls. In females, this was accompanied by an elevation in total protein in the 300, 600, and 1,200 mg/kg dose groups. Increased albumin production has not been known to occur in animals, and elevated levels of serum albumin are usually attributed to dehydration.

Serum levels of aspartate aminotransferase, lactate dehydrogenase, and sorbitol dehydrogenase in males receiving 1,200 mg/kg were significantly lower than those of controls, while the sorbitol dehydrogenase activity in 1,200 mg/kg females was significantly greater than that in controls. While statistically significant, these differences were slight and have no obvious explanation. The depressed enzyme levels in male rats may be related to the lower body weight gain in the 1,200 mg/kg group.

Cholinesterase values in males receiving 300, 600, and 1,200 mg/kg and in females receiving 600 and 1,200 mg/kg were significantly lower than those of controls (Table H2).

The absolute and relative liver and kidney weights of male and female rats that received 600 and 1,200 mg/kg were significantly greater than those of the controls (Table G1). Consistent with this observation, centrilobular hepatocellular hypertrophy was observed in male and female rats receiving 300 mg/kg or more (Table 5). The lesions ranged in severity from minimal to mild and consisted of slight hepatocyte enlargement, sometimes accompanied by slight nuclear enlargement of the cells surrounding the central vein.

Dose Selection Rationale: Because of mortality in both sexes and the lower mean body weight gain of males receiving 1,200 mg/kg, the high dose selected for the 2-year study was 600 mg/kg.

TABLE 5
Liver Lesions of Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin

Dose	0 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Male						
Liver[a]	10	10	10	10	10	10
Hepatocellular Hypertrophy[b]	0	0	0	10°°(1.3)[c]	10°°(1.0)	10°°(1.2)
Female						
Liver	10	10	10	10	10	9
Hepatocellular Hypertrophy	0	1	0	10°°(1.0)	10°°(1.0)	9°°(1.0)

°° Significantly different (P≤0.01) from the control group by the Fisher exact test
[a] Number of rats with organ examined microscopically.
[b] Number of rats with lesion.
[c] Average severity grade of lesion in affected rats: 1=minimal, 2=mild, 3=moderate, 4=marked

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 dosed female rats was similar to that of the controls. In contrast, the number of male rats surviving until the end of the study decreased with increasing dose, and the survival of each group of dosed males was significantly lower than that of controls. However, in each of the male dose groups, survival was greater than 50% until week 92. The reduced survival of dosed males was attributed to a chemical-related increased severity of nephropathy and renal failure.

Body Weights and Clinical Findings

Mean body weights of high-dose male rats were consistently about 5% to 10% lower than those of the controls after week 6. Body weights of other male dose groups and dosed female rats were similar to those of the controls (Tables 7 and 8, and Figure 3). Although there were no clinical findings attributed to chemical administration, the male rats resisted the daily gavage procedure.

TABLE 6
Survival of Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	9	10	10	10
Moribund	12	24	26	17
Accidental deaths[a]	2	1	1	2
Natural deaths	10[e]	13	15	29
Animals surviving to study termination	27	12	8	2
Percent probability of survival at end of study[b]	57	27	16	4
Mean survival (days)[c]	640	611	633	581
Survival analysis[d]	P<0.001	P=0.004	P<0.001	P<0.001
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	9	10	9
Moribund	13	17	20	19
Accidental deaths[a]	2	5	0	4
Natural deaths	4	8	4	5
Animals surviving to study termination	31	21	26	23
Percent probability of survival at end of study	65	46	52	50
Mean survival (days)	649	600	650	610
Survival analysis	P=0.213	P=0.106	P=0.300	P=0.134

[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.
[e] Includes one rat that died the last week of study

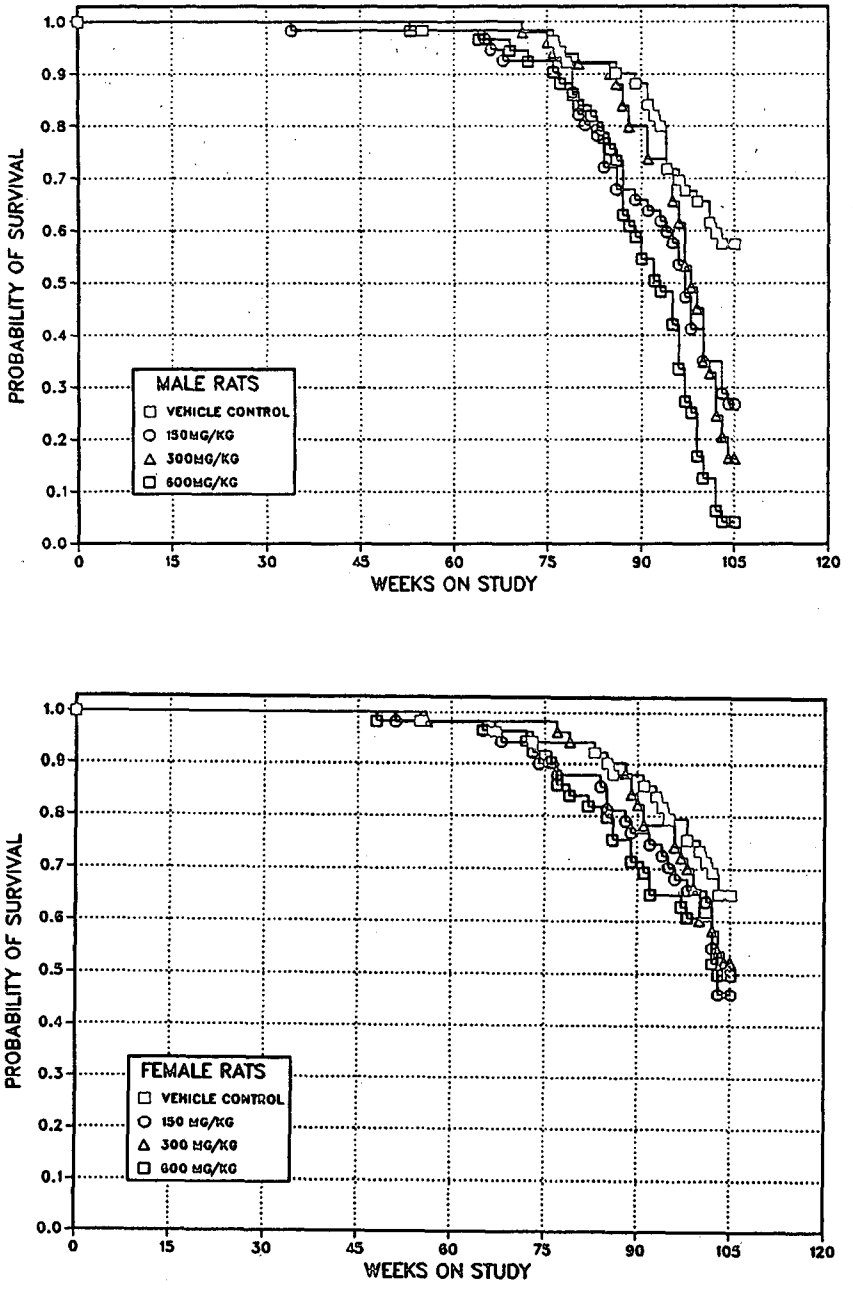


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered 3,4-Dihydrocoumarin in Corn Oil by Gavage for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Week on Study	Vehicle Control		150 mg/kg			300 mg/kg			600 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	128	60	125	98	60	129	101	60	125	98	60
2	184	60	181	99	60	185	101	60	182	99	60
3	229	60	226	99	60	231	101	60	226	99	60
4	250	60	247	99	60						
5	267	60	264	99	60	252	94	60	239	90	60
6	284	60	280	99	60	284	100	60	270	95	60
7	297	59	293	99	60	298	100	60	279	94	58
8	313	59	309	99	60	311	99	60	293	94	58
9	323	59	323	100	60	321	99	60	307	95	58
10	330	59	331	100	60	332	101	60	316	96	58
11	339	59	340	100	60	339	100	60	324	96	58
12	349	59	352	101	60	351	101	60	337	96	58
13	358	59	362	101	60	360	101	60	344	96	58
17	382	59	385	101	60	381	100	60	361	95	58
21	397	59	397	100	60	387	97	60	366	92	58
25	424	59	426	101	60	414	98	60	395	93	58
29	437	59	440	101	60	426	98	60	402	92	58
33	452	59	456	101	60	438	97	60	413	91	58
37	465	59	466	100	59	450	97	60	420	90	58
41	474	59	477	101	59	459	97	60	426	90	58
45	483	59	490	101	59	470	97	60	435	90	58
49	500	59	500	100	59	478	96	60	440	88	58
53	507	59	515	101	59	490	97	60	451	89	57
57	517	58	523	101	59	494	96	60	459	89	57
61	521	58	527	101	59	502	97	60	468	90	57
65	520	58	534	103	58	503	97	60	462	89	56
69[a]	529	49	541	102	46	516	98	50	468	89	46
73	529	49	552	104	46	522	99	49	475	90	44
77	517	47	540	104	46	513	99	47	467	90	42
81	522	45	539	103	40	526	101	46	481	92	40
85	510	45	543	107	35	511	100	45	476	93	36
90	494	43	540	109	32	516	105	39	471	95	28
93	480	39	526	110	30	502	104	36	455	95	24
97	471	33	503	107	23	487	104	26	454	96	13
102	459	30	490	107	16	471	103	15	436	95	6
103	459	28	486	106	13	471	103	10	414	90	2
Mean for weeks											
1-13	281		279	99		283	101		270	96	
14-52	446		449	101		434	97		406	91	
53-103	503		526	105		502	100		460	91	

[a] Interim evaluation occurred during week 65.

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Week on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	150 mg/kg Av. Wt. (g)	150 mg/kg Wt. (% of controls)	150 mg/kg No. of Survivors	300 mg/kg Av. Wt. (g)	300 mg/kg Wt. (% of controls)	300 mg/kg No. of Survivors	600 mg/kg Av. Wt. (g)	600 mg/kg Wt. (% of controls)	600 mg/kg No. of Survivors
1	103	60	105	103	60	104	101	60	102	100	60
2	130	60	132	102	59	133	103	60	131	101	60
3	148	60	148	100	59	151	102	60	150	102	60
4	156	60	159	102	59	160	103	60	160	102	60
5	166	60	169	102	59	171	103	60	169	102	60
6	172	60	174	101	59	176	102	60	175	102	59
7	176	60	179	101	59	182	103	60	181	102	59
8	184	60	185	101	58	188	102	60	184	100	59
9	187	60	189	101	58	192	103	60	189	101	59
10	192	60	195	101	58	196	102	60	194	101	59
11	195	60	197	101	57	202	104	60	201	103	59
13	199	60	204	103	57	207	104	60	207	104	59
14	201	60	208	103	57	211	105	60	208	103	58
17	209	60	215	103	57	214	103	60	210	101	58
21	208	60	215	103	57	216	104	60	215	103	58
25	216	60	222	103	57	224	103	60	223	103	58
29	228	60	234	103	57	234	103	60	235	103	58
33	231	60	240	104	57	241	104	60	240	104	58
37	238	60	249	105	57	247	104	60	244	102	58
41	245	60	256	104	57	253	103	60	247	101	58
45	251	60	262	105	56	262	105	60	252	101	58
49	259	60	274	106	56	265	102	60	256	99	57
53	267	60	283	106	55	280	105	60	267	100	57
57	276	59	293	106	55	290	105	59	269	98	57
61	283	59	299	106	55	300	106	59	278	98	57
65	291	59	307	106	54	308	106	59	281	96	56
69[a]	297	48	317	107	44	317	107	49	287	97	47
73	296	47	316	107	43	325	110	49	298	101	45
77	304	46	324	106	41	328	108	48	299	98	41
81	304	45	327	108	40	334	110	47	310	102	40
85	313	43	334	107	37	343	110	45	311	99	38
89	313	42	333	106	35	337	108	42	305	98	34
93	316	40	335	106	34	346	110	39	309	98	30
97	319	38	332	104	31	343	108	36	309	97	29
102	320	34	327	102	29	357	112	30	314	98	28
103	323	31	341	106	21	360	111	27	329	102	23
Mean for weeks											
1-13	167		170	102		172	103		170	102	
14-52	229		238	104		237	103		233	102	
53-103	302		319	106		326	108		298	99	

[a] Interim evaluation occurred during week 65.

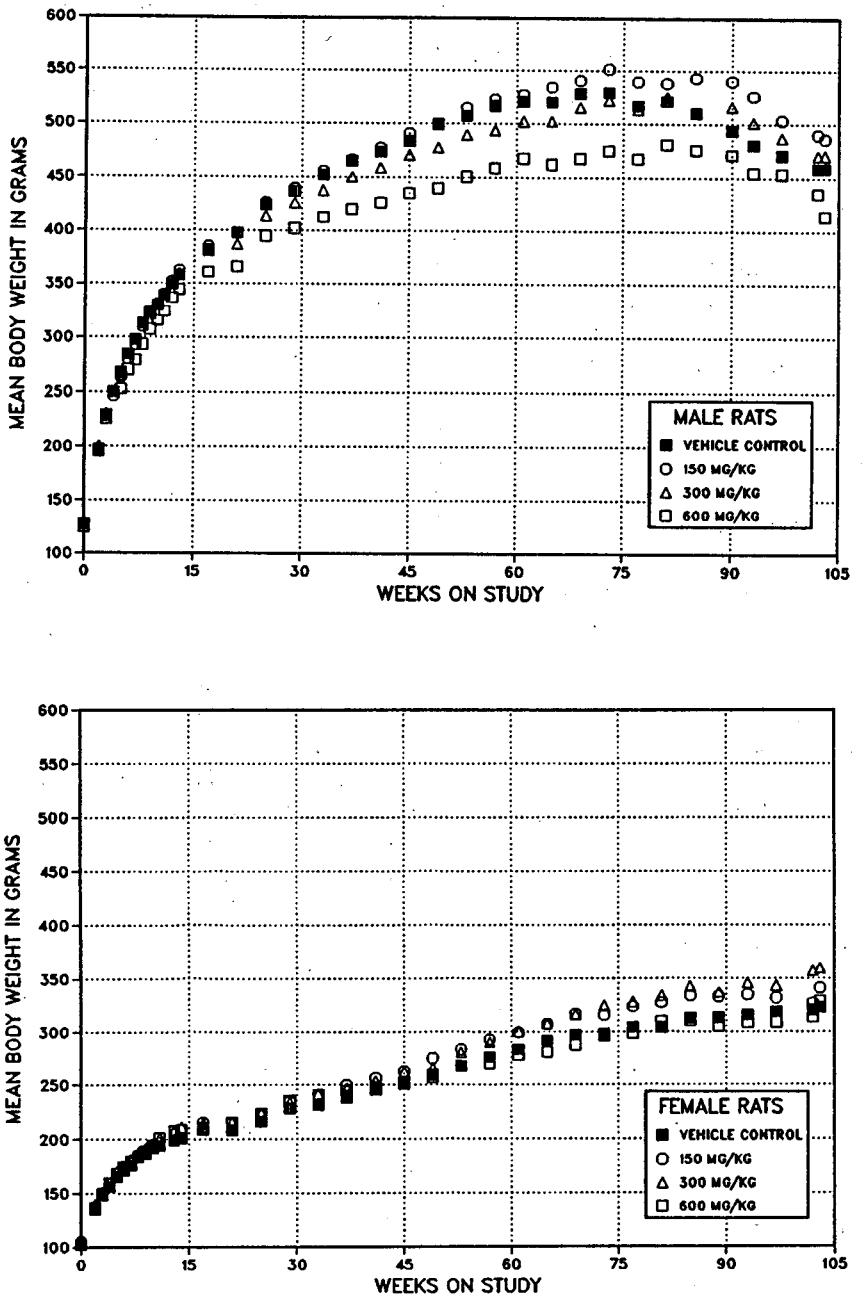


FIGURE 3
Growth Curves for Male and Female Rats Administered 3,4-Dihydrocoumarin in Corn Oil by Gavage for 2 Years

Hematology and Clinical Chemistry

At the 15-month interim evaluation, the hemoglobin concentrations, mean erythrocyte volumes, or mean erythrocyte hemoglobin concentrations in the 300 and 600 mg/kg female rats were slightly, but significantly, lower than those in the controls (Table H5). In males, only the hemoglobin concentration of the 600 mg/kg group was significantly lower. While these differences were statistically significant and possibly related to the anticoagulant effect of 3,4-dihydrocoumarin, they were not clinically important. The total leukocyte counts in 300 and 600 mg/kg females were higher, primarily because of an increase in the number of lymphocytes. The cause of this effect is unknown.

Serum activities of alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, or γ-glutamyltransferase were significantly higher in the 300 and 600 mg/kg male rats than those in controls (Table H5). In females, only alkaline phosphatase and γ-glutamyltransferase activities were significantly higher in the 600 mg/kg group. While elevated enzyme activities are usually associated with hepatic toxicity, hepatocellular degeneration or necrosis were not observed by light microscopy.

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 kidney, parathyroid gland, forestomach, adrenal gland, and pituitary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred at an incidence of at least 5% in at least one study group are presented in Appendixes A for male rats and B for female rats.

Kidney: The absolute and relative kidney weights of male and female rats receiving 300 and 600 mg/kg were significantly greater than those of controls at the 15-month interim evaluation (Table G4). While nephropathy occurred in nearly all dosed and control male rats, the average severity of nephropathy in each of the dose groups was significantly greater than that of controls at the 15-month interim evaluation and at the end of the 2-year study (Table 9). The more frequent occurrence of moderate or marked nephropathy in dosed males was the principal cause of reduced survival of these groups.

In female rats, there was no apparent response at the 15-month interim evaluation, but by the end of the study the incidences and average severities of nephropathy in the 300 and 600 mg/kg females were significantly greater than controls (Table 10).

Nephropathy was characterized by glomerulosclerosis, thickening of the tubule epithelium 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%.

In addition to the nephropathy described above, renal tubule adenomas were observed in one 150 and two 600 mg/kg male rats, and in one control, one 150, and one 300 mg/kg female rat (Tables 9, 10, A1, and B1). The 150 mg/kg female rat with an adenoma also had a renal tubule carcinoma, and an additional 300 mg/kg female had a renal tubule carcinoma. While the incidences of renal tubule adenoma in the dosed groups of male rats were not significantly greater than that of controls, no more than one has been seen in any group of NTP 2-year historical control male rats (8/1,019, 0.8%; Table A4a). Similarly, the occurrence of renal tubule adenomas or carcinomas (combined) in two 300 mg/kg females contrasts with the two seen in 1,018 NTP historical control female rats (Table B4a). Renal tubule hyperplasia, a possible precursor of adenoma, occurred in 150 and 600 mg/kg male rats and in one 600 mg/kg female (Tables 9, 10, A5, and B5). Transitional cell carcinomas of the renal pelvic urothelium were also observed in two 600 mg/kg male rats. Transitional cell carcinomas of the kidney have been observed in only 1 of 1,019 historical control male rats (Table A4b) from recent NTP studies.

The kidneys were initially sampled for histopathology by preparing a single hematoxylin and eosin stained section of each kidney. Primarily because of the unusual occurrence of renal tubule adenomas in 600 mg/kg males and 150 mg/kg females, additional step-sections of kidney were prepared from the

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Dose	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Single Sections (Standard Evaluation)				
15-Month Interim Evaluation				
Kidney[a]	9	10	10	10
Nephropathy[b]	9 (1.0)[c]	10 (1.8)**	10 (1.4)	10 (1.7)**
2-Year Study				
Kidney	50	48	47	50
Nephropathy	50 (2.2)	47 (2.9)**	47 (3.2)**	47 (3.2)**
Renal Tubule Hyperplasia	0	3	0	3
Renal Tubule Adenoma[d]	0	1	0	2
Transitional Cell Carcinoma[e]	0	0	0	2
Step Sections (Extended Evaluation)				
15-Month Interim Evaluation				
Kidney	9	10	10	10
Renal Tubule Hyperplasia	0	0	0	0
Renal Tubule Adenoma	0	1	0	0
2-Year Study				
Kidney	50	48	47	50
Renal Tubule Hyperplasia	0	3	6*	6**
Renal Tubule Adenoma	1	0	3	5*[f]
Single and Step Sections Combined				
15-Month Interim Evaluation				
Kidney	9	10	10	10
Renal Tubule Hyperplasia	0	0	0	0
Renal Tubule Adenoma	0	1	0	0
2-Year Study				
Kidney	50	48	47	50
Renal Tubule Hyperplasia	0	5*	6*	8**
Renal Tubule Adenoma	1	1	3	6*
Transitional Cell Carcinoma	0	0	0	2

* Significantly different ($P \leq 0.05$) 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)
** $P \leq 0.01$
[a] Number of rats with organ examined microscopically.
[b] Number of rats 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%
[e] Historical incidence: 1/1,019 (0.1% ± 0.5%); range 0%-2%
[f] One adenoma in the step section is the same adenoma seen in the original single section.

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Dose	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Single Sections (Standard Evaluation)				
15-Month Interim Evaluation				
Kidney[a]	10	9	10	9
Nephropathy[b]	2 (0.2)[c]	1 (0.1)	1 (0.1)	1 (0.1)
2-Year Study				
Kidney	50	49	49	49
Nephropathy	20 (0.5)	20 (0.4)	37**(1.0)**	31**(0.9)**
Renal Tubule Hyperplasia	0	0	0	1
Renal Tubule Adenoma	1	1	1	0
Renal Tubule Carcinoma	0	1	1	0
Renal Tubule Adenoma or Carcinoma[d]	1	1	2	0
Step Sections (Extended Evaluation)				
15-Month Interim Evaluation				
Kidney	10	9	10	9
Renal Tubule Hyperplasia	0	0	0	0
Renal Tubule Adenoma	0	0	0	0
2-Year Study				
Kidney	50	49	49	49
Renal Tubule Hyperplasia	0	0	0	1
Renal Tubule Adenoma	1[e]	1[e]	1[e]	0
Single and Step Sections Combined				
15-Month Interim Evaluation				
Kidney	10	9	10	9
Renal Tubule Hyperplasia	0	0	0	0
Renal Tubule Adenoma	0	0	0	0
2-Year Study				
Kidney	50	49	49	49
Renal Tubule Hyperplasia	0	0	0	2
Renal Tubule Adenoma	1	1	1	0
Renal Tubule Carcinoma	0	1	1	0
Renal Tubule Adenoma or Carcinoma	1	1	2	0

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test (2-year study) or Mann-Whitney U test (severity grades)
[a] Number of rats with organ examined microscopically.
[b] Number of rats with lesion.
[c] Group average severity grade of lesion: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Historical control 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 lesion in the step section is the same lesion seen in the original single section.

remaining formalin-fixed tissues. Approximately six to eight additional sections taken at 1 mm intervals were prepared for each male and female rat.

Additional rats, primarily dosed males, with focal hyperplasia or adenoma were identified. The incidences of these proliferative lesions in the step sections and in the single and step sections combined are shown in Table 9. The incidences of hyperplasia and adenoma increased with dose, and the incidences in the 600 mg/kg males were significantly greater than those of controls. No additional transitional cell carcinomas were found in males.

In female rats, renal tubule lesions occurred much less frequently, and the incidences in the dosed groups were not significantly greater than those of the controls (Table 10).

Renal tubule hyperplasia, as defined in this study, was distinguished from the regenerative epithelial changes commonly seen as a part of nephropathy and was considered a preneoplastic lesion. Renal tubule hyperplasia, adenoma, and carcinoma were part of a morphologic continuum and occurred in the cortex of the kidney. Hyperplasia of the renal 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 carcinomas were larger than the adenomas and exhibited cellular pleomorphism and atypia and central necrosis.

Parathyroid gland: The incidences of bilateral, diffuse parathyroid gland hyperplasia were significantly increased in dosed male rats (vehicle control, 0/47; 150 mg/kg, 15/41; 300 mg/kg, 26/48; 300 mg/kg, 19/41; Table A5); parathyroid gland hyperplasia also occurred in two female rats receiving 600 mg/kg (Table B5). Parathyroid gland hyperplasia was considered to be secondary to disturbances in calcium metabolism resulting from nephropathy and renal failure. The increased incidence of parathyroid gland hyperplasia in male rats was related to the increased severity of nephropathy in these groups.

Forestomach: There were no treatment-related increased incidences of forestomach ulcers in male or female rats at the 15-month interim evaluation; however, there was a significantly increased incidence of forestomach ulcers in dosed male rats at the end of the study (Table 11). These forestomach ulcers were characterized by focal necrosis of the mucosa and adjacent muscularis mucosa. Several of the forestomach ulcers had perforated the stomach wall. The squamous epithelium at the margin of the ulcers was usually thickened and hyperkeratotic (indicating areas of squamous hyperplasia), and the adjacent stomach wall was infiltrated with moderate numbers of mixed inflammatory cells, often mixed with proliferating fibrous tissue. Squamous hyperplasia and chronic inflammation also occurred in dosed males.

A squamous cell papilloma and a squamous cell carcinoma of the forestomach occurred in female rats receiving 600 mg/kg, but none occurred in the other dosed female groups or in the controls (Table 11). There were no squamous cell papillomas or squamous cell carcinomas of the forestomach in control or dosed male rats. The incidence of squamous cell papilloma or carcinoma (combined) of the forestomach in female rats that received 600 mg/kg exceeded the range for these neoplasms in control female rats from recent NTP 2-year gavage studies (Table B4b). However, because of the low incidence of these neoplasms and the low incidence of focal hyperplasia, these neoplasms could not be attributed to chemical administration.

TABLE 11
Incidences of Selected Lesions of the Forestomach of Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Dose	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Male				
Forestomach[a]	47	48	50	46
Ulcer[b]	4	14°	20°°	16°°
Squamous Hyperplasia	3	11°	14°°	11°
Inflammation, Chronic	3	8	15°°	8
Female				
Forestomach	50	49	50	49
Ulcer	3	1	1	1
Squamous Hyperplasia	1	0	1	2
Inflammation, Chronic	1	0	0	2
Squamous Cell Papilloma or Carcinoma[c]				
Overall rates[d]	0/50 (0%)	0/51 (0%)	0/50 (0%)	2/51 (4%)
Logistic regression tests[e]	P=0.037	–[f]	–	P=0.175

° Significantly different (P≤0.05) from the control group by the logistic regression test
°° P≤0.01
[a] Number of rats examined microscopically.
[b] Number of rats with lesion.
[c] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 3/1,020 (0.3% ± 0.7%); range 0%-2%
[d] Number of rats with neoplasm per number of rats with organ examined microscopically.
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal.
[f] Not applicable; no neoplasms in animal group

Adrenal gland: There was a marginally increased incidence of benign or malignant pheochromocytoma (combined) in low-dose female rats (2/50, 7/51, 6/49, 4/50; Table B3). All incidences fell within the historical range for control female rats from recent NTP 2-year gavage studies (range 0%-14%; 59/1,001, 5.9%; Table B4c), and the incidence of adrenal gland hyperplasia, a lesion generally considered to be the precursor to pheochromocytoma, was similar between control and female dosed groups (9/50, 10/51, 8/49, 8/50; Table B5). There was no increased incidence of benign or malignant pheochromocytoma (combined) in male rats (18/50, 11/49, 12/49, 8/50; Table A3). The slightly increased incidence of adrenal gland neoplasms in dosed female rats was not considered to be chemical related because the incidence was within the range of historical controls, the increased incidence was not dose related, and there was no treatment-related increased incidence of hyperplasia.

Pituitary gland: The incidences of adenomas of the pituitary gland pars distalis were significantly lower in the 300 and 600 mg/kg male rats and in the 600 mg/kg female rats than in the control groups (male: 24/49, 20/47, 13/46, 9/46; female: 31/49, 21/48, 27/49, 19/50; Tables A3 and B3). While the consistency of this finding in both sexes suggests it is chemical related, a potential mechanism for the effect is not apparent. Lower incidences of pituitary gland neoplasms are associated with lower body weights as a result of reduced feed consumption or toxicity, but the body weight of 600 mg/kg female rats, unlike male rats, was similar to that of the controls.

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/or bile duct carcinomas in male rats (Bär and Griepentrog, 1967; Griepentrog, 1973). Groups of 20 male rats were given 600 mg/kg 3,4-dihydrocoumarin for 9 or 15 months followed by administration of only the gavage vehicle until the end of the study. 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 evaluated at 9 or 15 months. To provide an additional measure of dose response as it relates 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 600 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 12. Eight males that received 600 mg/kg for 9 months and two males that received 600 mg/kg for 15 months survived until week 104. The decreased survival was attributed primarily to a chemical-related increase in the severity of renal disease.

TABLE 12
Survival of Male Rats in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin

	600 mg/kg (9-month exposure)	600 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	5	8
Moribund kills	6	10
Accidental deaths[a]	1	0
Animals surviving to study termination	8	2
Percent probability of survival at end of study[b]	42	10
Mean survival (days)[c]	651	617

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

Body Weights and Clinical Findings

The mean body weights of male rats in the 9- and 15-month stop-exposure groups are compared with the controls of the 2-year core study in Table 13. The mean body weight of the 9-month stop-exposure group was generally 5% to 10% lower than that of controls until week 40, when the administration of 3,4-dihydrocoumarin to this group ceased. The body weight gain of this group improved slightly thereafter, until the mean body weight was similar to controls at week 77. From week 90 until the end of the study the mean body weight of the 9-month stop-exposure group decreased at a slightly faster rate than did that of the controls.

The body weight gain of the 15-month stop-exposure group followed a similar pattern. The mean body weight of the 15-month stop-exposure group ranged from about 5% to 13% lower than that of the controls during the period that the rats received 3,4-dihydrocoumarin. The final mean body weight of this group was 15% lower than that of the controls.

TABLE 13
Mean Body Weights and Survival of Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin

Weeks on Study	Vehicle Control		600 mg/kg (9-month)			600 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	128	60	122	96	20	125	98	20
2	184	60	190	103	20	189	103	20
3	229	60	218	95	20	213	93	20
4	250	60	237	95	20	233	93	20
5	267	60	256	96	20	253	95	20
6	284	60	266	94	20	265	93	20
7	297	59	284	95	20	281	95	20
8	313	59	301	96	20	297	95	20
9	323	59	303	94	20	309	96	20
10	330	59	315	96	20	316	96	20
11	339	59	331	98	20	329	97	20
12	349	59	337	97	20	336	96	20
13	358	59	354	99	20	351	98	20
17	382	59	356	93	20	372	97	20
21	397	59	379	95	20	382	96	20
25	424	59	397	94	20	402	95	20
29	437	59	403	92	19	417	96	20
33	452	59	412	91	19	417	92	20
37	465	59	416	90	19	425	92	20
41	474	59	429	91	19	430	91	20
45	483	59	434	90	19	440	91	20
49	500	59	449	90	19	432	87	20
53	507	59	468	92	19	443	87	20
57	517	58	488	94	19	460	89	19
61	521	58	491	94	19	467	90	19
65	520	58	502	97	19	474	91	19
69	529	49[a]	503	95	19	487	92	18
73	529	49	507	96	19	484	91	17
77	517	47	509	98	19	469	91	13
81	522	45	511	98	16	465	89	13
85	510	45	503	99	16	451	88	13
89	494	43	486	98	16	431	87	12
93	480	39	454	94	15	420	87	10
97	471	33	425	90	11	396	84	7
101	459	30	438	95	8	391	85	6
103	459	28	422	92	8	390	85	3
Mean for weeks								
1-13	281		270	96		269	96	
14-52	446		408	91		413	93	
53-103	503		479	95		445	88	

[a] Interim evaluation occurred during week 65.

Pathology and Statistical Analysis 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 600 mg/kg for 2 years (Table E3b).

Progression or Regression of Chemical-Induced Lesions

Since 3,4-dihydrocoumarin administration 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. Consistent with the findings of the 2-year core study in male rats, chemical-related lesions were observed in the kidney. The average severity of nephropathy in male rats receiving 600 mg/kg for 9 or 15 months followed by the recovery period was significantly greater than that of the controls (Table 14). The severities of nephropathy in stop-exposure male rat groups at the end of the recovery period were also significantly greater than those at the respective interim evaluations (Tables 15 and 16). This is expected, since nephropathy is a progressive degenerative disease that naturally increases in severity with age. However, these findings indicate that renal damage caused by 9 or 15 months of exposure to 3,4-dihydrocoumarin was largely irreversible. Consistent with the increased average severity of renal disease, the incidence of

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney, Forestomach, and Parathyroid Gland of Male Rats in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin

Dose	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Single Sections (Standard Evaluation)			
9-Month Interim Evaluation			
Kidney[a]	19	19	
Nephropathy[b]	19 (1.0)[c]	18 (1.0)	
15-Month Interim Evaluation[d]			
Kidney	19		20
Nephropathy	19 (1.1)		20 (1.6)°°
Stop-Exposure Groups			
Kidney	50[e]	20	20
Nephropathy	50 (2.2)	19 (2.9)°°	20 (3.6)°°
Renal Tubule Hyperplasia	0	1	2
Renal Tubule Adenoma	0	0	0
Renal Tubule Oncocytoma	0	0	1
Parathyroid Gland	47	18	18
Hyperplasia	0	6°°	9°°
Forestomach	47	19	20
Ulcer	4	2	4

(continued)

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney, Forestomach, and Parathyroid Gland of Male Rats in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

Dose	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Step Sections (Extended Evaluation)			
15-Month Interim Evaluation			
Kidney	19		20
Renal Tubule Hyperplasia	0		1
Renal Tubule Adenoma	0		0
Stop-Exposure Groups			
Kidney	50	20	20
Renal Tubule Hyperplasia	0	0	2
Renal Tubule Adenoma	1	3*	2
Single and Step Sections Combined			
15-Month Interim Evaluation			
Kidney	19		20
Renal Tubule Hyperplasia	0		1
Renal Tubule Adenoma	0		1
Stop-Exposure Groups			
Kidney	50	20	20
Renal Tubule Hyperplasia	0	1	3*
Renal Tubule Adenoma	1	3*	2
Renal Tubule Oncocytoma	0	0	1

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test (stop-exposure groups), or Mann-Whitney U test (severity grades)
** ($P \leq 0.01$)
[a] Number of rats with organ examined microscopically.
[b] Number of rats 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 evaluation in the 2-year core study and the 15-month interim evaluation 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 15
Comparison of the 9-Month Interim Evaluation with the 9-Month Stop-Exposure Group in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin

Dose (600 mg/kg)	9-Month Interim Evaluation	9-Month Stop-Exposure Group
Kidney[a]	19	20
Nephropathy[b]	18 (1.0)[c]	19 (2.9)°°
Parathyroid Gland	15	18
Hyperplasia	0	6°
Stomach, Forestomach	19	19
Ulcer	0	2

° Significantly different (P≤0.05) from the 9-month interim group by the logistic regression test (incidence data) or Mann-Whitney U test (severity grades)
°° (P≤0.01)
[a] Number of rats with organ examined microscopically.
[b] Number of rats with lesion.
[c] Group average severity grade of lesion: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

TABLE 16
Comparison of the 15-Month Interim Evaluation with the 15-Month Stop-Exposure Group in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin

Dose (600 mg/kg)	15-Month Interim Evaluation[a]	15-Month Stop-Exposure Group
Kidney[b]	20	20
Nephropathy[c]	20 (1.6)[d]	20 (3.6)°°
Parathyroid Gland	19	18
Hyperplasia	0	9°°
Stomach, Forestomach	19	20
Ulcer	0	4°

° 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 evaluation in the 2-year core study and the 15-month interim evaluation in the stop-exposure evaluation.
[b] Number of rats with organ examined microscopically.
[c] Number of rats with lesion.
[d] Group average severity grade of lesion: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

parathyroid gland hyperplasia was greater in the stop-exposure groups than in the controls. Table 17 presents the kidney and parathyroid gland lesions in the stop-exposure groups and in the group receiving 600 mg/kg 3,4-dihydrocoumarin for 2 years.

In the standard evaluation of single sections, focal renal tubule hyperplasia was observed in one male in the 9-month stop-exposure group and in two males in the 15-month stop-exposure group (Table 14). While no renal tubule adenomas were found, an oncocytoma was identified in one male in the 15-month stop-exposure group. Microscopic examination of the additional step sections revealed additional males with hyperplasia and adenomas in these stop-exposure groups (Table 14).

TABLE 17
Incidences of Selected Lesions of the Kidney, Parathyroid Gland, and Stomach of Male Rats: Comparison of the 9- and 15-Month Stop-Exposure Groups with the 2-Year Core Group in the Gavage Study of 3,4-Dihydrocoumarin

Dose (600 mg/kg)	9-Month Stop-Exposure	15-Month Stop-Exposure	2-Year Core Group
Kidney[a]	20	20	50
Nephropathy[b]	19 (2.9)[c]	20 (3.6)	47 (3.2)
Renal Tubule Hyperplasia[d]	1	4	8
Renal Tubule Adenoma[d]	3	2	6
Renal Tubule Oncocytoma	0	1	0
Transitional Cell Carcinoma	0	0	2
Parathyroid Gland	18	18	41
Hyperplasia	6	9	19
Stomach, Forestomach	19	20	46
Ulcer	2	4	16

[a] Number of rats with organ examined microscopically.
[b] Number of rats with lesion.
[c] Group average severity grade of lesion: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Includes standard (single section) and extended (step section) evaluations.

MICE

16-DAY STUDY

All male and female mice receiving 2,250 mg/kg died during the first three days of dosing (Table 18). One female mouse that received 140 mg/kg died as the result of a gavage accident. Body weight gains and final mean body weights of surviving dosed male and female groups were similar to those of the controls. There were no treatment-related findings at necropsy, no differences in the hematologic parameters (Table H6), and no treatment-related clinical findings of toxicity. The high dose selected for the 13-week study was 1,600 mg/kg, just below the dose in which mortality was observed in the 16-day study.

TABLE 18
Survival and Mean Body Weights of Mice in the 16-Day Gavage Study of 3,4-Dihydrocoumarin

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	22.0 ± 0.9	23.4 ± 1.2	1.4 ± 0.4	
140	5/5	21.8 ± 1.0	23.6 ± 1.0	1.8 ± 0.2	101
280	5/5	23.0 ± 1.2	24.8 ± 1.1	1.8 ± 0.2	106
560	5/5	22.2 ± 0.7	24.2 ± 0.6	2.0 ± 0.3	103
1,125	5/5	22.2 ± 0.4	23.6 ± 1.3	1.4 ± 1.2	101
2,250	0/5[c]	23.0 ± 0.7	–	–	–
Female					
0	5/5	19.8 ± 0.7	21.0 ± 0.7	1.2 ± 0.2	
140	4/5[d]	19.0 ± 0.9	20.0 ± 0.8	1.5 ± 0.5	95
280	5/5	20.0 ± 0.5	21.2 ± 0.4	1.2 ± 0.2	101
560	5/5	19.6 ± 0.5	20.4 ± 0.4	0.8 ± 0.2	97
1,125	5/5	19.0 ± 0.5	20.8 ± 0.9	1.8 ± 0.7	99
2,250	0/5[e]	19.4 ± 0.5	–	–	–

[a] Number of mice surviving at 16 days/number initially in group
[b] Weights given as mean ± standard error. Subsequent calculations based on mice surviving to the end of the study. Differences from the control group are not significant by Dunnett's test.
[c] Day of death: 1, 2, 2, 2, 3
[d] Death attributed to gavage accident
[e] Day of death: 1, 2, 2, 2, 2

13-WEEK STUDY

Eight males and four females receiving 1,600 mg/kg died during the first week of the study, and one female receiving 1,600 mg/kg died during week 5 (Table 19). Deaths in the control and 100 mg/kg dose groups were attributed to gavage accidents. No treatment-related clinical findings were noted. While the body weight gain of the two surviving 1,600 mg/kg male mice was significantly lower than that of the controls, the final mean body weights of other dosed groups of male and female mice were similar to those of the controls. No treatment-related differences in hematologic parameters were observed (Table H7). Absolute and relative liver weights of surviving male and female mice that received 1,600 mg/kg and the relative kidney weight of surviving males that received 1,600 mg/kg were significantly greater than those of controls (Table G5). There were no chemical-related gross or microscopic lesions.

Dose Selection Rationale: Because of mortality at the 1,600 mg/kg dose level and the lack of a treatment-related response at the 800 mg/kg dose level, the high dose selected for the 2-year study was 800 mg/kg.

TABLE 19
Survival and Mean Body Weights of Mice in the 13-Week Gavage Study of 3,4-Dihydrocoumarin

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	9/10[c]	22.4 ± 0.6	30.9 ± 0.7	8.8 ± 0.5	
100	9/10[d]	22.5 ± 0.4	29.9 ± 0.5	7.6 ± 0.3	97
200	10/10	22.2 ± 0.4	30.8 ± 0.7	8.6 ± 0.7	100
400	10/10	21.8 ± 0.4	29.7 ± 0.8	7.9 ± 0.5	96
800	10/10	21.8 ± 0.5	30.3 ± 0.7	8.5 ± 0.5	98
1,600	2/10[e]	21.7 ± 0.4	27.0 ± 1.0	5.0 ± 0.0*	87
Female					
0	10/10	18.6 ± 0.3	25.1 ± 0.5	6.5 ± 0.4	
100	10/10	18.3 ± 0.5	25.5 ± 0.7	7.2 ± 0.4	102
200	10/10	18.9 ± 0.5	24.7 ± 0.8	5.8 ± 0.4	98
400	10/10	18.3 ± 0.4	23.9 ± 0.6	5.6 ± 0.5	95
800	10/10	18.8 ± 0.6	25.8 ± 0.7	7.0 ± 0.3	103
1,600	5/10[f]	17.7 ± 0.5	24.4 ± 0.2	6.8 ± 0.8	97

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
[a] Number of mice surviving/number initially in group.
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on mice surviving to the end of the study.
[c] Death attributed to gavage accident
[d] Death attributed to gavage accident
[e] Week of death: 1, 1, 1, 1, 1, 1, 1, 1
[f] Week of death: 1, 1, 1, 1, 5

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female mice are shown in Table 20 and in the Kaplan-Meier curves in Figure 4. Survival of dosed male and female mice was similar to that of the controls.

Body Weights and Clinical Findings

There were no treatment-related differences in the body weights of dosed male and female mice (Figure 5 and Tables 21 and 22). There were no clinical findings in mice that could be related to chemical administration.

TABLE 20
Survival of Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Male				
Animals initially in study	70	70	70	70
15-Month interim evaluation[a]	20	19	19	20
Moribund	3	3	8	4
Accidental deaths[a]	1	1	1	0
Natural deaths	4	8	8	8
Animals surviving to study termination	42	39	34	38
Percent probability of survival at end of study[b]	87	79	69	77
Mean survival (days)[c]	626	623	621	625
Survival analysis[d]	P=0.287	P=0.443	P=0.071	P=0.315
Female				
Animals initially in study	70	70	70	70
15-Month interim evaluation[a]	19	20	19	18
Moribund	5	9	4	5
Accidental deaths[a]	2	0	1	0
Natural deaths	8	2	5	19[e]
Animals surviving to study termination	36	39	41	28
Percent probability of survival at end of study	74	79	83	57
Mean survival (days)	612	638	639	603
Survival analysis	P=0.014	P=0.698N	P=0.396N	P=0.063

[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 mouse that died the last week of study

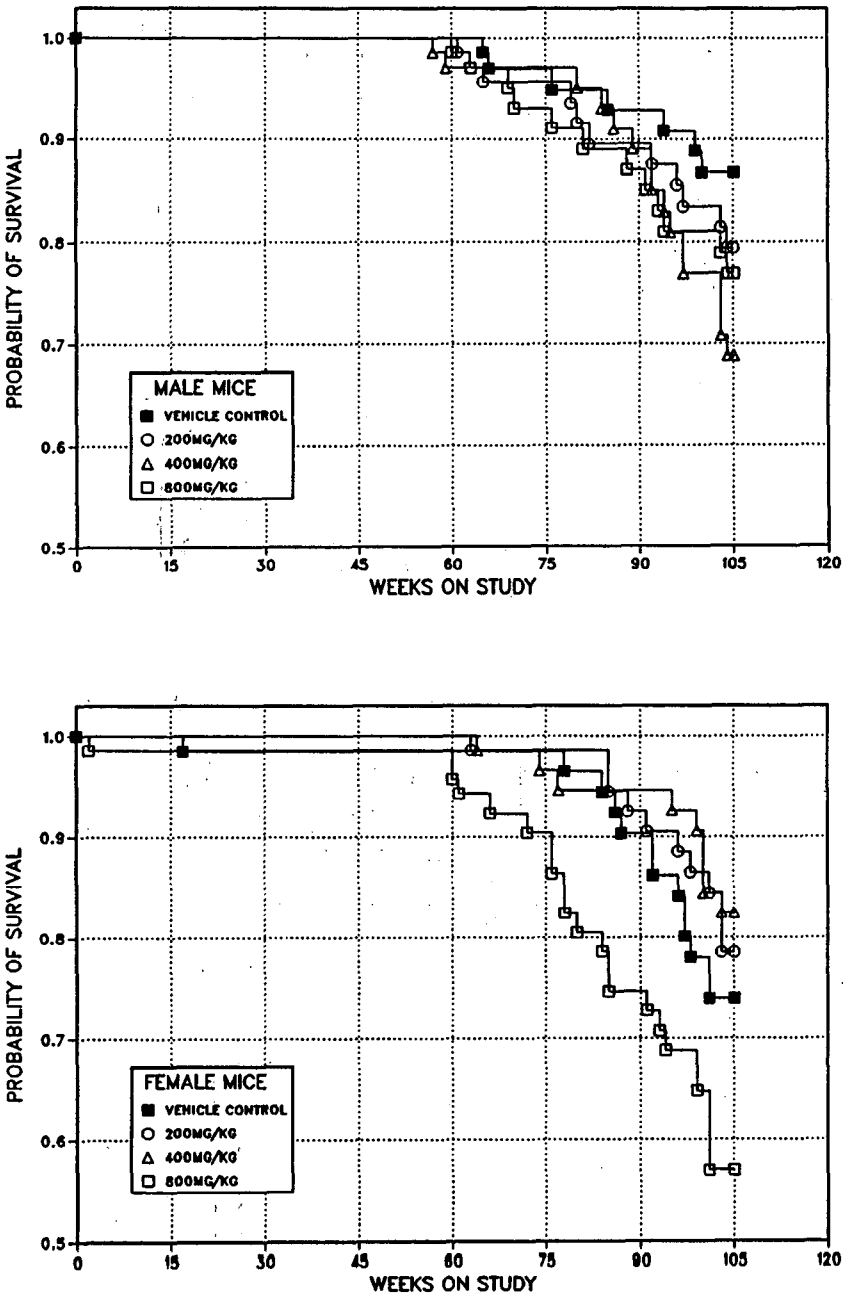
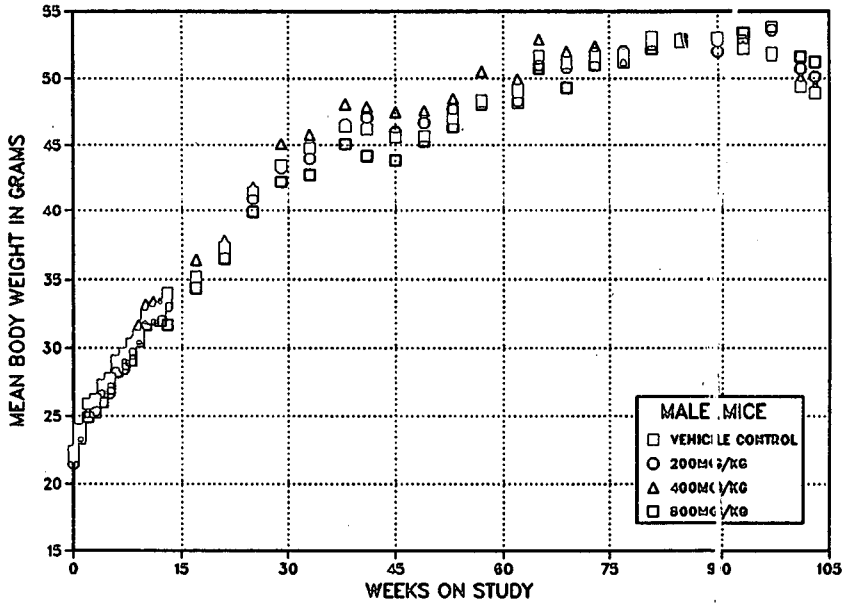


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered 3,4-Dihydrocoumarin in Corn Oil by Gavage for 2 Years



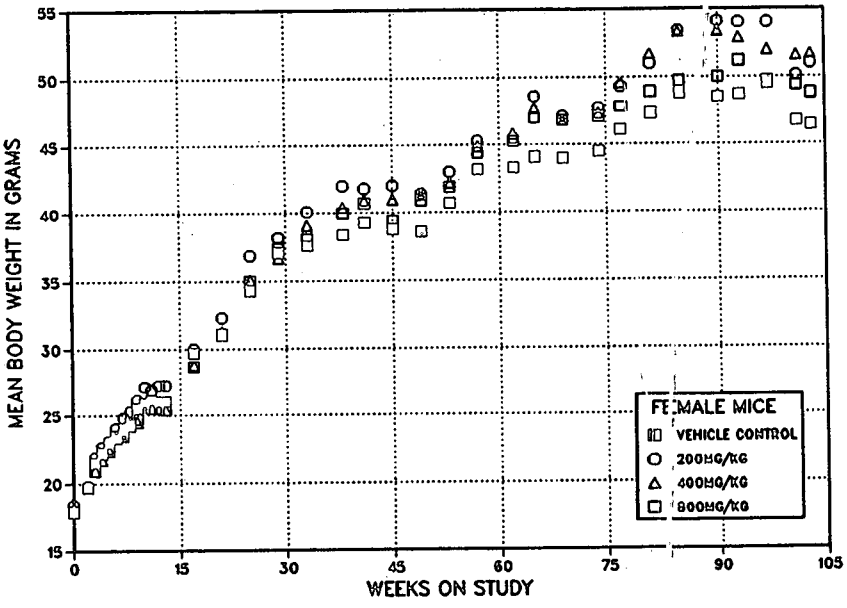


FIGURE 5
Growth Curves for Male and Female Mice Administered 3,4-Dihydrocoumarin in Corn Oil by Gavage for 2 Years

TABLE 21
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Week on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	200 mg/kg Av. Wt. (g)	200 mg/kg Wt. (% of controls)	200 mg/kg No. of Survivors	400 mg/kg Av. Wt. (g)	400 mg/kg Wt. (% of controls)	400 mg/kg No. of Survivors	800 mg/kg Av. Wt. (g)	800 mg/kg Wt. (% of controls)	800 mg/kg No. of Survivors
1	23.1	70	22.6	98	70	22.7	98	70	22.7	98	70
2	25.8	69	24.9	97	70	25.3	98	69	24.9	97	70
3	26.2	69	25.4	97	70	26.0	99	69	25.3	97	70
4	27.3	69	26.7	98	70	27.2	100	69	26.0	95	70
5	27.8	69	26.7	96	70	27.5	99	69	27.0	97	70
6	29.1	69	28.2	97	70	29.0	100	69	28.3	97	70
7	29.6	69	28.5	96	70	29.7	100	69	28.8	97	70
8	30.3	69	29.6	98	70	30.4	100	69	29.1	96	70
9	30.9	69	30.7	99	70	31.7	103	69	30.5	99	70
10	32.4	69	32.2	99	70	33.2	103	69	31.7	98	70
11	32.5	69	32.7	101	70	33.4	103	69	32.1	99	70
12	32.9	69	32.7	99	70	33.3	101	69	32.0	97	70
13	34.0	69	33.1	97	70	33.7	99	69	31.7	93	70
17	35.2	69	35.2	100	69	36.4	103	69	34.4	98	70
21	37.3	69	37.4	100	69	37.8	101	69	36.5	98	70
25	41.5	69	40.9	99	69	41.9	101	69	39.9	96	70
29	43.5	69	43.3	100	69	45.1	104	69	42.3	97	70
33	44.8	69	44.0	98	69	45.8	102	69	42.8	96	70
38	46.4	69	46.6	100	69	48.1	104	69	45.1	97	70
41	46.2	69	47.1	102	69	47.9	104	69	44.2	96	70
45	45.6	69	46.0	101	69	47.5	104	69	43.9	96	70
49	45.7	69	46.7	102	69	47.6	104	69	45.3	99	70
53	47.0	69	47.7	102	69	48.5	103	69	46.4	99	70
57	48.4	69	48.3	100	69	50.5	104	68	48.1	99	70
62	49.1	69	48.3	98	68	49.9	102	67	48.2	98	69
65[a]	51.7	64	51.0	99	60	52.9	102	62	50.7	98	63
69	51.1	47	50.8	99	47	52.0	102	48	49.3	97	47
73	51.6	47	51.9	101	47	52.4	102	48	51.0	99	46
77	51.8	46	52.0	100	47	51.2	99	48	51.3	99	45
81	53.1	46	52.5	99	45	52.8	99	47	52.2	98	44
85	52.7	45	52.9	100	44	53.0	101	46	52.9	100	44
90	53.0	45	52.0	98	44	52.9	100	44	53.0	100	43
93	52.2	45	52.8	101	43	52.4	100	42	53.4	102	41
97	51.9	44	53.6	103	41	51.7	100	39	53.8	104	40
101	49.4	42	50.7	103	41	50.0	101	38	51.6	105	40
103	48.9	42	50.1	103	40	49.4	101	35	51.2	105	39
Mean for weeks											
1-13	29.4		28.8	98		29.5	100		28.5	97	
14-52	42.9		43.0	100		44.2	103		41.6	97	
53-103	50.9		51.0	100		51.4	101		50.9	100	

[a] Interim evaluation s occurred during week s 65 and 66.

TABLE 22
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Week on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	200 mg/kg Av. Wt. (g)	200 mg/kg Wt. (% of controls)	200 mg/kg No. of Survivors	400 mg/kg Av. Wt. (g)	400 mg/kg Wt. (% of controls)	400 mg/kg No. of Survivors	800 mg/kg Av. Wt. (g)	800 mg/kg Wt. (% of controls)	800 mg/kg No. of Survivors
1	17.9	70	18.4	103	70	18.0	101	70	18.0	101	70
2	19.7	70	19.8	101	70	19.7	100	70	19.7	100	70
3	21.3	69	21.3	100	70	21.0	99	70	20.8	98	69
4	22.3	68	22.7	102	70	21.7	97	70	22.2	100	69
5	23.0	68	23.1	100	70	22.4	97	70	22.6	98	69
6	23.3	68	24.0	103	70	23.3	100	70	23.5	101	69
7	23.9	68	24.8	104	70	23.5	98	70	23.7	99	69
8	24.3	68	25.3	104	70	24.2	100	70	24.5	101	69
9	25.6	68	26.2	102	70	24.5	96	70	24.7	97	69
10	26.0	68	27.2	105	70	25.6	99	70	25.8	99	69
11	26.2	68	27.0	103	70	25.6	98	70	25.5	97	69
12	26.1	68	27.3	105	70	25.5	98	70	26.0	100	69
13	26.1	68	27.3	105	70	25.4	97	70	25.4	97	69
17	29.7	67	30.0	101	70	28.8	97	70	28.7	97	69
21	31.0	67	32.3	104	70	31.3	101	70	31.1	100	69
25	34.3	67	36.9	108	70	35.1	102	70	35.0	102	69
29	37.1	67	38.2	103	70	36.7	99	70	37.4	101	69
33	37.6	67	40.1	107	70	39.1	104	70	38.1	101	69
38	38.4	67	42.0	109	70	40.4	105	70	40.0	104	69
41	39.3	67	41.8	106	70	40.9	104	70	40.7	104	69
45	38.8	67	42.0	108	70	41.0	106	70	39.4	102	69
49	38.6	67	41.4	107	70	41.3	107	70	40.9	106	69
53	40.6	67	43.0	106	70	42.2	104	70	41.9	103	69
57	43.2	67	45.3	105	70	44.9	104	70	44.4	103	69
62	43.3	67	45.5	105	70	45.8	106	70	45.3	105	66
65[a]	44.1	63	48.6	110	67	47.7	108	67	47.0	107	64
69	44.0	48	47.1	107	49	46.8	106	50	46.8	106	47
74	44.5	48	47.7	107	49	47.3	106	50	47.1	106	46
77	46.1	48	49.3	107	49	49.6	108	47	47.8	104	44
81	47.3	47	51.0	108	49	51.7	109	47	48.9	103	41
85	48.8	46	53.4	109	47	53.3	109	47	49.8	102	38
90	48.5	44	54.1	112	46	53.4	110	47	50.0	103	38
93	48.7	42	54.0	111	45	52.9	109	47	51.2	105	36
97	49.5	39	54.0	109	44	52.0	105	46	49.7	100	35
101	46.7	36	50.1	107	42	51.6	111	42	49.4	106	29
103	46.4	36	51.0	110	39	51.7	111	41	48.8	105	29
Mean for weeks											
1-13	23.5		24.2	103		23.1	98		23.3	99	
14-52	36.1		38.3	106		37.2	103		36.8	102	
53-103	45.7		49.6	109		49.4	108		47.7	104	

[a] Interim evaluations occurred during weeks 65 and 66.

Hematology and Clinical Chemistry

There were no differences in hematology and clinical chemistry parameters at the 15-month interim evaluation that were considered to be biologically significant (Table H8).

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, lung, and kidney. Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal tumor diagnoses, and the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group are presented in Appendix C for male mice and Appendix D for female mice.

Liver: The relative liver weight of 800 mg/kg female mice was significantly greater than that of the controls at the 15-month interim evaluation (Table G6). There was a significantly increased incidence of hepatocellular adenoma in all dosed groups of female mice; the number of dosed female mice with multiple hepatocellular adenoma was also increased (Table 23). The incidence of hepatocellular carcinoma in dosed female mice was not significantly increased, but the incidence of hepatocellular adenoma or carcinoma (combined) in females receiving 400 or 800 mg/kg was significantly greater than that in controls (Table 23). There was no increased incidence of hepatocellular adenoma or carcinoma (combined) in male mice, but the number of males with multiple hepatocellular adenoma was moderately increased in the 400 and 800 mg/kg groups.

Hepatic foci of cytoplasmic alteration, hepatocellular adenoma, and hepatocellular carcinoma constitute 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). 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 or 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 23
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Dose	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Male				
15-Month Interim Evaluation				
Liver[a]	10	7	5	10
Basophilic Focus[b]	0	2	1	0
Clear Cell Focus	1	0	0	0
Mixed Cell Focus	0	0	1	0
Hepatocellular Adenoma	3	4	2	3
2-Year Study				
Liver	50	51	51	50
Basophilic Focus	3	1	4	4
Clear Cell Focus	2	7	14**	7
Eosinophilic Focus	9	8	13	12
Mixed Cell Focus	1	2	0	2
Multiple Hepatocellular Adenoma				
Overall rates[c]	8/50 (16%)	5/51 (10%)	19/51 (38%)	19/50 (38%)
Hepatocellular Adenoma				
Overall rates	29/50 (58%)	23/51 (45%)	36/51 (71%)	31/50 (62%)
Adjusted rates[d]	64.2%	54.6%	81.6%	71.8%
Terminal rates[e]	26/42 (62%)	20/39 (51%)	26/34 (76%)	26/38 (68%)
First incidence (days)	449	553	555	438
Logistic regression tests[f]	P=0.147	P=0.153N	P=0.105	P=0.410
Hepatocellular Carcinoma				
Overall rates	11/50 (22%)	11/51 (22%)	11/51 (22%)	6/50 (12%)
Adjusted rates	24.3%	23.3%	25.5%	13.4%
Terminal rates	8/42 (19%)	4/39 (10%)	4/34 (12%)	2/38 (5%)
First incidence (days)	591	423	583	477
Logistic regression tests	P=0.110N	P=0.566N	P=0.581N	P=0.144N
Hepatoblastoma				
Overall rates	0/50 (0%)	0/51 (0%)	0/51 (0%)	2/50 (4%)
Adjusted rates	0.0%	0.0%	0.0%	5.3%
Terminal rates	0/42 (0%)	0/39 (0%)	0/34 (0%)	2/38 (5%)
First incidence (days)	–[g]	–	–	729 (T)
Logistic regression tests	P=0.044	–	–	P=0.217
Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma (combined)[h]				
Overall rates	36/50 (72%)	30/51 (59%)	40/51 (78%)	34/50 (68%)
Adjusted rates	74.9%	63.7%	83.3%	75.3%
Terminal rates	30/42 (71%)	22/39 (56%)	26/34 (76%)	27/38 (71%)
First incidence (days)	449	423	555	438
Logistic regression tests	P=0.508N	P=0.125N	P=0.264	P=0.415N

TABLE 23
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver of Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

Dose	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Female				
15-Month Interim Evaluation				
Liver	9	10	9	9
Basophilic Focus	0	0	1	0
Hepatocellular Adenoma	2	0	2	2
2-Year Study				
Liver	51	50	50	52
Basophilic Focus	1	3	0	1
Clear Cell Focus	0	2	2	0
Eosinophilic Focus	8	11	9	8
Mixed Cell Focus	1	2	2	1
Multiple Hepatocellular Adenoma				
Overall rates	0/51 (0%)	6/50 (12%)	9/50 (18%)	9/52 (17%)
Hepatocellular Adenoma				
Overall rates	10/51 (20%)	20/50 (40%)	22/50 (44%)	20/52 (38%)
Adjusted rates	27.8%	45.2%	52.4%	56.1%
Terminal rates	10/36 (28%)	15/39 (38%)	21/41 (51%)	14/29 (48%)
First incidence (days)	729 (T)	594	700	420
Logistic regression tests	P=0.014	P=0.038	P=0.023	P=0.012
Hepatocellular Carcinoma				
Overall rates	3/51 (6%)	2/50 (4%)	4/50 (8%)	6/52 (12%)
Adjusted rates	7.7%	4.8%	9.2%	15.7%
Terminal rates	1/36 (3%)	1/39 (3%)	3/41 (7%)	2/29 (7%)
First incidence (days)	674	685	444	504
Logistic regression tests	P=0.131	P=0.490N	P=0.470	P=0.254
Hepatocellular Adenoma or Carcinoma (combined)[i]				
Overall rates	13/51 (25%)	21/50 (42%)	25/50 (50%)	24/52 (46%)
Adjusted rates	34.1%	46.5%	58.0%	60.3%
Terminal rates	11/36 (31%)	15/39 (38%)	23/41 (56%)	14/29 (48%)
First incidence (days)	674	594	444	420
Logistic regression tests	P=0.013	P=0.100	P=0.020	P=0.014

** Significantly different (P≤0.01) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of mice necropsied.
[b] Number of mice with lesion.
[c] Number of mice with neoplasm per number of mice with organ examined microscopically.
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.
[g] Not applicable; no neoplasms in animal group
[h] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 370/901 (41.1% ± 15.5%); range 14%-72%
[i] Historical incidence: 129/898 (14.4% ± 8.1%); range 2%-34%

Lung: The incidences of alveolar/bronchiolar adenoma in the 200 and 400 mg/kg male mice were marginally greater than that of the controls (Table 24). The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in these groups also exceeded the range for these neoplasms in NTP historical controls (Table C4b). However, because the increased incidence of pulmonary neoplasms in these groups was marginal and there was no corresponding increase in the 800 mg/kg group, it was not considered chemical related.

Kidney: In the standard evaluation of single sections of kidney, focal hyperplasia, adenoma, or carcinoma of the renal tubule were identified in several dosed male mice, but not in the controls (Table 25).

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung of Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Dose	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Male				
15-Month Interim Evaluation				
Lung[a]	10	7	5	10
Alveolar Epithelium Hyperplasia[b]	1	1	0	1
Alveolar/bronchiolar Adenoma	1	1	1	1
Alveolar/bronchiolar Adenoma, Multiple	0	0	1	0
2-Year Study				
Lung	50	50	51	50
Alveolar Epithelium Hyperplasia	0	3	0	1
Alveolar/bronchiolar Adenoma				
Overall rates[c]	8/50 (16%)	15/50 (30%)	15/51 (29%)	10/50 (20%)
Adjusted rates[d]	19.0%	38.5%	41.4%	25.5%
Terminal rates[e]	8/42 (19%)	15/39 (38%)	13/34 (38%)	9/38 (24%)
First incidence (days)	729 (T)	729 (T)	679	634
Logistic regression tests[f]	P=0.423	P=0.047	P=0.038	P=0.345
Alveolar/bronchiolar Carcinoma				
Overall rates	1/50 (2%)	3/50 (6%)	1/51 (2%)	3/50 (6%)
Adjusted rates	2.3%	7.2%	2.6%	7.2%
Terminal rates	0/42 (0%)	1/39 (3%)	0/34 (0%)	2/38 (5%)
First incidence (days)	690	643	715	477
Logistic regression tests	P=0.313	P=0.303	P=0.762N	P=0.296
Alveolar/bronchiolar Adenoma or Carcinoma (combined)[g]				
Overall rates	9/50 (18%)	18/50 (36%)	16/51 (31%)	13/50 (26%)
Adjusted rates	20.9%	43.8%	43.0%	32.0%
Terminal rates	8/42 (19%)	16/39 (41%)	13/34 (38%)	11/38 (29%)
First incidence (days)	690	643	679	477
Logistic regression tests	P=0.327	P=0.024	P=0.047	P=0.218

(continued)

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung of Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

Dose	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Female				
15-Month Interim Evaluation				
Lung	9	10	9	9
Alveolar Epithelium Hyperplasia	0	0	0	0
Alveolar/bronchiolar Adenoma	0	0	0	0
2-Year Study				
Lung	51	50	48	51
Alveolar Epithelium Hyperplasia	0	0	0	1
Alveolar/bronchiolar Adenoma				
Overall rates	2/51 (4%)	5/50 (10%)	1/48 (2%)	3/51 (6%)
Adjusted rates	5.6%	12.3%	2.4%	9.5%
Terminal rates	2/36 (6%)	4/39 (10%)	1/41 (2%)	2/28 (7%)
First incidence (days)	729 (T)	671	729 (T)	595
Logistic regression tests	P=0.554	P=0.245	P=0.455N	P=0.460
Alveolar/bronchiolar Carcinoma				
Overall rates	0/51 (0%)	1/50 (2%)	0/48 (0%)	0/51 (0%)
Alveolar/bronchiolar Adenoma or Carcinoma (combined)				
Overall rates	2/51 (4%)	6/50 (12%)	1/48 (2%)	3/51 (6%)
Adjusted rates	5.6%	14.1%	2.4%	9.5%
Terminal rates	2/36 (6%)	4/39 (10%)	1/41 (2%)	2/28 (7%)
First incidence (days)	729 (T)	615	729 (T)	595
Logistic regression tests	P=0.531N	P=0.143	P=0.455N	P=0.460

(T)Terminal sacrifice
[a] Number of mice necropsied.
[b] Number of mice with lesion.
[c] Number of mice with neoplasms per number of mice examined microscopically.
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[e] Observed incidence in mice surviving until the end of the study.
[f] 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.
[g] Historical incidence for 2-year corn oil gavage studies with vehicle control groups (mean ± standard deviation): 166/900 (18.4% ± 5.9%); range 6%-28%

Although the incidences of these lesions in dosed male mice were low, no more than one renal neoplasm has been observed in a group of 50 historical controls. The incidence and severity of nephropathy, a spontaneous age-related degenerative disease, was similar among dosed and control mice.

Because the incidence of renal tubule adenoma in the 400 mg/kg males exceeded the range in NTP historical control groups, additional step sections of kidney were prepared from the remaining formalin-fixed tissue. Approximately four to six additional sections taken at 0.5 μm intervals were prepared for each male mouse. Additional males with focal hyperplasia or adenoma were identified in the dosed groups. The incidences of these proliferative lesions in the step sections and in the single and step sections combined are shown in Table 25. While renal tubule neoplasms occurred only in dosed males, the incidence in each of the dose groups was not significantly greater than that of controls, and did not increase with dose. Therefore, the low number of renal tubule neoplasms in dosed male mice was not considered chemical related.

TABLE 25
Incidences of Selected Lesions of the Kidney of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

Dose	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Single Sections (Standard Evaluation)				
Kidney[a]	50	51	51	49
Nephropathy[b]	45 (1.3)[c]	46 (1.2)	45 (1.4)	43 (1.1)
Renal Tubule Hyperplasia	0	1	1	0
Renal Tubule Adenoma[d]	0	0	2	0
Renal Tubule Carcinoma[e]	0	1	0	1
Step Sections (Extended Evaluation)				
Kidney	50	51	51	49
Renal Tubule Hyperplasia	0	0	3	1
Renal Tubule Adenoma	0	0	1[f]	1
Single and Step Sections Combined				
Kidney	50	51	51	49
Renal Tubule Hyperplasia	0	1	3	1
Renal Tubule Adenoma	0	0	2	1
Renal Tubule Carcinoma	0	1	0	1
Renal Tubule Adenoma or Carcinoma	0	1	2	2

[a] Number of mice with kidney examined microscopically.
[b] Number of mice with lesion.
[c] Average severity grade of lesion in affected mice: 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): 3/899 (0.3% ± 0.8%); range 0%-2%
[e] Historical incidence: 0/899
[f] The adenoma in the step section is the same adenoma seen in the original single section.

GENETIC TOXICOLOGY

3,4-Dihydrocoumarin (10 to 6,666 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in a pre-incubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983; Table F1). In cytogenetic tests with Chinese hamster ovary cells, 3,4-dihydrocoumarin (effective doses, 50 to 300 μg/mL) induced a dose-related increase in sister chromatid exchanges in the absence of S9; with S9, a significant increase in sister chromatid exchanges was observed only at the highest doses tested (1,600 and 2,000 μg/mL) in each of two trials (Table F2). The response in the second trial with S9 was dose-related. In the second sister chromatid exchange trial with S9, cytotoxicity was apparent at the 2,000 μg/mL dose level and only 36 cells could be scored. 3,4-Dihydrocoumarin did not induce chromosomal aberrations in Chinese hamster ovary cells at doses up to 500 μg/mL without S9 or up to 1,600 μg/mL with S9 (Table F3). No increases in the frequencies of micronucleated normochromatic erythrocytes were noted in peripheral blood samples obtained from male and female mice at the end of the 13-week toxicity study (Table F4). The elevated micronucleated erythrocyte frequency observed in male mice in the high-dose group was based on counts obtained from only two animals (8 out of 10 mice died at this dose). These data were not included in the overall analysis.

In conclusion, 3,4-dihydrocoumarin does not appear to be mutagenic and does not induce chromosomal damage *in vitro* or *in vivo*. However, 3,4-dihydrocoumarin induced sister chromatid exchanges in cultured Chinese hamster ovary cells *in vitro*.

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 hydroxy 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-γ-pyrone derivative resembling the 1,2-benzopyrone moiety in coumarin.

3,4-Dihydrocoumarin was nominated by the Food and Drug Administration and the National Cancer Institute for study because of its widespread use as a flavoring agent in beverages, gelatins, puddings, candy, and other food items; as a fragrance in perfumes, creams, and cosmetics; and because of the interest in chemical structure-biologic 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 3,4-dihydrocoumarin in F344/N rats and $B6C3F_1$ mice. The results of the NTP toxicity and carcinogenicity studies of coumarin are reported separately (NTP, 1993).

Treatment with 3,4-dihydrocoumarin resulted in an increase in the severity of nephropathy in dosed male rats at the 15-month interim evaluation, which progressed during the last half of the study in male rats from the 2-year core study and the stop-exposure evaluation. At the end of the 2-year study, 600 mg/kg female rats also had a marginal increase in the severity of nephropathy. Nephropathy in the untreated Fischer rat is a chronic, progressive, degenerative lesion with increased inflammation, degeneration and necrosis, and increased renal epithelial cell turnover. Changes in glomerular permeability resulting in proteinuria, progressive glomerular sclerosis, tubule damage, inflammation, and interstitial fibrosis are associated with the process of aging in rats. This background level of kidney disease, which is most severe in the male rat, may make the male rat particularly susceptible to chemical toxicity at this site.

The incidence of parathyroid gland hyperplasia was not increased in dosed male rats at the 9- or 15-month interim evaluations, but by the end of 2 years the incidence was increased, an indication that the nephropathy was severe enough to compromise renal function. Hyperparathyroidism frequently accompanies severe nephropathy in rats because the progressive loss of renal function disrupts calcium and phosphorus homeostasis, which leads to prolonged parathyroid gland stimulation. This results in hyperplasia and elevated levels of parathyroid hormone.

Coumarin had a similar effect in the kidney of rats causing an increase in the severity of nephropathy. Treatment-related kidney toxicity was not observed in $B6C3F_1$ mice treated with either 3,4-dihydrocoumarin or coumarin. The mouse kidney has a lower background of nephropathy and in these studies was less susceptible to chemical-induced nephropathy. Treatment-related kidney toxicity has not been reported in the previous long-term studies of coumarin in male rats (Osborne-Mendel or Sprague-Dawley) receiving coumarin at 2,500 or 5,000 ppm (Griepentrog, 1973; Evans *et al.*, 1989). Factors contributing to nephropathy in F344/N rats given 3,4-dihydrocoumarin or coumarin may be related to the strain of rat and the route of administration.

Forestomach ulcers were observed in male rats receiving 3,4-dihydrocoumarin or coumarin during the last half of the 2-year studies. There was no evidence for a direct toxic effect on the forestomach with these chemicals in the 13-week studies even though higher doses of the chemicals were administered. Male rats in the coumarin and 3,4-dihydrocoumarin studies resisted the daily gavage procedure and also had an increase in the severity of nephropathy. Studies on stress-related ulcers in rats have generally focused on findings in the glandular stomach, and findings in the forestomach have not been extensively reported (Paré, 1986; Rozman and Hänninen, 1986; Kleiman *et al*, 1988). Factors contributing to the forestomach ulcers may include

direct toxicity of the chemical at this site after long-term administration or changes in the physiologic state of the animals due to kidney disease and/or stress.

Coumarin caused toxic liver lesions after 13 weeks in rats receiving 150 and 300 mg/kg, and death in rats receiving 300 mg/kg. In contrast, no treatment-related toxic liver lesions were observed in rats that received 600 mg/kg 3,4-dihydrocoumarin. In the 13-week mouse studies, decreased weight gain and/or mortality were observed in mice receiving 300 mg/kg coumarin, while no general toxicity was observed in mice that received 3,4-dihydrocoumarin at doses up to 800 mg/kg. In the 13-week studies of 3,4-dihydrocoumarin, there were increases in the absolute liver and kidney weights of rats, and mortality was observed in rats receiving 1,200 mg/kg and mice receiving 1,600 mg/kg.

In the 2-year study, survival was reduced in all male rat dose groups as a result of kidney toxicity. Survival was greater than 50% in all dosed groups of male rats up to week 92 of the study, which was considered to be adequate for the determination of the potential carcinogenicity of 3,4-dihydrocoumarin in rats. Survival in dosed groups of female rats was also somewhat reduced, but not as much as that observed in male rats. Body weight gain was reduced in the 600 mg/kg male rats. Although treatment-related mortality was observed in mice receiving 1,600 mg/kg in the 13-week study, treatment with 800 mg/kg in the 2-year study did not cause statistically significant differences in survival or body weights.

3,4-Dihydrocoumarin did not cause extensive liver lesions as were found in the coumarin studies. The differences in the chemical structures and metabolism of 3,4-dihydrocoumarin and coumarin are probably the reasons for the different toxic responses in the liver. Lake (1984) presented supporting evidence for this hypothesis in a set of experiments in which coumarin treatment was shown to produce hepatotoxic changes in rats within 24 hours after administration, but when rats were pretreated with cobaltous chloride, a treatment that is reported to block cytochrome P-450-dependent biotransformations, the same hepatotoxic changes were not observed. 3,4-Dihydrocoumarin, a coumarin saturated at the 3,4-position, does not produce toxic liver lesions and probably cannot be metabolized at the 3,4-position to the metabolite responsible for liver toxicity.

The evidence of a carcinogenic response in rats was seen primarily in the kidney of males. In the standard evaluation of single sections of the kidneys from male rats, renal tubule adenomas were identified in one 150 and two 600 mg/kg animals, and transitional cell carcinomas were observed in two 600 mg/kg animals. In addition, three male rats receiving 150 mg/kg and three male rats receiving 600 mg/kg had renal tubule hyperplasia. The renal tubule hyperplasia in this study was distinguished from background regenerative hyperplasia, which commonly accompanies the degenerative tubule changes of age-related nephropathy, on the basis of cellular atypia and prominent stratification of the epithelium. These cytologic features suggest a loss of cell growth regulation and failure of cellular differentiation. This lesion is similar to those induced by potent renal carcinogens and appears to represent the early stages of renal tubule adenoma and carcinoma development (Hard, 1986; Tsuda *et al.*, 1986). The only kidney neoplasm observed in the initial evaluations of the stop-exposure male rats was one renal tubule oncocytoma. In the original evaluation of the kidneys in female rats, there was one tubule cell adenoma in each of the control, 150 mg/kg, and 300 mg/kg groups, and one renal tubule carcinoma in each of the 150 and 600 mg/kg groups.

The NTP has found that multiple sectioning of the kidney may allow a more precise evaluation of the potential chemical-related induction of renal proliferative lesions than single sectioning does. The majority of renal neoplasms in the original evaluation of the kidney in these 3,4-dihydrocoumarin studies 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.

Additional renal tubule proliferative lesions were identified by the step sections, and the majority were seen in the dosed male rats. The combined incidence of renal tubule adenomas in male rats from the single-section evaluation and the step-section evaluation was: controls, 1/50; 150 mg/kg, 1/48; 300 mg/kg, 3/47; 600 mg/kg, 6/50; 9-month stop-exposure, 3/20; 15-month stop-exposure, 2/20. Focal hyperplasia was also observed in dosed male rats with incidences that

generally paralleled the incidences of renal neoplasms.

The incidences of focal hyperplasia and renal tubule adenoma were significantly increased in dosed male rats as indicated by the incidental tumor and life table tests. These increased incidences were considered to be some evidence of a carcinogenic response because of the statistical significance and because the incidence of renal tubule adenomas in all dosed groups of male rats exceeded the incidence of this neoplasm in historical controls (8/1,019). However, this was not considered to be clear evidence of a carcinogenic response because there was no evidence of malignant renal tubule neoplasms, the incidence of renal tubule neoplasms in female rats was not significantly increased, and there was no supportive evidence for a neoplastic response in the step-section evaluation.

The step-section evaluation showed no additional evidence for a treatment-related response in the transitional cells in the kidney of male rats, and the biological significance of the two transitional cell carcinomas found in the original evaluation of the kidneys of 600 mg/kg male rats was uncertain.

In the original evaluations of the kidney in male mice there were a few renal tubule neoplasms in dosed animals: one tubule cell carcinoma was found in a 200 mg/kg male mouse, two renal tubule adenomas were found in 400 mg/kg male mice, and one renal tubule carcinoma was found in a 400 mg/kg male mouse. The combined incidence of renal tubule adenoma or carcinoma (combined) in male mice from the original single-section analysis and the step-section analysis was: controls, 0/50; 200 mg/kg, 1/51; 400 mg/kg, 2/51; 800 mg/kg, 2/49. Because of the low incidence of these neoplasms and the lack of a dose-response trend, they were not considered to be related to chemical treatment. There were no kidney neoplasms in either control or dosed female mice.

In female mice there was some evidence of a carcinogenic response in the liver based on a significantly increased incidence of hepatocellular adenoma in all dosed groups by both the life table and incidental tumor tests. Dosed female mice also had increased incidences of multiple hepatocellular adenomas. The increased incidences of hepatocellular neoplasms were not considered to be clear evidence of a carcinogenic response because there was no increased incidence of malignant neoplasms of the liver. The incidence of hepatocellular adenomas and/or carcinomas were not significantly increased in male mice.

In male mice, there were a few more alveolar/bronchiolar adenomas in the 200 and 400 mg/kg groups than in the controls; these were not considered to be related to treatment because the increase was not significant by the trend test, there was no increased incidence in the 600 mg/kg group, and there was no increased incidence of alveolar/bronchiolar adenoma or carcinoma (combined). In addition, there was no supportive evidence of a carcinogenic response in the lungs of dosed female mice.

3,4-Dihydrocoumarin was not mutagenic in the *Salmonella* test with or without metabolic activation, did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, and did not cause chromosomal damage (either structural alterations such as breaks, or aneuploidy events leading to genomic imbalance) in the peripheral blood samples obtained from mice at the end of the 13-week study. The only evidence for genetic toxicity of 3,4-dihydrocoumarin consists of positive results from an *in vivo* sister chromatid exchange test in cultured Chinese hamster ovary cells, but a positive result in this test provides little positive predictivity for carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). The accumulated data from *in vivo* mouse micronucleus assays have not yet been evaluated with respect to its sensitivity, specificity, and predictivity for carcinogenicity in rats and mice. The genetic toxicity data available for 3,4-dihydrocoumarin indicate little potential or direct interaction with cellular DNA.

Coumarin, a mutagenic chemical, caused lung neoplasms in female mice, while 3,4-dihydrocoumarin, a nonmutagenic chemical, did not increase the incidence of lung neoplasms. Ashby and Tennant (1991) report that most chemicals that cause a carcinogenic response in the lung of mice are mutagenic in the *Salmonella* test, and the lack of a carcinogenic response at this site with 3,4-dihydrocoumarin correlated with its negative response in the *Salmonella* test.

3,4-Dihydrocoumarin and coumarin both produced treatment-related preneoplastic lesions and neoplasms of the renal tubule epithelium. These lesions were observed at coumarin doses of 25, 50, and

100 mg/kg, and at 3,4-dihydrocoumarin doses of 150, 300, and 600 mg/kg. The similarity of the response with these two chemicals at this site suggests that the mechanism for the formation of these neoplasms may be related. Konishi and Ward (1989) have demonstrated increased ^{3}H-thymidine labeling indices in the renal tubule epithelium with increased severity of nephropathy. The increased severity of nephropathy in male rats in both the coumarin and 3,4-dihydrocoumarin studies may have increased the rate of cell proliferation at this site. Cell proliferation is an essential component of the multistage process of carcinogenesis (Cohen and Ellwein, 1990), and may have played a role in the development of kidney neoplasms in the male rat. Other coumarin derivations such as 8-methoxypsoralen (NTP, 1989a) (a furanocoumarin), ochratoxin A (NTP, 1989b) (a dihydrocoumarin), and quercetin (NTP, 1992) (a benzo-γ-pyrone derivative resembling the 1,2-benzopyrone moiety in coumarin) were also nephrotoxic and produced renal tubule neoplasms.

Both 3,4-dihydrocoumarin and coumarin produced an increased incidence of hepatocellular neoplasms in female mice. The increased incidence was observed in females receiving 50 and 100 mg/kg coumarin or 400 and 800 mg/kg 3,4-dihydrocoumarin. 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. Additional studies would help clarify the possible role of other mechanisms in the formation of liver neoplasms such as alterations in gene expression through changes in DNA methylation (Goodman *et al.*, 1991).

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of 3,4-dihydrocoumarin in male F344/N rats based on increased incidences of renal tubule adenomas and focal hyperplasia. The transitional cell carcinomas in two 600 mg/kg males may also have been chemical related. There was *no evidence of carcinogenic activity* of 3,4-dihydrocoumarin in female F344/N rats receiving 150, 300, or 600 mg/kg. There was *no evidence of carcinogenic activity* of 3,4-dihydrocoumarin in male B6C3F$_1$ mice receiving 200, 400, or 800 mg/kg. There was *some evidence of carcinogenic activity* in female B6C3F$_1$ mice based on increased incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined).

3,4-Dihydrocoumarin caused ulcers, hyperplasia, and inflammation of the forestomach, parathyroid gland hyperplasia, and increased severity of nephropathy in male rats.

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

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF 3,4-DIHYDROCOUMARIN

TABLE A1	Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	77
TABLE A2	Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	82
TABLE A3	Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	106
TABLE A4a	Historical Incidence of Renal Tubule Neoplasms in Male F344/N Rats Receiving Corn Oil by Gavage	111
TABLE A4b	Historical Incidence of Transitional Cell Neoplasms of the Kidney in Male F344/N Rats Receiving Corn Oil by Gavage	111
TABLE A5	Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	112

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	10	10	10
Early deaths				
Moribund	12	24	26	17
Accidental deaths	2	1	1	2
Natural deaths	9	13	15	29
Survivors				
Died last week of study	1			
Terminal sacrifice	27	12	8	2
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(2)	(4)	(10)
Hepatocellular adenoma			1 (25%)	
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(9)	(1)	(2)	(10)
Pars distalis, adenoma		1 (100%)	1 (50%)	
Pars intermedia, adenoma	1 (11%)			
General Body System				
None				
Genital System				
Testes	(9)	(3)	(2)	(10)
Interstitial cell, adenoma	5 (56%)	2 (67%)	2 (100%)	4 (40%)
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 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	(41)	(42)	(41)	(24)
Intestine large, colon	(44)	(42)	(43)	(30)
Intestine large, rectum	(44)	(44)	(44)	(32)
Intestine small, duodenum	(43)	(44)	(45)	(33)
Intestine small, ileum	(42)	(43)	(42)	(23)
Intestine small, jejunum	(41)	(42)	(43)	(30)
Liver	(49)	(47)	(49)	(50)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma		1 (2%)	1 (2%)	2 (4%)
Leiomyosarcoma				1 (2%)
Mesentery	(17)	(15)	(10)	(6)
Leiomyosarcoma				1 (17%)
Pancreas	(49)	(47)	(48)	(38)
Adenoma	2 (4%)	5 (11%)	2 (4%)	2 (5%)
Leiomyosarcoma				1 (3%)
Acinar cell, adenoma			2 (4%)	
Salivary glands	(51)	(50)	(47)	(42)
Stomach, forestomach	(47)	(48)	(50)	(46)
Leiomyosarcoma, metastatic			1 (2%)	
Stomach, glandular	(46)	(47)	(50)	(43)
Leiomyosarcoma			1 (2%)	
Tongue		(1)		(1)
Papilloma squamous		1 (100%)		1 (100%)
Tooth				(1)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal gland, cortex	(50)	(49)	(49)	(50)
Adrenal gland, medulla	(50)	(49)	(49)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma complex		1 (2%)		
Pheochromocytoma benign	17 (34%)	10 (20%)	11 (22%)	8 (16%)
Bilateral, pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(49)	(47)	(48)	(42)
Adenoma	4 (8%)	2 (4%)	4 (8%)	1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(49)	(47)	(46)	(46)
Pars distalis, adenoma	24 (49%)	20 (43%)	13 (28%)	9 (20%)
Thyroid gland	(50)	(48)	(49)	(40)
C-cell, adenoma	1 (2%)	1 (2%)		1 (3%)
Follicle, adenoma	1 (2%)	2 (4%)	1 (2%)	1 (3%)
Follicle, carcinoma		1 (2%)		
Follicular cell, adenocarcinoma	1 (2%)			
General Body System				
Tissue NOS		(1)	(1)	(1)
Fibroma			1 (100%)	
Genital System				
Epididymis	(49)	(50)	(48)	(47)
Preputial gland	(47)	(49)	(48)	(49)
Adenocarcinoma	1 (2%)			
Adenoma	8 (17%)	1 (2%)	1 (2%)	1 (2%)
Carcinoma	2 (4%)	3 (6%)		1 (2%)
Prostate	(45)	(48)	(46)	(49)
Seminal vesicle	(49)	(49)	(46)	(49)
Testes	(49)	(49)	(49)	(46)
Interstitial cell, adenoma	43 (88%)	39 (80%)	39 (80%)	42 (91%)
Hematopoietic System				
Blood		(1)	(1)	(1)
Bone marrow	(47)	(49)	(50)	(46)
Lymph node	(51)	(49)	(50)	(48)
Lymph node, mandibular	(51)	(48)	(44)	(42)
Lymph node, mesenteric	(50)	(49)	(50)	(47)
Spleen	(49)	(48)	(45)	(45)
Thymus	(46)	(47)	(47)	(45)
Integumentary System				
Mammary gland	(46)	(46)	(47)	(44)
Adenoma	1 (2%)			
Fibroadenoma	3 (7%)	2 (4%)		
Skin	(51)	(50)	(48)	(49)
Basosquamous tumor benign	1 (2%)			
Fibroma	1 (2%)	4 (8%)		
Fibrosarcoma	1 (2%)			
Keratoacanthoma	2 (4%)	3 (6%)	2 (4%)	
Lipoma			1 (2%)	
Neurofibroma		1 (2%)		
Papilloma squamous	2 (4%)	1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(51)	(50)	(50)	(50)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Nervous System				
Brain	(48)	(49)	(46)	(47)
Cerebrum, meningioma benign	1 (2%)			
Meninges, meningioma benign	1 (2%)			
Spinal cord	(2)	(4)	(8)	(4)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	1 (2%)	
Trachea	(51)	(50)	(50)	(48)
Special Senses System				
Ear		(1)	(1)	(2)
Fibroma				1 (50%)
Papilloma				1 (50%)
Zymbal's gland			(1)	
Squamous cell carcinoma			1 (100%)	
Urinary System				
Kidney	(50)	(48)	(47)	(50)
Cortex, lipoma				1 (2%)
Renal tubule, adenoma		1 (2%)		2 (4%)
Transitional epithelium, carcinoma				2 (4%)
Urinary bladder	(49)	(48)	(44)	(38)
Systemic Lesions				
Multiple organs[b]	(51)	(50)	(50)	(50)
Leukemia mononuclear	10 (20%)	5 (10%)	8 (16%)	4 (8%)
Lymphoma malignant		2 (4%)		
Mesothelioma benign		2 (4%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	6	3	4	4
2-Year study	48	46	47	45
Total primary neoplasms				
15-Month interim evaluation	6	3	4	4
2-Year study	130	109	93	83
Total animals with benign neoplasms				
15-Month interim evaluation	6	3	4	4
2-Year study	48	45	46	44
Total benign neoplasms				
15-Month interim evaluation	6	3	4	4
2-Year study	114	98	83	73
Total animals with malignant neoplasms				
2-Year study	16	12	11	8
Total malignant neoplasms				
2-Year study	16	12	11	10

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Neoplasm Summary (continued)				
Total animals with metastatic neoplasms				
2-Year study			1	
Total metastatic neoplasms				
2-Year study			1	

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 2 5	0 0 3 3	0 0 3 4	0 0 3 5	0 0 5 1	0 0 5 4	0 0 7 2	0 0 7 4	0 0 7 5	0 0 8 3	0 0 9 3	0 0 9 4	0 0 0 4	0 1 2 2	0 1 1 1	0 0 1 3	0 0 2 4	0 0 4 3	0 0 4 5	0 0 6 2	0 0 6 4	0 0 7 1	0 0 8 1	0 0 9 1	0 1 0 5	0 1 1 3	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery		+			+					+		+									+			+			17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X	X																			2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																											1
Pheochromocytoma benign			X				X	X		X	X								X		X	X		X	X	X	X	17
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X				X						X						X						4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X			X	X	X	X					X	X	X		X	X	X			X			24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																											1
Follicle, adenoma	X																										1
Follicular cell, adenocarcinoma																				X							1
General Body System																											
None																											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	0 4 5	3 7 9	5 2 6	5 3 4	5 4 0	5 4 1	5 9 6	6 1 9	6 3 4	6 3 7	6 3 9	6 4 8	6 5 4	6 5 4	6 5 5	6 5 6	6 7 0	6 7 8	6 9 0	7 0 4	7 0 5	7 1 1	7 1 7	7 2 9	7 2 9
Carcass ID Number	0 0 5 2	0 0 4 1	0 0 1 4	0 0 4 2	0 0 2 2	0 1 0 3	0 0 7 3	0 0 4 4	0 0 8 2	0 1 1 2	0 0 6 5	0 1 2 1	0 0 8 4	0 0 8 5	0 0 6 1	0 0 9 2	0 1 1 5	0 1 1 4	0 0 5 3	0 1 2 4	0 0 6 3	0 0 2 1	0 0 5 5	0 0 1 2	0 0 1 5
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	M	+	+	+	+
Adenocarcinoma																									X
Adenoma																				X					
Carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	+	+	+	+	A	+	A	+	+	A	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Adenoma																									
Fibroadenoma								X																	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Fibroma																									
Fibrosarcoma																									
Keratoacanthoma																									
Papilloma squamous															X	X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Cerebrum, meningioma benign																	X								
Meninges, meningioma benign																	X								
Peripheral nerve		+																							
Spinal cord		+																							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	00023	00033	00034	00035	00051	00054	00072	00074	00075	00083	00093	00094	00104	00112	00122	00131	00133	00142	00143	00155	00162	00164	00171	00181	00191	00205	00213	Total Tissues/ Tumors
Genital System																												
Coagulating gland			+												+													2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																												1
Adenoma							X	X							X	X	X								X	X		8
Carcinoma																						X						2
Prostate	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	X	X	43
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																												
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma			X																									1
Fibroadenoma																X												3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basosquamous tumor benign																			X									1
Fibroma					X																							1
Fibrosarcoma																		X										1
Keratoacanthoma																										X	X	2
Papilloma squamous																												2
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cerebrum, meningioma benign																												1
Meninges, meningioma benign																												1
Peripheral nerve																						+						2
Spinal cord																						+						2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 2 5	0 0 3 3	0 0 3 4	0 0 3 5	0 0 5 1	0 0 5 4	0 0 7 2	0 0 7 4	0 0 7 5	0 0 8 3	0 0 9 3	0 0 9 4	0 0 0 4	0 1 4 4	0 1 2 2	0 0 2 1	0 0 1 3	0 0 1 4	0 0 2 4	0 0 4 3	0 0 4 5	0 0 6 2	0 0 6 4	0 0 7 1	0 0 8 1	0 0 9 1	0 1 0 5	0 1 1 3	Total Tissues/ Tumors
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X							X													2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																												
Eye																												1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear						X					X																	10

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg
(continued)

Number of Days on Study	6 7 3	6 7 7	6 8 1	6 8 1	6 8 5	6 9 4	6 9 5	6 9 5	7 1 8	7 2 1	7 2 1	7 2 1	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 8 3	0 2 3 2	0 1 8 2	0 2 3 5	0 1 6 2	0 2 0 5	0 1 5 4	0 2 2 4	0 2 1 2	0 1 6 3	0 2 2 1	0 1 5 1	0 1 3 1	0 1 4 1	0 1 4 4	0 1 5 3	0 1 7 3	0 1 8 5	0 2 2 2	0 2 3 3	0 2 4 4	0 1 5 2	0 1 7 2	0 1 8 1	0 2 1 3	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular adenoma																		X									1
Mesentery		+	+			+				+	+					+	+		+								15
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma						X											X		X								5
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tongue																											1
Papilloma squamous																											1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma complex								X																			1
Pheochromocytoma benign			X	X	X							X				X		X			X		X			10
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma														X													2
Parathyroid gland	+	M	+	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Pars distalis, adenoma				X	X	X	X			X		X		X	X		X	X		X				X	X		20
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma													X														1
Follicle, adenoma										X														X			2
Follicle, carcinoma																						X					1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg
(continued)

Number of Days on Study	2	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6
	3	5	6	7	4	4	4	5	5	5	6	7	8	8	8	9	9	2	3	4	5	6	6	7
	8	5	2	2	3	8	9	0	6	7	7	6	4	4	8	9	9	3	4	5	7	2	8	3
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	2	2	1	1	2	1	1	1	1	2	1	1	2	2	1	1	2	1	2	2	1	1	1
	6	0	4	9	3	0	4	7	7	4	1	6	8	3	3	9	9	4	3	1	1	3	6	7
	1	3	5	5	3	1	3	1	4	2	1	4	4	4	1	1	2	3	5	4	5	2	5	5
General Body System																								
Tissue NOS			+									M												
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma												X	X	X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Fibroadenoma													X						X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																	X							
Keratoacanthoma																			X					
Neurofibroma																								
Papilloma squamous																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg
(continued)

Number of Days on Study	6 7 3	6 7 7	6 8 1	6 8 1	6 8 5	6 9 4	6 9 5	6 9 5	7 1 8	7 2 1	7 2 1	7 2 1	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	3 4 0	
Carcass ID Number	0 1 8 3	0 2 3 2	0 1 8 2	0 2 3 5	0 1 6 2	0 2 0 5	0 1 5 4	0 2 2 4	0 2 1 2	0 1 6 3	0 2 5 1	0 1 3 1	0 1 4 1	0 1 4 4	0 1 5 3	0 1 7 3	0 1 8 5	0 2 2 2	0 2 3 3	0 2 4 4	0 2 5 2	0 1 7 2	0 1 8 1	0 2 1 3	Total Tissues/ Tumors	
General Body System																										
Tissue NOS																									1	
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma																						X			1	
Carcinoma																									3	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
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	39	
Hematopoietic System																										
Blood																									1	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Fibroadenoma																									2	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Fibroma							X						X					X							4	
Keratoacanthoma			X	X																					3	
Neurofibroma																			X						1	
Papilloma squamous			X																						1	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Skeletal muscle																		+							1	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg
(continued)

Number of Days on Study	2	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6
	3	5	6	7	4	4	4	5	5	5	6	7	8	8	8	9	9	2	3	4	5	6	6	6	7
	8	5	2	2	3	8	9	0	6	7	7	6	4	4	8	9	9	3	4	5	7	2	8	8	3
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	2	2	1	1	2	1	1	1	1	2	1	1	2	2	1	1	2	1	2	2	1	1	1	1
	6	0	4	9	3	0	4	7	7	4	1	6	8	3	3	9	9	4	3	1	1	3	6	7	3
	1	3	5	5	3	1	3	1	4	2	1	4	4	4	1	1	2	3	5	4	5	2	5	5	4
Nervous System																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																			+						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																		+							
Eye																									
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X										X							X
Lymphoma malignant			X													X									
Mesothelioma benign									X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg (continued)

Number of Days on Study	6 7 3	6 7 7	6 8 1	6 8 1	6 8 5	6 9 4	6 9 5	6 9 5	7 1 8	7 2 1	7 2 1	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	3 4 0	
Carcass ID Number	0 1 8 3	0 2 3 2	0 1 8 2	0 2 3 5	0 1 6 2	0 2 0 5	0 1 5 4	0 2 2 4	0 2 1 2	0 1 6 3	0 2 2 1	0 1 5 1	0 1 3 1	0 1 4 1	0 1 4 4	0 1 5 3	0 1 7 3	0 1 8 5	0 2 2 2	0 2 3 3	0 2 4 4	0 1 5 2	0 1 7 2	0 1 8 1	0 2 1 3	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve				+																						1
Spinal cord				+			+								+											4
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye				+																+						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X									X						5
Lymphoma malignant																										2
Mesothelioma benign								X																		2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg
(continued)

Number of Days on Study	6 8 4	6 9 0	6 9 1	6 9 4	6 9 4	6 9 5	6 9 7	6 9 7	7 0 1	7 0 8	7 0 9	7 0 9	7 0 9	7 1 6	7 2 0	7 2 3	7 2 5	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 2 5 2	0 2 5 4	0 3 4 5	0 3 1 1	0 3 3 4	0 2 6 4	0 2 8 1	0 3 0 5	0 2 7 4	0 2 5 5	0 2 6 5	0 2 9 4	0 3 2 3	0 3 0 4	0 3 0 2	0 2 9 1	0 2 9 2	0 2 7 1	0 2 7 5	0 3 2 4	0 3 6 2	0 2 5 3	0 2 6 1	0 3 1 2	0 3 2 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	43
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																									1
Hepatocellular adenoma				X																					1
Mesentery		+					+										M					+		+	10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma											X														2
Acinar cell, adenoma													X												2
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic	X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma	X																								1
Cardiovascular System																									
Blood vessel						+											+								2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign					X	X			X				X						X		X				11
Bilateral, pheochromocytoma benign																	X								1
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma								X				X							X						4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma					X	X		X	X		X	X		X								X			13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicle, adenoma									X																1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg
(continued)

Number of Days on Study	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	9	2	2	5	9	9	0	0	1	1	1	3	3	3	5	6	6	6	6	7	7	7	7	8
	4	2	7	4	2	6	3	5	3	5	9	3	4	4	4	2	2	5	6	0	4	5	8	9	1
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
	2	3	3	3	3	3	3	2	3	2	2	3	2	3	3	3	3	2	3	3	2	2	3	3	3
	9	4	5	3	4	0	2	8	1	5	7	6	8	1	6	3	3	6	1	5	6	7	6	2	5
	3	1	1	2	4	1	2	2	4	1	2	1	3	5	4	3	5	2	3	2	3	3	3	5	4
General Body System																									
Tissue NOS															+										
Fibroma															X										
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Lipoma							X																		
Papilloma squamous																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+																		
Spinal cord							+																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg (continued)

Number of Days on Study	6 8 4	6 9 0	6 9 1	6 9 4	6 9 4	6 9 5	6 9 7	6 9 7	7 0 1	7 0 8	7 0 9	7 0 9	7 0 9	7 1 6	7 2 0	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 2 5 2	0 2 5 4	0 3 4 5	0 3 1 1	0 3 3 4	0 2 6 4	0 2 8 1	0 3 0 5	0 2 7 4	0 2 5 5	0 2 6 5	0 2 9 4	0 2 3 3	0 3 2 4	0 3 0 4	0 3 0 2	0 2 9 1	0 2 9 2	0 2 7 1	0 2 7 5	0 3 2 4	0 3 6 2	0 2 5 3	0 2 6 1	0 3 1 2	0 3 2 1	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Fibroma																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																								X		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	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	39
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Keratoacanthoma	X																					X				2
Lipoma																										1
Papilloma squamous													X													1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Peripheral nerve				+		+		M				+		+			+					+				7
Spinal cord				+		+		+				+		+			+					+				8

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg
(continued)

Number of Days on Study	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	9	2	2	5	9	9	0	0	1	1	1	3	3	3	5	6	6	6	6	7	7	7	7	7	8	
	4	2	7	4	2	6	3	5	3	5	9	3	4	4	4	2	2	5	6	0	4	5	8	9	1	
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
	2	3	3	3	3	3	3	2	3	2	2	3	2	3	3	3	3	2	3	3	2	2	3	3	3	
	9	4	5	3	4	0	2	8	1	5	7	6	8	1	6	3	3	6	1	5	6	7	6	2	5	
	3	1	1	2	4	1	2	2	4	1	2	1	3	5	4	3	5	2	3	2	3	3	3	5	4	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Ear																										
Zymbal's gland																										
Squamous cell carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear							X							X	X	X									X	
Mesothelioma benign																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg (continued)

Number of Days on Study	6 8 4	6 9 0	6 9 1	6 9 4	6 9 4	6 9 5	6 9 7	6 9 7	7 0 1	7 0 1	7 0 8	7 0 9	7 0 9	7 0 9	7 1 6	7 2 0	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 2 5 2	0 2 5 4	0 3 4 5	0 3 1 1	0 3 3 4	0 2 6 4	0 2 8 1	0 3 0 5	0 2 7 4	0 2 5 5	0 2 6 5	0 2 9 4	0 3 2 3	0 3 0 4	0 3 0 2	0 2 9 1	0 2 9 2	0 2 7 1	0 2 7 5	0 3 2 4	0 3 6 2	0 2 5 3	0 2 6 1	0 3 1 2	0 3 2 1	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			1
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																		+								1
Zymbal's gland		+																								1
Squamous cell carcinoma		X																								1
Urinary System																										
Kidney	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X			X		X		8
Mesothelioma benign					X																					1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg
(continued)

Number of Days on Study	6 4 0	6 5 1	6 5 9	6 6 2	6 6 3	6 6 8	6 6 8	6 7 2	6 7 2	6 7 3	6 7 3	6 7 7	6 7 7	6 8 1	6 8 7	6 8 8	6 9 0	6 9 0	6 9 4	6 9 6	7 1 0	7 1 1	7 1 2	7 2 0	7 3 0	7 3 0	
Carcass ID Number	0 4 8 1	0 4 6 5	0 4 5 5	0 4 3 4	0 3 7 4	0 3 9 4	0 4 0 5	0 4 0 3	0 4 7 4	0 3 9 1	0 4 6 3	0 4 2 1	0 4 2 3	0 4 4 3	0 4 7 3	0 3 9 2	0 3 9 3	0 4 4 2	0 4 6 1	0 4 0 4	0 4 5 3	0 4 7 5	0 3 7 5	0 4 1 1	0 3 7 1	0 4 5 2	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	A	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	A	A	A	+	A	+	+		32
Intestine large, cecum	+	+	A	+	A	+	+	+	+	A	A	+	+	+	A	+	A	+	A	A	A	A	A	+	+		24
Intestine large, colon	+	+	A	+	A	+	+	+	+	A	A	+	+	+	A	+	+	+	A	A	A	+	A	+	+		30
Intestine large, rectum	+	+	A	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	A	A	A	+	A	+	+		32
Intestine small	+	+	A	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	A	A	+	+	A	+	+		33
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	A	A	+	+	A	+	+		33
Intestine small, ileum	+	+	A	+	A	+	+	+	+	A	A	+	+	+	A	+	A	+	A	A	A	A	A	+	+		23
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	A	A	+	A	A	+	+		30
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular adenoma					X																						2
Leiomyosarcoma																		X									1
Mesentery				,											+		+	+			+				+	+	6
Leiomyosarcoma																		X									1
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Adenoma																						X					2
Leiomyosarcoma																		X									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Tongue																+											1
Papilloma squamous																X											1
Tooth																											1
Cardiovascular System																											
Blood vessel																											1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X	X				X				X										X						X	8
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenoma							X																				1
Parathyroid gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma																X		X			X	X	X	X			9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	40
C-cell, adenoma															X												1
Follicle, adenoma																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg
(continued)

Number of Days on Study	0	0	3	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
	4	4	6	4	8	0	2	3	5	5	6	7	8	9	9	0	0	0	0	0	1	1	2	2	4
	4	5	5	4	3	1	8	7	2	4	9	7	4	3	8	5	5	5	6	7	6	8	5	7	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
	4	4	4	4	4	4	3	4	3	4	3	4	4	4	4	4	4	4	4	4	4	4	4	3	4
	1	0	4	1	3	4	8	5	8	2	8	1	4	7	8	0	1	6	8	8	5	7	8	7	6
	2	1	5	3	2	1	2	1	4	2	1	4	4	2	5	2	5	4	3	2	4	1	4	3	2
General Body System																									
Tissue NOS																+									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Testes	+	+	+	A	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma					X	X	X	X	X	X		X	X			X	X	X	X	X	X	X	X	X	X
Hematopoietic System																									
Blood												+													
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	+	+	M	M	+	+	+	M	+	M	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg
(continued)

Number of Days on Study	6 4 0	6 5 1	6 5 9	6 6 2	6 6 3	6 6 8	6 6 8	6 7 2	6 7 2	6 7 3	6 7 3	6 7 7	6 8 1	6 8 7	6 8 8	6 9 0	6 9 0	6 9 4	6 9 6	7 1 0	7 1 1	7 1 2	7 2 0	7 3 0	7 3 0	
Carcass ID Number	0 4 8 1	0 4 6 5	0 4 5 5	0 4 3 4	0 3 7 4	0 3 9 4	0 4 0 5	0 4 0 3	0 4 7 4	0 3 9 1	0 4 6 3	0 4 2 1	0 4 2 3	0 4 4 3	0 4 7 2	0 3 9 3	0 3 4 2	0 4 4 3	0 4 6 2	0 4 0 1	0 4 5 4	0 3 7 3	0 4 7 5	0 3 1 1	0 4 5 2	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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																										
Blood																										1
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	46
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	M	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+		44
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Peripheral nerve						+		+					+													3
Spinal cord						+		+		+			+													4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg
(continued)

Number of Days on Study	0	0	3	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	
	4	4	6	4	8	0	2	3	5	5	6	7	8	9	9	0	0	0	0	0	1	1	2	2	4
	4	5	5	4	3	1	8	7	2	4	9	7	4	3	8	5	5	5	6	7	6	8	5	7	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
	4	4	4	4	4	4	3	4	3	4	3	4	4	4	4	4	4	4	4	4	4	4	4	3	4
	1	0	4	1	3	4	8	5	8	2	8	1	4	7	8	0	1	6	8	8	5	7	8	7	6
	2	1	5	3	2	1	2	1	4	2	1	4	4	2	5	2	5	4	3	2	4	1	4	3	2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																								+	
Fibroma																									
Papilloma																								X	
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, lipoma																									
Renal tubule, adenoma																	X								
Transitional epithelium, carcinoma				X			X																		
Urinary bladder	+	+	+	A	+	+	+	+	+	A	+	+	+	A	A	+	A	+	A	A	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X						X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg
(continued)

Number of Days on Study	6 4 0	6 5 1	6 5 9	6 6 2	6 6 3	6 6 8	6 6 8	6 7 2	6 7 2	6 7 3	6 7 3	6 7 7	6 8 1	6 8 7	6 8 8	6 9 0	6 9 0	6 9 4	6 9 6	7 1 0	7 1 1	7 1 2	7 2 0	7 3 0	7 3 0	
Carcass ID Number	0 4 8 1	0 4 6 5	0 4 5 5	0 4 3 4	0 3 7 4	0 3 9 4	0 4 0 5	0 4 0 3	0 4 7 4	0 3 9 1	0 4 6 3	0 4 2 1	0 4 2 3	0 4 4 3	0 3 7 2	0 3 9 3	0 4 4 2	0 4 6 1	0 4 0 4	0 4 5 3	0 4 7 5	0 3 7 5	0 4 1 1	0 3 7 1	0 4 5 2	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Ear																		+								2
Fibroma																		X								1
Papilloma																										1
Eye										+																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, lipoma																		X								1
Renal tubule, adenoma																		X								2
Transitional epithelium, carcinoma																										2
Urinary bladder	+	+	A	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	38
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X										X										4

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	17/50 (34%)	10/49 (20%)	12/49 (24%)	8/50 (16%)
Adjusted rates[b]	52.5%	48.2%	55.3%	66.0%
Terminal rates[c]	13/28 (46%)	4/13 (31%)	2/8 (25%)	1/2 (50%)
First incidence (days)	634	668	615	577
Life table tests[d]	P=0.024	P=0.474	P=0.123	P=0.030
Logistic regression tests[d]	P=0.341N	P=0.356N	P=0.420N	P=0.345N
Cochran-Armitage test[d]	P=0.042N			
Fisher exact test[d]		P=0.098N	P=0.207N	P=0.032N
Adrenal Medulla: Benign, Malignant, or Complex Pheochromocytoma				
Overall rates	18/50 (36%)	11/49 (22%)	12/49 (24%)	8/50 (16%)
Adjusted rates	53.8%	50.9%	55.3%	66.0%
Terminal rates	13/28 (46%)	4/13 (31%)	2/8 (25%)	1/2 (50%)
First incidence (days)	634	668	615	577
Life table tests	P=0.043	P=0.443	P=0.180	P=0.058
Logistic regression tests	P=0.238N	P=0.355N	P=0.312N	P=0.242N
Cochran-Armitage test	P=0.024N			
Fisher exact test		P=0.104N	P=0.152N	P=0.020N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rates	0/50 (0%)	1/48 (2%)	0/47 (0%)	2/50 (4%)
Adjusted rates	0.0%	3.6%	0.0%	15.0%
Terminal rates	0/28 (0%)	0/13 (0%)	0/8 (0%)	0/2 (0%)
First incidence (days)	–[e]	668	–	605
Life table tests	P=0.060	P=0.455	–	P=0.090
Logistic regression tests	P=0.128	P=0.489	–	P=0.217
Cochran-Armitage test	P=0.143			
Fisher exact test		P=0.490	–	P=0.247
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rates	1/50 (2%)	1/48 (2%)	3/47 (6%)	6/50 (12%)
Adjusted rates	3.4%	3.6%	14.9%	69.3%
Terminal rates	0/28 (0%)	0/13 (0%)	0/8 (0%)	1/2 (50%)
First incidence (days)	717	668	694	605
Life table tests	P<0.001	P=0.675	P=0.124	P<0.001
Logistic regression tests	P=0.002	P=0.723	P=0.210	P=0.013
Cochran-Armitage test	P=0.013			
Fisher exact test		P=0.742	P=0.285	P=0.056
Kidney (Transitional Epithelium): Carcinoma				
Overall rates	0/50 (0%)	0/48 (0%)	0/47 (0%)	2/50 (4%)
Adjusted rates	0.0%	0.0%	0.0%	4.4%
Terminal rates	0/28 (0%)	0/13 (0%)	0/8 (0%)	0/2 (0%)
First incidence (days)	–	–	–	444
Life table tests	P=0.043	–	–	P=0.226
Logistic regression tests	P=0.105	–	–	P=0.378
Cochran-Armitage test	P=0.048			
Fisher exact test		–	–	P=0.247

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Mammary Gland: Fibroadenoma				
Overall rates	3/51 (6%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rates	9.3%	5.7%	0.0%	0.0%
Terminal rates	2/28 (7%)	0/13 (0%)	0/8 (0%)	0/2 (0%)
First incidence (days)	619	584	–	–
Life table tests	P=0.128N	P=0.661	P=0.291N	P=0.485N
Logistic regression tests	P=0.041N	P=0.512N	P=0.133N	P=0.193N
Cochran-Armitage test	P=0.040N			
Fisher exact test		P=0.509N	P=0.125N	P=0.125N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	4/51 (8%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rates	12.7%	5.7%	0.0%	0.0%
Terminal rates	3/28 (11%)	0/13 (0%)	0/8 (0%)	0/2 (0%)
First incidence (days)	619	584	–	–
Life table tests	P=0.094N	P=0.580N	P=0.227N	P=0.445N
Logistic regression tests	P=0.021N	P=0.365N	P=0.080N	P=0.148N
Cochran-Armitage test	P=0.019N			
Fisher exact test		P=0.348N	P=0.061N	P=0.061N
Pancreatic Islets: Adenoma				
Overall rates	4/49 (8%)	2/47 (4%)	4/48 (8%)	1/42 (2%)
Adjusted rates	14.3%	11.0%	24.8%	5.0%
Terminal rates	4/28 (14%)	1/13 (8%)	1/8 (13%)	0/2 (0%)
First incidence (days)	729 (T)	668	662	668
Life table tests	P=0.295	P=0.665N	P=0.165	P=0.577
Logistic regression tests	P=0.523N	P=0.545N	P=0.424	P=0.647N
Cochran-Armitage test	P=0.234N			
Fisher exact test		P=0.359N	P=0.631	P=0.232N
Pancreas: Adenoma				
Overall rates	2/49 (4%)	5/47 (11%)	4/48 (8%)	2/38 (5%)
Adjusted rates	7.1%	24.2%	18.7%	21.9%
Terminal rates	2/28 (7%)	2/13 (15%)	0/8 (0%)	0/2 (0%)
First incidence (days)	729 (T)	549	662	537
Life table tests	P=0.127	P=0.063	P=0.102	P=0.144
Logistic regression tests	P=0.510	P=0.152	P=0.243	P=0.555
Cochran-Armitage test	P=0.574N			
Fisher exact test		P=0.201	P=0.329	P=0.590
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	24/49 (49%)	20/47 (43%)	13/46 (28%)	9/46 (20%)
Adjusted rates	63.4%	73.7%	50.6%	74.9%
Terminal rates	15/28 (54%)	7/13 (54%)	1/8 (13%)	0/2 (0%)
First incidence (days)	534	557	527	483
Life table tests	P=0.216	P=0.112	P=0.494	P=0.149
Logistic regression tests	P=0.006N	P=0.572N	P=0.039N	P=0.021N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.335N	P=0.031N	P=0.002N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Preputial Gland: Adenoma				
Overall rates	8/47 (17%)	1/49 (2%)	1/48 (2%)	1/49 (2%)
Adjusted rates	27.3%	7.7%	12.5%	7.7%
Terminal rates	7/28 (25%)	1/13 (8%)	1/8 (13%)	0/2 (0%)
First incidence (days)	704	729 (T)	729 (T)	681
Life table tests	P=0.392N	P=0.141N	P=0.298N	P=0.689
Logistic regression tests	P=0.146N	P=0.082N	P=0.140N	P=0.336N
Cochran-Armitage test	P=0.008N			
Fisher exact test		P=0.013N	P=0.014N	P=0.013N
Preputial Gland: Carcinoma				
Overall rates	3/47 (6%)	3/49 (6%)	0/48 (0%)	1/49 (2%)
Adjusted rates	9.3%	7.7%	0.0%	2.6%
Terminal rates	2/28 (7%)	0/13 (0%)	0/8 (0%)	0/2 (0%)
First incidence (days)	619	576	–	577
Life table tests	P=0.307N	P=0.481	P=0.291N	P=0.734
Logistic regression tests	P=0.110N	P=0.630N	P=0.125N	P=0.328N
Cochran-Armitage test	P=0.128N			
Fisher exact test		P=0.641N	P=0.117N	P=0.293N
Preputial Gland: Adenoma or Carcinoma				
Overall rates	11/47 (23%)	4/49 (8%)	1/48 (2%)	2/49 (4%)
Adjusted rates	35.8%	14.8%	12.5%	10.1%
Terminal rates	9/28 (32%)	1/13 (8%)	1/8 (13%)	0/2 (0%)
First incidence (days)	619	576	729 (T)	577
Life table tests	P=0.218N	P=0.313N	P=0.124N	P=0.639
Logistic regression tests	P=0.006N	P=0.061N	P=0.012N	P=0.068N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.037N	P=0.002N	P=0.006N
Skin: Fibroma				
Overall rates	1/51 (2%)	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted rates	3.6%	22.1%	0.0%	0.0%
Terminal rates	1/28 (4%)	2/13 (15%)	0/8 (0%)	0/2 (0%)
First incidence (days)	729 (T)	599	–	–
Life table tests	P=0.507N	P=0.049	P=0.748N	P=0.959N
Logistic regression tests	P=0.208N	P=0.115	P=0.748N	P=0.959N
Cochran-Armitage test	P=0.128N			
Fisher exact test		P=0.175	P=0.505N	P=0.505N
Skin: Keratoacanthoma				
Overall rates	2/51 (4%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rates	7.1%	11.5%	16.0%	0.0%
Terminal rates	2/28 (7%)	0/13 (0%)	1/8 (13%)	0/2 (0%)
First incidence (days)	729 (T)	634	684	–
Life table tests	P=0.540N	P=0.282	P=0.319	P=0.855N
Logistic regression tests	P=0.244N	P=0.419	P=0.521	P=0.855N
Cochran-Armitage test	P=0.138N			
Fisher exact test		P=0.491	P=0.684	P=0.252N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Skin: Keratoacanthoma or Squamous Papilloma				
Overall rates	4/51 (8%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rates	12.2%	11.5%	21.6%	0.0%
Terminal rates	2/28 (7%)	0/13 (0%)	1/8 (13%)	0/2 (0%)
First incidence (days)	655	634	684	–
Life table tests	P=0.322N	P=0.588	P=0.470	P=0.299N
Logistic regression tests	P=0.097N	P=0.562N	P=0.580N	P=0.114N
Cochran-Armitage test	P=0.052N			
Fisher exact test		P=0.511N	P=0.511N	P=0.061N
Testes: Adenoma				
Overall rates	43/49 (88%)	39/49 (80%)	39/49 (80%)	42/46 (91%)
Adjusted rates	100.0%	97.3%	100.0%	100.0%
Terminal rates	28/28 (100%)	12/13 (92%)	8/8 (100%)	2/2 (100%)
First incidence (days)	526	462	522	483
Life table tests	P<0.001	P=0.009	P<0.001	P<0.001
Logistic regression tests	P=0.039	P=0.395N	P=0.178N	P=0.062
Cochran-Armitage test	P=0.273			
Fisher exact test		P=0.207N	P=0.207N	P=0.411
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	2/50 (4%)	3/48 (6%)	1/49 (2%)	1/40 (3%)
Adjusted rates	7.1%	20.7%	5.9%	3.7%
Terminal rates	2/28 (7%)	2/13 (15%)	0/8 (0%)	0/2 (0%)
First incidence (days)	729 (T)	721	701	627
Life table tests	P=0.272	P=0.196	P=0.651	P=0.513
Logistic regression tests	P=0.623N	P=0.231	P=0.686N	P=0.727N
Cochran-Armitage test	P=0.348N			
Fisher exact test		P=0.480	P=0.508N	P=0.584N
All Organs: Mononuclear Cell Leukemia				
Overall rates	10/51 (20%)	5/50 (10%)	8/50 (16%)	4/50 (8%)
Adjusted rates	25.5%	21.2%	46.0%	19.8%
Terminal rates	2/28 (7%)	1/13 (8%)	3/8 (38%)	0/2 (0%)
First incidence (days)	526	550	603	605
Life table tests	P=0.402	P=0.388N	P=0.382	P=0.604N
Logistic regression tests	P=0.131N	P=0.139N	P=0.415N	P=0.094N
Cochran-Armitage test	P=0.104N			
Fisher exact test		P=0.141N	P=0.416N	P=0.080N
All Organs: Benign Neoplasms				
Overall rates	48/51 (94%)	47/50 (94%)	48/50 (96%)	45/50 (90%)
Adjusted rates	100.0%	97.9%	100.0%	100.0%
Terminal rates	28/28 (100%)	12/13 (92%)	8/8 (100%)	2/2 (100%)
First incidence (days)	526	238	522	45
Life table tests	P<0.001	P=0.003	P<0.001	P<0.001
Logistic regression tests	P=0.582N	P=0.631	P=0.664N	P=0.677N
Cochran-Armitage test	P=0.257N			
Fisher exact test		P=0.652N	P=0.509	P=0.346N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
All Organs: Malignant Neoplasms				
Overall rates	16/51 (31%)	12/50 (24%)	11/50 (22%)	8/50 (16%)
Adjusted rates	40.1%	39.9%	51.9%	33.6%
Terminal rates	6/28 (21%)	2/13 (15%)	3/8 (38%)	0/2 (0%)
First incidence (days)	526	462	603	444
Life table tests	P=0.325	P=0.450	P=0.430	P=0.362
Logistic regression tests	P=0.049N	P=0.261N	P=0.204N	P=0.065N
Cochran-Armitage test	P=0.047N			
Fisher exact test		P=0.273N	P=0.201N	P=0.056N
All Organs: Benign or Malignant Neoplasms				
Overall rates	48/51 (94%)	48/50 (96%)	49/50 (98%)	46/50 (92%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	13/13 (100%)	8/8 (100%)	2/2 (100%)
First incidence (days)	526	238	522	45
Life table tests	P<0.001	P=0.002	P<0.001	P<0.001
Logistic regression tests	P=0.502	P=0.436	P=0.614	P=0.562
Cochran-Armitage test	P=0.364N			
Fisher exact test		P=0.509	P=0.316	P=0.489N

(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 test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE 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 Transistional Cell Neoplasms of the Kidney in Male F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	0/1,019 (0.0%)	1/1,019 (0.1%)	1/1,019 (0.1%)
Standard deviation		0.5%	0.5%
Range		0%-2%	0%-2%

[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 3,4-Dihydrocoumarin[a]

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	10	10	10
Early deaths				
Moribund	12	24	26	17
Accidental deaths	2	1	1	2
Natural deaths	9	13	15	29
Survivors				
Died last week of study	1			
Terminal sacrifice	27	12	8	2
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(2)	(4)	(10)
Basophilic focus	1 (11%)			
Clear cell focus				3 (30%)
Fatty change		1 (50%)		
Inflammation, chronic	1 (11%)			
Inflammation, suppurative	1 (11%)			
Necrosis, coagulative				2 (20%)
Bile duct, cyst				1 (10%)
Bile duct, hyperplasia	5 (56%)			3 (30%)
Centrilobular, inflammation, necrotizing				1 (10%)
Centrilobular, necrosis, coagulative				1 (10%)
Periductular, inflammation, chronic	4 (44%)			1 (10%)
Portal, pigmentation, hemosiderin	1 (11%)			
Mesentery	(2)	(1)	(1)	(1)
Fat, necrosis, coagulative	2 (100%)	1 (100%)	1 (100%)	1 (100%)
Pancreas	(9)			(10)
Atrophy	2 (22%)			
Inflammation, chronic	1 (11%)			
Interstitium, infiltration cellular, lymphocyte				1 (10%)
Cardiovascular System				
Heart	(9)			(10)
Cardiomyopathy	9 (100%)			8 (80%)
Endocrine System				
Pituitary gland	(9)	(1)	(2)	(10)
Pars distalis, cyst			1 (50%)	1 (10%)
Pars intermedia, cyst	1 (11%)			
Thyroid gland	(9)			(10)
Follicle, cyst				1 (10%)
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
15-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(9)			(10)
Inflammation, chronic	1 (11%)			2 (20%)
Inflammation, suppurative				1 (10%)
Duct, dilatation	1 (11%)			1 (10%)
Duct, inflammation, suppurative				1 (10%)
Testes	(9)	(3)	(2)	(10)
Atrophy	1 (11%)	1 (33%)	1 (50%)	
Interstitial cell, hyperplasia	3 (33%)			4 (40%)
Hematopoietic System				
Lymph node, mandibular	(8)			(10)
Hyperplasia, lymphoid				1 (10%)
Integumentary System				
Skin	(9)			(10)
Inflammation, chronic	1 (11%)			
Ulcer	1 (11%)			
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(9)			(10)
Alveolar epithelium, hyperplasia				1 (10%)
Special Senses System				
None				
Urinary System				
Kidney	(9)	(10)	(10)	(10)
Nephropathy	9 (100%)	10 (100%)	10 (100%)	10 (100%)
2-Year Study				
Alimentary System				
Intestine large	(45)	(44)	(44)	(32)
Circumanal gland, hyperplasia, glandular		1 (2%)		
Intestine large, cecum	(41)	(42)	(41)	(24)
Inflammation, suppurative				1 (4%)
Submucosa, edema				1 (4%)
Submucosa, inflammation, suppurative			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Intestine small, jejunum	(41)	(42)	(43)	(30)
Hemorrhage			1 (2%)	
Liver	(49)	(47)	(49)	(50)
Angiectasis		3 (6%)	1 (2%)	
Basophilic focus	1 (2%)	1 (2%)		
Clear cell focus	3 (6%)		1 (2%)	1 (2%)
Congestion	1 (2%)			
Cytologic alterations	1 (2%)			
Developmental malformation	6 (12%)	5 (11%)	2 (4%)	5 (10%)
Fatty change	9 (18%)	6 (13%)		
Infiltration cellular, histiocyte		1 (2%)		
Inflammation, chronic	5 (10%)			1 (2%)
Inflammation, chronic active		1 (2%)		
Inflammation, necrotizing			1 (2%)	
Inflammation, suppurative		1 (2%)		
Mixed cell focus	1 (2%)			
Necrosis, coagulative		4 (9%)	1 (2%)	2 (4%)
Regeneration				1 (2%)
Artery, dilatation				1 (2%)
Bile duct, hyperplasia	24 (49%)	17 (36%)	13 (27%)	7 (14%)
Centrilobular, necrosis, coagulative	2 (4%)	1 (2%)	8 (16%)	4 (8%)
Hepatocyte, hyperplasia		1 (2%)	3 (6%)	1 (2%)
Periductular, fibrosis	7 (14%)	6 (13%)	9 (18%)	4 (8%)
Periductular, infiltration cellular, lymphocyte		1 (2%)		
Periductular, inflammation, chronic		1 (2%)		
Periportal, necrosis, coagulative	1 (2%)			
Periportal, pigmentation, hemosiderin	1 (2%)			
Mesentery	(17)	(15)	(10)	(6)
Fat, inflammation, chronic	1 (6%)	1 (7%)	1 (10%)	
Fat, inflammation, chronic active			2 (20%)	
Fat, inflammation, granulomatous	1 (6%)			
Fat, inflammation, suppurative	1 (6%)			
Fat, inflammation, fibrinopurulent		3 (20%)		
Fat, necrosis, coagulative	11 (65%)	10 (67%)	5 (50%)	5 (83%)
Pancreas	(49)	(47)	(48)	(38)
Atrophy	7 (14%)	4 (9%)	1 (2%)	1 (3%)
Ectopic tissue		1 (2%)		
Hemorrhage			1 (2%)	
Hyperplasia		5 (11%)	4 (8%)	4 (11%)
Inflammation, chronic			1 (2%)	1 (3%)
Inflammation, necrotizing		1 (2%)		
Inflammation, suppurative				1 (3%)
Necrosis, liquifactive				1 (3%)
Polyarteritis			1 (2%)	
Acinar cell, hyperplasia	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(47)	(48)	(50)	(46)
Cyst epithelial inclusion	1 (2%)	1 (2%)		
Hemorrhage			1 (2%)	
Hyperkeratosis			1 (2%)	1 (2%)
Hyperplasia, squamous	3 (6%)	11 (23%)	14 (28%)	11 (24%)
Inflammation, chronic	3 (6%)	8 (17%)	15 (30%)	8 (17%)
Inflammation, suppurative	1 (2%)			
Ulcer	4 (9%)	14 (29%)	20 (40%)	16 (35%)
Stomach, glandular	(46)	(47)	(50)	(43)
Erosion	1 (2%)	3 (6%)	4 (8%)	4 (9%)
Hemorrhage		1 (2%)		
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Mineralization		1 (2%)		
Ulcer		1 (2%)	1 (2%)	1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	36 (72%)	33 (66%)	34 (68%)	32 (64%)
Necrosis, Zenker's			1 (2%)	
Atrioventricular valve, fibrosis				1 (2%)
Atrioventricular valve, thrombus			1 (2%)	
Atrium, inflammation, suppurative				1 (2%)
Atrium, thrombus		1 (2%)	2 (4%)	2 (4%)
Endocrine System				
Adrenal gland, cortex	(50)	(49)	(49)	(50)
Basophilic focus	1 (2%)			
Cytoplasmic alteration		1 (2%)		1 (2%)
Hemorrhage		1 (2%)		
Vacuolization cytoplasmic		6 (12%)	2 (4%)	
Adrenal gland, medulla	(50)	(49)	(49)	(50)
Cyst	1 (2%)	1 (2%)		
Hyperplasia	3 (6%)	2 (4%)	5 (10%)	2 (4%)
Inflammation, suppurative				1 (2%)
Necrosis, coagulative	1 (2%)			
Necrosis, liquifactive		1 (2%)		
Parathyroid gland	(47)	(41)	(48)	(41)
Hyperplasia		15 (37%)	26 (54%)	19 (46%)
Pituitary gland	(49)	(47)	(46)	(46)
Inflammation, suppurative		1 (2%)		
Pars distalis, cyst	2 (4%)	4 (9%)	6 (13%)	
Pars distalis, cyst multilocular	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pars distalis, hemorrhage, acute			1 (2%)	
Pars distalis, hemorrhage, chronic		1 (2%)		
Pars distalis, hyperplasia	2 (4%)			
Thyroid gland	(50)	(48)	(49)	(40)
C-cell, hyperplasia	2 (4%)	4 (8%)	3 (6%)	3 (8%)
Follicle, cyst				1 (3%)
Follicle, hyperplasia	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
General Body System				
Tissue NOS		(1)	(1)	(1)
Hemorrhage		1 (100%)		
Genital System				
Coagulating gland	(2)			
Inflammation, suppurative	1 (50%)			
Lumen, dilatation	1 (50%)			
Epididymis	(49)	(50)	(48)	(47)
Polyarteritis		1 (2%)		
Preputial gland	(47)	(49)	(48)	(49)
Hyperplasia	3 (6%)	2 (4%)	6 (13%)	2 (4%)
Inflammation, chronic		1 (2%)	1 (2%)	
Inflammation, chronic active	1 (2%)			
Inflammation, suppurative	4 (9%)	9 (18%)	7 (15%)	6 (12%)
Duct, dilatation		2 (4%)	2 (4%)	1 (2%)
Duct, inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Prostate	(45)	(48)	(46)	(49)
Hyperplasia	1 (2%)		1 (2%)	
Inflammation, suppurative	9 (20%)	8 (17%)	12 (26%)	5 (10%)
Interstitium, hemorrhage, acute				1 (2%)
Seminal vesicle	(49)	(49)	(46)	(49)
Inflammation, suppurative	3 (6%)			1 (2%)
Lumen, dilatation	1 (2%)			
Testes	(49)	(49)	(49)	(46)
Atrophy	3 (6%)	2 (4%)	3 (6%)	3 (7%)
Infiltration cellular, lymphocyte	1 (2%)			
Polyarteritis		1 (2%)		
Interstitial cell, hyperplasia		1 (2%)	2 (4%)	
Hematopoietic System				
Bone marrow	(47)	(49)	(50)	(46)
Hypercellularity		1 (2%)		
Hyperplasia, neutrophil			1 (2%)	
Myelofibrosis			1 (2%)	
Lymph node	(51)	(49)	(50)	(48)
Lumbar, congestion			1 (2%)	
Mediastinal, congestion			1 (2%)	2 (4%)
Mediastinal, inflammation, suppurative			1 (2%)	
Mediastinal, pigmentation, hemosiderin			1 (2%)	
Pancreatic, hyperplasia, plasma cell			1 (2%)	
Renal, hyperplasia, plasma cell		1 (2%)		
Lymph node, mandibular	(51)	(48)	(44)	(42)
Congestion				1 (2%)
Hyperplasia, lymphoid	2 (4%)	4 (8%)		1 (2%)
Hyperplasia, plasma cell	2 (4%)	2 (4%)	2 (5%)	1 (2%)
Inflammation, suppurative			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(49)	(50)	(47)
Congestion			1 (2%)	
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid		2 (4%)		
Inflammation, suppurative			1 (2%)	
Pigmentation, hemosiderin	1 (2%)			
Spleen	(49)	(48)	(45)	(45)
Atrophy	2 (4%)			
Congestion	4 (8%)	3 (6%)	2 (4%)	
Congestion, diffuse			1 (2%)	
Developmental malformation	1 (2%)	2 (4%)	1 (2%)	
Fibrosis		1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)	
Hyperplasia, macrophage			2 (4%)	
Infiltration cellular, mononuclear cell		1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
Necrosis, liquifactive				2 (4%)
Pigmentation, hemosiderin		1 (2%)		1 (2%)
Perivascular, fibrosis		1 (2%)		
Subcapsular, hemorrhage				1 (2%)
Thymus	(46)	(47)	(47)	(45)
Congestion		1 (2%)		
Hemorrhage		1 (2%)		1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, suppurative			1 (2%)	
Capsule, inflammation, suppurative				1 (2%)
Integumentary System				
Mammary gland	(46)	(46)	(47)	(44)
Galactocele		2 (4%)	1 (2%)	
Skin	(51)	(50)	(48)	(49)
Alopecia		1 (2%)	2 (4%)	1 (2%)
Cyst epithelial inclusion	1 (2%)		1 (2%)	1 (2%)
Hyperkeratosis			1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, suppurative			1 (2%)	
Ulcer		1 (2%)		
Subcutaneous tissue, developmental malformation			1 (2%)	
Musculoskeletal System				
Bone	(51)	(50)	(50)	(50)
Degeneration	1 (2%)			
Skeletal muscle		(1)		
Metaplasia, osseous		1 (100%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Nervous System				
Brain	(48)	(49)	(46)	(47)
Hemorrhage		1 (2%)		
Hypothalamus, hemorrhage, acute			1 (2%)	
Meninges, congestion		1 (2%)		
Thalamus, compression	2 (4%)			
Thalamus, necrosis				1 (2%)
Peripheral nerve	(2)	(1)	(7)	(3)
Degeneration, secondary wallerian	1 (50%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar epithelium, hyperplasia	4 (8%)	3 (6%)	3 (6%)	2 (4%)
Alveolus, congestion				1 (2%)
Alveolus, edema	1 (2%)	2 (4%)		1 (2%)
Alveolus, foreign body				1 (2%)
Alveolus, hemorrhage		2 (4%)	2 (4%)	1 (2%)
Alveolus, inflammation, chronic	2 (4%)			
Alveolus, inflammation, suppurative	2 (4%)	2 (4%)		2 (4%)
Bronchiole, inflammation, suppurative	1 (2%)			1 (2%)
Nose	(50)	(50)	(48)	(49)
Autolysis			1 (2%)	
Fungus	1 (2%)		2 (4%)	1 (2%)
Inflammation, chronic			1 (2%)	
Metaplasia, squamous	1 (2%)			
Lumen, foreign body	1 (2%)			2 (4%)
Lumen, fungus	3 (6%)	5 (10%)	6 (13%)	4 (8%)
Lumen, inflammation, suppurative	8 (16%)	8 (16%)	9 (19%)	8 (16%)
Mucosa, inflammation, suppurative	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Mucosa, septum, inflammation, chronic	1 (2%)			
Nasolacrimal duct, inflammation, suppurative			2 (4%)	1 (2%)
Trachea	(51)	(50)	(50)	(48)
Inflammation, suppurative		2 (4%)	1 (2%)	1 (2%)
Special Senses System				
Ear		(1)	(1)	(2)
Acanthosis			1 (100%)	
Pinna, perforation		1 (100%)		
Eye	(1)	(2)		(1)
Anterior chamber, hemorrhage, chronic	1 (100%)			
Bilateral, lens, cataract		1 (50%)		
Lens, cataract		1 (50%)		1 (100%)
Retina, degeneration		1 (50%)		1 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(48)	(47)	(50)
Fibrosis				1 (2%)
Inflammation, suppurative				1 (2%)
Nephropathy	50 (100%)	47 (98%)	47 (100%)	47 (94%)
Cortex, cyst	3 (6%)			1 (2%)
Cortex, infarct			1 (2%)	1 (2%)
Pelvis, inflammation, chronic				1 (2%)
Pelvis, inflammation, suppurative	2 (4%)			1 (2%)
Renal tubule, hyperplasia		3 (6%)		3 (6%)
Renal tubule, hyperplasia, cystic	1 (2%)		2 (4%)	1 (2%)
Renal tubule, hyperplasia, oncocytic	1 (2%)		1 (2%)	
Ureter	(1)			
Mucosa, inflammation, suppurative	1 (100%)			
Urinary bladder	(49)	(48)	(44)	(38)
Mucosa, inflammation, suppurative	1 (2%)	1 (2%)		
Serosa, inflammation, suppurative		1 (2%)		
Submucosa, infiltration cellular, lymphocyte			1 (2%)	
Submucosa, inflammation, suppurative	1 (2%)			

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

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF 3,4-DIHYDROCOUMARIN

TABLE B1 Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 123

TABLE B2 Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 128

TABLE B3 Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 152

TABLE B4a Historical Incidence of Renal Tubule Neoplasms in Female F344/N Rats Receiving Corn Oil by Gavage 156

TABLE B4b Historical Incidence of Forestomach Neoplasms in Female F344/N Rats Receiving Corn Oil by Gavage 156

TABLE B4c Historical Incidence of Adrenal Medulla Pheochromocytomas in Female F344/N Rats Receiving Corn Oil by Gavage 156

TABLE B5 Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 157

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	10	9
Early deaths				
Moribund	13	17	20	19
Accidental deaths	2	5	0	4
Natural deaths	4	8	4	5
Survivors				
Terminal sacrifice	31	21	26	23
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(1)	(3)	(9)
Pars distalis, adenoma	5 (50%)		1 (33%)	1 (11%)
Thyroid gland	(10)		(1)	(9)
C-cell, adenoma			1 (100%)	
General Body System				
None				
Genital System				
Uterus	(10)	(3)	(5)	(9)
Polyp	2 (20%)	2 (67%)	3 (60%)	
Hematopoietic System				
None				
Integumentary System				
Mammary gland	(10)	(1)		(9)
Fibroadenoma	1 (10%)	1 (100%)		
Musculoskeletal System				
None				
Nervous System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
Ear			(1)	
Pinna, fibroma			1 (100%)	
Urinary System				
None				
2-Year Study				
Alimentary System				
Intestine large, colon	(47)	(46)	(47)	(48)
Intestine small, ileum	(46)	(42)	(45)	(48)
Liver	(50)	(51)	(50)	(50)
Fibrous histiocytoma				1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Hepatocyte, adenoma				1 (2%)
Mesentery	(6)	(5)	(4)	(6)
Adenocarcinoma, metastatic, uterus		1 (20%)		
Pancreas	(48)	(46)	(49)	(49)
Adenoma			1 (2%)	
Salivary glands	(50)	(51)	(50)	(50)
Stomach, forestomach	(50)	(49)	(50)	(49)
Papilloma squamous				1 (2%)
Squamous cell carcinoma				1 (2%)
Stomach, glandular	(50)	(48)	(48)	(48)
Tongue		(2)	(1)	
Papilloma squamous		1 (50%)		
Cardiovascular System				
Heart	(50)	(51)	(50)	(50)
Fibrous histiocytoma				1 (2%)
Endocrine System				
Adrenal gland, cortex	(50)	(51)	(49)	(50)
Adenoma	1 (2%)	1 (2%)		
Adrenal gland, medulla	(50)	(51)	(49)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign	1 (2%)	5 (10%)	5 (10%)	3 (6%)
Bilateral, pheochromocytoma benign		2 (4%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(46)	(50)	(49)
Adenoma	2 (4%)		1 (2%)	1 (2%)
Parathyroid gland	(42)	(44)	(46)	(45)
Adenoma				1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(49)	(48)	(49)	(50)
Adenoma			1 (2%)	1 (2%)
Pars distalis, adenoma	31 (63%)	21 (44%)	26 (53%)	18 (36%)
Thyroid gland	(49)	(48)	(49)	(50)
C-cell, adenoma	1 (2%)	4 (8%)		2 (4%)
Follicle, adenocarcinoma			1 (2%)	1 (2%)
Follicle, adenoma		1 (2%)		
General Body System				
Tissue NOS		(1)		
Sarcoma		1 (100%)		
Genital System				
Clitoral gland	(47)	(50)	(50)	(50)
Adenocarcinoma	2 (4%)	1 (2%)		
Adenoma	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Carcinoma		3 (6%)		1 (2%)
Squamous cell carcinoma		1 (2%)		
Ovary	(50)	(51)	(50)	(50)
Oviduct	(1)	(1)		(4)
Uterus	(50)	(51)	(50)	(51)
Adenocarcinoma		1 (2%)		
Leiomyoma	1 (2%)			
Leiomyosarcoma		1 (2%)		
Polyp	9 (18%)	11 (22%)	6 (12%)	8 (16%)
Sarcoma stromal				1 (2%)
Cervix, leiomyoma		1 (2%)		
Cervix, sarcoma stromal				1 (2%)
Vagina		(5)		(3)
Leiomyosarcoma		2 (40%)		
Sarcoma				1 (33%)
Hematopoietic System				
Blood	(1)	(1)		(1)
Bone marrow	(49)	(50)	(50)	(50)
Lymph node	(50)	(51)	(50)	(50)
Deep cervical, histiocytic sarcoma	1 (2%)			
Thoracic, histiocytic sarcoma	1 (2%)			
Lymph node, mandibular	(48)	(51)	(49)	(50)
Histiocytic sarcoma	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(49)	(49)	(49)
Histiocytic sarcoma	1 (2%)			
Thymus	(44)	(47)	(50)	(49)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Integumentary System				
Mammary gland	(49)	(49)	(49)	(50)
Adenocarcinoma			1 (2%)	
Fibroadenoma	14 (29%)	9 (18%)	22 (45%)	6 (12%)
Skin	(50)	(50)	(50)	(50)
Fibroma			1 (2%)	2 (4%)
Fibrous histiocytoma		1 (2%)		1 (2%)
Keratoacanthoma			2 (4%)	
Papilloma squamous				2 (4%)
Sarcoma	1 (2%)	1 (2%)		
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(48)	(49)
Cerebellum, astrocytoma benign				1 (2%)
Spinal cord	(1)	(9)	(3)	(4)
Respiratory System				
Lung	(50)	(51)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma			1 (2%)	
Fibrous histiocytoma				1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal gland	1 (2%)			
Nose	(50)	(51)	(50)	(50)
Special Senses System				
None				
Urinary System				
Kidney	(50)	(49)	(49)	(49)
Renal tubule, adenocarcinoma		1 (2%)	1 (2%)	
Renal tubule, adenoma	1 (2%)	1 (2%)	1 (2%)	
Urinary bladder	(48)	(50)	(48)	(49)
Fibrous histiocytoma				1 (2%)
Papilloma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(51)	(50)	(51)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	10 (20%)	10 (20%)	12 (24%)	12 (24%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	5	3	5	1
2-Year study	46	43	48	39
Total primary neoplasms				
15-Month interim evaluation	8	3	6	1
2-Year study	80	81	86	73
Total animals with benign neoplasms				
15-Month interim evaluation	5	3	5	1
2-Year study	41	35	45	31
Total benign neoplasms				
15-Month interim evaluation	8	3	6	1
2-Year study	65	58	70	50
Total animals with malignant neoplasms				
2-Year study	15	20	15	16
Total malignant neoplasms				
2-Year study	15	23	16	23
Total animals with metastatic neoplasms				
2-Year study	1	2		
Total metastatic neoplasms				
2-Year study	1	3		

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 7 9 2	0 7 9 4	0 6 9 1	0 6 9 3	0 6 9 5	0 7 0 3	0 7 0 5	0 7 1 1	0 7 1 4	0 7 3 4	0 7 4 4	0 7 5 4	0 7 6 5	0 7 7 4	0 7 8 3	0 7 9 1	0 8 0 3	0 7 1 3	0 7 2 3	0 7 4 3	0 7 6 2	0 7 6 3	0 7 8 1	0 8 0 1	0 8 0 2	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+					+									+							6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																											1
Pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X				X																		2
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	M	+	M	+	+	M	+	+	+		42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X	X	X	X			X		X		X		X		X	X	X			X		X		31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma									X																		1
General Body System																											
None																											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	3 8 5	4 6 6	5 0 6	5 3 3	5 4 2	5 8 0	5 8 9	5 9 8	6 3 1	6 5 1	6 5 2	6 6 5	6 8 0	6 8 0	6 9 6	7 0 3	7 0 9	7 1 6	7 1 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 7 4 1	0 7 5 3	0 7 8 4	0 6 9 2	0 7 3 5	0 7 7 5	0 7 3 3	0 7 2 4	0 7 4 5	0 7 0 4	0 7 9 5	0 7 2 2	0 6 9 4	0 7 7 3	0 7 2 5	0 8 0 4	0 7 9 3	0 7 6 1	0 7 3 2	0 7 0 1	0 7 0 2	0 7 1 2	0 7 5 2	0 7 5 5	0 7 8 5
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma			X																						
Adenoma											X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct			+																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																X									
Polyp																				X			X		
Hematopoietic System																									
Blood							+																		
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, histiocytic sarcoma																									
Thoracic, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma								X			X					X		X	X		X				X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord									+																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 0 7 9 2	0 0 7 9 4	0 0 6 9 1	0 0 6 9 3	0 0 6 9 5	0 0 7 0 3	0 0 7 0 5	0 0 7 1 1	0 0 7 1 4	0 0 7 3 4	0 0 7 4 4	0 0 7 5 4	0 0 7 6 5	0 0 7 7 4	0 0 7 8 3	0 0 7 9 1	0 0 8 0 3	0 0 7 1 3	0 0 7 2 3	0 0 7 4 3	0 0 7 6 2	0 0 7 6 3	0 0 7 8 1	0 0 8 0 1	0 0 8 0 2	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Adenocarcinoma																				X						2
Adenoma		X																				X				3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Polyp		X										X				X				X	X		X	X		9
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deep cervical, histiocytic sarcoma																									X	1
Thoracic, histiocytic sarcoma																									X	1
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																									X	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									X	1
Thymus	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma						X			X		X	X	X			X						X				14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	3	4	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	
	8	6	0	3	4	8	8	9	3	5	5	6	8	8	9	0	0	1	1	3	3	3	3	3	3	
	5	6	6	3	2	0	9	8	1	1	2	5	0	0	6	3	9	6	7	0	0	0	0	0	0	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	7	7	7	6	7	7	7	7	7	7	7	7	6	7	7	8	7	7	7	7	7	7	7	7	7	
	4	5	8	9	3	7	3	2	4	0	9	2	9	7	2	0	9	6	3	0	0	1	5	5	8	
	1	3	4	2	5	5	3	4	5	4	5	2	4	3	5	4	3	1	2	1	2	2	2	5	5	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																										
Pheochromocytoma malignant, metastatic, adrenal gland																								X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																										
Leukemia mononuclear							X		X	X	X	X	X													

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 7 9 2	0 7 9 4	0 6 9 1	0 6 9 3	0 6 9 5	0 7 0 3	0 7 0 5	0 7 1 1	0 7 1 4	0 7 3 4	0 7 4 4	0 7 5 4	0 7 6 5	0 7 7 4	0 7 8 3	0 8 9 1	0 7 0 3	0 7 1 3	0 7 2 3	0 7 4 3	0 7 6 2	0 7 6 3	0 7 8 1	0 8 0 1	0 8 0 2	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									X	1
Leukemia mononuclear					X									X		X	X									10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg (continued)

Number of Days on Study	7 1 0	7 1 5	7 1 6	7 1 6	7 1 7	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 8 6 3	0 9 1 4	0 8 1 2	0 8 3 3	0 8 4 3	0 8 7 5	0 8 8 4	0 8 2 4	0 8 2 5	0 8 3 1	0 8 4 1	0 8 6 2	0 8 0 3	0 9 0 4	0 8 5 4	0 8 6 1	0 8 9 3	0 9 0 1	0 9 2 2	0 8 2 3	0 8 3 2	0 8 5 1	0 8 5 3	0 8 9 4	0 9 0 5	0 9 1 1	0 8 1 2	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrous histiocytoma, metastatic, skin																											1
Mesentery							+			+		+															5
Adenocarcinoma, metastatic, uterus																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																				+							2
Papilloma squamous																											1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																					X						1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign											X			X				X					X	X			5
Bilateral, pheochromocytoma benign	X																								X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X	X	X						X			X			X	X	X	X	X	X			X	X	X	X	21
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma			X					X									X				X							4
Follicle, adenoma																									X		1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg (continued)

Number of Days on Study	7 1 0	7 1 5	7 1 6	7 1 6	7 1 7	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 8 6 3	0 9 1 4	0 8 1 2	0 8 3 3	0 8 4 3	0 8 7 5	0 8 8 4	0 8 2 4	0 8 2 5	0 8 3 1	0 8 4 1	0 8 6 2	0 9 0 3	0 8 5 4	0 8 6 1	0 8 9 3	0 9 0 1	0 9 2 2	0 8 2 3	0 8 3 2	0 8 5 1	0 8 5 3	0 8 9 4	0 9 0 5	0 9 1 1	0 8 2 2	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Sarcoma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																								X		1
Adenoma																										1
Carcinoma				X																	X					3
Squamous cell carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma																										1
Leiomyosarcoma																										1
Polyp							X		X					X	X	X		X					X			11
Cervix, leiomyoma																										1
Vagina											+															5
Leiomyosarcoma																										2
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma		X	X		X			X	X						X						X			X		9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg
(continued)

Number of Days on Study	0	0	0	3	3	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7		
	0	4	7	0	5	5	7	0	1	3	4	8	9	9	1	1	4	5	6	8	0	1	1	1		
	6	9	3	0	7	5	1	8	3	7	2	8	0	1	2	8	4	7	4	7	2	1	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		
	8	8	8	8	8	8	8	8	9	8	8	8	8	9	8	9	9	8	9	8	8	8	8	8		
	6	8	5	4	3	1	7	1	2	6	1	4	8	1	7	1	0	9	0	8	8	9	2	3	5	
	4	3	5	5	4	1	1	5	1	5	3	4	1	2	4	3	4	1	2	5	2	5	1	5	2	
Nervous System																										
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Peripheral nerve																				+	+					
Spinal cord																				+	+			M		
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrous histiocytoma, metastatic, skin																							X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye															+											
Lacrimal gland															+											
Urinary System																										
Kidney	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Renal tubule, adenocarcinoma																										
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear					X	X						X	X	X	X									X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 150 mg/kg (continued)

Number of Days on Study	7 1 0	7 1 5	7 1 6	7 1 6	7 1 7	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 8 6 3	0 9 1 4	0 8 1 2	0 8 3 3	0 8 4 3	0 8 7 5	0 8 8 4	0 8 2 4	0 8 2 5	0 8 3 1	0 8 4 1	0 8 6 2	0 8 9 3	0 9 0 4	0 8 5 1	0 8 6 1	0 8 9 3	0 9 0 1	0 9 2 2	0 8 2 3	0 8 3 2	0 8 5 1	0 8 5 3	0 8 9 4	0 9 0 5	0 9 1 1	0 8 1 2	Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve						+	+	+	M	+		+							+							+	9
Spinal cord						+	+	+	+	+		+							I							+	9
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrous histiocytoma, metastatic, skin																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye																											1
Lacrimal gland																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenocarcinoma	X																										1
Renal tubule, adenoma	X																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear	X													X								X					10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg

Number of Days on Study	3 8 7	5 3 8	5 5 2	5 8 0	5 9 5	6 1 1	6 1 8	6 2 2	6 2 4	6 3 1	6 3 3	6 6 7	6 7 2	6 7 8	6 8 0	6 8 9	6 9 2	6 9 5	6 9 6	7 0 0	7 1 0	7 1 7	7 1 7	7 2 4	7 2 9
Carcass ID Number	1 0 4 5	1 0 4 4	0 9 7 2	0 9 4 2	1 0 1 2	0 9 1 1	0 9 4 4	1 0 8 2	1 0 3 1	1 0 3 2	0 9 0 2	0 9 3 2	0 9 6 4	0 0 1 3	1 0 1 1	1 0 0 4	0 9 6 1	1 0 4 2	0 9 8 1	0 9 7 5	0 9 5 2	1 0 1 5	1 0 3 5	0 9 4 3	0 9 3 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	A	A	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+	+		+																				
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign				X			X																		
Bilateral, pheochromocytoma benign					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Pars distalis, adenoma		X	X		X		X				X	X	X		X				X	X	X		X		X
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenocarcinoma																									
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg (continued)

Number of Days on Study	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	
Carcass ID Number	0 9 8 3	0 9 9 5	0 9 3 1	0 9 4 5	0 9 5 3	0 9 7 1	0 9 8 5	0 9 9 4	0 1 0 5	1 0 3 4	1 0 4 1	0 9 6 2	0 9 6 3	0 9 9 3	1 0 3 3	0 9 3 5	0 9 5 1	0 9 5 4	0 9 5 5	1 0 0 1	1 0 0 3	1 0 2 1	1 0 2 5	0 9 9 2	1 0 2 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																			+							4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																						X				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue					+																					1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign				X										X					X							5
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Pars distalis, adenoma		X	X				X		X	X	X			X	X		X	X	X		X			X		26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicle, adenocarcinoma				X																						1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg
(continued)

Number of Days on Study	3 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 8 3 5 8 9 1 1 2 2 3 3 6 7 7 8 8 9 9 9 0 1 1 1 2 2 7 8 2 0 5 1 8 2 4 1 3 7 2 8 0 9 2 5 6 0 0 7 7 4 9
Carcass ID Number	1 1 0 0 1 0 0 1 1 1 0 0 0 1 1 1 0 1 0 0 0 1 1 0 0 0 0 9 9 0 9 9 0 0 0 9 9 9 0 0 0 9 0 9 9 9 0 0 9 9 4 4 7 4 1 4 8 3 3 0 8 3 6 1 1 0 6 4 8 7 5 1 3 4 3 5 4 2 2 2 1 4 2 1 2 2 2 4 3 1 4 1 2 1 5 2 5 5 3 4
Genital System	
Clitoral gland	+ +
Adenoma	X
Ovary	+ +
Uterus	+ +
Polyp	X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, mandibular	A +
Lymph node, mesenteric	+ +
Spleen	A +
Thymus	+ +
Integumentary System	
Mammary gland	+ +
Adenocarcinoma	X
Fibroadenoma	X X X X X X X X X X X
Skin	+ +
Fibroma	
Keratoacanthoma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	A + + + + + + + + + + + + + + + + + + A + + + + +
Peripheral nerve	+ + + + M +
Spinal cord	+ + + +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar carcinoma	
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+ +

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg (continued)

Number of Days on Study	729	729	730	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	09983	09995	09913	09945	09953	09971	09985	09994	10005	10034	10041	10096	09923	09933	09973	10033	10035	10051	10144	10154	10155	10001	10003	10021	10022	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp	X											X			X			X				X				6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Fibroadenoma				X	X	X	X	X	X						X		X	X		X		X			X	22
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																X										1
Keratoacanthoma		X															X									2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Peripheral nerve																										4
Spinal cord																										3
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg
(continued)

Number of Days on Study	3	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7		
	8	3	5	8	9	1	1	2	2	3	3	6	7	7	8	8	9	9	9	0	1	1	1	2		
	7	8	2	0	5	1	8	2	4	1	3	7	2	8	0	9	2	5	6	0	0	7	7	4	9	
Carcass ID Number	1	1	0	0	1	0	0	1	1	1	0	0	0	1	1	1	0	1	0	0	0	1	1	0	0	
	0	0	9	9	0	9	9	0	0	0	9	9	9	0	0	0	9	0	9	9	9	0	0	9	9	
	4	4	7	4	1	4	8	3	3	0	8	3	6	1	1	0	6	4	8	7	5	1	3	4	3	
	5	4	2	2	2	1	4	2	1	2	2	2	4	3	1	4	1	2	1	5	2	5	5	3	4	
Urinary System																										
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Renal tubule, adenocarcinoma									X																	
Renal tubule, adenoma																										
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear				X	X	X			X					X		X	X	X	X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg (continued)

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	731	731	731	731	734	734	734	734	734	734	734	734	735	735	
Carcass ID Number	09 89 35	09 99 55	09 93 11	09 94 55	09 95 33	09 97 11	09 98 55	09 99 44	10 00 55	10 00 44	10 00 41	10 09 62	10 09 63	10 09 33	10 09 35	10 03 31	10 03 35	10 05 11	10 05 44	10 05 55	10 10 51	10 10 03	10 11 31	10 12 25	10 09 23	10 10 23	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenocarcinoma																										1
Renal tubule, adenoma												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear														X					X				X			12

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg (continued)

Number of Days on Study	7 1 0	7 1 1	7 1 7	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 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	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 8 1	1 1 1 1	1 1 5 2	1 0 9 5	1 1 0 4	1 1 5 4	1 0 7 1	1 0 7 2	1 0 9 2	1 0 9 4	1 1 4 1	1 1 4 2	1 1 6 3	1 0 6 5	1 0 7 5	1 1 7 2	1 1 3 3	1 1 6 1	1 1 6 5	1 0 5 1	1 0 5 3	1 0 5 4	1 1 0 1	1 1 2 5	1 1 5 3	1 1 6 2	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																											1
Hepatocyte, adenoma															X												1
Mesentery																		+		+						+	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																								X			1
Squamous cell carcinoma																				X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																											1
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X								X											X					3
Bilateral, pheochromocytoma benign																										X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																		1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	45
Adenoma																								X			1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																											1
Pars distalis, adenoma					X					X		X			X		X		X	X		X		X	X		18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																X		X									2
Follicle, adenocarcinoma																											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg
(continued)

Number of Days on Study	0 4 1	0 9 0	3 3 1	4 5 5	5 0 4	5 0 6	5 2 1	5 3 1	5 3 3	5 3 5	5 5 3	5 7 0	5 9 1	5 9 6	6 0 2	6 1 8	6 1 8	6 3 1	6 3 8	6 3 9	6 3 9	6 7 8	6 8 0	7 0 8	7 1 0
Carcass ID Number	1 0 9 3	1 1 1 4	1 1 2 4	1 1 0 2	1 1 3 5	1 1 1 5	1 1 1 3	1 1 0 5	1 0 5 2	1 1 2 3	1 1 3 1	1 1 5 1	1 1 2 2	1 1 0 3	1 1 4 3	1 0 8 5	1 0 9 1	1 0 8 4	1 1 3 4	1 0 6 2	1 0 6 4	1 1 6 4	1 1 4 4	1 1 5 4	1 0 7 4
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																						X			
Ovary	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct		+		+								+			+										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp					X											X					X	X			
Sarcoma stromal				X																					
Cervix, sarcoma stromal				X																					
Vagina				+														+		+					
Sarcoma				X																					
Hematopoietic System																									
Blood								+																	
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							X						X			X									
Skin	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrous histiocytoma										X															
Papilloma squamous																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg (continued)

Number of Days on Study	7 1 0	7 1 1	7 1 7	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 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	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 8 1	1 1 1 1	1 1 5 2	1 0 9 5	1 1 0 4	1 1 5 4	1 0 7 1	1 0 7 2	1 0 9 2	1 0 9 4	1 1 4 1	1 1 4 2	1 1 6 3	1 0 6 5	1 0 7 5	1 1 2 2	1 1 3 3	1 1 6 1	1 1 6 5	1 0 5 1	1 0 5 3	1 0 5 4	1 1 0 1	1 1 2 5	1 1 5 3	1 1 6 2	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																						1
Carcinoma																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oviduct																											4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp				X															X				X		X		8
Sarcoma stromal																											1
Cervix, sarcoma stromal																											1
Vagina																											3
Sarcoma																											1
Hematopoietic System																											
Blood																											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																	X				X			X			6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma			X																				X				2
Fibrous histiocytoma																											1
Papilloma squamous												X											X				2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg
(continued)

Number of Days on Study	0 4 1	0 9 0	3 3 1	4 5 5	5 0 4	5 0 6	5 2 1	5 3 1	5 3 3	5 3 5	5 5 3	5 7 0	5 9 1	5 9 6	6 0 2	6 1 8	6 1 8	6 3 1	6 3 8	6 3 9	6 3 9	6 7 8	6 8 0	7 0 8	7 1 0
Carcass ID Number	1 0 9 3	1 1 1 4	1 1 2 4	1 1 0 2	1 1 3 5	1 1 1 5	1 1 1 3	1 1 0 5	1 0 5 2	1 1 2 3	1 1 3 1	1 1 5 1	1 1 2 2	1 1 0 3	1 1 4 3	1 0 8 5	1 0 9 1	1 0 8 4	1 1 3 4	1 0 6 2	1 0 6 4	1 1 6 4	1 1 4 4	1 1 5 5	1 0 7 4
Nervous System																									
Brain	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebellum, astrocytoma benign															X										
Peripheral nerve																									
Spinal cord												+						+							
Respiratory System																									
Lung	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma									X																
Nose	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma										X															
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X						X		X			X	X	X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 600 mg/kg (continued)

Number of Days on Study	7 1 0	7 1 1	7 1 7	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 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 0 8 1	1 1 1 1	1 1 5 2	1 0 9 5	1 1 0 4	1 1 5 4	1 0 7 1	1 0 7 2	1 0 9 2	1 0 9 4	1 1 4 1	1 1 4 2	1 1 6 3	1 0 6 5	1 0 7 5	1 1 2 3	1 1 3 6	1 1 6 1	1 1 6 5	1 0 5 1	1 0 5 3	1 0 5 4	1 1 0 1	1 1 2 5	1 1 5 3	1 1 6 2	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cerebellum, astrocytoma benign																										1
Peripheral nerve											+												+			2
Spinal cord											+												+			4
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																							+			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma																										1
Papilloma									X																	1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear	X					X				X		X														12

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	1/50 (2%)	7/51 (14%)	6/49 (12%)	4/50 (8%)
Adjusted rates[b]	3.0%	31.0%	17.2%	16.7%
Terminal rates[c]	0/31 (0%)	6/21 (29%)	3/26 (12%)	3/23 (13%)
First incidence (days)	716	710	580	717
Life table tests[d]	P=0.234	P=0.009	P=0.052	P=0.105
Logistic regression tests[d]	P=0.269	P=0.012	P=0.053	P=0.110
Cochran-Armitage test[d]	P=0.333			
Fisher exact test[d]		P=0.032	P=0.053	P=0.181
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rates	2/50 (4%)	7/51 (14%)	6/49 (12%)	4/50 (8%)
Adjusted rates	6.2%	31.0%	17.2%	16.7%
Terminal rates	1/31 (3%)	6/21 (29%)	3/26 (12%)	3/23 (13%)
First incidence (days)	716	710	580	717
Life table tests	P=0.329	P=0.024	P=0.115	P=0.213
Logistic regression tests	P=0.370	P=0.032	P=0.127	P=0.224
Cochran-Armitage test	P=0.445			
Fisher exact test		P=0.085	P=0.128	P=0.339
Clitoral Gland: Adenoma				
Overall rates	3/47 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rates	9.0%	2.9%	7.2%	4.3%
Terminal rates	2/30 (7%)	0/20 (0%)	1/26 (4%)	1/23 (4%)
First incidence (days)	652	657	717	729 (T)
Life table tests	P=0.346N	P=0.409N	P=0.550N	P=0.407N
Logistic regression tests	P=0.295N	P=0.324N	P=0.478N	P=0.344N
Cochran-Armitage test	P=0.262N			
Fisher exact test		P=0.285N	P=0.470N	P=0.285N
Clitoral Gland: Carcinoma				
Overall rates	2/47 (4%)	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted rates	5.3%	16.5%	0.0%	3.3%
Terminal rates	1/30 (3%)	2/20 (10%)	0/26 (0%)	0/23 (0%)
First incidence (days)	506	682	–[e]	678
Life table tests	P=0.249N	P=0.217	P=0.253N	P=0.562N
Logistic regression tests	P=0.194N	P=0.322	P=0.240N	P=0.452N
Cochran-Armitage test	P=0.185N			
Fisher exact test		P=0.369	P=0.232N	P=0.477N
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	5/47 (11%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rates	14.1%	19.0%	7.2%	7.5%
Terminal rates	3/30 (10%)	2/20 (10%)	1/26 (4%)	1/23 (4%)
First incidence (days)	506	657	717	678
Life table tests	P=0.171N	P=0.445	P=0.261N	P=0.322N
Logistic regression tests	P=0.113N	P=0.607	P=0.192N	P=0.211N
Cochran-Armitage test	P=0.098N			
Fisher exact test		P=0.590N	P=0.193N	P=0.193N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Kidney (Renal Tubule): Adenoma				
Overall rates	1/50 (2%)	1/49 (2%)	1/49 (2%)	0/49 (0%)
Adjusted rates	3.2%	3.4%	3.8%	0.0%
Terminal rates	1/31 (3%)	0/21 (0%)	1/26 (4%)	0/23 (0%)
First incidence (days)	729 (T)	710	729 (T)	–
Life table tests	P=0.359N	P=0.702	P=0.723	P=0.560N
Logistic regression tests	P=0.353N	P=0.719	P=0.723	P=0.560N
Cochran-Armitage test	P=0.315N			
Fisher exact test		P=0.747	P=0.747	P=0.505N
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rates	1/50 (2%)	1/49 (2%)	2/49 (4%)	0/49 (0%)
Adjusted rates	3.2%	3.4%	6.1%	0.0%
Terminal rates	1/31 (3%)	0/21 (0%)	1/26 (4%)	0/23 (0%)
First incidence (days)	729 (T)	710	624	–
Life table tests	P=0.420N	P=0.702	P=0.459	P=0.560N
Logistic regression tests	P=0.392N	P=0.719	P=0.495	P=0.560N
Cochran-Armitage test	P=0.371N			
Fisher exact test		P=0.747	P=0.492	P=0.505N
Mammary Gland: Fibroadenoma				
Overall rates	14/50 (28%)	9/51 (18%)	22/50 (44%)	6/51 (12%)
Adjusted rates	38.3%	35.4%	59.2%	19.5%
Terminal rates	9/31 (29%)	5/21 (24%)	12/26 (46%)	3/23 (13%)
First incidence (days)	598	710	611	521
Life table tests	P=0.271N	P=0.484N	P=0.042	P=0.142N
Logistic regression tests	P=0.160N	P=0.308N	P=0.069	P=0.062N
Cochran-Armitage test	P=0.102N			
Fisher exact test		P=0.158N	P=0.072	P=0.035N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	31/49 (63%)	21/48 (44%)	27/49 (55%)	19/50 (38%)
Adjusted rates	73.0%	68.7%	67.5%	55.3%
Terminal rates	20/31 (65%)	12/21 (57%)	14/26 (54%)	10/23 (43%)
First incidence (days)	385	471	538	455
Life table tests	P=0.205N	P=0.428N	P=0.513N	P=0.190N
Logistic regression tests	P=0.036N	P=0.076N	P=0.269N	P=0.014N
Cochran-Armitage test	P=0.022N			
Fisher exact test		P=0.042N	P=0.269N	P=0.010N
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rates	0/50 (0%)	0/51 (0%)	0/50 (0%)	2/51 (4%)
Adjusted rates	0.0%	0.0%	0.0%	8.7%
Terminal rates	0/31 (0%)	0/21 (0%)	0/26 (0%)	2/23 (9%)
First incidence (days)	–	–	–	729 (T)
Life table tests	P=0.037	–	–	P=0.175
Logistic regression tests	P=0.037	–	–	P=0.175
Cochran-Armitage test	P=0.047			
Fisher exact test		–	–	P=0.252

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Thyroid Gland (C-cell): Adenoma				
Overall rates	1/49 (2%)	4/48 (8%)	0/49 (0%)	2/50 (4%)
Adjusted rates	3.2%	17.9%	0.0%	8.7%
Terminal rates	1/31 (3%)	3/21 (14%)	0/26 (0%)	2/23 (9%)
First incidence (days)	729 (T)	716	–	729 (T)
Life table tests	P=0.544	P=0.086	P=0.535N	P=0.396
Logistic regression tests	P=0.550	P=0.105	P=0.535N	P=0.396
Cochran-Armitage test	P=0.566N			
Fisher exact test		P=0.175	P=0.500N	P=0.508
Uterus: Stromal Polyp				
Overall rates	9/50 (18%)	11/51 (22%)	6/50 (12%)	8/51 (16%)
Adjusted rates	29.0%	40.6%	21.9%	26.4%
Terminal rates	9/31 (29%)	7/21 (33%)	5/26 (19%)	4/23 (17%)
First incidence (days)	729 (T)	513	710	504
Life table tests	P=0.500N	P=0.131	P=0.416N	P=0.473
Logistic regression tests	P=0.405N	P=0.273	P=0.380N	P=0.595
Cochran-Armitage test	P=0.317N			
Fisher exact test		P=0.421	P=0.288N	P=0.482N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	9/50 (18%)	11/51 (22%)	6/50 (12%)	9/51 (18%)
Adjusted rates	29.0%	40.6%	21.9%	27.9%
Terminal rates	9/31 (29%)	7/21 (33%)	5/26 (19%)	4/23 (17%)
First incidence (days)	729 (T)	513	710	455
Life table tests	P=0.488	P=0.131	P=0.416N	P=0.371
Logistic regression tests	P=0.500N	P=0.273	P=0.380N	P=0.534
Cochran-Armitage test	P=0.425N			
Fisher exact test		P=0.421	P=0.288N	P=0.584N
All Organs: Mononuclear Cell Leukemia				
Overall rates	10/50 (20%)	10/51 (20%)	12/50 (24%)	12/51 (24%)
Adjusted rates	25.0%	27.4%	30.3%	34.9%
Terminal rates	4/31 (13%)	2/21 (10%)	3/26 (12%)	3/23 (13%)
First incidence (days)	589	357	580	531
Life table tests	P=0.206	P=0.401	P=0.353	P=0.217
Logistic regression tests	P=0.454	P=0.544N	P=0.524N	P=0.465
Cochran-Armitage test	P=0.336			
Fisher exact test		P=0.579N	P=0.405	P=0.426
All Organs: Benign Neoplasms				
Overall rates	43/50 (86%)	37/51 (73%)	46/50 (92%)	31/51 (61%)
Adjusted rates	95.5%	94.7%	97.8%	84.8%
Terminal rates	29/31 (94%)	19/21 (90%)	25/26 (96%)	18/23 (78%)
First incidence (days)	385	455	538	455
Life table tests	P=0.339N	P=0.201	P=0.120	P=0.376N
Logistic regression tests	P=0.014N	P=0.314N	P=0.280	P=0.015N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.077N	P=0.262	P=0.004N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
All Organs: Malignant Neoplasms				
Overall rates	16/50 (32%)	20/51 (39%)	15/50 (30%)	16/51 (31%)
Adjusted rates	39.1%	50.1%	38.6%	42.7%
Terminal rates	8/31 (26%)	4/21 (19%)	5/26 (19%)	4/23 (17%)
First incidence (days)	506	357	580	455
Life table tests	P=0.441	P=0.110	P=0.550	P=0.311
Logistic regression tests	P=0.273N	P=0.272	P=0.313N	P=0.577N
Cochran-Armitage test	P=0.391N			
Fisher exact test		P=0.292	P=0.500N	P=0.558N
All Organs: Benign or Malignant Neoplasms				
Overall rates	47/50 (94%)	43/51 (84%)	48/50 (96%)	39/51 (76%)
Adjusted rates	95.9%	95.5%	98.0%	90.3%
Terminal rates	29/31 (94%)	19/21 (90%)	25/26 (96%)	19/23 (83%)
First incidence (days)	385	357	538	455
Life table tests	P=0.466	P=0.129	P=0.213	P=0.421
Logistic regression tests	P=0.028N	P=0.370N	P=0.511	P=0.042N
Cochran-Armitage test	P=0.015N			
Fisher exact test		P=0.106N	P=0.500	P=0.013N

(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 test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE 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 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 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 B4c
Historical Incidence of Adrenal Medulla Pheochromocytomas in Female F344/N Rats Receiving Corn Oil by Gavage[a]

	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Overall Historical Incidence			
Total	50/1,001 (5.0%)	8/1,001 (0.8%)	59/1,001[b] (5.9%)
Standard deviation	3.0%	1.4%	3.9%
Range	0%-10%	0%-4%	0%-14%

[a] Data as of 17 December 1991
[b] Includes one complex pheochromocytoma

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	10	9
Early deaths				
Moribund	13	17	20	19
Accidental deaths	2	5	0	4
Natural deaths	4	8	4	5
Survivors				
Terminal sacrifice	31	21	26	23
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Esophagus	(10)			(9)
Inflammation, suppurative				1 (11%)
Liver	(10)	(1)	(2)	(9)
Basophilic focus	1 (10%)			
Developmental malformation			1 (50%)	
Inflammation, chronic	2 (20%)			
Bile duct, hyperplasia				2 (22%)
Periductular, fibrosis			1 (50%)	
Periductular, inflammation, chronic	4 (40%)			3 (33%)
Mesentery	(1)			
Fat, necrosis, coagulative	1 (100%)			
Pancreas	(10)			(9)
Interstitium, fibrosis				2 (22%)
Salivary glands	(10)			(9)
Periductular, infiltration cellular, lymphocyte	1 (10%)			
Stomach, forestomach	(10)			(9)
Mineralization	2 (20%)			3 (33%)
Cardiovascular System				
Heart	(10)		(1)	(9)
Cardiomyopathy	3 (30%)		1 (100%)	2 (22%)
Endocrine System				
Pituitary gland	(10)	(1)	(3)	(9)
Pars distalis, cyst	1 (10%)		1 (33%)	
Pars distalis, hemorrhage		1 (100%)		1 (11%)
Pars distalis, hyperplasia	1 (10%)			1 (11%)
Thyroid gland	(10)		(1)	(9)
C-cell, hyperplasia	1 (10%)			
General Body System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)			(9)
Duct, dilatation	1 (10%)			
Uterus	(10)	(3)	(5)	(9)
Hydrometra	1 (10%)	1 (33%)	2 (40%)	3 (33%)
Hematopoietic System				
Lymph node	(10)		(2)	(9)
Hyperplasia, lymphoid			1 (50%)	
Lumbar, pigmentation, hemosiderin			1 (50%)	
Integumentary System				
Skin	(10)	(1)		(9)
Inflammation, suppurative		1 (100%)		
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(1)		(9)
Alveolar epithelium, hyperplasia		1 (100%)		1 (11%)
Nose	(10)			(9)
Mucosa, inflammation, suppurative				1 (11%)
Special Senses System				
Eye			(1)	(1)
Iris, synechia			1 (100%)	
Retina, dysplasia			1 (100%)	
Urinary System				
Kidney	(10)	(1)	(1)	(9)
Nephropathy	2 (20%)	1 (100%)	1 (100%)	1 (11%)
Collecting tubule, mineralization	1 (10%)			
Interstitium, infiltration cellular, lymphocyte	2 (20%)			
2-Year Study				
Alimentary System				
Intestine large, cecum	(46)	(43)	(47)	(48)
Inflammation, suppurative		1 (2%)	1 (2%)	
Intestine small, duodenum	(48)	(45)	(47)	(48)
Ulcer			1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(51)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)		
Basophilic focus	2 (4%)	4 (8%)		
Clear cell focus	3 (6%)	1 (2%)	6 (12%)	8 (16%)
Congestion			1 (2%)	1 (2%)
Developmental malformation	8 (16%)	6 (12%)	5 (10%)	4 (8%)
Eosinophilic focus		1 (2%)		1 (2%)
Fatty change	3 (6%)	7 (14%)	6 (12%)	1 (2%)
Inflammation, chronic	21 (42%)	18 (35%)	20 (40%)	10 (20%)
Mixed cell focus			1 (2%)	1 (2%)
Necrosis, coagulative		7 (14%)	4 (8%)	2 (4%)
Bile duct, hyperplasia	6 (12%)	5 (10%)	5 (10%)	5 (10%)
Central vein, dilatation	1 (2%)			
Centrilobular, necrosis, coagulative		2 (4%)		2 (4%)
Hepatocyte, cytoplasmic alteration				1 (2%)
Hepatocyte, hyperplasia	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Periductular, fibrosis	1 (2%)	4 (8%)		2 (4%)
Periductular, infiltration cellular, lymphocyte			2 (4%)	
Periductular, inflammation, suppurative				1 (2%)
Sinusoid, dilatation	1 (2%)			
Mesentery	(6)	(5)	(4)	(6)
Fat, inflammation, chronic	1 (17%)	2 (40%)		
Fat, inflammation, chronic active				1 (17%)
Fat, necrosis, coagulative	5 (83%)	2 (40%)	3 (75%)	3 (50%)
Fat, necrosis, liquifactive				1 (17%)
Pancreas	(48)	(46)	(49)	(49)
Atrophy	2 (4%)	7 (15%)	5 (10%)	5 (10%)
Ectopic tissue		1 (2%)	1 (2%)	
Hemorrhage, chronic		1 (2%)		
Hyperplasia		2 (4%)		
Infiltration cellular, lymphocyte	1 (2%)			
Inflammation, chronic		3 (7%)		1 (2%)
Necrosis, coagulative		1 (2%)		
Salivary glands	(50)	(51)	(50)	(50)
Submandibular gland, inflammation, chronic	1 (2%)			
Stomach, forestomach	(50)	(49)	(50)	(49)
Fibrosis				1 (2%)
Hyperkeratosis			1 (2%)	
Hyperplasia, squamous	1 (2%)		1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)			2 (4%)
Inflammation, suppurative	1 (2%)		1 (2%)	
Ulcer	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(48)	(48)	(48)
Erosion			1 (2%)	
Inflammation, chronic			1 (2%)	
Inflammation, suppurative				1 (2%)
Ulcer	1 (2%)	1 (2%)		3 (6%)
Mucosa, dilatation			1 (2%)	
Tongue		(2)	(1)	
Hyperkeratosis		1 (50%)		
Hyperplasia, squamous			1 (100%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(51)	(50)	(50)
Cardiomyopathy	10 (20%)	16 (31%)	17 (34%)	8 (16%)
Inflammation, suppurative	1 (2%)			
Atrioventricular valve, fibrosis			1 (2%)	
Atrium, thrombus			1 (2%)	1 (2%)
Endocrine System				
Adrenal gland, cortex	(50)	(51)	(49)	(50)
Angiectasis			1 (2%)	
Clear cell focus	1 (2%)			
Congestion				1 (2%)
Cyst	1 (2%)			
Hemorrhage			1 (2%)	
Infarct			1 (2%)	
Necrosis, coagulative		1 (2%)		
Vacuolization cytoplasmic		4 (8%)		1 (2%)
Adrenal gland, medulla	(50)	(51)	(49)	(50)
Cyst	1 (2%)			
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	9 (18%)	10 (20%)	8 (16%)	8 (16%)
Infiltration cellular, lymphocyte	1 (2%)			
Islets, pancreatic	(50)	(46)	(50)	(49)
Infiltration cellular, lymphocyte		1 (2%)		
Necrosis, coagulative		1 (2%)		
Parathyroid gland	(42)	(44)	(46)	(45)
Hyperplasia				2 (4%)
Pituitary gland	(49)	(48)	(49)	(50)
Congestion				1 (2%)
Pars distalis, cyst	3 (6%)	6 (13%)	2 (4%)	8 (16%)
Pars distalis, cyst multilocular	6 (12%)	4 (8%)	2 (4%)	
Pars distalis, cytoplasmic alteration		1 (2%)		
Pars distalis, hemorrhage			1 (2%)	
Pars distalis, pigmentation, hemosiderin			1 (2%)	
Pars intermedia, hemorrhage			1 (2%)	
Pars nervosa, cyst	1 (2%)			
Thyroid gland	(49)	(48)	(49)	(50)
C-cell, hyperplasia	5 (10%)	4 (8%)	7 (14%)	2 (4%)
Follicle, cyst	2 (4%)		1 (2%)	1 (2%)
Follicle, dilatation			1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(47)	(50)	(50)	(50)
Hyperplasia	2 (4%)	3 (6%)	2 (4%)	
Inflammation, suppurative	3 (6%)	4 (8%)	5 (10%)	4 (8%)
Duct, dilatation	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Duct, inflammation, suppurative			1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Genital System (continued)				
Ovary	(50)	(51)	(50)	(50)
Follicle, cyst	4 (8%)	4 (8%)	3 (6%)	4 (8%)
Uterus	(50)	(51)	(50)	(51)
Hemorrhage	1 (2%)			
Hydrometra	4 (8%)	5 (10%)	4 (8%)	5 (10%)
Hyperplasia, cystic		2 (4%)	6 (12%)	3 (6%)
Cervix, inflammation, suppurative			1 (2%)	1 (2%)
Vagina		(5)		(3)
Hyperkeratosis		1 (20%)		
Hyperplasia, squamous		1 (20%)		
Inflammation, suppurative		2 (40%)		3 (100%)
Metaplasia, squamous		1 (20%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hyperplasia, neutrophil		1 (2%)		
Myelofibrosis				1 (2%)
Lymph node	(50)	(51)	(50)	(50)
Inguinal, hyperplasia, plasma cell		1 (2%)		
Lumbar, hyperplasia, histiocytic				1 (2%)
Mediastinal, congestion				1 (2%)
Mediastinal, hemorrhage		1 (2%)		
Mediastinal, hyperplasia, histiocytic				1 (2%)
Mediastinal, hyperplasia, macrophage			1 (2%)	
Mediastinal, hyperplasia, plasma cell				1 (2%)
Mediastinal, necrosis, coagulative		1 (2%)		
Prefemoral, hyperplasia, lymphoid	1 (2%)		1 (2%)	
Lymph node, mandibular	(48)	(51)	(49)	(50)
Hyperplasia, lymphoid	2 (4%)	2 (4%)		3 (6%)
Hyperplasia, plasma cell		1 (2%)		2 (4%)
Inflammation, suppurative	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Spleen	(50)	(49)	(49)	(49)
Atrophy	1 (2%)			
Congestion	1 (2%)		3 (6%)	4 (8%)
Depletion lymphoid	1 (2%)			
Developmental malformation				1 (2%)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation		2 (4%)		
Hyperplasia, lymphoid		2 (4%)	1 (2%)	
Hyperplasia, plasma cell		1 (2%)		
Hyperplasia, reticulum cell		1 (2%)		1 (2%)
Necrosis, coagulative		1 (2%)		
Necrosis, liquifactive	1 (2%)			
Pigmentation, hemosiderin				2 (4%)
Capsule, hemorrhage		1 (2%)		
Thymus	(44)	(47)	(50)	(49)
Epithelial cell, cyst	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Integumentary System				
Mammary gland	(49)	(49)	(49)	(50)
Galactocele	3 (6%)	2 (4%)	3 (6%)	
Lactation	1 (2%)	1 (2%)	1 (2%)	
Acinus, hyperplasia	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
Subcutaneous tissue, cyst epithelial inclusion				1 (2%)
Subcutaneous tissue, inflammation, chronic		1 (2%)		
Tail, hyperkeratosis				1 (2%)
Tail, inflammation, suppurative				1 (2%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(48)	(49)
Hemorrhage	1 (2%)	2 (4%)		1 (2%)
Hydrocephalus	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis, liquifactive		1 (2%)		
Cerebellum, gliosis				1 (2%)
Hypothalamus, compression	1 (2%)		3 (6%)	
Meninges, inflammation, chronic	1 (2%)			
Thalamus, compression	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Thalamus, necrosis, coagulative			1 (2%)	
Respiratory System				
Lung	(50)	(51)	(50)	(50)
Congestion		2 (4%)		1 (2%)
Edema		2 (4%)		2 (4%)
Alveolar epithelium, hyperplasia	3 (6%)	3 (6%)	3 (6%)	
Alveolus, edema	1 (2%)			
Alveolus, foreign body				2 (4%)
Alveolus, hemorrhage	1 (2%)			
Alveolus, inflammation, chronic	10 (20%)	1 (2%)	1 (2%)	1 (2%)
Alveolus, inflammation, suppurative		1 (2%)		
Nose	(50)	(51)	(50)	(50)
Congestion				1 (2%)
Lumen, fungus	2 (4%)		2 (4%)	
Lumen, inflammation, chronic	1 (2%)			
Lumen, inflammation, suppurative	3 (6%)	2 (4%)	1 (2%)	5 (10%)
Mucosa, inflammation, chronic active	1 (2%)			
Mucosa, inflammation, suppurative	1 (2%)		1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, chronic				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
2-Year Study (continued)				
Special Senses System				
Eye	(1)	(1)	(2)	(1)
Lens, cataract	1 (100%)		1 (50%)	1 (100%)
Posterior chamber, hemorrhage			1 (50%)	
Retina, atrophy	1 (100%)			
Lacrimal gland		(1)		
Pigmentation, porphyrin		1 (100%)		
Urinary System				
Kidney	(50)	(49)	(49)	(49)
Hydronephrosis		2 (4%)		
Nephropathy	20 (40%)	20 (41%)	37 (76%)	31 (63%)
Cortex, cyst	1 (2%)		1 (2%)	
Cortex, necrosis, coagulative	1 (2%)			
Pelvis, inflammation, chronic		1 (2%)	1 (2%)	1 (2%)
Pelvis, mineralization		1 (2%)		
Renal tubule, hyperplasia				1 (2%)
Urinary bladder	(48)	(50)	(48)	(49)
Developmental malformation				1 (2%)
Infiltration cellular, lymphocyte			1 (2%)	

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

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF 3,4-DIHYDROCOUMARIN

TABLE C1	Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	166
TABLE C2	Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	172
TABLE C3	Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	196
TABLE C4a	Historical Incidence of Liver Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage	201
TABLE C4b	Historical Incidence of Alveolar/bronchiolar Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage	201
TABLE C4c	Historical Incidence of Renal Tubule Neoplasms in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage	201
TABLE C5	Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	202

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Disposition summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	20	19	19	20
Early deaths				
Moribund	3	3	8	4
Accidental deaths	1	1	1	0
Natural deaths	4	8	8	8
Survivors				
Terminal sacrifice	42	39	34	38
Animals examined microscopically	60	58	56	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(5)	(4)	(10)
Hepatocellular adenoma	3 (30%)	4 (80%)	2 (50%)	3 (30%)
Cardiovascular System				
None				
Endocrine System				
Thyroid gland	(10)			(10)
Follicular cell, adenoma	1 (10%)			
General Body System				
None				
Genital System				
None				
Hematopoietic System				
Lymph node, mesenteric	(10)		(1)	(10)
Lymphoma malignant			1 (100%)	
Spleen	(10)		(1)	(10)
Lymphoma malignant			1 (100%)	
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
Lung	(10)	(2)	(2)	(10)
Alveolar/bronchiolar adenoma	1 (10%)	1 (50%)	1 (50%)	1 (10%)
Alveolar/bronchiolar adenoma, multiple			1 (50%)	
Special Senses System				
Harderian gland		(1)		
Adenoma		1 (100%)		
Urinary System				
None				
Systemic Lesions				
Multiple organs[c]	(10)	(7)	(5)	(10)
Lymphoma malignant			1 (20%)	
2-Year Study				
Alimentary System				
Intestine large, cecum	(47)	(46)	(43)	(44)
Intestine small, ileum	(47)	(46)	(43)	(44)
Adenocarcinoma	1 (2%)		1 (2%)	
Intestine small, jejunum	(47)	(45)	(43)	(44)
Adenocarcinoma	2 (4%)			
Adenoma	1 (2%)			
Sarcoma	1 (2%)			
Liver	(50)	(51)	(51)	(50)
Hemangiosarcoma	1 (2%)			
Hemangiosarcoma, multiple	1 (2%)			
Hepatoblastoma				2 (4%)
Hepatocellular carcinoma	10 (20%)	11 (22%)	11 (22%)	6 (12%)
Hepatocellular carcinoma, multiple	1 (2%)			
Hepatocellular adenoma	21 (42%)	18 (35%)	17 (33%)	12 (24%)
Hepatocellular adenoma, multiple	8 (16%)	5 (10%)	19 (37%)	19 (38%)
Hepatocholangiocarcinoma				1 (2%)
Histiocytic sarcoma		1 (2%)		
Mesentery	(1)	(2)	(2)	(1)
Hemangioma		1 (50%)		
Pancreas	(48)	(50)	(48)	(49)
Stomach, forestomach	(49)	(49)	(46)	(48)
Papilloma squamous	2 (4%)		5 (11%)	2 (4%)
Squamous cell carcinoma	1 (2%)	1 (2%)		2 (4%)
Stomach, glandular	(48)	(47)	(43)	(46)
Squamous cell carcinoma, metastatic	1 (2%)	1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(51)	(51)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			1 (2%)
Hemangiosarcoma, metastatic, spleen	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Sarcoma			1 (2%)	
Endocrine System				
Adrenal gland	(50)	(50)	(48)	(49)
Spindle cell, adenoma	1 (2%)			
Adrenal gland, cortex	(49)	(50)	(48)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Adrenal gland, medulla	(49)	(49)	(48)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Islets, pancreatic	(49)	(50)	(49)	(50)
Adenoma		2 (4%)		
Pituitary gland	(47)	(46)	(45)	(45)
Pars distalis, adenoma			1 (2%)	1 (2%)
Thyroid gland	(49)	(49)	(49)	(50)
Follicular cell, adenoma				2 (4%)
General Body System				
Tissue NOS	(1)	(5)		(1)
Liposarcoma				1 (100%)
Thoracic, hemangioma		1 (20%)		
Thoracic, hepatocellular carcinoma, metastatic, liver		1 (20%)		
Genital System				
Epididymis	(49)	(49)	(48)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Squamous cell carcinoma, metastatic, stomach		1 (2%)		
Seminal vesicle	(49)	(48)	(47)	(48)
Testes	(49)	(48)	(48)	(48)
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(49)	(51)	(50)	(49)
Histiocytic sarcoma		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(50)	(49)	(50)	(50)
Bronchial, sarcoma			1 (2%)	
Bronchial, squamous cell carcinoma, metastatic		1 (2%)		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Mediastinal, hepatocellular carcinoma, metastatic, liver		1 (2%)		
Mediastinal, hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Mediastinal, sarcoma			1 (2%)	
Lymph node, mandibular	(47)	(41)	(49)	(44)
Lymph node, mesenteric	(49)	(48)	(43)	(47)
Spleen	(49)	(50)	(46)	(48)
Hemangioma			1 (2%)	
Hemangiosarcoma	1 (2%)		1 (2%)	2 (4%)
Histiocytic sarcoma		1 (2%)		
Thymus	(41)	(49)	(39)	(46)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Integumentary System				
Skin	(49)	(49)	(49)	(48)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Subcutaneous tissue, hemangioma				1 (2%)
Musculoskeletal System				
Bone	(50)	(51)	(51)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)	1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Skeletal muscle	(1)			(2)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (100%)			
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung				1 (50%)
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(51)	(50)
Adenocarcinoma, metastatic, harderian gland		1 (2%)		
Alveolar/bronchiolar adenoma	7 (14%)	14 (28%)	12 (24%)	10 (20%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	3 (6%)	
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)	3 (6%)	2 (4%)	1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Respiratory System (continued)				
Lung (continued)				
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Liposarcoma, metastatic, tissue NOS				1 (2%)
Neoplasm NOS, metastatic, liver				1 (2%)
Nose	(50)	(51)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Special Senses System				
Eye	(3)	(3)	(2)	(2)
Adenocarcinoma, metastatic, harderian gland		1 (33%)		
Harderian gland	(5)	(4)	(2)	(2)
Adenocarcinoma		1 (25%)		
Adenoma	5 (100%)	3 (75%)	2 (100%)	2 (100%)
Lacrimal gland	(1)	(1)	(1)	
Adenoma			1 (100%)	
Urinary System				
Kidney	(50)	(51)	(51)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			1 (2%)
Hepatocellular carcinoma, metastatic		1 (2%)		
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)		
Squamous cell carcinoma, metastatic, stomach		1 (2%)		
Renal tubule, adenoma			2 (4%)	
Renal tubule, carcinoma		1 (2%)		1 (2%)
Systemic Lesions				
Multiple organs	(50)	(51)	(51)	(50)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant			2 (4%)	3 (6%)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	4	6	4	3
2-Year study	42	40	44	44
Total primary neoplasms				
15-Month interim evaluation	5	6	5	4
2-Year study	67	63	84	71
Total animals with benign neoplasms				
15-Month interim evaluation	4	6	4	3
2-Year study	35	30	39	37
Total benign neoplasms				
15-Month interim evaluation	5	6	4	4
2-Year study	47	45	63	49
Total animals with malignant neoplasms				
15-Month interim evaluation			1	
2-Year study	17	17	15	20
Total malignant neoplasms				
15-Month interim evaluation			1	
2-Year study	20	18	21	22
Total animals with metastatic neoplasms				
2-Year study	4	5	2	5
Total metastatic neoplasms				
2-Year study	11	16	2	13

[a] Number of animals examined microscopically at site and number of animals with lesion
[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 3,4-Dihydrocoumarin: Vehicle Control

Number of Days on Study	0 1 1	4 4 9	4 5 6	5 2 8	5 9 1	6 5 8	6 9 0	6 9 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 0 4 1	0 0 8 1	0 2 2 1	0 3 5 1	0 4 4 1	0 4 2 1	0 2 0 1	0 6 4 1	0 0 2 1	0 0 5 1	0 0 7 1	0 0 9 1	0 1 0 1	0 1 1 1	0 1 5 1	0 2 4 1	0 2 7 1	0 3 0 1	0 3 4 1	0 3 7 1	0 3 8 1	0 4 1 1	0 4 3 1	0 5 2 1	0 5 3 1
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	A	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	A	+	+	A	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X																			
Intestine small, jejunum	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Adenoma																									X	
Sarcoma							X																			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X							
Hemangiosarcoma, multiple			X																							
Hepatocellular carcinoma					X	X	X				X															
Hepatocellular carcinoma, multiple																										
Hepatocellular adenoma		X	X	X						X				X			X	X	X		X		X	X	
Hepatocellular adenoma, multiple									X						X	X						X				
Mesentery				+																						
Pancreas	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																X										
Squamous cell carcinoma				X																						
Stomach, glandular	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic				X																						
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																			
Hemangiosarcoma, metastatic, spleen																		X								

+: 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 3,4-Dihydrocoumarin: 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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 5 4 1	0 5 8 1	0 6 1 1	0 6 6 1	0 6 8 1	0 7 0 1	0 0 1 1	0 0 3 1	0 1 2 1	0 1 4 1	0 1 6 1	0 1 7 1	0 2 1 1	0 2 3 1	0 2 6 1	0 2 8 1	0 2 9 1	0 3 3 1	0 3 9 1	0 4 0 1	0 4 7 1	0 4 9 1	0 5 1 1	0 5 5 1	0 6 7 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+		44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma							X									X										2
Adenoma																										1
Sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma	X			X											X		X		X				X			10
Hepatocellular carcinoma, multiple								X																		1
Hepatocellular adenoma	X		X			X	X	X	X							X	X			X				X		21
Hepatocellular adenoma, multiple					X													X	X			X				8
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																						X				2
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma, metastatic, spleen																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	0 1 1	4 4 9	4 5 6	5 2 8	5 9 1	6 5 8	6 9 0	6 9 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 0 4 1	0 0 8 1	0 2 2 1	0 3 5 1	0 4 4 1	0 4 2 1	0 2 0 1	0 6 4 1	0 0 2 1	0 0 5 1	0 0 7 1	0 0 9 1	0 1 0 1	0 1 1 1	0 1 5 1	0 2 4 1	0 2 7 1	0 3 0 1	0 3 4 1	0 3 7 1	0 3 8 1	0 4 1 1	0 4 3 1	0 5 2 1	0 5 3 1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																										
Adrenal gland, cortex	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																			
Adrenal gland, medulla	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																			
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	M	+	M	+	M	+	+	
Pituitary gland	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
General Body System																										
Tissue NOS																									+	
Genital System																										
Epididymis	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																			
Preputial gland																+				+	+	+			+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																					X					
Hematopoietic System																										
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X								
Thymus	+	+	+	I	I	A	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																			
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	+	M	M	+	+	M	M	M	M	M	M	+	M	M	M	M	M	M	
Skin	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 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 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 5 4 1	0 5 8 1	0 6 1 1	0 6 6 1	0 6 8 1	0 7 0 1	0 0 1 3 1	0 0 1 3 2 1	0 1 1 4 1	0 1 1 6 1	0 1 1 7 1	0 2 1 1	0 2 2 3 1	0 2 2 6 1	0 2 2 8 1	0 2 3 9 1	0 3 3 1	0 3 9 1	0 4 0 1	0 4 7 1	0 4 9 1	0 5 1 1	0 6 5 1	0 6 7 1	Total Tissues/ Tumors
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma		X																							1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	I	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																									
Tissue NOS																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Preputial gland		+										+	+	+	+				+		+				12
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																									1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	I	I	+	I	M	+	+	+	+	I	+	+	41
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	0 1 1	4 4 9	4 5 6	5 2 8	5 9 1	6 5 8	6 9 0	6 9 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 1	0 8 1	0 2 1	0 3 1	0 4 1	0 4 1	0 2 1	0 6 1	0 0 1	0 0 1	0 0 1	0 0 1	0 1 1	0 1 1	0 1 1	0 2 1	0 2 1	0 3 1	0 3 1	0 3 1	0 3 1	0 4 1	0 4 1	0 5 1	0 5 1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Skeletal muscle							+																		
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Nervous System																									
Brain	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X		X			X							X			X
Alveolar/bronchiolar adenoma, multiple																					X				
Alveolar/bronchiolar carcinoma							X																		
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																+	+								
Harderian gland																+	+		+						
Adenoma																X	X		X						
Lacrimal gland																									
Zymbal's gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	05441	05811	06161	06661	06881	07201	07001	07331	01121	01141	01161	01171	02211	02231	02661	02281	02391	03331	03901	04041	04771	04991	05111	05611	05731	06671	Total Tissues/ Tumors
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Skeletal muscle																											1
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X						X							7
Alveolar/bronchiolar adenoma, multiple																											1
Alveolar/bronchiolar carcinoma																											1
Hepatocellular carcinoma, metastatic, liver	X																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																										+	3
Harderian gland											+															+	5
Adenoma											X															X	5
Lacrimal gland											+																1
Zymbal's gland											+																1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg

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

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 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	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	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	
Carcass ID Number	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	Total
	1	1	2	2	2	2	3	3	4	7	7	7	7	8	9	9	9	9	0	0	2	2	2	2	3	3	Tissues/
	1	7	2	5	7	9	4	6	0	5	6	8	9	4	1	5	8	9	0	9	0	1	3	8	3	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	1	
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	I	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma	X						X		X																		11
Hepatocellular adenoma		X			X			X	X					X	X		X		X		X			X			18
Hepatocellular adenoma, multiple				X		X												X							X		5
Histiocytic sarcoma																											1
Mesentery																			+					+			2
Hemangioma																			X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma										X																	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic										X																	1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X										X			2
Parathyroid gland	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg (continued)

Number of Days on Study	1 4 4 4 5 5 5 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 0 2 3 4 5 5 6 4 6 7 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 7 3 8 9 3 8 8 3 6 3 8 3 9 9 9 9 9 9 9 9 9 9 9 9 9
Carcass ID Number	0 1 1 1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0 0 1 1 1 1 1 7 1 2 1 3 3 1 2 1 3 0 8 7 8 8 9 9 9 9 9 0 0 0 0 0 1 5 4 2 0 5 4 6 6 1 6 7 2 2 5 0 2 3 6 7 1 2 4 5 8 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
General Body System	
Tissue NOS	+ + + + + + +
Thoracic, hemangioma	
Thoracic, hepatocellular carcinoma, metastatic, liver	X
Genital System	
Epididymis	+ + + A + + + + + A + + + + + + + + + + + + + +
Squamous cell carcinoma, metastatic, stomach	
Preputial gland	+ + + +
Prostate	+ + + M + I + A + A + + + + + + + + + + + + + + +
Seminal vesicle	+ + + A + + + A + A + + + + + + + + + + + + + + +
Testes	+ + + A + + + A + A + + + + + + + + + + + + + + +
Hematopoietic System	
Bone marrow	+ +
Histiocytic sarcoma	X
Lymph node	+ + + + + + + M + M + + + + + + + + + + + + + + +
Bronchial, squamous cell carcinoma, metastatic	
Mediastinal, hepatocellular carcinoma, metastatic, liver	X
Lymph node, mandibular	+ I + M + + M M M M + + + + + + + + + + + + + + +
Lymph node, mesenteric	+ + + + + + + M + M + M + + + + + + + + + + + + +
Spleen	+ + + + + + + A + + + + + + + + + + + + + + + + +
Histiocytic sarcoma	X
Thymus	+ + + + + + + + + + I + + + + + + + + + + + + + +
Hepatocellular carcinoma, metastatic, liver	X
Integumentary System	
Mammary gland	M M M M M M M M M M M M M M M M M + M M M M M M M
Skin	+ + + + + + + A + A + + + + + + + + + + + + + + +
Musculoskeletal System	
Bone	+ +
Alveolar/bronchiolar carcinoma, metastatic, lung	X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 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 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 1 1 1	1 1 7 1	1 2 2 1	1 2 5 1	1 2 7 1	1 2 9 1	1 3 4 1	1 3 6 1	1 4 0 1	0 7 5 1	0 7 6 1	0 7 8 1	0 7 9 1	0 8 4 1	0 9 1 1	0 9 5 1	0 9 8 1	0 9 9 1	1 0 9 1	1 0 0 1	1 0 2 1	1 2 2 1	1 2 3 1	1 2 8 1	1 3 3 1	1 3 7 1	Total Tissues/ Tumors
General Body System																											
Tissue NOS								+																			5
Thoracic, hemangioma								X																			1
Thoracic, hepatocellular carcinoma, metastatic, liver																											1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, stomach										X																	1
Preputial gland	+			+								+						+								+	8
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bronchial, squamous cell carcinoma, metastatic										X																	1
Mediastinal, hepatocellular carcinoma, metastatic, liver																											1
Lymph node, mandibular	M	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																											1
Integumentary System																											
Mammary gland	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar carcinoma, metastatic, lung																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 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 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 1 1 1	1 1 7 1	1 2 2 1	1 2 5 1	1 2 7 1	1 2 9 1	1 3 4 1	1 3 6 1	1 4 0 1	0 7 5 1	0 7 6 1	0 7 8 1	0 7 9 1	0 8 4 1	0 9 1 1	0 9 5 1	0 9 8 1	0 9 9 1	1 0 0 1	1 0 9 1	1 1 0 1	1 2 2 1	1 2 3 1	1 2 8 1	1 3 3 1	1 3 7 1	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																										1
Alveolar/bronchiolar adenoma				X		X										X	X				X	X		X	X	X	14
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										2
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye						+																				3
Adenocarcinoma, metastatic, harderian gland																										1
Harderian gland						+												+								4
Adenocarcinoma																										1
Adenoma						X												X								3
Lacrimal gland																		+								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Squamous cell carcinoma, metastatic, stomach										X																1
Renal tubule, carcinoma																X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	17711	17712	17715	17911	20011	20061	20071	14011	14031	14061	14071	15011	15031	15061	16021	17711	17781	17911	18011	18031	18041	18091	19071	20021	20031	20041	20091	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma																									X			1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma							X			X								X			X							11
Hepatocellular adenoma			X				X				X			X				X		X		X					X	17
Hepatocellular adenoma, multiple					X	X		X	X	X		X			X	X	X		X				X		X			19
Mesentery																					+					+		2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Papilloma squamous	X											X										X				X		5
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma																												1
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	45
Pars distalis, adenoma																	X											1
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																												
None																												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

Number of Days on Study	0 1 4	3 9 3	4 1 0	5 5 5	5 8 3	5 9 9	6 1 8	6 3 9	6 4 0	6 5 5	6 5 9	6 7 5	6 7 9	7 1 5	7 1 8	7 1 8	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
Carcass ID Number	1 8 8 1	1 5 6 1	2 1 0 1	1 8 6 1	1 6 0 1	1 9 1 1	1 7 0 1	2 0 4 1	1 9 6 1	2 0 5 1	1 8 7 1	1 5 9 1	1 9 2 1	1 4 4 1	1 5 5 1	1 7 6 1	1 7 3 1	1 4 2 1	1 4 5 1	1 5 1 1	1 5 8 1	1 6 1 1	1 6 4 1	1 6 6 1	1 6 8 1
Genital System																									
Coagulating gland																									
Epididymis	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland				+					+									+					+	+	+
Prostate	+	+	+	+	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, sarcoma													X												
Mediastinal, sarcoma													X												
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	M	M	+	+	A	A	A	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Thymus	+	A	+	+	M	+	A	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
Skin	+	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X			X		X		X		X	X
Alveolar/bronchiolar adenoma, multiple													X												
Alveolar/bronchiolar carcinoma														X											
Hepatocellular carcinoma, metastatic, liver							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 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 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 7 1 1	1 7 2 1	1 7 5 1	1 9 9 1	2 0 1 1	2 0 6 1	2 0 7 1	1 4 1 1	1 4 3 1	1 4 6 1	1 4 7 1	1 5 0 1	1 5 3 1	1 6 2 1	1 7 7 1	1 7 8 1	1 7 9 1	1 8 1 1	1 8 3 1	1 8 4 1	1 8 9 1	1 9 7 1	2 0 2 1	2 0 3 1	2 0 8 1	2 0 9 1	Total Tissues/ Tumors
Genital System																											
Coagulating gland			+																								1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland		+							+								+			+		+			+	+	13
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, sarcoma																											1
Mediastinal, sarcoma																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangioma	X																										1
Hemangiosarcoma																X											1
Thymus	I	+	+	I	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	39
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	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma					X		X					X		X		X			X								12
Alveolar/bronchiolar adenoma, multiple			X												X												3
Alveolar/bronchiolar carcinoma																											1
Hepatocellular carcinoma, metastatic, liver							X																				2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	17711	17721	17751	19911	20011	20061	20071	14111	14431	14661	14711	15011	15031	15051	16021	17711	17811	17911	18111	18311	18411	18911	19711	20221	20321	20811	20911	Total Tissues/ Tumors
Special Senses System																												
Ear				+																+								2
Eye																												2
Harderian gland																												2
Adenoma																												2
Lacrimal gland																				+								1
Adenoma																				X								1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Renal tubule, adenoma														X														2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant																							X					2
Lymphoma malignant lymphocytic																												1
Lymphoma malignant mixed																												1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 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 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 5 8 1	2 6 2 1	2 6 7 1	2 7 0 1	2 7 2 1	2 7 9 1	2 8 0 1	2 1 5 1	2 1 6 1	2 1 7 1	2 2 0 1	2 4 3 1	2 4 7 1	2 4 9 1	2 5 2 1	2 5 3 1	2 5 6 1	2 6 0 1	2 6 3 1	2 6 4 1	2 6 8 1	2 6 9 1	2 7 4 1	2 7 5 1	2 7 7 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma				X																					X	2
Hepatocellular carcinoma					X																				X	6
Hepatocellular adenoma					X		X							X					X							12
Hepatocellular adenoma, multiple			X			X					X	X	X	X		X	X				X	X	X	X	X	19
Hepatocholangiocarcinoma																										1
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																						X				2
Squamous cell carcinoma											X															2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	M	+	M	42
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg (continued)

Number of Days on Study	4 1 7	4 3 8	4 7 7	4 8 9	5 2 7	5 6 1	6 1 3	6 3 4	6 4 5	6 5 2	7 1 6	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 2 9	7 2 9
Carcass ID Number	2 3 3 1	2 4 2 1	2 2 2 1	2 4 4 1	2 1 1 1	2 3 2 1	2 6 5 1	2 2 9 1	2 5 4 1	2 5 7 1	2 5 9 1	2 4 0 1	2 1 3 1	2 1 4 1	2 2 1 1	2 2 3 1	2 2 6 1	2 3 8 1	2 3 5 1	2 3 7 1	2 3 8 1	2 4 1 1	2 4 5 1	2 5 0 1	2 5 5 1
General Body System																									
Tissue NOS																									
Liposarcoma																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland							+	+					+				+				+				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Mediastinal, hepatocholangiocarcinoma, metastatic, liver				X																					
Lymph node, mandibular	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X								X																
Thymus	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Integumentary System																									
Mammary gland	M	M	+	+	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Subcutaneous tissue, hemangioma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Skeletal muscle			+																						
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung			X																						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 500 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	25811	26211	26711	27011	27711	27911	28011	28111	28511	28611	28711	28011	28311	28411	28711	28911	29211	29311	29611	29011	29311	29411	29811	29911	30411	30711	Total Tissues/ Tumors
General Body System																											
Tissue NOS																				+							1
Liposarcoma																				X							1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland			+						+		+				+							+		+			11
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																											1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																											1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+		44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+		47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Hemangiosarcoma																											2
Thymus	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																											1
Subcutaneous tissue, hemangioma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Skeletal muscle								+																			2
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg (continued)

Number of Days on Study	4 1 7	4 3 8	4 7 7	4 8 9	5 2 7	5 6 1	6 1 3	6 3 4	6 4 5	6 5 2	7 1 6	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 2 9	7 2 9
Carcass ID Number	2 3 3 1	2 4 2 1	2 2 2 1	2 4 4 1	2 1 1 1	2 3 2 1	2 6 5 1	2 2 9 1	2 5 4 1	2 5 7 1	2 5 9 1	2 4 0 1	2 1 3 1	2 1 4 1	2 2 1 1	2 2 3 1	2 2 6 1	2 3 8 1	3 5 1 1	3 7 1 1	3 8 1 1	4 1 1 1	4 5 1 1	5 0 1 1	5 5 1 1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X												X		X			
Alveolar/bronchiolar carcinoma			X																						
Hepatocellular carcinoma, metastatic, liver										X															
Hepatocholangiocarcinoma, metastatic, liver				X																					
Liposarcoma, metastatic, tissue NOS																									
Neoplasm nos, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye												+												+	
Harderian gland												+												+	
Adenoma												X												X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Hepatocholangiocarcinoma, metastatic, liver				X																					
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant							X	X												X					
Lymphoma malignant histiocytic																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	25811	26211	26711	27011	27711	27911	28011	21511	21611	21711	22011	24311	24711	24911	25211	25311	25611	26011	26311	26411	26811	26911	27411	27511	27711		Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma					X		X		X				X	X		X					X						10
Alveolar/bronchiolar carcinoma								X																X			3
Hepatocellular carcinoma, metastatic, liver																											1
Hepatocholangiocarcinoma, metastatic, liver																											1
Liposarcoma, metastatic, tissue NOS																			X								1
Neoplasm NOS, metastatic, liver				X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Eye																											2
Harderian gland																											2
Adenoma																											2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Hepatocholangiocarcinoma, metastatic, liver																											1
Renal tubule, carcinoma						X																					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant																											3
Lymphoma malignant histiocytic																		X									1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Harderian Gland: Adenoma				
Overall rates[a]	5/50 (10%)	3/51 (6%)	2/51 (4%)	2/50 (4%)
Adjusted rates[b]	11.9%	7.4%	5.4%	5.1%
Terminal rates[c]	5/42 (12%)	2/39 (5%)	1/34 (3%)	1/38 (3%)
First incidence (days)	729 (T)	718	675	722
Life table tests[d]	P=0.196N	P=0.395N	P=0.303N	P=0.259N
Logistic regression tests[d]	P=0.175N	P=0.379N	P=0.238N	P=0.246N
Cochran-Armitage test[d]	P=0.158N			
Fisher exact test[d]		P=0.346N	P=0.210N	P=0.218N
Harderian Gland: Adenoma or Carcinoma				
Overall rates	5/50 (10%)	4/51 (8%)	2/51 (4%)	2/50 (4%)
Adjusted rates	11.9%	9.3%	5.4%	5.1%
Terminal rates	5/42 (12%)	2/39 (5%)	1/34 (3%)	1/38 (3%)
First incidence (days)	729 (T)	438	675	722
Life table tests	P=0.168N	P=0.537N	P=0.303N	P=0.259N
Logistic regression tests	P=0.135N	P=0.490N	P=0.238N	P=0.246N
Cochran-Armitage test	P=0.133N			
Fisher exact test		P=0.487N	P=0.210N	P=0.218N
Kidney (Renal Tubule): Adenoma				
Overall rates	0/50 (0%)	0/51 (0%)	2/51 (4%)	0/49 (0%)
Adjusted rates	0.0%	0.0%	5.9%	0.0%
Terminal rates	0/42 (0%)	0/39 (0%)	2/34 (6%)	0/38 (0%)
First incidence (days)	–[e]	–	729 (T)	–
Life table tests	P=0.572	–	P=0.193	–
Logistic regression tests	P=0.572	–	P=0.193	–
Cochran-Armitage test	P=0.591			
Fisher exact test		–	P=0.252	–
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rates	0/50 (0%)	1/51 (2%)	2/51 (4%)	1/49 (2%)
Adjusted rates	0.0%	2.6%	5.9%	2.6%
Terminal rates	0/42 (0%)	1/39 (3%)	2/34 (6%)	1/38 (3%)
First incidence (days)	–	729 (T)	729 (T)	729 (T)
Life table tests	P=0.340	P=0.485	P=0.193	P=0.480
Logistic regression tests	P=0.340	P=0.485	P=0.193	P=0.480
Cochran-Armitage test	P=0.358			
Fisher exact test		P=0.505	P=0.252	P=0.495
Liver: Hepatoblastoma				
Overall rates	0/50 (0%)	0/51 (0%)	0/51 (0%)	2/50 (4%)
Adjusted rates	0.0%	0.0%	0.0%	5.3%
Terminal rates	0/42 (0%)	0/39 (0%)	0/34 (0%)	2/38 (5%)
First incidence (days)	–	–	–	729 (T)
Life table tests	P=0.044	–	–	P=0.217
Logistic regression tests	P=0.044	–	–	P=0.217
Cochran-Armitage test	P=0.045			
Fisher exact test		–	–	P=0.247

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Liver: Hepatocellular Adenoma				
Overall rates	29/50 (58%)	23/51 (45%)	36/51 (71%)	31/50 (62%)
Adjusted rates	64.2%	54.6%	81.6%	71.8%
Terminal rates	26/42 (62%)	20/39 (51%)	26/34 (76%)	26/38 (68%)
First incidence (days)	449	553	555	438
Life table tests	P=0.077	P=0.262N	P=0.015	P=0.236
Logistic regression tests	P=0.147	P=0.153N	P=0.105	P=0.410
Cochran-Armitage test	P=0.165			
Fisher exact test		P=0.136N	P=0.133	P=0.419
Liver: Hepatocellular Carcinoma				
Overall rates	11/50 (22%)	11/51 (22%)	11/51 (22%)	6/50 (12%)
Adjusted rates	24.3%	23.3%	25.5%	13.4%
Terminal rates	8/42 (19%)	4/39 (10%)	4/34 (12%)	2/38 (5%)
First incidence (days)	591	423	583	477
Life table tests	P=0.171N	P=0.540	P=0.450	P=0.202N
Logistic regression tests	P=0.110N	P=0.566N	P=0.581N	P=0.144N
Cochran-Armitage test	P=0.110N			
Fisher exact test		P=0.574N	P=0.574N	P=0.143N
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rates	11/50 (22%)	11/51 (22%)	11/51 (22%)	7/50 (14%)
Adjusted rates	24.3%	23.3%	25.5%	15.8%
Terminal rates	8/42 (19%)	4/39 (10%)	4/34 (12%)	3/38 (8%)
First incidence (days)	591	423	583	477
Life table tests	P=0.246N	P=0.540	P=0.450	P=0.289N
Logistic regression tests	P=0.173N	P=0.566N	P=0.581N	P=0.218N
Cochran-Armitage test	P=0.172N			
Fisher exact test		P=0.574N	P=0.574N	P=0.218N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	36/50 (72%)	30/51 (59%)	40/51 (78%)	33/50 (66%)
Adjusted rates	74.9%	63.7%	83.3%	73.1%
Terminal rates	30/42 (71%)	22/39 (56%)	26/34 (76%)	26/38 (68%)
First incidence (days)	449	423	555	438
Life table tests	P=0.351	P=0.305N	P=0.054	P=0.568
Logistic regression tests	P=0.504N	P=0.125N	P=0.264	P=0.334N
Cochran-Armitage test	P=0.504N			
Fisher exact test		P=0.118N	P=0.302	P=0.333N
Liver: Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma				
Overall rates	36/50 (72%)	30/51 (59%)	40/51 (78%)	34/50 (68%)
Adjusted rates	74.9%	63.7%	83.3%	75.3%
Terminal rates	30/42 (71%)	22/39 (56%)	26/34 (76%)	27/38 (71%)
First incidence (days)	449	423	555	438
Life table tests	P=0.284	P=0.305N	P=0.054	P=0.491
Logistic regression tests	P=0.508N	P=0.125N	P=0.264	P=0.415N
Cochran-Armitage test	P=0.486			
Fisher exact test	P=0.118N	P=0.302	P=0.414N	

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	8/50 (16%)	15/50 (30%)	15/51 (29%)	10/50 (20%)
Adjusted rates	19.0%	38.5%	41.4%	25.5%
Terminal rates	8/42 (19%)	15/39 (38%)	13/34 (38%)	9/38 (24%)
First incidence (days)	729 (T)	729 (T)	679	634
Life table tests	P=0.381	P=0.047	P=0.022	P=0.312
Logistic regression tests	P=0.423	P=0.047	P=0.038	P=0.345
Cochran-Armitage test	P=0.503			
Fisher exact test		P=0.077	P=0.085	P=0.398
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	1/50 (2%)	3/50 (6%)	1/51 (2%)	3/50 (6%)
Adjusted rates	2.3%	7.2%	2.6%	7.2%
Terminal rates	0/42 (0%)	1/39 (3%)	0/34 (0%)	2/38 (5%)
First incidence (days)	690	643	715	477
Life table tests	P=0.289	P=0.290	P=0.733	P=0.284
Logistic regression tests	P=0.313	P=0.303	P=0.762N	P=0.296
Cochran-Armitage test	P=0.313			
Fisher exact test		P=0.309	P=0.748N	P=0.309
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	9/50 (18%)	18/50 (36%)	16/51 (31%)	13/50 (26%)
Adjusted rates	20.9%	43.8%	43.0%	32.0%
Terminal rates	8/42 (19%)	16/39 (41%)	13/34 (38%)	11/38 (29%)
First incidence (days)	690	643	679	477
Life table tests	P=0.265	P=0.023	P=0.027	P=0.170
Logistic regression tests	P=0.327	P=0.024	P=0.047	P=0.218
Cochran-Armitage test	P=0.377			
Fisher exact test		P=0.035	P=0.092	P=0.235
Small Intestine: Adenoma or Carcinoma				
Overall rates	4/50 (8%)	0/51 (0%)	1/51 (2%)	0/50 (0%)
Adjusted rates	9.3%	0.0%	2.9%	0.0%
Terminal rates	3/42 (7%)	0/39 (0%)	1/34 (3%)	0/38 (0%)
First incidence (days)	690	–	729 (T)	–
Life table tests	P=0.050N	P=0.075N	P=0.246N	P=0.078N
Logistic regression tests	P=0.043N	P=0.065N	P=0.195N	P=0.067N
Cochran-Armitage test	P=0.039N			
Fisher exact test		P=0.056N	P=0.175N	P=0.059N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	2/50 (4%)	0/51 (0%)	5/51 (10%)	2/50 (4%)
Adjusted rates	4.8%	0.0%	14.7%	5.3%
Terminal rates	2/42 (5%)	0/39 (0%)	5/34 (15%)	2/38 (5%)
First incidence (days)	729 (T)	–	729 (T)	729 (T)
Life table tests	P=0.344	P=0.255N	P=0.139	P=0.658
Logistic regression tests	P=0.344	P=0.255N	P=0.139	P=0.658
Cochran-Armitage test	P=0.384			
Fisher exact test		P=0.243N	P=0.226	P=0.691N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Stomach (Forestomach): Squamous Cell Carcinoma				
Overall rates	1/50 (2%)	1/51 (2%)	0/51 (0%)	2/50 (4%)
Adjusted rates	2.1%	2.6%	0.0%	5.1%
Terminal rates	0/42 (0%)	1/39 (3%)	0/34 (0%)	1/38 (3%)
First incidence (days)	528	729 (T)	–	722
Life table tests	P=0.346	P=0.752	P=0.496N	P=0.475
Logistic regression tests	P=0.364	P=0.756N	P=0.487N	P=0.493
Cochran-Armitage test	P=0.365			
Fisher exact test		P=0.748N	P=0.495N	P=0.500
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rates	3/50 (6%)	1/51 (2%)	5/51 (10%)	4/50 (8%)
Adjusted rates	6.8%	2.6%	14.7%	10.3%
Terminal rates	2/42 (5%)	1/39 (3%)	5/34 (15%)	3/38 (8%)
First incidence (days)	528	729 (T)	729 (T)	722
Life table tests	P=0.226	P=0.327N	P=0.262	P=0.453
Logistic regression tests	P=0.251	P=0.296N	P=0.357	P=0.498
Cochran-Armitage test	P=0.261			
Fisher exact test		P=0.301N	P=0.369	P=0.500
All Organs: Hemangiosarcoma				
Overall rates	3/50 (6%)	0/51 (0%)	1/51 (2%)	2/50 (4%)
Adjusted rates	6.7%	0.0%	2.9%	4.3%
Terminal rates	2/42 (5%)	0/39 (0%)	1/34 (3%)	0/38 (0%)
First incidence (days)	456	–	729 (T)	417
Life table tests	P=0.576N	P=0.133N	P=0.364N	P=0.522N
Logistic regression tests	P=0.579N	P=0.114N	P=0.292N	P=0.549N
Cochran-Armitage test	P=0.558N			
Fisher exact test		P=0.118N	P=0.301N	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	3/50 (6%)	2/51 (4%)	2/51 (4%)	2/50 (4%)
Adjusted rates	6.7%	5.1%	5.9%	4.3%
Terminal rates	2/42 (5%)	2/39 (5%)	2/34 (6%)	0/38 (0%)
First incidence (days)	456	729 (T)	729 (T)	417
Life table tests	P=0.466N	P=0.529N	P=0.576N	P=0.522N
Logistic regression tests	P=0.440N	P=0.487N	P=0.486N	P=0.549N
Cochran-Armitage test	P=0.433N			
Fisher exact test		P=0.491N	P=0.491N	P=0.500N
All Organs: Malignant Lymphoma and Histiocytic Sarcoma				
Overall rates	0/50 (0%)	1/51 (2%)	3/51 (6%)	4/50 (8%)
Adjusted rates	0.0%	2.4%	8.0%	9.6%
Terminal rates	0/42 (0%)	0/39 (0%)	1/34 (3%)	2/38 (5%)
First incidence (days)	–	673	659	613
Life table tests	P=0.023	P=0.491	P=0.098	P=0.058
Logistic regression tests	P=0.025	P=0.506	P=0.120	P=0.062
Cochran-Armitage test	P=0.025			
Fisher exact test		P=0.505	P=0.125	P=0.059

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)				
Overall rates	0/50 (0%)	0/51 (0%)	3/51 (6%)	4/50 (8%)
Adjusted rates	0.0%	0.0%	8.0%	9.6%
Terminal rates	0/42 (0%)	0/39 (0%)	1/34 (3%)	2/38 (5%)
First incidence (days)	–	–	659	613
Life table tests	P=0.011	–	P=0.098	P=0.058
Logistic regression tests	P=0.011	–	P=0.120	P=0.062
Cochran-Armitage test	P=0.011			
Fisher exact test		–	P=0.125	P=0.059
All Organs: Benign Neoplasms				
Overall rates	35/50 (70%)	30/51 (59%)	39/51 (76%)	37/50 (74%)
Adjusted rates	77.6%	69.7%	88.5%	82.0%
Terminal rates	32/42 (76%)	26/39 (67%)	29/34 (85%)	30/38 (79%)
First incidence (days)	449	553	555	417
Life table tests	P=0.073	P=0.356N	P=0.026	P=0.195
Logistic regression tests	P=0.161	P=0.200N	P=0.243	P=0.408
Cochran-Armitage test	P=0.185			
Fisher exact test		P=0.167N	P=0.305	P=0.412
All Organs: Malignant Neoplasms				
Overall rates	17/50 (34%)	17/51 (33%)	15/51 (29%)	20/50 (40%)
Adjusted rates	36.0%	34.6%	34.9%	41.4%
Terminal rates	12/42 (29%)	7/39 (18%)	7/34 (21%)	10/38 (26%)
First incidence (days)	456	423	583	417
Life table tests	P=0.239	P=0.510	P=0.547	P=0.271
Logistic regression tests	P=0.292	P=0.536N	P=0.392N	P=0.357
Cochran-Armitage test	P=0.293			
Fisher exact test		P=0.555N	P=0.389N	P=0.339
All Organs: Benign or Malignant Neoplasms				
Overall rates	42/50 (84%)	40/51 (78%)	44/51 (86%)	44/50 (88%)
Adjusted rates	87.5%	81.6%	91.7%	89.7%
Terminal rates	36/42 (86%)	30/39 (77%)	30/34 (88%)	33/38 (87%)
First incidence (days)	449	423	555	417
Life table tests	P=0.114	P=0.529	P=0.056	P=0.178
Logistic regression tests	P=0.225	P=0.341N	P=0.423	P=0.389
Cochran-Armitage test	P=0.219			
Fisher exact test		P=0.323N	P=0.483	P=0.387

(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 test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

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

	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Carcinoma or Hepatoblastoma
Overall Historical Incidence				
Total	249/901 (27.6%)	155/901 (17.2%)	2/901 (0.2%)	370/901 (41.4%)
Standard deviation	15.0%	5.8%	0.7%	15.5%
Range	4%-58%	8%-32%	0%-2%	14%-72%

[a] Data as of 17 December 1991

TABLE C4b
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 (15.6%)	34/900 (3.7%)	166/900 (18.4%)
Standard deviation	5.7%	3.6%	5.9%
Range	4%-20%	0%-12%	6%-26%

[a] Data as of 17 December 1991

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

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	3/899 (0.3%)	0/899 (0.0%)	3/899 (0.3%)
Standard deviation	0.7%		0.7%
Range	0%-2%		0%-2%

[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 3,4-Dihydrocoumarin[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	20	19	19	20
Early deaths				
Moribund	3	3	8	4
Accidental deaths	1	1	1	0
Natural deaths	4	8	8	8
Survivors				
Terminal sacrifice	42	39	34	38
Animals examined microscopically	60	58	56	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(5)	(4)	(10)
Basophilic focus			1 (25%)	
Clear cell focus	1 (10%)			
Fatty change	2 (20%)	1 (20%)		3 (30%)
Hemorrhage				1 (10%)
Mixed cell focus			1 (25%)	
Mesentery	(2)	(1)		
Fat, necrosis	2 (100%)	1 (100%)		
Salivary glands	(10)			(10)
Infiltration cellular, lymphocyte	2 (20%)			3 (30%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Preputial gland		(2)		
Duct, dilatation		2 (100%)		
Hematopoietic System				
None				
Integumentary System				
Skin	(10)	(1)		(10)
Alopecia	3 (30%)	1 (100%)		2 (20%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(2)	(2)	(10)
Alveolar epithelium, hyperplasia	1 (10%)	1 (50%)		1 (10%)
Special Senses System				
None				
Urinary System				
Kidney	(10)			(10)
Hydronephrosis	1 (10%)			
Infiltration cellular, lymphocyte	3 (30%)			
Urinary bladder	(10)			(10)
Infiltration cellular, lymphocyte				1 (10%)
2-Year Study				
Alimentary System				
Gallbladder	(45)	(40)	(41)	(40)
Hemorrhage		1 (3%)		
Intestine large, cecum	(47)	(46)	(43)	(44)
Hyperplasia, lymphoid	6 (13%)	2 (4%)	8 (19%)	3 (7%)
Inflammation, chronic				1 (2%)
Inflammation, suppurative			1 (2%)	
Intestine large, rectum	(44)	(46)	(43)	(46)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, suppurative			1 (2%)	
Intestine small, ileum	(47)	(46)	(43)	(44)
Hyperplasia, lymphoid	1 (2%)			
Intestine small, jejunum	(47)	(45)	(43)	(44)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Liver	(50)	(51)	(51)	(50)
Angiectasis	1 (2%)	4 (8%)		
Basophilic focus	3 (6%)	1 (2%)	4 (8%)	4 (8%)
Clear cell focus	2 (4%)	7 (14%)	14 (27%)	7 (14%)
Eosinophilic focus	9 (18%)	8 (16%)	13 (25%)	12 (24%)
Fatty change		1 (2%)	1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	
Infiltration cellular, lymphocyte	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic			1 (2%)	
Inflammation, suppurative		2 (4%)		1 (2%)
Mixed cell focus	1 (2%)	2 (4%)		2 (4%)
Necrosis		3 (6%)	3 (6%)	1 (2%)
Vacuolization cytoplasmic	1 (2%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(1)	(2)	(2)	(1)
Fat, inflammation, chronic active			2 (100%)	
Fat, inflammation, suppurative	1 (100%)			
Fat, necrosis		1 (50%)	1 (50%)	1 (100%)
Pancreas	(48)	(50)	(48)	(49)
Atrophy	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Cyst	1 (2%)	1 (2%)		
Infiltration cellular, lymphocyte	1 (2%)	3 (6%)		1 (2%)
Inflammation, chronic			1 (2%)	
Polyarteritis			1 (2%)	
Salivary glands	(50)	(50)	(50)	(49)
Infiltration cellular, lymphocyte	19 (38%)	23 (46%)	18 (36%)	12 (24%)
Duct, dilatation			1 (2%)	
Stomach	(49)	(49)	(46)	(48)
Serosa, inflammation, suppurative	1 (2%)			
Stomach, forestomach	(49)	(49)	(46)	(48)
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis				2 (4%)
Hyperplasia, squamous	10 (20%)	8 (16%)	9 (20%)	16 (33%)
Inflammation, chronic	1 (2%)			
Inflammation, suppurative	4 (8%)	4 (8%)	1 (2%)	6 (13%)
Stomach, glandular	(48)	(47)	(43)	(46)
Cyst		1 (2%)		
Inflammation, suppurative		2 (4%)		
Mineralization		1 (2%)		
Cardiovascular System				
Heart	(50)	(51)	(51)	(50)
Cardiomyopathy	2 (4%)		5 (10%)	1 (2%)
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Mineralization			2 (4%)	
Atrium, thrombus	1 (2%)	1 (2%)		
Perivascular, infiltration cellular, lymphocyte		1 (2%)		
Endocrine System				
Adrenal gland	(50)	(50)	(48)	(49)
Capsule, inflammation, suppurative	1 (2%)			
Adrenal gland, cortex	(49)	(50)	(48)	(49)
Accessory adrenal cortical nodule				1 (2%)
Hyperplasia	3 (6%)	1 (2%)		1 (2%)
Hypertrophy	4 (8%)	7 (14%)	1 (2%)	5 (10%)
Infarct			1 (2%)	
Pigmentation, ceroid			1 (2%)	
Adrenal gland, medulla	(49)	(49)	(48)	(47)
Hyperplasia	4 (8%)	2 (4%)	1 (2%)	2 (4%)
Islets, pancreatic	(49)	(50)	(49)	(50)
Hyperplasia		1 (2%)		
Pituitary gland	(47)	(46)	(45)	(45)
Pars distalis, cyst	1 (2%)		1 (2%)	1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(49)	(49)	(49)	(50)
Follicle, cyst			1 (2%)	
Follicle, degeneration		1 (2%)		
Follicular cell, hyperplasia	2 (4%)		2 (4%)	3 (6%)
General Body System				
Tissue NOS	(1)	(5)		(1)
Hemorrhage		1 (20%)		
Necrosis	1 (100%)	1 (20%)		
Abdominal, inflammation, suppurative		1 (20%)		
Genital System				
Epididymis	(49)	(49)	(48)	(49)
Granuloma sperm	1 (2%)			
Infiltration cellular, lymphocyte	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)		
Mineralization		1 (2%)		
Preputial gland	(12)	(8)	(13)	(11)
Inflammation, chronic			1 (8%)	1 (9%)
Inflammation, suppurative	1 (8%)	3 (38%)		1 (9%)
Duct, dilatation	11 (92%)	5 (63%)	13 (100%)	9 (82%)
Prostate	(50)	(47)	(48)	(50)
Infiltration cellular, lymphocyte	1 (2%)	1 (2%)		1 (2%)
Inflammation, suppurative				1 (2%)
Seminal vesicle	(49)	(48)	(47)	(48)
Dilatation	1 (2%)		2 (4%)	
Inflammation, chronic		1 (2%)		
Testes	(49)	(48)	(48)	(48)
Atrophy	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Mineralization		1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(51)	(50)	(49)
Hyperplasia, neutrophil		1 (2%)		1 (2%)
Lymph node	(50)	(49)	(50)	(50)
Mediastinal, hyperplasia, plasma cell			1 (2%)	
Lymph node, mandibular	(47)	(41)	(49)	(44)
Hyperplasia, lymphoid		2 (5%)	5 (10%)	1 (2%)
Hyperplasia, macrophage				1 (2%)
Lymph node, mesenteric	(49)	(48)	(43)	(47)
Congestion	5 (10%)	1 (2%)	4 (9%)	1 (2%)
Hemorrhage				2 (4%)
Inflammation, suppurative		1 (2%)		
Sinus, dilatation			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(49)	(50)	(46)	(48)
Congestion	1 (2%)		1 (2%)	
Cyst				1 (2%)
Developmental malformation	2 (4%)	1 (2%)	1 (2%)	6 (13%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid	5 (10%)	4 (8%)	4 (9%)	2 (4%)
Inflammation, suppurative		1 (2%)	1 (2%)	
Inflammation, pyogranulomatous			1 (2%)	
Thymus	(41)	(49)	(39)	(46)
Atrophy		1 (2%)		
Inflammation, suppurative		1 (2%)	1 (3%)	
Integumentary System				
Skin	(49)	(49)	(49)	(48)
Alopecia	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Cyst epithelial inclusion		1 (2%)		
Fibrosis			1 (2%)	
Hyperkeratosis	1 (2%)			
Inflammation, chronic active			1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Parakeratosis			1 (2%)	
Ulcer				1 (2%)
Sebaceous gland, metaplasia, squamous			1 (2%)	
Musculoskeletal System				
Bone	(50)	(51)	(51)	(50)
Hyperostosis	1 (2%)			
Inflammation, suppurative		1 (2%)		
Skeletal muscle	(1)			(2)
Hemorrhage				1 (50%)
Nervous System				
Brain	(48)	(49)	(48)	(50)
Infiltration cellular, lymphocyte	2 (4%)			
Respiratory System				
Lung	(50)	(50)	(51)	(50)
Congestion	1 (2%)	2 (4%)	2 (4%)	
Edema	1 (2%)			1 (2%)
Emphysema		1 (2%)		
Hemorrhage			1 (2%)	
Hyperplasia, macrophage		2 (4%)		
Inflammation, chronic active	1 (2%)	1 (2%)		
Inflammation, suppurative		1 (2%)	2 (4%)	
Pigmentation		1 (2%)		
Alveolar epithelium, hyperplasia		3 (6%)		1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Respiratory System (continued)				
Lung (continued)				
Alveolus, giant cell		1 (2%)		
Peribronchiolar, infiltration cellular, lymphocyte		1 (2%)		
Nose	(50)	(51)	(50)	(50)
Inflammation, suppurative		1 (2%)	1 (2%)	2 (4%)
Nasolacrimal duct, hyperplasia, squamous				1 (2%)
Vomeronasal organ, inflammation, proliferative			1 (2%)	
Special Senses System				
Ear			(2)	
Pinna, hyperplasia, squamous			1 (50%)	
Pinna, inflammation, suppurative			2 (100%)	
Eye	(3)	(3)	(2)	(2)
Cataract	1 (33%)	1 (33%)		1 (50%)
Anterior chamber, edema				1 (50%)
Cornea, edema				1 (50%)
Cornea, inflammation, chronic			1 (50%)	
Urinary System				
Kidney	(50)	(51)	(51)	(49)
Amyloid deposition			1 (2%)	
Infarct			1 (2%)	1 (2%)
Infiltration cellular, lymphocyte	3 (6%)	1 (2%)	3 (6%)	
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous				1 (2%)
Mineralization				1 (2%)
Necrosis, coagulative	1 (2%)			
Nephropathy	45 (90%)	46 (90%)	45 (88%)	43 (88%)
Cortex, cyst	2 (4%)	1 (2%)	5 (10%)	4 (8%)
Medulla, mineralization				1 (2%)
Pelvis, epithelium, hyperplasia			1 (2%)	
Renal tubule, hyperplasia		1 (2%)	1 (2%)	
Renal tubule, hyperplasia, cystic	2 (4%)	1 (2%)	4 (8%)	2 (4%)
Urinary bladder	(50)	(47)	(46)	(48)
Dilatation	1 (2%)			
Infiltration cellular, lymphocyte	2 (4%)	4 (9%)	5 (11%)	2 (4%)
Inflammation, suppurative				1 (2%)

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Of the animals designated for the 15-month interim evaluation, only 5-10 per group were examined microscopically.

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF 3,4-DIHYDROCOUMARIN

TABLE D1	Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	211
TABLE D2	Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	216
TABLE D3	Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	240
TABLE D4	Historical Incidence of Liver Neoplasms in Female B6C3F$_1$ Mice Receiving Corn Oil by Gavage	244
TABLE D5	Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin	245

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	19	20	19	18
Early deaths				
Moribund	5	9	4	5
Accidental deaths	2		1	
Natural deaths	8	2	5	17
Survivors				
Died last week of study				1
Terminal sacrifice	36	39	41	28
Animals examined microscopically	60	60	59	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)		(3)	(9)
Hepatocellular adenoma	2 (22%)		1 (33%)	2 (22%)
Hepatocyte, hepatocellular adenoma			1 (33%)	
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 Feed Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Gallbladder	(45)	(50)	(44)	(35)
Intestine large, cecum	(44)	(50)	(46)	(40)
Intestine large, colon	(45)	(50)	(46)	(40)
Intestine small, duodenum	(45)	(50)	(46)	(37)
Intestine small, ileum	(45)	(50)	(45)	(40)
Intestine small, jejunum	(47)	(50)	(45)	(39)
Liver	(51)	(50)	(50)	(52)
Hemangiosarcoma				2 (4%)
Hepatocellular carcinoma	3 (6%)	2 (4%)	4 (8%)	6 (12%)
Hepatocellular adenoma	10 (20%)	14 (28%)	13 (26%)	11 (21%)
Hepatocellular adenoma, multiple		6 (12%)	9 (18%)	9 (17%)
Histiocytic sarcoma	1 (2%)			
Neoplasm NOS			1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)
Pancreas	(50)	(50)	(48)	(47)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Salivary glands	(51)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(47)	(48)
Papilloma squamous	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Stomach, glandular	(44)	(50)	(45)	(41)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Endocrine System				
Adrenal gland, cortex	(49)	(50)	(47)	(48)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Adrenal gland, medulla	(47)	(50)	(47)	(48)
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(50)	(50)	(48)	(47)
Adenoma		1 (2%)		
Pituitary gland	(47)	(48)	(47)	(47)
Pars distalis, adenoma	9 (19%)	5 (10%)	3 (6%)	3 (6%)
Thyroid gland	(48)	(50)	(49)	(49)
Bilateral, follicular cell, adenoma				1 (2%)
Follicular cell, adenoma		1 (2%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
General Body System				
Tissue NOS			(1)	(1)
Fibroma			1 (100%)	
Genital System				
Clitoral gland			(2)	
Carcinoma			1 (50%)	
Ovary	(50)	(50)	(49)	(50)
Cystadenoma	1 (2%)	2 (4%)	1 (2%)	
Granulosa cell tumor benign	1 (2%)			
Luteoma			1 (2%)	1 (2%)
Oviduct	(2)			(2)
Uterus	(51)	(50)	(49)	(51)
Polyp		2 (4%)		
Sarcoma stromal	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(48)	(47)
Lymph node	(50)	(50)	(48)	(48)
Lumbar, carcinoma, metastatic, clitoral gland			1 (2%)	
Lymph node, mandibular	(49)	(48)	(40)	(43)
Lymph node, mesenteric	(47)	(50)	(45)	(41)
Spleen	(51)	(50)	(49)	(46)
Hemangiosarcoma				2 (4%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Thymus	(45)	(48)	(47)	(48)
Integumentary System				
Mammary gland	(51)	(47)	(48)	(50)
Adenoma	1 (2%)			
Skin	(51)	(50)	(48)	(51)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)	1 (2%)	
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Musculoskeletal System				
Bone	(51)	(50)	(50)	(52)
Osteosarcoma			1 (2%)	
Nervous System				
Brain	(49)	(50)	(47)	(48)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(51)	(50)	(48)	(51)
Alveolar/bronchiolar adenoma	2 (4%)	5 (10%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	2 (4%)		1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)
Special Senses System				
Harderian gland	(2)	(3)	(3)	(1)
Adenoma	1 (50%)	3 (100%)	3 (100%)	1 (100%)
Urinary System				
Kidney	(48)	(50)	(48)	(47)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Ureter	(1)			
Urinary bladder	(45)	(50)	(47)	(45)
Systemic Lesions				
Multiple organs[c]	(51)	(50)	(50)	(52)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	1 (2%)	3 (6%)		3 (6%)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	4 (8%)	4 (8%)	2 (4%)
Lymphoma malignant mixed	1 (2%)	2 (4%)		1 (2%)
Lymphoma malignant undifferentiated cell	2 (4%)			
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	2		2	2
2-Year study	24	36	36	38
Total primary neoplasms				
15-Month interim evaluation	2		2	
2-Year study	38	55	47	48
Total animals with benign neoplasms				
15-Month interim evaluation	2		2	2
2-Year study	17	29	27	25
Total benign neoplasms				
15-Month interim evaluation	2		2	2
2-Year study	27	42	35	30
Total animals with malignant neoplasms				
2-Year study	9	11	11	16
Total malignant neoplasms				
2-Year study	11	13	11	18
Total animals with metastatic neoplasms				
2-Year study	2		3	1
Total metastatic neoplasms				
2-Year study	2		3	8

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Neoplasm Summary (continued)				
Total animals with malignant neoplasms uncertain primary site				
2-Year study				1
Total animals with neoplasms uncertain-benign or malignant				
2-Year study			1	
Total uncertain neoplasms				
2-Year study			1	

[a] Number of animals examined microscopically at site and number of animals with lesion
[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 3,4-Dihydrocoumarin: Vehicle Control

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 0 7 1	3 0 9 1	3 0 1 1	3 1 0 1	3 1 2 1	3 1 7 1	3 2 5 1	3 2 7 1	3 2 9 1	3 3 2 1	3 4 3 1	3 4 5 1	3 4 6 1	3 4 7 1	3 4 8 1	3 2 8 1	3 2 8 1	3 2 7 1	3 2 8 1	3 2 8 1	3 0 9 1	3 0 1 1	3 1 4 1	3 3 1 1	3 3 6 1	3 3 7 1	3 3 8 1	3 4 4 1	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma																												3
Hepatocellular adenoma	X								X	X	X						X	X						X			X	10
Histiocytic sarcoma						X																						1
Mesentery																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous									X														X					2
Stomach, glandular	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	38
Pituitary gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma						X			X			X						X					X	X				9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																												
None																												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	0 1 5	0 2 4	1 1 7	5 4 5	5 8 7	5 9 7	6 0 5	6 3 9	6 4 3	6 6 8	6 7 4	6 7 4	6 8 0	7 0 4	7 0 7	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
Carcass ID Number	2 8 4 1 1	2 8 1 1 1	3 4 2 1 1	2 8 3 1 1	2 9 6 1 1	3 1 9 1 1	2 9 9 1 1	3 2 3 1 1	3 2 0 1 1	3 2 1 1 1	2 4 1 1 1	3 9 0 1 1	3 1 9 1 1	2 9 6 1 1	3 0 7 1 1	3 0 5 1 1	3 0 3 1 1	3 1 6 1 1	3 4 3 1 1	3 5 9 1 1	2 8 0 1 1	2 9 5 1 1	2 9 1 1 1	2 9 2 1 1	3 0 0 1 1
Genital System																								
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Granulosa cell tumor benign																						X		
Oviduct	+	+																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal																								
Hematopoietic System																								
Blood													+											
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	A	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	I	+	+	+	+	A	+	I	A	I	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, schwannoma malignant								X																
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X	X			
Hepatocellular carcinoma, metastatic, liver												X										X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 0 7 1	3 0 9 1	3 1 0 1	3 1 2 1	3 1 7 1	3 2 5 1	3 2 7 1	3 2 9 1	3 3 2 1	3 4 3 1	3 4 5 1	3 4 6 1	3 4 7 1	3 4 8 1	3 4 8 1	2 8 2 1	2 8 7 1	2 8 8 1	2 8 9 1	3 0 1 1	3 0 4 1	3 1 4 1	3 3 1 1	3 3 6 1	3 3 7 1	3 3 8 1	3 4 4 1	Total Tissues/ Tumors
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma											X																1
Granulosa cell tumor benign																											1
Oviduct																											2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma stromal						X																					1
Hematopoietic System																											
Blood																											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma						X																					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, schwannoma malignant																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																											2
Hepatocellular carcinoma, metastatic, liver																											2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: Vehicle Control (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 0 7 1	3 0 9 1	3 1 0 1	3 1 2 1	3 1 7 1	3 2 5 1	3 2 7 1	3 2 9 1	3 3 2 1	3 4 3 1	3 4 5 1	3 4 6 1	3 4 7 1	3 4 8 1	3 8 2 1	2 8 7 1	2 8 8 1	2 8 9 1	2 0 1 1	3 0 4 1	3 1 4 1	3 3 1 1	3 3 6 1	3 3 7 1	3 3 8 1	3 4 4 1	Total Tissues/ Tumors
Special Senses System																											
Ear																											1
Eye																											3
Harderian gland																											2
Adenoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ureter																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma						X																					1
Lymphoma malignant																											1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																											1
Lymphoma malignant undifferentiated cell type																											2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 7 5 1	3 7 7 1	3 7 8 1	3 8 2 1	3 8 7 1	3 8 8 1	3 9 2 1	3 9 3 1	3 9 6 1	3 9 7 1	3 9 9 1	4 0 0 1	4 0 3 1	4 0 4 1	4 1 3 1	4 1 5 1	4 1 8 1	4 2 0 1	3 5 5 1	3 5 7 1	3 8 0 1	4 0 2 1	4 0 6 1	4 0 8 1	4 1 1 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Hepatocellular adenoma		X	X				X			X						X									X	14
Hepatocellular adenoma, multiple						X																				6
Mesentery											+												+			3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	+	M	+	M	+	+	+	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Pars distalis, adenoma												X												X		5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 7 5 1	3 7 7 1	3 8 1 1	3 8 2 1	3 8 7 1	3 8 8 1	3 9 2 1	3 9 3 1	3 9 6 1	3 9 7 1	3 9 9 1	4 0 0 1	4 0 3 1	4 0 4 1	4 1 3 1	4 1 5 1	4 1 8 1	4 2 0 1	3 5 5 1	3 5 7 1	3 8 0 1	4 0 2 1	4 0 6 1	4 0 8 1	4 1 1 1	Total Tissues/ Tumors
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																								X		2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp																							X			2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X		X				X								5
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								2
Harderian gland		+																								3
Adenoma		X																								3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 200 mg/kg (continued)

Number of Days on Study	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0730	0731	0731	0731	0731	0731	0731	0731	
Carcass ID Number	3751	3771	3781	3882	3887	3898	3992	3993	3996	3997	3999	4001	4003	4041	4043	4055	4081	4102	4205	4357	4370	4402	4406	4408	4411	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										3
Lymphoma malignant lymphocytic																										4
Lymphoma malignant mixed																			X							2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 5 5 1	4 5 7 1	4 6 2 1	4 6 3 1	4 6 5 1	4 7 0 1	4 7 3 1	4 7 5 1	4 7 6 1	4 8 1 1	4 8 3 1	4 8 4 1	4 2 9 1	4 3 0 1	4 3 1 1	4 3 9 1	4 5 0 1	4 5 9 1	4 6 0 1	4 6 1 1	4 7 7 1	4 7 8 1	4 8 0 1	4 8 2 1	4 8 8 1	4 8 9 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																							X			X	4
Hepatocellular adenoma											X					X	X	X			X		X			13
Hepatocellular adenoma, multiple								X		X		X								X					X		9
Neoplasm NOS																											1
Mesentery																											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma squamous																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	M	I	+	M	+	+	+	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma				X				X																			3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma					X																						1
General Body System																											
Tissue NOS																									+		1
Fibroma																									X		1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

Number of Days on Study	4 4 4	5 1 5	5 3 8	6 6 5	6 8 7	6 9 4	6 9 4	7 0 0	7 1 7	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 3 2 1	4 2 5 1	4 8 6 1	4 4 4 1	4 5 1 1	4 4 9 1	4 5 2 1	4 7 1 1	4 4 6 1	4 3 8 1	4 8 5 1	4 2 1 1	4 2 3 1	4 2 4 1	4 2 6 1	4 2 8 1	4 3 3 1	4 3 4 1	4 3 6 1	4 4 1 1	4 4 2 1	4 4 3 1	4 4 7 1	4 5 3 1
Genital System																								
Clitoral gland					+				+															
Carcinoma					X																			
Ovary	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Luteoma															X									
Uterus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, carcinoma, metastatic, clitoral gland					X																			
Lymph node, mandibular	+	+	+	A	+	+	+	+	+	M	+	+	M	+	+	+	+	I	M	+	M	+	M	+
Lymph node, mesenteric	+	+	M	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma									X															
Subcutaneous tissue, hemangioma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma		X																						
Skeletal muscle						+																		
Nervous System																								
Brain	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+																						
Respiratory System																								
Lung	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X							
Hepatocellular carcinoma, metastatic, liver																								
Osteosarcoma, metastatic, bone		X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 5 5 1	4 5 7 1	4 5 2 1	4 6 3 1	4 6 5 1	4 7 0 1	4 7 3 1	4 7 5 1	4 7 6 1	4 8 1 1	4 8 3 1	4 8 4 1	4 2 9 1	4 3 0 1	4 3 1 1	4 3 9 1	4 5 0 1	4 5 9 1	4 6 0 1	4 6 1 1	4 7 7 1	4 7 8 1	4 8 0 1	4 8 2 1	4 8 8 1	4 8 9 1	Total Tissues/ Tumors
Genital System																											
Clitoral gland																											2
Carcinoma																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma															X												1
Luteoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lumbar, carcinoma, metastatic, clitoral gland																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, hemangioma																	X										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																											1
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma																											1
Hepatocellular carcinoma, metastatic, liver																										X	1
Osteosarcoma, metastatic, bone																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 400 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 5 5 1	4 5 7 1	4 6 2 1	4 6 3 1	4 6 5 1	4 7 0 1	4 7 3 1	4 7 5 1	4 7 6 1	4 8 1 1	4 8 3 1	4 8 4 1	4 2 9 1	4 3 0 1	4 3 1 1	4 3 9 1	4 5 0 1	4 5 9 1	4 6 0 1	4 6 1 1	4 7 7 1	4 7 8 1	4 8 0 1	4 8 2 1	4 8 8 1	4 8 9 1	Total Tissues/ Tumors
Special Senses System																											
Eye		M														+										1
Harderian gland		+								+						+										3
Adenoma		X								X						X										3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic								X																			4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg (continued)

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	
Carcass ID Number	51177	49211	49411	49711	50111	50311	50411	50711	51011	51111	51811	52111	52211	52411	52511	53711	54011	54311	54511	55211	55411	55811	56011	56311	56611	56911	57011	57311	57411	57611	57711	Total Tissues/ Tumors
Alimentary System																																
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine large	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																											X					2
Hepatocellular carcinoma											X					X																6
Hepatocellular adenoma	X									X	X					X				X						X						11
Hepatocellular adenoma, multiple				X		X						X			X	X		X	X													9
Sarcoma, metastatic, uncertain primary site																																1
Mesentery																																2
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, uncertain primary site																																1
Salivary glands	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																																1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Cardiovascular System																																
Heart	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma, metastatic, uncertain primary site																																1
Endocrine System																																
Adrenal gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, uncertain primary site																																1
Adrenal gland, medulla	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	39
Pituitary gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma		X																														3
Thyroid gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, follicular cell, adenoma																																1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg (continued)

Number of Days on Study	0 4 4 4 4 5 5 5 5 5 5 5 5 5 6 6 6 6 6 7 7 7 7 7 7 0 1 2 2 6 0 2 2 4 4 5 8 9 9 3 4 5 8 9 0 0 0 0 2 2 9 9 0 2 2 4 6 9 0 5 4 3 2 5 7 6 4 9 2 1 3 3 4 9 9
Carcass ID Number	5 5 5 5 5 5 5 4 5 5 5 5 5 5 5 4 5 5 5 5 5 5 5 5 5 2 4 1 3 4 3 5 9 4 5 4 4 1 0 2 9 0 3 3 3 0 5 2 1 1 6 7 5 2 5 1 7 8 2 5 6 8 9 5 0 5 6 3 9 4 9 1 8 2 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	
Ovary	+ M + +
Luteoma	
Oviduct	+
Uterus	+ +
Hematopoietic System	
Bone marrow	+ + + + + + + + + + + + + A + + + A + A + + A + +
Lymph node	+ + + + M + A + + + + + + + + M + + + + + + + + +
Lymph node, mandibular	+ + + M M + M + + + + + + + + M + + + + + + M + + +
Lymph node, mesenteric	+ + + + M + A I + + + + + + A M + M A + A + + A + +
Spleen	+ + + + + + A + + + A + A + + + + + + A + + A + +
Hemangiosarcoma	X X
Sarcoma, metastatic, uncertain primary site	X
Thymus	+ + + + + + + + + + A + + + M + + + + M + + + + +
Integumentary System	
Mammary gland	+ + + + + + M + + + + + + + + + + + + + + + + + +
Skin	+ +
Sarcoma, metastatic, uncertain primary site	X
Subcutaneous tissue, hemangiosarcoma	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ + + + + + + + + + A + A + + + + + + A + + + + +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Sarcoma, metastatic, uncertain primary site	X
Nose	+ +
Trachea	+ +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg (continued)

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	51771	49211	49411	49711	50111	50311	50411	50711	51011	51111	51811	52111	52211	52411	52511	53111	53411	54411	55211	55311	55411	55811	56011	56111	56311	56411	56611	Total Tissues/ Tumors
General Body System																												
Tissue NOS																												1
Genital System																												
Ovary	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Luteoma					X																							1
Oviduct										+																		2
Uterus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	41
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangiosarcoma																												2
Sarcoma, metastatic, uncertain primary site																												1
Thymus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																												
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma, metastatic, uncertain primary site																												1
Subcutaneous tissue, hemangiosarcoma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Nervous System																												
Brain	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																												
Lung	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma								X		X																		3
Sarcoma, metastatic, uncertain primary site																												1
Nose	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 800 mg/kg (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 300 mg/kg (continued)

Number of Days on Study	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 7 1	4 9 2 1	4 9 4 1	4 9 7 1	5 0 1 1	5 0 3 1	5 0 4 1	5 0 7 1	5 1 0 1	5 1 1 1	5 1 8 1	5 2 1 1	5 2 2 1	5 2 4 1	5 2 5 1	5 3 7 1	5 4 0 1	5 4 3 1	5 5 2 1	5 5 3 1	5 5 4 1	5 5 8 1	5 0 0 1	5 1 3 1	5 3 0 1	5 4 9 1	5 6 0 1	Total Tissues/ Tumors
Special Senses System																												
Harderian gland				+																								1
Adenoma				X																								1
Urinary System																												
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, uncertain primary site																												1
Urinary bladder	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymphoma malignant							X									X									X			3
Lymphoma malignant histiocytic																												1
Lymphoma malignant lymphocytic																						X						2
Lymphoma malignant mixed																												1

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Harderian Gland: Adenoma				
Overall rates[a]	1/51 (2%)	3/50 (6%)	3/50 (6%)	1/52 (2%)
Adjusted rates[b]	2.4%	7.2%	7.3%	3.4%
Terminal rates[c]	0/36 (0%)	2/39 (5%)	3/41 (7%)	1/29 (3%)
First incidence (days)	674	671	729 (T)	729 (T)
Life table tests[d]	P=0.589N	P=0.337	P=0.353	P=0.718
Logistic regression tests[d]	P=0.544N	P=0.308	P=0.324	P=0.752
Cochran-Armitage test[d]	P=0.490N			
Fisher exact test[d]		P=0.301	P=0.301	P=0.748N
Liver: Hepatocellular Adenoma				
Overall rates	10/51 (20%)	20/50 (40%)	22/50 (44%)	20/52 (38%)
Adjusted rates	27.8%	45.2%	52.4%	56.1%
Terminal rates	10/36 (28%)	15/39 (38%)	21/41 (51%)	14/29 (48%)
First incidence (days)	729 (T)	594	700	420
Life table tests	P=0.005	P=0.049	P=0.022	P=0.005
Logistic regression tests	P=0.014	P=0.038	P=0.023	P=0.012
Cochran-Armitage test	P=0.057			
Fisher exact test		P=0.021	P=0.007	P=0.029
Liver: Hepatocellular Carcinoma				
Overall rates	3/51 (6%)	2/50 (4%)	4/50 (8%)	6/52 (12%)
Adjusted rates	7.7%	4.8%	9.2%	15.7%
Terminal rates	1/36 (3%)	1/39 (3%)	3/41 (7%)	2/29 (7%)
First incidence (days)	674	685	444	504
Life table tests	P=0.067	P=0.455N	P=0.561	P=0.178
Logistic regression tests	P=0.131	P=0.490N	P=0.470	P=0.254
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.509N	P=0.489	P=0.254
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	13/51 (25%)	21/50 (42%)	25/50 (50%)	24/52 (46%)
Adjusted rates	34.1%	46.5%	58.0%	60.3%
Terminal rates	11/36 (31%)	15/39 (38%)	23/41 (56%)	14/29 (48%)
First incidence (days)	674	594	444	420
Life table tests	P=0.002	P=0.135	P=0.037	P=0.005
Logistic regression tests	P=0.013	P=0.100	P=0.020	P=0.014
Cochran-Armitage test	P=0.030			
Fisher exact test		P=0.061	P=0.009	P=0.023
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	2/51 (4%)	5/50 (10%)	1/48 (2%)	3/51 (6%)
Adjusted rates	5.6%	12.3%	2.4%	9.5%
Terminal rates	2/36 (6%)	4/39 (10%)	1/41 (2%)	2/28 (7%)
First incidence (days)	729 (T)	671	729 (T)	595
Life table tests	P=0.489	P=0.252	P=0.455N	P=0.395
Logistic regression tests	P=0.554	P=0.245	P=0.455N	P=0.460
Cochran-Armitage test	P=0.562N			
Fisher exact test		P=0.210	P=0.523N	P=0.500

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	0/51 (0%)	1/50 (2%)	0/48 (0%)	0/51 (0%)
Adjusted rates	0.0%	2.1%	0.0%	0.0%
Terminal rates	0/36 (0%)	0/39 (0%)	0/41 (0%)	0/28 (0%)
First incidence (days)	–[e]	615	–	–
Life table tests	P=0.593N	P=0.513	–	–
Logistic regression tests	P=0.558N	P=0.450	–	–
Cochran-Armitage test	P=0.567N			
Fisher exact test		P=0.495	–	–
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	2/51 (4%)	6/50 (12%)	1/48 (2%)	3/51 (6%)
Adjusted rates	5.6%	14.1%	2.4%	9.5%
Terminal rates	2/36 (6%)	4/39 (10%)	1/41 (2%)	2/28 (7%)
First incidence (days)	729 (T)	615	729 (T)	595
Life table tests	P=0.546	P=0.165	P=0.455N	P=0.395
Logistic regression tests	P=0.531N	P=0.143	P=0.455N	P=0.460
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.128	P=0.523N	P=0.500
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	9/47 (19%)	5/48 (10%)	3/47 (6%)	3/47 (6%)
Adjusted rates	26.2%	12.4%	7.3%	9.7%
Terminal rates	8/33 (24%)	3/37 (8%)	3/41 (7%)	2/28 (7%)
First incidence (days)	704	703	729 (T)	646
Life table tests	P=0.061N	P=0.139N	P=0.026N	P=0.108N
Logistic regression tests	P=0.056N	P=0.127N	P=0.027N	P=0.095N
Cochran-Armitage test	P=0.040N			
Fisher exact test		P=0.181N	P=0.060N	P=0.060N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	2/51 (4%)	2/50 (4%)	1/50 (2%)	1/52 (2%)
Adjusted rates	5.6%	5.1%	2.4%	2.2%
Terminal rates	2/36 (6%)	2/39 (5%)	1/41 (2%)	0/29 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	529
Life table tests	P=0.397N	P=0.666N	P=0.455N	P=0.557N
Logistic regression tests	P=0.336N	P=0.666N	P=0.455N	P=0.494N
Cochran-Armitage test	P=0.330N			
Fisher exact test		P=0.684	P=0.508N	P=0.493N
All Organs: Hemangiosarcoma				
Overall rates	0/51 (0%)	0/50 (0%)	0/50 (0%)	4/52 (8%)
Adjusted rates	0.0%	0.0%	0.0%	12.0%
Terminal rates	0/36 (0%)	0/39 (0%)	0/41 (0%)	2/29 (7%)
First incidence (days)	–	–	–	583
Life table tests	P=0.001	–	–	P=0.045
Logistic regression tests	P=0.003	–	–	P=0.060
Cochran-Armitage test	P=0.004			
Fisher exact test		–	–	P=0.061

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin
(continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	0/51 (0%)	0/50 (0%)	1/50 (2%)	4/52 (8%)
Adjusted rates	0.0%	0.0%	2.4%	12.0%
Terminal rates	0/36 (0%)	0/39 (0%)	1/41 (2%)	2/29 (7%)
First incidence (days)	–	–	729 (T)	583
Life table tests	P=0.002	–	P=0.526	P=0.045
Logistic regression tests	P=0.006	–	P=0.526	P=0.060
Cochran-Armitage test	P=0.006			
Fisher exact test		–	P=0.495	P=0.061
All Organs: Malignant Lymphoma and Histiocytic Sarcoma				
Overall rates	5/51 (10%)	8/50 (16%)	4/50 (8%)	7/52 (13%)
Adjusted rates	11.9%	17.9%	9.0%	20.5%
Terminal rates	2/36 (6%)	3/39 (8%)	2/41 (5%)	4/29 (14%)
First incidence (days)	587	590	538	419
Life table tests	P=0.312	P=0.343	P=0.445N	P=0.277
Logistic regression tests	P=0.465	P=0.260	P=0.544N	P=0.384
Cochran-Armitage test	P=0.461			
Fisher exact test		P=0.264	P=0.513N	P=0.394
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	4/51 (8%)	8/50 (16%)	4/50 (8%)	7/52 (13%)
Adjusted rates	9.3%	17.9%	9.0%	20.5%
Terminal rates	1/36 (3%)	3/39 (8%)	2/41 (5%)	4/29 (14%)
First incidence (days)	587	590	538	419
Life table tests	P=0.228	P=0.235	P=0.592N	P=0.187
Logistic regression tests	P=0.365	P=0.160	P=0.597	P=0.269
Cochran-Armitage test	P=0.359			
Fisher exact test		P=0.169	P=0.631	P=0.274
All Organs: Benign Neoplasms				
Overall rates	17/51 (33%)	29/50 (58%)	27/50 (54%)	25/52 (48%)
Adjusted rates	44.6%	65.8%	64.3%	66.6%
Terminal rates	15/36 (42%)	24/39 (62%)	26/41 (63%)	17/29 (59%)
First incidence (days)	674	594	700	420
Life table tests	P=0.017	P=0.037	P=0.096	P=0.015
Logistic regression tests	P=0.052	P=0.026	P=0.090	P=0.040
Cochran-Armitage test	P=0.194			
Fisher exact test		P=0.011	P=0.029	P=0.093
All Organs: Malignant Neoplasms				
Overall rates	9/51 (18%)	11/50 (22%)	11/50 (22%)	16/52 (31%)
Adjusted rates	20.6%	23.6%	23.0%	40.3%
Terminal rates	3/36 (8%)	4/39 (10%)	5/41 (12%)	7/29 (24%)
First incidence (days)	587	590	444	419
Life table tests	P=0.027	P=0.483	P=0.503	P=0.047
Logistic regression tests	P=0.083	P=0.367	P=0.321	P=0.091
Cochran-Armitage test	P=0.072			
Fisher exact test		P=0.383	P=0.383	P=0.093

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rates	24/51 (47%)	36/50 (72%)	36/50 (72%)	38/52 (73%)
Adjusted rates	54.3%	73.5%	74.9%	82.5%
Terminal rates	16/36 (44%)	26/39 (67%)	29/41 (71%)	21/29 (72%)
First incidence (days)	587	590	444	419
Life table tests	P<0.001	P=0.079	P=0.101	P=0.002
Logistic regression tests	P=0.007	P=0.019	P=0.017	P=0.003
Cochran-Armitage test	P=0.012			
Fisher exact test		P=0.009	P=0.009	P=0.006

(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 test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4
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 D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
15-Month interim evaluation[b]	19	20	19	18
Early deaths				
Moribund	5	9	4	5
Accidental deaths	2		1	
Natural deaths	8	2	5	17
Survivors				
Died last week of study				1
Terminal sacrifice	36	39	41	28
Animals examined microscopically	60	60	59	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)		(3)	(9)
Basophilic focus			1 (33%)	
Infiltration cellular, lymphocyte	1 (11%)			1 (11%)
Central vein, dilatation	1 (11%)			
Mesentery	(1)			
Fat, necrosis	1 (100%)			
Pancreas	(9)			(9)
Infiltration cellular, lymphocyte	2 (22%)			2 (22%)
Salivary glands	(9)			(9)
Infiltration cellular, lymphocyte	5 (56%)			5 (56%)
Stomach, forestomach	(9)		(1)	(9)
Hyperkeratosis			1 (100%)	
Cardiovascular System				
Heart	(9)			(9)
Valve, pigmentation, melanin, multifocal	1 (11%)			
Endocrine System				
None				
General Body System				
None				
Genital System				
Ovary	(9)	(1)	(1)	(9)
Pigmentation, ceroid	1 (11%)			
Follicle, cyst		1 (100%)	1 (100%)	2 (22%)
Uterus	(9)	(6)	(7)	(9)
Hydrometra	2 (22%)	2 (33%)	3 (43%)	1 (11%)
Hyperplasia, cystic	5 (56%)	4 (67%)	4 (57%)	8 (89%)
Inflammation, suppurative	1 (11%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
15-Month Interim Evaluation (continued)				
Hematopoietic System				
None				
Integumentary System				
Skin	(9)	(2)	(2)	(9)
Alopecia	2 (22%)	2 (100%)	2 (100%)	
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(9)			(9)
Infiltration cellular, lymphocyte	4 (44%)			4 (44%)
Urinary bladder	(9)			(9)
Infiltration cellular, lymphocyte	5 (56%)			6 (67%)
2-Year Study				
Alimentary System				
Gallbladder	(45)	(50)	(44)	(35)
Infiltration cellular, lymphocyte	1 (2%)	1 (2%)		
Inflammation, chronic		1 (2%)		
Intestine large, cecum	(44)	(50)	(46)	(40)
Hyperplasia, lymphoid	1 (2%)	6 (12%)	2 (4%)	
Inflammation, suppurative		1 (2%)		
Intestine large, colon	(45)	(50)	(46)	(40)
Edema	1 (2%)			
Intestine small, duodenum	(45)	(50)	(46)	(37)
Hyperplasia, lymphoid		1 (2%)		
Intestine small, ileum	(45)	(50)	(45)	(40)
Hyperplasia, lymphoid	2 (4%)			
Intestine small, jejunum	(47)	(50)	(45)	(39)
Hyperplasia, lymphoid	1 (2%)	2 (4%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(51)	(50)	(50)	(52)
Autolysis			1 (2%)	
Basophilic focus	1 (2%)	3 (6%)		1 (2%)
Clear cell focus		2 (4%)	2 (4%)	
Eosinophilic focus	8 (16%)	11 (22%)	9 (18%)	8 (15%)
Infiltration cellular, lymphocyte	8 (16%)	8 (16%)	8 (16%)	4 (8%)
Inflammation, chronic	2 (4%)			
Inflammation, suppurative			2 (4%)	1 (2%)
Mixed cell focus	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Necrosis	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Vacuolization cytoplasmic	1 (2%)	1 (2%)		
Bile duct, cyst	1 (2%)	1 (2%)		
Perivascular, fibrosis				1 (2%)
Mesentery	(1)	(3)	(2)	(2)
Fat, infiltration cellular, lymphocyte		1 (33%)		
Fat, inflammation, chronic active	1 (100%)	1 (33%)		
Fat, necrosis		2 (67%)	2 (100%)	1 (50%)
Pancreas	(50)	(50)	(48)	(47)
Atrophy	2 (4%)		1 (2%)	3 (6%)
Infiltration cellular, lymphocyte	8 (16%)	13 (26%)	10 (21%)	10 (21%)
Inflammation, suppurative				1 (2%)
Duct, dilatation				1 (2%)
Salivary glands	(51)	(50)	(50)	(50)
Infiltration cellular, lymphocyte	16 (31%)	20 (40%)	23 (46%)	18 (36%)
Stomach, forestomach	(49)	(50)	(47)	(48)
Hyperplasia, squamous	14 (29%)	6 (12%)	9 (19%)	6 (13%)
Inflammation, chronic active	1 (2%)		2 (4%)	
Inflammation, suppurative	12 (24%)	2 (4%)	2 (4%)	3 (6%)
Stomach, glandular	(44)	(50)	(45)	(41)
Infiltration cellular, lymphocyte			2 (4%)	
Mineralization	1 (2%)	1 (2%)		1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Cardiomyopathy		3 (6%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocyte		1 (2%)		4 (8%)
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)	2 (4%)		2 (4%)
Necrosis				1 (2%)
Polyarteritis		2 (4%)		
Atrioventricular valve, fibrosis				1 (2%)
Atrium, thrombus		1 (2%)		
Endocrine System				
Adrenal gland	(49)	(50)	(47)	(48)
Corticomedullary junction, hemorrhage	2 (4%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal gland, cortex	(49)	(50)	(47)	(48)
Congestion	1 (2%)			
Cyst		1 (2%)		
Hyperplasia	1 (2%)	1 (2%)		
Hypertrophy	1 (2%)	1 (2%)	1 (2%)	
Pigmentation, ceroid	1 (2%)	1 (2%)		
Adrenal gland, medulla	(47)	(50)	(47)	(48)
Congestion	1 (2%)			1 (2%)
Hemorrhage		1 (2%)		
Hyperplasia		1 (2%)	1 (2%)	
Necrosis	1 (2%)			
Islets, pancreatic	(50)	(50)	(48)	(47)
Infiltration cellular, lymphocyte				1 (2%)
Parathyroid gland	(38)	(38)	(33)	(39)
Hyperplasia	1 (3%)			1 (3%)
Pituitary gland	(47)	(48)	(47)	(47)
Congestion	1 (2%)			
Pars distalis, cyst				2 (4%)
Pars distalis, hyperplasia		1 (2%)		2 (4%)
Pars distalis, hypertrophy	1 (2%)			
Thyroid gland	(48)	(50)	(49)	(49)
Infiltration cellular, lymphocyte			2 (4%)	2 (4%)
Inflammation, suppurative	1 (2%)			
Follicle, cyst		1 (2%)	2 (4%)	
Follicular cell, hyperplasia	5 (10%)	2 (4%)	2 (4%)	2 (4%)
General Body System				
Tissue NOS			(1)	(1)
Fat, pelvic, hemorrhage				1 (100%)
Genital System				
Ovary	(50)	(50)	(49)	(50)
Pigmentation, ceroid	1 (2%)	1 (2%)		1 (2%)
Follicle, cyst	11 (22%)	9 (18%)	9 (18%)	7 (14%)
Follicle, hematocyst	5 (10%)	12 (24%)	4 (8%)	5 (10%)
Periovarian tissue, hemorrhage		1 (2%)		
Uterus	(51)	(50)	(49)	(51)
Congestion		1 (2%)		1 (2%)
Hydrometra	1 (2%)	1 (2%)	2 (4%)	5 (10%)
Hyperplasia, cystic	41 (80%)	48 (96%)	43 (88%)	39 (76%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(48)	(47)
Hyperplasia, erythrocyte			1 (2%)	
Hyperplasia, mononuclear cell	1 (2%)			
Hyperplasia, neutrophil	1 (2%)	1 (2%)		
Lymph node	(50)	(50)	(48)	(48)
Mediastinal, hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(48)	(40)	(43)
Congestion		1 (2%)		
Hyperplasia, lymphoid	3 (6%)	4 (8%)	3 (8%)	1 (2%)
Hyperplasia, macrophage	1 (2%)			
Lymph node, mesenteric	(47)	(50)	(45)	(41)
Congestion				1 (2%)
Hyperplasia, lymphoid	2 (4%)	6 (12%)	4 (9%)	1 (2%)
Hyperplasia, macrophage	1 (2%)	1 (2%)		
Inflammation, suppurative		1 (2%)		
Spleen	(51)	(50)	(49)	(46)
Congestion				1 (2%)
Developmental malformation	2 (4%)	3 (6%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, erythrocyte			1 (2%)	
Hyperplasia, lymphoid	12 (24%)	12 (24%)	6 (12%)	3 (7%)
Hyperplasia, macrophage	1 (2%)			
Inflammation, suppurative	1 (2%)	1 (2%)		
Capsule, fibrosis	1 (2%)			
Thymus	(45)	(48)	(47)	(48)
Atrophy			1 (2%)	2 (4%)
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)	
Necrosis	1 (2%)			
Integumentary System				
Mammary gland	(51)	(47)	(48)	(50)
Lactation	3 (6%)			1 (2%)
Skin	(51)	(50)	(48)	(51)
Alopecia	5 (10%)		3 (6%)	3 (6%)
Hyperplasia, squamous			1 (2%)	
Inflammation, chronic active		1 (2%)	1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)		
Musculoskeletal System				
Bone	(51)	(50)	(50)	(52)
Hyperplasia			1 (2%)	
Inflammation, chronic		1 (2%)		
Necrosis			1 (2%)	
Osteopetrosis		1 (2%)	1 (2%)	
Skeletal muscle			(1)	
Necrosis			1 (100%)	
Nervous System				
Brain	(49)	(50)	(47)	(48)
Compression	2 (4%)			2 (4%)
Hydrocephalus	1 (2%)	1 (2%)		
Cerebellum, necrosis, coagulative		1 (2%)		
Meninges, inflammation, suppurative	1 (2%)			
Spinal cord			(1)	
Degeneration			1 (100%)	
Demyelination			1 (100%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
2-Year Study (continued)				
Respiratory System				
Lung	(51)	(50)	(48)	(51)
Congestion			1 (2%)	
Hemorrhage	3 (6%)			1 (2%)
Hyperplasia, macrophage			1 (2%)	
Infiltration cellular, lymphocyte	2 (4%)	2 (4%)	1 (2%)	
Inflammation, chronic		1 (2%)		
Inflammation, suppurative	2 (4%)			
Alveolar epithelium, hyperplasia				1 (2%)
Nose	(51)	(50)	(50)	(51)
Inflammation, suppurative	1 (2%)			1 (2%)
Trachea	(50)	(50)	(49)	(51)
Infiltration cellular, lymphocyte		1 (2%)		
Special Senses System				
Ear	(1)			
Inflammation, suppurative	1 (100%)			
Eye	(3)	(2)	(1)	
Cornea, edema	1 (33%)			
Harderian gland	(2)	(3)	(3)	(1)
Inflammation, suppurative	1 (50%)			
Urinary System				
Kidney	(48)	(50)	(48)	(47)
Fatty change				1 (2%)
Glomerulosclerosis	1 (2%)		1 (2%)	
Infarct				1 (2%)
Infiltration cellular, lymphocyte	8 (17%)	7 (14%)	10 (21%)	5 (11%)
Metaplasia, cartilagenous			1 (2%)	1 (2%)
Necrosis, coagulative		2 (4%)	3 (6%)	1 (2%)
Nephropathy		5 (10%)	4 (8%)	5 (11%)
Cortex, cyst	1 (2%)			1 (2%)
Urinary bladder	(45)	(50)	(47)	(45)
Dilatation			1 (2%)	
Infiltration cellular, lymphocyte	12 (27%)	22 (44%)	19 (40%)	13 (29%)

[a] Number of animals examined microscopically at site and number of animals with lesion
[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 3,4-DIHYDROCOUMARIN

TABLE E1	Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin	252
TABLE E2a	Individual Animal Tumor Pathology of Male Rats in the 9-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin	258
TABLE E2b	Individual Animal Tumor Pathology of Male Rats in the 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin	260
TABLE E3a	Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 2-Year Vehicle Control Group versus Stop-Exposure 600 mg/kg Dose Groups	262
TABLE E3b	Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 3,4-Dihydrocoumarin: 2-Year 600 mg/kg Dose Group versus Stop-Exposure 600 mg/kg Dose Groups	267
TABLE E4	Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin	271

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin[a]

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Disposition Summary			
Animals initially in study	30	40	30
9-Month interim evaluation	19	20	
15-Month interim evaluation	10		10
Early deaths			
Moribund		6	10
Accidental deaths	1	1	
Natural deaths		5	8
Survivors			
Died last week of study		1	
Terminal sacrifice		7	2
Animals examined microscopically	30	39	30
9-Month Interim Evaluation			
Alimentary System			
None			
Cardiovascular System			
None			
Endocrine System			
Pituitary gland	(19)	(19)	
Pars distalis, adenoma	1 (5%)		
General Body System			
None			
Genital System			
Preputial gland	(1)		
Carcinoma	1 (100%)		
Hematopoietic System			
None			
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
9-Month Interim Evaluation (continued)			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
None			
15-Month Interim Evaluation			
Alimentary System			
None			
Cardiovascular System			
None			
Endocrine System			
Islets, pancreatic	(10)		(10)
Adenoma	1 (10%)		
Pituitary gland	(9)		(10)
Pars distalis, adenoma	1 (11%)		
Thyroid gland	(10)		(10)
Follicular cell, adenoma			1 (10%)
General Body System			
None			
Genital System			
Testes	(10)		(10)
Interstitial cell, adenoma	8 (80%)		7 (70%)
Hematopoietic System			
None			
Integumentary System			
Skin	(10)		(10)
Keratoacanthoma	1 (10%)		
Musculoskeletal System			
None			

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
15-Month Interim Evaluation (continued)			
Nervous System			
None			
Respiratory System			
Lung	(10)		(10)
Alveolar/bronchiolar adenoma	1 (10%)		
Bronchiole, alveolus, adenoma			1 (10%)
Special Senses System			
None			
Urinary System			
None			
Stop-Exposure Evaluation[b]			
Alimentary System			
Intestine large, cecum	(41)	(13)	(16)
Intestine large, colon	(44)	(13)	(17)
Intestine large, rectum	(44)	(16)	(18)
Intestine small, duodenum	(43)	(14)	(19)
Intestine small, ileum	(42)	(12)	(18)
Intestine small, jejunum	(41)	(14)	(19)
Leiomyoma		1 (7%)	
Liver	(49)	(19)	(19)
Hepatocellular adenoma		1 (5%)	
Mesentery	(17)	(3)	
Pancreas	(49)	(19)	(20)
Adenoma	2 (4%)		
Stomach, forestomach	(47)	(19)	(20)
Stomach, glandular	(46)	(18)	(20)
Cardiovascular System			
Heart	(50)	(20)	(20)
Schwannoma NOS		1 (5%)	
Endocrine System			
Adrenal gland, cortex	(50)	(20)	(20)
Osteosarcoma, metastatic, bone			1 (5%)
Adrenal gland, medulla	(50)	(20)	(20)
Osteosarcoma, metastatic, bone			1 (5%)
Pheochromocytoma malignant	1 (2%)		
Pheochromocytoma benign	17 (34%)	5 (25%)	4 (20%)
Islets, pancreatic	(49)	(18)	(20)
Adenoma	4 (8%)	1 (6%)	1 (5%)
Parathyroid gland	(47)	(18)	(18)
Adenoma		1 (6%)	

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Stop-Exposure Evaluation (continued)			
Endocrine System (continued)			
Pituitary gland	(49)	(18)	(18)
Pars distalis, adenoma	24 (49%)	6 (33%)	3 (17%)
Thyroid gland	(50)	(18)	(18)
C-cell, adenoma	1 (2%)		
Follicle, adenoma	1 (2%)	1 (6%)	
Follicular cell, adenocarcinoma	1 (2%)		
General Body System			
None			
Genital System			
Preputial gland	(47)	(20)	(20)
Adenocarcinoma	1 (2%)		
Adenoma	8 (17%)		
Carcinoma	2 (4%)		
Prostate	(45)	(20)	(20)
Seminal vesicle	(49)	(17)	(20)
Testes	(49)	(20)	(20)
Interstitial cell, adenoma	43 (88%)	16 (80%)	16 (80%)
Hematopoietic System			
Bone marrow	(47)	(19)	(20)
Lymph node	(51)	(20)	(20)
Lymph node, mandibular	(51)	(19)	(18)
Lymph node, mesenteric	(50)	(18)	(20)
Spleen	(49)	(19)	(20)
Thymus	(46)	(18)	(19)
Integumentary System			
Mammary gland	(46)	(19)	(15)
Adenoma	1 (2%)		
Fibroadenoma	3 (7%)	2 (11%)	
Skin	(51)	(20)	(20)
Basal cell adenoma			3 (15%)
Basosquamous tumor benign	1 (2%)		
Fibroma	1 (2%)	1 (5%)	2 (10%)
Fibrosarcoma	1 (2%)		
Keratoacanthoma	2 (4%)		
Squamous cell papilloma	2 (4%)	1 (5%)	
Musculoskeletal System			
Bone	(51)	(20)	(20)
Osteosarcoma			1 (5%)

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Stop-Exposure Evaluation (continued)			
Nervous System			
Brain	(48)	(19)	(18)
Cerebrum, meningioma benign	1 (2%)		
Meninges, meningioma benign	1 (2%)		
Respiratory System			
Lung	(50)	(20)	(20)
Alveolar/bronchiolar adenoma	2 (4%)		1 (5%)
Osteosarcoma, metastatic, bone			1 (5%)
Special Senses System			
None			
Urinary System			
Kidney	(50)	(20)	(20)
Osteosarcoma, metastatic, bone			1 (5%)
Renal tubule, oncocytoma benign			1 (5%)
Urinary bladder	(49)	(20)	(20)
Systemic Lesions			
Multiple organs[c]	(51)	(20)	(20)
Leukemia mononuclear	10 (20%)	6 (30%)	2 (10%)
Neoplasm Summary			
Total animals with primary neoplasms[d]			
9-Month interim evaluation	2		
15-Month interim evaluation	9	7	
Stop-exposure evaluation	48	19	18
Total primary neoplasms			
9-Month interim evaluation	2		
15-Month interim evaluation	12	9	
Stop-exposure evaluation	130	43	34
Total animals with benign neoplasms			
9-Month interim evaluation	1		
15-Month interim evaluation	9	7	
Stop-exposure evaluation	48	18	17
Total benign neoplasms			
9-Month interim evaluation	1		
15-Month interim evaluation	12	9	
Stop-exposure evaluation	114	36	31
Total animals with malignant neoplasms			
9-Month interim evaluation	1		
15-Month interim evaluation			
Stop-exposure evaluation	16	6	3

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the 9- and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Neoplasm Summary (continued)			
Total malignant neoplasms			
9-Month interim evaluation	1		
Stop-exposure evaluation	16	6	3
Total animals with metastatic neoplasms			
Stop-exposure evaluation			1
Total metastatic neoplasms			
Stop-exposure evaluation			4
Total animals with neoplasms uncertain-benign or malignant			
Stop-exposure evaluation		1	
Total uncertain neoplasms			
Stop-exposure evaluation		1	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Vehicle controls in stop-exposure evaluation are 2-year core study vehicle controls.
[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 Evaluation of 3,4-Dihydrocoumarin: 600 mg/kg

Number of Days on Study	1 8 6	5 4 0	5 5 4	5 5 9	6 5 1	6 5 4	6 5 5	6 5 5	6 6 9	6 8 0	6 9 0	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	
Carcass ID Number	0 5 7 5	0 5 7 2	0 5 8 1	0 5 7 3	0 6 0 5	0 6 0 4	0 5 7 4	0 5 8 5	0 5 8 2	0 5 9 5	0 5 7 1	0 5 8 3	0 5 8 4	0 5 9 1	0 5 9 2	0 5 9 3	0 5 9 4	0 6 0 1	0 6 0 2	0 6 0 3	Total Tissues/ Tumors
Alimentary System																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large	+	A	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	16
Intestine large, cecum	A	A	+	A	+	A	+	+	A	+	+	A	+	A	+	+	+	+	+	+	13
Intestine large, colon	A	A	+	A	+	A	+	+	A	+	+	A	+	A	+	+	+	+	+	+	13
Intestine large, rectum	+	A	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	16
Intestine small	A	A	+	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	15
Intestine small, duodenum	A	A	+	A	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	14
Intestine small, ileum	M	A	+	A	+	A	+	A	A	+	+	A	+	A	+	+	+	+	+	+	12
Intestine small, jejunum	A	A	+	A	+	+	+	A	A	+	+	M	+	+	+	+	+	+	+	+	14
Leiomyoma														X							1
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	19
Hepatocellular adenoma																		X			1
Mesentery							+				+								+		3
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	19
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	19
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	19
Stomach, glandular	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	18
Tongue														+							1
Cardiovascular System																					
Blood vessel												+		+		+					3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Schwannoma NOS											X										1
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Pheochromocytoma benign											X			X		X			X	X	5
Islets, pancreatic	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	18
Adenoma																			X		1
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18
Adenoma														X							1
Pituitary gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	18
Pars distalis, adenoma			X										X			X	X		X	X	6
Thyroid gland	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	18
Follicle, adenoma									X												1
General Body System																					
None																					

+: 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 Evaluation of 3,4-Dihydrocoumarin: 600 mg/kg (continued)

Number of Days on Study	18 46	15 04	15 54	15 59	16 05	16 14	16 25	16 55	16 69	16 80	16 90	17 01	17 29	17 29	17 29	17 29	17 29	17 29	17 29	17 29	
Carcass ID Number	05 57	05 72	05 81	05 73	06 05	06 04	05 74	05 85	05 82	05 95	05 71	05 83	05 84	05 91	05 92	05 93	05 94	06 01	06 02	06 03	Total Tissues/ Tumors
Genital System																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Seminal vesicle	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	17
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Interstitial cell, adenoma		X		X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	16
Hematopoietic System																					
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	19
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	19
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	18
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	19
Thymus	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	18
Integumentary System																					
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Fibroadenoma															X	X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Fibroma																			X		1
Squamous cell papilloma																		X			1
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Skeletal muscle											+										1
Nervous System																					
Brain	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	19
Respiratory System																					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Special Senses System																					
Eye													+								1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Leukemia mononuclear					X	X	X						X			X		X			6

TABLE E2b
Individual Animal Tumor Pathology of Male Rats in the 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin: 600 mg/kg

Number of Days on Study	3 8 5	4 5 5	5 0 7	5 2 8	5 2 8	5 2 9	5 2 9	6 0 4	6 3 4	6 3 8	6 5 5	6 6 1	6 6 1	6 6 1	6 9 7	7 1 6	7 1 8	7 1 8	7 2 4	7 2 9	7 2 9	
Carcass ID Number	0 6 8 3	0 6 7 1	0 6 7 3	0 6 5 3	0 6 5 5	0 6 7 2	0 6 8 1	0 6 8 4	0 6 6 5	0 6 6 4	0 6 5 2	0 6 6 1	0 6 7 5	0 6 7 4	0 6 5 1	0 6 6 2	0 6 6 3	0 6 6 5	0 6 8 4	0 6 5 2	0 6 8 2	Total Tissues/ Tumors
Alimentary System																						
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+		18
Intestine large, cecum	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	A	+	+		16
Intestine large, colon	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	A	+	+		17
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+		18
Intestine small	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		19
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		19
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+		18
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		19
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+		19
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Salivary glands	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+		18
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Cardiovascular System																						
Blood vessel				+						+							+	+				4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Endocrine System																						
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Osteosarcoma, metastatic, bone		X																				1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Osteosarcoma, metastatic, bone		X																				1
Pheochromocytoma benign						X			X				X				X					4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		20
Adenoma													X									1
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+		18
Pituitary gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+		18
Pars distalis, adenoma							X						X		X							3
Thyroid gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+		18
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		X	X	16

TABLE E2b
Individual Animal Tumor Pathology of Male Rats in the 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin: 600 mg/kg (continued)

Number of Days on Study	3 8 5	4 5 5	5 0 7	5 2 8	5 2 8	5 2 9	5 2 9	6 0 4	6 3 4	6 3 8	6 5 5	6 6 1	6 6 1	6 9 7	7 1 6	7 1 8	7 1 8	7 2 4	7 2 9	7 2 9	
Carcass ID Number	0 6 8 3	0 6 7 1	0 6 7 3	0 6 5 3	0 6 5 5	0 6 7 2	0 6 8 1	0 6 8 4	0 6 6 5	0 6 6 4	0 6 5 2	0 6 6 1	0 6 7 5	0 6 7 4	0 6 5 1	0 6 6 2	0 6 6 3	0 6 8 5	0 6 5 4	0 6 8 2	Total Tissues/ Tumors
Hematopoietic System																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	18
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	19
Integumentary System																					
Mammary gland	+	+	M	+	M	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	15
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Basal cell adenoma													X	X			X				3
Fibroma													X				X				2
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Osteosarcoma		X																			1
Nervous System																					
Brain	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	18
Respiratory System																					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Alveolar/bronchiolar adenoma													X								1
Osteosarcoma, metastatic, bone		X																			1
Nose	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	18
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Special Senses System																					
None																					
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Osteosarcoma, metastatic, bone		X																			1
Renal tubule, oncocytoma benign									X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Leukemia mononuclear								X												X	2

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year Vehicle Control Group versus Stop-Exposure 600 mg/kg Dose Groups

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	17/50 (34%)	5/20 (25%)	4/20 (20%)
Adjusted rates[b]	52.5%	55.0%	39.2%
Terminal rates[c]	13/28 (46%)	4/8 (50%)	0/2 (0%)
First incidence (days)	634	690	529
Life table tests[d]	P=0.178	P=0.610	P=0.192
Logistic regression tests[d]	P=0.425N	P=0.526N	P=0.484N
Cochran-Armitage test[d]	P=0.137N		
Fisher exact test[d]		P=0.332N	P=0.195N
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rates	18/50 (36%)	5/20 (25%)	4/20 (20%)
Adjusted rates	53.8%	55.0%	39.2%
Terminal rates	13/28 (46%)	4/8 (50%)	0/2 (0%)
First incidence (days)	634	690	529
Life table tests	P=0.241	P=0.569N	P=0.251
Logistic regression tests	P=0.336N	P=0.432N	P=0.401N
Cochran-Armitage test	P=0.102N		
Fisher exact test		P=0.277N	P=0.154N
Kidney (Renal Tubule): Adenoma (Single and Step Sections)			
Overall rates	1/50 (2%)	3/20 (15%)	2/20 (10%)
Adjusted rates	3.4%	33.3%	28.0%
Terminal rates	0/28 (0%)	2/8 (25%)	0/2 (0%)
First incidence (days)	717	701	655
Life table tests	P=0.007	P=0.024	P=0.064
Logistic regression tests	P=0.021	P=0.030	P=0.111
Cochran-Armitage test	P=0.081		
Fisher exact test		P=0.067	P=0.194
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	2/50 (4%)	0/20 (0%)	1/20 (5%)
Adjusted rates	7.1%	0.0%	11.1%
Terminal rates	2/28 (7%)	0/8 (0%)	0/2 (0%)
First incidence (days)	729 (T)	–[e]	661
Life table tests	P=0.380	P=0.538N	P=0.380
Logistic regression tests	P=0.537	P=0.538N	P=0.573
Cochran-Armitage test	P=0.640N		
Fisher exact test		P=0.507N	P=0.642
Mammary Gland: Fibroadenoma			
Overall rates	3/51 (6%)	2/20 (10%)	0/20 (0%)
Adjusted rates	9.3%	25.0%	0.0%
Terminal rates	2/28 (7%)	2/8 (25%)	0/2 (0%)
First incidence (days)	619	729 (T)	–
Life table tests	P=0.595	P=0.352	P=0.612N
Logistic regression tests	P=0.463N	P=0.413	P=0.386N
Cochran-Armitage test	P=0.326N		
Fisher exact test		P=0.436	P=0.364N

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year Vehicle Control Group versus Stop-Exposure 600 mg/kg Dose Groups (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Mammary Gland: Fibroadenoma or Adenoma			
Overall rates	4/51 (8%)	2/20 (10%)	0/20 (0%)
Adjusted rates	12.7%	25.0%	0.0%
Terminal rates	3/28 (11%)	2/8 (25%)	0/2 (0%)
First incidence (days)	619	729 (T)	–
Life table tests	P=0.602N	P=0.450	P=0.558N
Logistic regression tests	P=0.365N	P=0.511	P=0.320N
Cochran-Armitage test	P=0.225N		
Fisher exact test		P=0.546	P=0.257N
Pancreatic Islets: Adenoma			
Overall rates	4/49 (8%)	1/18 (6%)	1/20 (5%)
Adjusted rates	14.3%	12.5%	11.1%
Terminal rates	4/28 (14%)	1/8 (13%)	0/2 (0%)
First incidence (days)	729 (T)	729 (T)	661
Life table tests	P=0.393	P=0.672N	P=0.482
Logistic regression tests	P=0.598	P=0.672N	P=0.704
Cochran-Armitage test	P=0.399N		
Fisher exact test		P=0.592N	P=0.547N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	24/49 (49%)	6/18 (33%)	3/18 (17%)
Adjusted rates	63.4%	73.0%	30.9%
Terminal rates	15/28 (54%)	5/7 (71%)	0/2 (0%)
First incidence (days)	534	554	529
Life table tests	P=0.460N	P=0.477N	P=0.534N
Logistic regression tests	P=0.032N	P=0.259N	P=0.046N
Cochran-Armitage test	P=0.010N		
Fisher exact test		P=0.194N	P=0.015N
Preputial Gland: Adenoma			
Overall rates	8/47 (17%)	0/20 (0%)	0/20 (0%)
Adjusted rates	27.3%	0.0%	0.0%
Terminal rates	7/28 (25%)	0/8 (0%)	0/2 (0%)
First incidence (days)	704	–	–
Life table tests	P=0.083N	P=0.122N	P=0.429N
Logistic regression tests	P=0.045N	P=0.102N	P=0.214N
Cochran-Armitage test	P=0.012N		
Fisher exact test		P=0.048N	P=0.048N
Preputial Gland: Carcinoma			
Overall rates	3/47 (6%)	0/20 (0%)	0/20 (0%)
Adjusted rates	9.3%	0.0%	0.0%
Terminal rates	2/28 (7%)	0/8 (0%)	0/2 (0%)
First incidence (days)	619	–	–
Life table tests	P=0.266N	P=0.386N	P=0.612N
Logistic regression tests	P=0.152N	P=0.318N	P=0.362N
Cochran-Armitage test	P=0.131N		
Fisher exact test		P=0.338N	P=0.338N

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year Vehicle Control Group versus Stop-Exposure 600 mg/kg Dose Groups (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Preputial Gland: Adenoma or Carcinoma			
Overall rates	11/47 (23%)	0/20 (0%)	0/20 (0%)
Adjusted rates	35.8%	0.0%	0.0%
Terminal rates	9/28 (32%)	0/8 (0%)	0/2 (0%)
First incidence (days)	619	–	–
Life table tests	P=0.034N	P=0.057N	P=0.287N
Logistic regression tests	P=0.009N	P=0.033N	P=0.076N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.014N	P=0.014N
Skin: Fibroma			
Overall rates	1/51 (2%)	1/20 (5%)	2/20 (10%)
Adjusted rates	3.6%	12.5%	28.9%
Terminal rates	1/28 (4%)	1/8 (13%)	0/2 (0%)
First incidence (days)	729 (T)	729 (T)	661
Life table tests	P=0.013	P=0.462	P=0.035
Logistic regression tests	P=0.044	P=0.462	P=0.097
Cochran-Armitage test	P=0.121		
Fisher exact test		P=0.487	P=0.189
Skin: Squamous Cell Papilloma			
Overall rates	2/51 (4%)	1/20 (5%)	0/20 (0%)
Adjusted rates	5.4%	12.5%	0.0%
Terminal rates	0/28 (0%)	1/8 (13%)	0/2 (0%)
First incidence (days)	655	729 (T)	–
Life table tests	P=0.533N	P=0.629	P=0.561N
Logistic regression tests	P=0.397N	P=0.669	P=0.458N
Cochran-Armitage test	P=0.365N		
Fisher exact test		P=0.636	P=0.513N
Skin: Basal Cell Adenoma			
Overall rates	0/51 (0%)	0/20 (0%)	3/20 (15%)
Adjusted rates	0.0%	0.0%	39.0%
Terminal rates	0/28 (0%)	0/8 (0%)	0/2 (0%)
First incidence (days)	–	–	661
Life table tests	P<0.001	–	P=0.002
Logistic regression tests	P=0.002	–	P=0.004
Cochran-Armitage test	P=0.006		
Fisher exact test		–	P=0.020
Skin: Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Papilloma			
Overall rates	4/51 (8%)	1/20 (5%)	3/20 (15%)
Adjusted rates	12.2%	12.5%	39.0%
Terminal rates	2/28 (7%)	1/8 (13%)	0/2 (0%)
First incidence (days)	655	729 (T)	661
Life table tests	P=0.057	P=0.629N	P=0.066
Logistic regression tests	P=0.164	P=0.572N	P=0.197
Cochran-Armitage test	P=0.289		
Fisher exact test		P=0.564N	P=0.306

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year Vehicle Control Group versus Stop-Exposure 600 mg/kg Dose Groups (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Testes: Adenoma			
Overall rates	43/49 (88%)	16/20 (80%)	16/20 (80%)
Adjusted rates	100.0%	94.1%	100.0%
Terminal rates	28/28 (100%)	7/8 (88%)	2/2 (100%)
First incidence (days)	526	540	507
Life table tests	P<0.001	P=0.240	P<0.001
Logistic regression tests	P=0.564	P=0.427N	P=0.595
Cochran-Armitage test	P=0.232N		
Fisher exact test		P=0.315N	P=0.315N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rates	2/50 (4%)	1/18 (6%)	0/18 (0%)
Adjusted rates	7.1%	8.3%	0.0%
Terminal rates	2/28 (7%)	0/8 (0%)	0/2 (0%)
First incidence (days)	729 (T)	669	–
Life table tests	P=0.642N	P=0.609	P=0.855N
Logistic regression tests	P=0.491N	P=0.635	P=0.855N
Cochran-Armitage test	P=0.390N		
Fisher exact test		P=0.609	P=0.538N
All Organs: Mononuclear Cell Leukemia			
Overall rates	10/51 (20%)	6/20 (30%)	2/20 (10%)
Adjusted rates	25.5%	49.2%	53.8%
Terminal rates	2/28 (7%)	3/8 (38%)	1/2 (50%)
First incidence (days)	526	651	604
Life table tests	P=0.336	P=0.182	P=0.651
Logistic regression tests	P=0.373N	P=0.260	P=0.268N
Cochran-Armitage test	P=0.329N		
Fisher exact test		P=0.261	P=0.276N
All Organs: Benign Neoplasms			
Overall rates	48/51 (94%)	18/20 (90%)	17/20 (85%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	8/8 (100%)	2/2 (100%)
First incidence (days)	526	540	507
Life table tests	P=0.001	P=0.242	P=0.001
Logistic regression tests	P=0.379N	P=0.623N	P=0.501N
Cochran-Armitage test	P=0.156N		
Fisher exact test		P=0.436N	P=0.215N
All Organs: Malignant Neoplasms			
Overall rates	16/51 (31%)	7/20 (35%)	3/20 (15%)
Adjusted rates	40.1%	54.3%	56.3%
Terminal rates	6/28 (21%)	3/8 (38%)	1/2 (50%)
First incidence (days)	526	651	455
Life table tests	P=0.417	P=0.328	P=0.620
Logistic regression tests	P=0.180N	P=0.474	P=0.137N
Cochran-Armitage test	P=0.150N		
Fisher exact test		P=0.489	P=0.134N

TABLE E3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year Vehicle Control Group versus Stop-Exposure 600 mg/kg Dose Groups (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
All Organs: Benign or Malignant Neoplasms			
Overall rates	48/51 (94%)	19/20 (95%)	18/20 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	8/8 (100%)	2/2 (100%)
First incidence (days)	526	540	455
Life table tests	P<0.001	P=0.164	P<0.001
Logistic regression tests	P=0.616N	P=0.551	P=0.677N
Cochran-Armitage test	P=0.389N		
Fisher exact test		P=0.686	P=0.436N

[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 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 test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE E3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year 600 mg/kg Dose Group versus Stop-Exposure 600 mg/kg Dose Groups

	600 mg/kg (24-month exposure)	600 mg/kg (15-month exposure)	600 mg/kg (9-month exposure)
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	8/50 (16%)	4/20 (20%)	5/20 (25%)
Adjusted rates[b]	66.0%	39.2%	55.0%
Terminal rates[c]	1/2 (50%)	0/2 (0%)	4/8 (50%)
First incidence (days)	577	529	690
Life table tests[d]	P=0.158N	P=0.599N	P=0.134N
Logistic regression tests[d]	P=0.398	P=0.494	P=0.574
Cochran-Armitage test[d]	P=0.237		
Fisher exact test[d]		P=0.466	P=0.289
Liver: Hepatocellular Adenoma			
Overall rates	2/50 (4%)	0/19 (0%)	1/19 (5%)
Adjusted rates	8.4%	0.0%	12.5%
Terminal rates	0/2 (0%)	0/2 (0%)	1/8 (13%)
First incidence (days)	640	–[e]	729 (T)
Life table tests	P=0.345N	P=0.482N	P=0.478N
Logistic regression tests	P=0.556N	P=0.466N	P=0.720N
Cochran-Armitage test	P=0.626		
Fisher exact test		P=0.522N	P=0.626
Kidney (Renal Tubule): Adenoma (Single Sections)			
Overall rates	2/50 (4%)	0/20 (0%)	0/20 (0%)
Adjusted rates	15.0%	0.0%	0.0%
Terminal rates	0/2 (0%)	0/2 (0%)	0/8 (0%)
First incidence (days)	605	–	–
Life table tests	P=0.149N	P=0.369N	P=0.307N
Logistic regression tests	P=0.213N	P=0.448N	P=0.425N
Cochran-Armitage test	P=0.233N		
Fisher exact test		P=0.507N	P=0.507N
Kidney (Renal Tubule): Adenoma (Single and Step Sections)			
Overall rates	6/50 (12%)	2/20 (10%)	3/20 (15%)
Adjusted rates	69.3%	28.0%	33.3%
Terminal rates	1/2 (50%)	0/2 (0%)	2/8 (25%)
First incidence (days)	605	655	701
Life table tests	P=0.070N	P=0.261N	P=0.092N
Logistic regression tests	P=0.307N	P=0.501N	P=0.448N
Cochran-Armitage test	P=0.509		
Fisher exact test		P=0.588N	P=0.505
Mammary Gland: Fibroadenoma			
Overall rates	0/50 (0%)	0/20 (0%)	2/20 (10%)
Adjusted rates	0.0%	0.0%	25.0%
Terminal rates	0/2 (0%)	0/2 (0%)	2/8 (25%)
First incidence (days)	–	–	729 (T)
Life table tests	P=0.314	–	P=0.574
Logistic regression tests	P=0.314	–	P=0.574
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 Evaluation of 3,4-Dihydrocoumarin: 2-Year 600 mg/kg Dose Group versus Stop-Exposure 600 mg/kg Dose Groups (continued)

	600 mg/kg (24-month exposure)	600 mg/kg (15-month exposure)	600 mg/kg (9-month exposure)
Pancreas: Adenoma			
Overall rates	2/38 (5%)	0/20 (0%)	0/19 (0%)
Adjusted rates	21.9%	0.0%	0.0%
Terminal rates	0/2 (0%)	0/2 (0%)	0/8 (0%)
First incidence (days)	537	–	–
Life table tests	P=0.128N	P=0.335N	P=0.265N
Logistic regression tests	P=0.190N	P=0.387N	P=0.401N
Cochran-Armitage test	P=0.191N		
Fisher exact test		P=0.425N	P=0.440N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	9/46 (20%)	3/18 (17%)	6/18 (33%)
Adjusted rates	74.9%	30.9%	73.0%
Terminal rates	0/2 (0%)	0/2 (0%)	5/7 (71%)
First incidence (days)	483	529	554
Life table tests	P=0.105N	P=0.184N	P=0.091N
Logistic regression tests	P=0.294	P=0.543N	P=0.371
Cochran-Armitage test	P=0.193		
Fisher exact test		P=0.549N	P=0.198
Skin: Fibroma			
Overall rates	0/50 (0%)	2/20 (10%)	1/20 (5%)
Adjusted rates	0.0%	28.9%	12.5%
Terminal rates	0/2 (0%)	0/2 (0%)	1/8 (13%)
First incidence (days)	–	661	729 (T)
Life table tests	P=0.523	P=0.189	P=0.773
Logistic regression tests	P=0.310	P=0.096	P=0.773
Cochran-Armitage test	P=0.140		
Fisher exact test		P=0.079	P=0.286
Skin: Basal Cell Adenoma			
Overall rates	0/50 (0%)	3/20 (15%)	0/20 (0%)
Adjusted rates	0.0%	39.0%	0.0%
Terminal rates	0/2 (0%)	0/2 (0%)	0/8 (0%)
First incidence (days)	–	661	–
Life table tests	P=0.580N	P=0.104	–
Logistic regression tests	P=0.523	P=0.027	–
Cochran-Armitage test	P=0.360		
Fisher exact test		P=0.021	–
Skin: Squamous Cell Papilloma or Basal Cell Adenoma			
Overall rates	0/50 (0%)	3/20 (15%)	1/20 (5%)
Adjusted rates	0.0%	39.0%	12.5%
Terminal rates	0/2 (0%)	0/2 (0%)	1/8 (13%)
First incidence (days)	–	661	729 (T)
Life table tests	P=0.554	P=0.104	P=0.773
Logistic regression tests	P=0.306	P=0.027	P=0.773
Cochran-Armitage test	P=0.125		
Fisher exact test		P=0.021	P=0.286

TABLE E3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year 600 mg/kg Dose Group versus Stop-Exposure 600 mg/kg Dose Groups (continued)

	600 mg/kg (24-month exposure)	600 mg/kg (15-month exposure)	600 mg/kg (9-month exposure)
Testes: Adenoma			
Overall rates	42/46 (91%)	16/20 (80%)	16/20 (80%)
Adjusted rates	100.0%	100.0%	94.1%
Terminal rates	2/2 (100%)	2/2 (100%)	7/8 (88%)
First incidence (days)	483	507	540
Life table tests	P<0.001N	P=0.142N	P=0.001N
Logistic regression tests	P=0.017N	P=0.168N	P=0.036N
Cochran-Armitage test	P=0.118N		
Fisher exact test		P=0.186N	P=0.186N
All Organs: Mononuclear Cell Leukemia			
Overall rates	4/50 (8%)	2/20 (10%)	6/20 (30%)
Adjusted rates	19.8%	53.8%	49.2%
Terminal rates	0/2 (0%)	1/2 (50%)	3/8 (38%)
First incidence (days)	605	604	651
Life table tests	P=0.352	P=0.668	P=0.394
Logistic regression tests	P=0.046	P=0.594	P=0.060
Cochran-Armitage test	P=0.018		
Fisher exact test		P=0.556	P=0.027
All Organs: Benign Neoplasms			
Overall rates	45/50 (90%)	17/20 (85%)	18/20 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	2/2 (100%)	2/2 (100%)	8/8 (100%)
First incidence (days)	45	507	540
Life table tests	P<0.001N	P=0.131N	P=0.001N
Logistic regression tests	P=0.365N	P=0.339N	P=0.565N
Cochran-Armitage test	P=0.527N		
Fisher exact test		P=0.412N	P=0.652N
All Organs: Malignant Neoplasms			
Overall rates	9/50 (18%)	3/20 (15%)	7/20 (35%)
Adjusted rates	66.8%	56.3%	54.3%
Terminal rates	1/2 (50%)	1/2 (50%)	3/8 (38%)
First incidence (days)	444	455	651
Life table tests	P=0.369N	P=0.370N	P=0.433N
Logistic regression tests	P=0.141	P=0.519N	P=0.157
Cochran-Armitage test	P=0.113		
Fisher exact test		P=0.534N	P=0.114
All Organs: Benign or Malignant Neoplasms			
Overall rates	46/50 (92%)	18/20 (90%)	19/20 (95%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	2/2 (100%)	2/2 (100%)	8/8 (100%)
First incidence (days)	45	455	540
Life table tests	P=0.002N	P=0.162N	P=0.002N
Logistic regression tests	P=0.609N	P=0.488N	P=0.677
Cochran-Armitage test	P=0.468		
Fisher exact test		P=0.556N	P=0.556

TABLE E3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Evaluation of 3,4-Dihydrocoumarin: 2-Year 600 mg/kg Dose Group versus Stop-Exposure 600 mg/kg Dose Groups (continued)

[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 after adjustment for intercurrent mortality.
[c] Observed incidence at terminal kill.
[d] Beneath the 24-month exposure group incidence are the P values associated with the trend test. Beneath the 15-month and 9-month exposure group incidences are the P values corresponding to pairwise comparisons between the 24-month exposure group and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin[a]

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Disposition Summary			
Animals initially in study	30	40	30
9-Month interim evaluation	19	20	
15-Month interim evaluation	10		10
Early deaths			
Moribund		6	10
Accidental deaths	1	1	
Natural deaths		5	8
Survivors			
Died last week of study		1	
Terminal sacrifice	30	7	2
Animals examined microscopically	30	39	30
9-Month Interim Evaluation			
Alimentary System			
Liver	(19)	(19)	
Developmental malformation		1 (5%)	
Fatty change	10 (53%)		
Necrosis, coagulative	1 (5%)		
Bile duct, hyperplasia	2 (11%)	6 (32%)	
Kupffer cell, hyperplasia		1 (5%)	
Mesentery	(1)		
Granuloma	1 (100%)		
Pancreas	(19)	(19)	
Atrophy	2 (11%)		
Inflammation, chronic		1 (5%)	
Stomach, forestomach	(19)	(19)	
Hyperplasia, squamous		1 (5%)	
Cardiovascular System			
Heart	(19)	(19)	
Cardiomyopathy	17 (89%)	13 (68%)	
Endocrine System			
None			
General Body System			
None			
Genital System			
Prostate	(19)	(19)	
Inflammation, chronic active		4 (21%)	
Inflammation, suppurative	1 (5%)		

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
9-Month Interim Evaluation (continued)			
Genital System (continued)			
Testes	(19)	(19)	
Degeneration	1 (5%)		
Interstitial cell, hyperplasia	11 (58%)	9 (47%)	
Seminiferous tubule, degeneration		3 (16%)	
Hematopoietic System			
None			
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung	(19)	(19)	
Alveolar epithelium, hyperplasia	1 (5%)		
Special Senses System			
None			
Urinary System			
Kidney	(19)	(19)	
Nephropathy	19 (100%)	18 (95%)	
15-Month Interim Evaluation			
Alimentary System			
Liver	(10)		(10)
Clear cell focus	1 (10%)		
Fatty change	1 (10%)		
Inflammation, chronic	1 (10%)		
Bile duct, hyperplasia	4 (40%)		1 (10%)
Periductular, inflammation, chronic	1 (10%)		
Mesentery	(1)		(1)
Fat, inflammation, chronic	1 (100%)		
Fat, necrosis, chronic			1 (100%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats
in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
15-Month Evaluation (continued)			
Alimentary System (continued)			
Pancreas	(10)		(10)
Fibrosis	2 (20%)		1 (10%)
Interstitium, infiltration cellular, lymphocyte			1 (10%)
Stomach, glandular	(10)		(10)
Erosion			1 (10%)
Cardiovascular System			
Heart	(10)		(10)
Cardiomyopathy	6 (60%)		8 (80%)
Endocrine System			
Adrenal gland, medulla	(9)		(10)
Infiltration cellular, lymphocyte			1 (10%)
Pituitary gland	(9)		(10)
Pars distalis, congestion			1 (10%)
Pars distalis, cyst			2 (20%)
Pars distalis, hypertrophy	2 (22%)		
General Body System			
None			
Genital System			
Preputial gland	(10)		(10)
Abscess			1 (10%)
Inflammation, chronic			2 (20%)
Testes	(10)		(10)
Interstitial cell, hyperplasia	2 (20%)		3 (30%)
Hematopoietic System			
None			
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
15-Month Evaluation (continued)			
Respiratory System			
Lung	(10)		(10)
Alveolar epithelium, hyperplasia	1 (10%)		
Alveolus, inflammation, suppurative	1 (10%)		
Nose	(10)		(10)
Inflammation, chronic	3 (30%)		
Inflammation, suppurative			2 (20%)
Lumen, fungus	3 (30%)		
Special Senses System			
None			
Urinary System			
Kidney	(10)		(10)
Nephropathy	10 (100%)		10 (100%)
Stop-Exposure Evaluation[b]			
Alimentary System			
Intestine large, colon	(44)	(13)	(17)
Polyarteritis		1 (8%)	
Intestine large, rectum	(44)	(16)	(18)
Polyarteritis		1 (6%)	
Intestine small, jejunum	(41)	(14)	(19)
Diverticulum			1 (5%)
Liver	(49)	(19)	(19)
Angiectasis			1 (5%)
Basophilic focus	1 (2%)		
Clear cell focus	3 (6%)		
Congestion	1 (2%)		
Cytologic alterations	1 (2%)		
Developmental malformation	6 (12%)		1 (5%)
Ectasia			1 (5%)
Fatty change	9 (18%)	2 (11%)	1 (5%)
Inflammation, chronic	5 (10%)		
Inflammation, suppurative		2 (11%)	1 (5%)
Mixed cell focus	1 (2%)		
Necrosis, coagulative		2 (11%)	
Bile duct, hyperplasia	24 (49%)	2 (11%)	1 (5%)
Centrilobular, necrosis, coagulative	2 (4%)		
Hepatocyte, hyperplasia		1 (5%)	
Periductular, fibrosis	7 (14%)		
Periportal, necrosis, coagulative	1 (2%)		
Periportal, pigmentation, hemosiderin	1 (2%)		

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Stop-Exposure Evaluation (continued)			
Alimentary System (continued)			
Mesentery	(17)	(3)	
Polyarteritis		1 (33%)	
Fat, inflammation, chronic	1 (6%)		
Fat, inflammation, granulomatous	1 (6%)		
Fat, inflammation, suppurative	1 (6%)		
Fat, necrosis, coagulative	11 (65%)	3 (100%)	
Pancreas	(49)	(19)	(20)
Atrophy	7 (14%)		1 (5%)
Hyperplasia			3 (15%)
Polyarteritis		1 (5%)	
Acinar cell, hyperplasia	1 (2%)		
Stomach, forestomach	(47)	(19)	(20)
Cyst epithelial inclusion	1 (2%)		
Hyperplasia, squamous	3 (6%)	2 (11%)	1 (5%)
Inflammation, chronic	3 (6%)	2 (11%)	4 (20%)
Inflammation, suppurative	1 (2%)		
Ulcer	4 (9%)	2 (11%)	4 (20%)
Stomach, glandular	(46)	(18)	(20)
Erosion	1 (2%)		1 (5%)
Inflammation, chronic	1 (2%)		
Mineralization		1 (6%)	5 (25%)
Polyarteritis		1 (6%)	
Ulcer			1 (5%)
Tongue		(1)	
Parenchyma, edema		1 (100%)	
Cardiovascular System			
Blood vessel		(3)	(4)
Aorta, mineralization		1 (33%)	2 (50%)
Pulmonary artery, mineralization			1 (25%)
Heart	(50)	(20)	(20)
Cardiomyopathy	36 (72%)	8 (40%)	9 (45%)
Necrosis, Zenker's		1 (5%)	1 (5%)
Polyarteritis		1 (5%)	
Artery, mineralization			1 (5%)
Atrioventricular valve, fibrosis		1 (5%)	
Atrium, thrombosis		1 (5%)	
Valve, fibrosis		1 (5%)	
Endocrine System			
Adrenal gland, cortex	(50)	(20)	(20)
Basophilic focus	1 (2%)		
Clear cell focus		1 (5%)	
Cytoplasmic alteration		1 (5%)	
Vacuolization cytoplasmic		1 (5%)	1 (5%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Stop-Exposure Eevaluation (continued)			
Endocrine System (continued)			
Adrenal gland, medulla	(50)	(20)	(20)
Cyst	1 (2%)		
Hyperplasia	3 (6%)	1 (5%)	1 (5%)
Necrosis, coagulative	1 (2%)		
Necrosis, liquifactive			1 (5%)
Parathyroid gland	(47)	(18)	(18)
Hyperplasia		6 (33%)	9 (50%)
Pituitary gland	(49)	(18)	(18)
Pars distalis, cyst	2 (4%)		1 (6%)
Pars distalis, cyst multilocular	1 (2%)		
Pars distalis, hemorrhage, acute			1 (6%)
Pars distalis, hyperplasia	2 (4%)		
Thyroid gland	(50)	(18)	(18)
Polyarteritis		1 (6%)	
C-cell, hyperplasia	2 (4%)	1 (6%)	1 (6%)
Follicle, cyst		1 (6%)	1 (6%)
Follicle, hyperplasia	1 (2%)		
General Body System			
None			
Genital System			
Coagulating gland	(2)		
Inflammation, suppurative	1 (50%)		
Lumen, dilatation	1 (50%)		
Preputial gland	(47)	(20)	(20)
Abscess		1 (5%)	
Hyperplasia	3 (6%)		2 (10%)
Inflammation, chronic active	1 (2%)		
Inflammation, suppurative	4 (9%)	1 (5%)	3 (15%)
Polyarteritis		1 (5%)	
Duct, dilatation		1 (5%)	
Duct, inflammation, chronic			1 (5%)
Duct, inflammation, suppurative			1 (5%)
Prostate	(45)	(20)	(20)
Hyperplasia	1 (2%)		
Inflammation, suppurative	9 (20%)	3 (15%)	3 (15%)
Seminal vesicle	(49)	(17)	(20)
Inflammation, suppurative	3 (6%)		
Lumen, dilatation	1 (2%)		
Testes	(49)	(20)	(20)
Atrophy	3 (6%)		1 (5%)
Infiltration cellular, lymphocyte	1 (2%)		
Interstitial cell, hyperplasia		1 (5%)	1 (5%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats
in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Stop-Exposure Evaluation (continued)			
Hematopoietic System			
Lymph node	(51)	(20)	(20)
Hyperplasia, plasma cell		1 (5%)	
Mediastinal, hemorrhage, acute			1 (5%)
Mediastinal, polyarteritis		1 (5%)	
Renal, congestion			1 (5%)
Renal, hyperplasia, macrophage		1 (5%)	
Renal, pigmentation, hemosiderin		1 (5%)	
Lymph node, mandibular	(51)	(19)	(18)
Angiectasis			1 (6%)
Hyperplasia, lymphoid	2 (4%)		
Hyperplasia, plasma cell	2 (4%)		
Lymph node, mesenteric	(50)	(18)	(20)
Angiectasis			1 (5%)
Pigmentation, hemosiderin	1 (2%)		
Spleen	(49)	(19)	(20)
Atrophy	2 (4%)		
Congestion	4 (8%)	1 (5%)	
Developmental malformation	1 (2%)		
Fibrosis			1 (5%)
Hyperplasia, lymphoid	1 (2%)	1 (5%)	
Inflammation, chronic	1 (2%)		
Pigmentation, hemosiderin		1 (5%)	
Thymus	(46)	(18)	(19)
Hemorrhage		1 (6%)	
Integumentary System			
Mammary gland	(46)	(19)	(15)
Galactocele			1 (7%)
Lactation		1 (5%)	
Skin	(51)	(20)	(20)
Cyst epithelial inclusion	1 (2%)		1 (5%)
Hemorrhage			1 (5%)
Inflammation, chronic active		1 (5%)	
Polyarteritis		1 (5%)	
Musculoskeletal System			
Bone	(51)	(20)	(20)
Degeneration	1 (2%)		
Degeneration, cystic			1 (5%)
Fibrous osteodystrophy		1 (5%)	
Skeletal muscle		(1)	
Polyarteritis		1 (100%)	

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Stop-Exposure Evaluation (continued)			
Nervous System			
Brain	(48)	(19)	(18)
Hydrocephalus		1 (5%)	
Polyarteritis		1 (5%)	
Hypothalamus, compression			1 (6%)
Thalamus, compression	2 (4%)		
Peripheral nerve	(2)		
Degeneration, secondary wallerian	1 (50%)		
Respiratory System			
Lung	(50)	(20)	(20)
Polyarteritis		1 (5%)	
Alveolar epithelium, hyperplasia	4 (8%)		1 (5%)
Alveolus, congestion			1 (5%)
Alveolus, edema	1 (2%)	1 (5%)	1 (5%)
Alveolus, hemorrhage			1 (5%)
Alveolus, inflammation, chronic	2 (4%)		1 (5%)
Alveolus, inflammation, suppurative	2 (4%)		
Bronchiole, inflammation, suppurative	1 (2%)		1 (5%)
Nose	(50)	(20)	(18)
Fungus	1 (2%)		
Metaplasia, squamous	1 (2%)		
Lumen, foreign body	1 (2%)		
Lumen, fungus	3 (6%)		1 (6%)
Lumen, inflammation, suppurative	8 (16%)	1 (5%)	1 (6%)
Mucosa, inflammation, suppurative	1 (2%)		2 (11%)
Mucosa, metaplasia, squamous			1 (6%)
Mucosa, septum, inflammation, chronic	1 (2%)		
Trachea	(51)	(20)	(20)
Inflammation, suppurative		1 (5%)	
Special Senses System			
Eye	(1)	(1)	
Anterior chamber, hemorrhage, chronic	1 (100%)		
Lens, cataract		1 (100%)	
Retina, degeneration		1 (100%)	
Urinary System			
Kidney	(50)	(20)	(20)
Nephropathy	50 (100%)	19 (95%)	20 (100%)
Polyarteritis		1 (5%)	
Cortex, cyst	3 (6%)		3 (15%)
Pelvis, inflammation, suppurative	2 (4%)		
Renal tubule, hyperplasia		1 (5%)	2 (10%)
Renal tubule, hyperplasia, cystic	1 (2%)		
Renal tubule, hyperplasia, oncocytic	1 (2%)		
Ureter	(1)		
Mucosa, inflammation, suppurative	1 (100%)		

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats
in the 9-Month and 15-Month Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	600 mg/kg (9-month exposure)	600 mg/kg (15-month exposure)
Stop-Exposure Evaluation (continued)			
Urinary System (continued)			
Urinary bladder	(49)	(20)	(20)
Mucosa, inflammation, suppurative	1 (2%)		
Submucosa, inflammation, suppurative	1 (2%)		

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Vehicle controls in stop-exposure evaluation are 2-year core study vehicle controls.

APPENDIX F
GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL 282
CHINESE HAMSTER OVARY CELL CYTOGENETICS TEST PROTOCOLS 282
MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL 283
RESULTS 284
TABLE F1 Mutagenicity of 3,4-Dihydrocoumarin in *Salmonella typhimurium* 285
TABLE F2 Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 3,4-Dihydrocoumarin 287
TABLE F3 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 3,4-Dihydrocoumarin 289
TABLE F4 Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Treated with 3,4-Dihydrocoumarin for 13 Weeks by Gavage 290

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). 3,4-Dihydrocoumarin was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls, and of at least five doses of 3,4-dihydrocoumarin. The high dose was limited by toxicity. All positive trials were repeated under the conditions that elicited the positive response. If no positive responses were seen, all negative trials were repeated.

In this test, a positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants that was not dose related, not reproducible, or was of insufficient magnitude to support a determination of mutagenicity. A response is judged negative when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS TEST PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). 3,4-Dihydrocoumarin 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. Cell 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 3,4-dihydrocoumarin; 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 3,4-dihydrocoumarin 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 3,4-dihydrocoumarin was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2.5 hours. Cells were harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with 3,4-dihydrocoumarin, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no 3,4-dihydrocoumarin, 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. Because significant chemical-induced cell cycle delay was seen at the top dose with S9, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves (Galloway *et al.*, 1987). For individual doses, an SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.05$) 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 3,4-dihydrocoumarin for 10 hours; Colcemid was added and incubation continued for 2 hours. The cells were harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with 3,4-dihydrocoumarin 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. Harvesting and staining were the same as for cells treated without S9.

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

Chromosomal aberration data are presented as percentage of cells with aberrations. Statistical analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) are considered weak evidence for a positive response; 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).

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 end of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol. They were later 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) for 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

3,4-Dihydrocoumarin (10 to 6,666 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983; Table F1). In cytogenetic tests with Chinese hamster ovary (CHO) cells, 3,4-dihydrocoumarin (effective doses, 50 to 300 μg/mL) induced a dose-related increase in SCE in the absence of S9; with S9, a significant increase in SCE was observed only at the highest doses tested (1,600 and 2,000 μg/mL) in each of two trials (Table F2); the response in the second trial with S9 was dose-related. In the second SCE trial with S9, cytotoxicity was apparent at the 2,000 μg/mL dose level and only 36 cells could be scored. 3,4-Dihydrocoumarin did not induce chromosomal aberrations in CHO cells, at doses up to 500 μg/mL without S9 and up to 1,600 μg/mL with S9 (Table F3). No increases in the frequencies of micronucleated normochromatic erythrocytes were noted in peripheral blood samples obtained from male and female mice at the end of the 13-week toxicity study (Table F4). The elevated micronucleated erythrocyte frequency seen in male mice in the high-dose group was based on counts obtained from only 2 animals (8 out of 10 mice died at this dose). These data were not included in the overall analysis.

In conclusion, 3,4-dihydrocoumarin does not appear to be mutagenic and does not induce chromosomal damage *in vitro* or *in vivo*. However, 3,4-dihydrocoumarin induced SCEs in CHO cells *in vitro*.

TABLE F1
Mutagenicity of 3,4-Dihydrocoumarin 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	121 ± 7.8	128 ± 6.5	114 ± 7.0	137 ± 8.4	120 ± 8.1	145 ± 5.5
	10	126 ± 3.8	119 ± 12.7				
	33	130 ± 6.2	121 ± 11.0		118 ± 6.9		133 ± 4.4
	100	138 ± 7.0	130 ± 7.2	114 ± 4.5	121 ± 9.5	104 ± 2.1	122 ± 7.7
	333	103 ± 0.6	121 ± 7.0	98 ± 2.8	93 ± 4.7	122 ± 12.3	125 ± 3.8
	1,000	122 ± 8.5[c]	116 ± 7.8[c]	95 ± 0.7	116 ± 5.0	132 ± 4.6	128 ± 6.6
	3,333			102 ± 11.7		108 ± 8.1[c]	121 ± 11.2[c]
	4,500				73 ± 7.2[c]		
	6,666			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		2,115 ± 43.6	1,410 ± 41.6	1,311 ± 94.2	2,282 ± 54.3	1,278 ± 89.2	1,197 ± 10.1
TA1535	0	26 ± 4.7	26 ± 1.5	11 ± 0.9	11 ± 2.0	14 ± 0.9	14 ± 2.3
	10	22 ± 3.2	22 ± 2.7				
	33	21 ± 1.8	22 ± 1.7		11 ± 1.2		16 ± 2.6
	100	22 ± 3.2	26 ± 1.2	11 ± 1.5	9 ± 1.5	11 ± 0.9	9 ± 1.5
	333	25 ± 3.8	17 ± 2.4	10 ± 2.0	11 ± 1.2	15 ± 2.3	11 ± 0.9
	1,000	18 ± 1.2[c]	18 ± 2.8[c]	14 ± 1.5	9 ± 3.4	7 ± 1.0	9 ± 1.5
	3,333			11 ± 1.9		12 ± 4.4	7 ± 2.6
	4,500				5 ± 2.0[c]		
	6,666			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,354 ± 3.2	1,103 ± 11.7	147 ± 10.5	170 ± 4.8	103 ± 8.1	107 ± 13.7
TA1537	0	8 ± 2.6	8 ± 1.5	9 ± 1.2	10 ± 0.9	10 ± 2.6	6 ± 3.0
	10	10 ± 2.3	7 ± 0.7				
	33	9 ± 0.6	6 ± 1.8		10 ± 1.5		8 ± 2.4
	100	8 ± 0.9	9 ± 1.5	11 ± 2.6	9 ± 1.7	10 ± 2.3	8 ± 1.2
	333	9 ± 1.7	7 ± 3.0	9 ± 1.8	10 ± 2.0	9 ± 0.6	6 ± 2.7
	1,000	7 ± 1.8[c]	7 ± 1.7[c]	11 ± 0.6	8 ± 2.3	10 ± 0.6	8 ± 1.2
	3,333			10 ± 1.0		6 ± 0.7	9 ± 1.9
	4,500				4 ± 0.7[c]		
	6,666			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		399 ± 34.2	245 ± 20.1	162 ± 9.8	243 ± 26.8	109 ± 11.4	86 ± 2.6
TA98	0	25 ± 1.2	19 ± 0.3	34 ± 2.1	34 ± 3.8	36 ± 0.5	36 ± 1.2
	10	27 ± 1.5	23 ± 1.0				
	33	22 ± 4.0	18 ± 2.6		37 ± 3.0		30 ± 7.0
	100	22 ± 2.4	19 ± 2.1	39 ± 5.0	38 ± 2.1	33 ± 2.9	29 ± 3.8
	333	25 ± 1.9	18 ± 2.0	29 ± 0.9	31 ± 4.3	37 ± 2.1	35 ± 4.4
	1,000	21 ± 3.0	17 ± 4.2	26 ± 0.3	32 ± 1.5	32 ± 1.5	30 ± 1.7
	3,333			27 ± 1.8		28 ± 2.7[c]	30 ± 2.6
	4,500				16 ± 1.7[c]		
	6,666			20 ± 1.5[c]		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,445 ± 20.2	1,754 ± 64.6	1,471 ± 16.7	2,640 ± 184.3	1,402 ± 27.7	1,108 ± 84.4

TABLE F1
Mutagenicity of 3,4-Dihydrocoumarin in *Salmonella typhimurium* (continued)

[a] Study performed at EG&G Mason Research Institute. The detailed protocol and these data are presented in Haworth *et al.* (1983). 0 μg/plate dose is the solvent control.
[b] Revertants are presented as mean ± the standard error from three plates.
[c] Slight toxicity
[d] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 3,4-Dihydrocoumarin[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	1,050	491	0.46	9.8	26.5	
Mitomycin-C	0.0005	50	1,049	574	0.54	11.5	26.5	17.02
	0.0050	10	210	329	1.56	32.9	26.5	235.04
3,4-Dihydrocoumarin	5	50	1,051	414	0.39	8.3	26.5	-15.76
	16	50	1,048	415	0.39	8.3	26.5	-15.32
	50	50	1,048	506	0.48	10.1	26.5	3.25
	160	50	1,048	589	0.56	11.8	26.5	20.19°
	500	0					26.5	
								P≤0.001[c]
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,048	427	0.40	8.5	26.0	
Mitomycin-C	0.0005	50	1,050	569	0.54	11.4	26.0	33.00
	0.0050	10	209	329	1.57	32.9	26.0	286.35
3,4-Dihydrocoumarin	50	50	1,046	523	0.50	10.5	26.0	22.72°
	100	50	1,048	528	0.50	10.6	26.0	23.65°
	160	50	1,049	563	0.53	11.3	26.0	31.72°
	300	50	1,051	780	0.74	15.6	31.0[d]	82.15°
								P≤0.001

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 3,4-Dihydrocoumarin
(continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
+S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,046	518	0.49	10.4	26.0	
Cyclophosphamide	0.1	50	1,046	629	0.60	12.6	26.0	21.43
	0.6	10	209	274	1.31	27.4	26.0	164.74
3,4-Dihydrocoumarin	50	50	1,049	468	0.44	9.4	26.0	-9.91
	160	50	1,049	526	0.50	10.5	26.0	1.25
	500	50	1,042	520	0.49	10.4	26.0	0.77
	1,600	50	1,037	667	0.64	13.3	26.0	29.88*
								P≤0.001
Trial 2								
Summary: Weak positive								
Dimethylsulfoxide		50	1,046	514	0.49	10.3	26.0	
Cyclophosphamide	0.15	50	1,051	731	0.69	14.6	26.0	41.54
	0.60	10	210	238	1.13	23.8	26.0	130.64
3,4-Dihydrocoumarin	500	50	1,048	536	0.51	10.7	26.0	4.08
	1,000	50	1,049	544	0.51	10.9	26.0	5.53
	1,600	50	1,048	593	0.56	11.9	26.0	15.15
	2,000	36[e]	754	551	0.73	15.3	31.0[d]	48.71*
								P≤0.001

* Positive (≥20% increase over solvent control)
[a] Study performed at Environmental Health Research & Testing. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987).
[b] SCEs/chromosome of culture exposed to 3,4-dihydrocoumarin 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
[d] Because 3,4-dihydrocoumarin induced a significant cell cycle delay, incubation times were lengthened as needed to ensure a sufficient number of scorable second-division metaphase cells.
[e] Only 36 cells could be scored due to the toxicity of 3,4-dihydrocoumarin.

TABLE F3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 3,4-Dihydrocoumarin[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Trial 1 – Harvest time: 12.0 hours Summary: Negative					Trial 1 – Harvest time: 13.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	3	0.02	1.5		200	1	0.01	0.5
Mitomycin-C					Cyclophosphamide				
0.0625	200	30	0.15	13.0	2.5	200	36	0.18	16.5
0.2500	50	27	0.54	34.0	5.0	50	11	0.22	22.0
3,4-Dihydrocoumarin					3,4-Dihydrocoumarin				
100	200	3	0.02	1.5	500	200	3	0.02	1.5
160	200	4	0.02	1.5	1,000	200	2	0.01	1.0
500	200	3	0.02	1.5	1,600	200	5	0.03	2.5
				P=0.500[b]					P=0.077

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

TABLE F4
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Treated with 3,4-Dihydrocoumarin for 13 Weeks by Gavage[a]

Dose (mg/kg)	Micronucleated Normochromatic Erythrocytes/1,000 Cells[b]	Number of Mice
Male		
0	0.49 ± 0.10	9
400	0.55 ± 0.12	9
800	0.54 ± 0.09	10
1,600	1.78*	2
Female		
0	0.32 ± 0.07	10
400	0.42 ± 0.08	10
800	0.41 ± 0.10	10
1,600	0.27 ± 0.11	4

* Significantly different from control ($P \leq 0.01$)
[a] Values are presented as mean ± standard error. Micronucleus frequency of each treated group was compared to the concurrent control by Student's *t*-test.
[b] 10,000 normochromatic erythrocytes scored per animal.

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 3,4-Dihydrocoumarin 292

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 Evaluation of 3,4-Dihydrocoumarin 294

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 Evaluation of 3,4-Dihydrocoumarin 295

TABLE G4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 296

TABLE G5 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of 3,4-Dihydrocoumarin 297

TABLE G6 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 299

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Male						
n	9	10	10	10	10	8
Necropsy body wt	321 ± 8	328 ± 3	325 ± 6	327 ± 9	317 ± 7	279 ± 8**
Brain						
Absolute	1.83 ± 0.02	1.82 ± 0.02	1.83 ± 0.02	1.82 ± 0.03	1.80 ± 0.03	1.75 ± 0.02
Relative	5.72 ± 0.13	5.56 ± 0.09	5.65 ± 0.12	5.59 ± 0.10	5.72 ± 0.16	6.31 ± 0.13**
Heart						
Absolute	1.063 ± 0.023	1.078 ± 0.024	1.090 ± 0.027	1.070 ± 0.039	1.112 ± 0.025	1.000 ± 0.033
Relative	3.33 ± 0.11	3.29 ± 0.08	3.36 ± 0.09	3.27 ± 0.11	3.52 ± 0.11	3.59 ± 0.10
R. Kidney						
Absolute	1.09 ± 0.02	1.13 ± 0.02	1.16 ± 0.04	1.19 ± 0.03*	1.27 ± 0.04**	1.28 ± 0.04**
Relative	3.40 ± 0.09	3.44 ± 0.07	3.56 ± 0.08	3.66 ± 0.10	4.03 ± 0.11**	4.58 ± 0.07**
Liver						
Absolute	9.07 ± 0.21	9.65 ± 0.18	10.00 ± 0.30	10.27 ± 0.36*	10.89 ± 0.35**	12.04 ± 0.54**
Relative	28.3 ± 0.5	29.4 ± 0.6	30.8 ± 0.8**	31.3 ± 0.6**	34.3 ± 0.6**	43.1 ± 0.9**
Lungs						
Absolute	1.49 ± 0.05	1.44 ± 0.05	1.39 ± 0.06	1.38 ± 0.04	1.36 ± 0.04	1.39 ± 0.06
Relative	4.66 ± 0.15	4.40 ± 0.17	4.28 ± 0.16	4.24 ± 0.12	4.29 ± 0.13	4.98 ± 0.15
R. Testis						
Absolute	1.43 ± 0.03	1.48 ± 0.02	1.47 ± 0.03	1.44 ± 0.05	1.42 ± 0.03	1.31 ± 0.01*
Relative	4.47 ± 0.15	4.51 ± 0.04	4.55 ± 0.06	4.41 ± 0.12	4.48 ± 0.08	4.70 ± 0.11
Thymus						
Absolute	0.254 ± 0.013	0.230 ± 0.011	0.254 ± 0.016	0.278 ± 0.018[b]	0.240 ± 0.011	0.228 ± 0.013
Relative	0.79 ± 0.04	0.70 ± 0.03	0.78 ± 0.05	0.86 ± 0.05[b]	0.76 ± 0.03	0.82 ± 0.04

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Female						
n	10	10	10	10	10	5
Necropsy body wt	182 ± 2	187 ± 3	194 ± 2°	190 ± 3°	192 ± 3°	195 ± 3°
Brain						
Absolute	1.72 ± 0.02	1.73 ± 0.02	1.72 ± 0.02	1.66 ± 0.02	1.72 ± 0.02	1.62 ± 0.02°°
Relative	9.42 ± 0.12	9.29 ± 0.22	8.88 ± 0.11°	8.76 ± 0.11°	8.98 ± 0.14°	8.30 ± 0.22°°
Heart						
Absolute	0.718 ± 0.015	0.703 ± 0.012	0.734 ± 0.017	0.712 ± 0.017	0.747 ± 0.019	0.767 ± 0.026
Relative	3.95 ± 0.10	3.77 ± 0.08	3.79 ± 0.08	3.74 ± 0.07	3.89 ± 0.08	3.94 ± 0.16
R. Kidney						
Absolute	0.634 ± 0.013	0.646 ± 0.012	0.666 ± 0.011	0.655 ± 0.019[b]	0.758 ± 0.010°°	0.885 ± 0.012°°
Relative	3.47 ± 0.04	3.46 ± 0.05	3.44 ± 0.07	3.44 ± 0.07[b]	3.95 ± 0.04°°	4.54 ± 0.05°°
Liver						
Absolute	4.93 ± 0.12	4.97 ± 0.15	5.19 ± 0.12	5.22 ± 0.16	6.19 ± 0.14°°	8.05 ± 0.28°°
Relative	27.0 ± 0.6	26.6 ± 0.6	26.7 ± 0.4	27.4 ± 0.6	32.3 ± 0.6°°	41.3 ± 1.3°°
Lungs						
Absolute	1.00 ± 0.05[b]	1.06 ± 0.03	1.07 ± 0.03	1.01 ± 0.02	1.12 ± 0.03	1.10 ± 0.03
Relative	5.46 ± 0.26[b]	5.67 ± 0.14	5.51 ± 0.12	5.30 ± 0.11	5.83 ± 0.17	5.63 ± 0.22
Thymus						
Absolute	0.236 ± 0.015	0.234 ± 0.012	0.255 ± 0.013	0.255 ± 0.007[b]	0.254 ± 0.007	0.262 ± 0.021
Relative	1.30 ± 0.10	1.25 ± 0.06	1.31 ± 0.06	1.34 ± 0.04[b]	1.33 ± 0.05	1.35 ± 0.13

° 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 Evaluation of 3,4-Dihydrocoumarin[a]

	Vehicle Control	600 mg/kg
n	19	19
Necropsy body wt	475 ± 8	425 ± 10**
Brain		
Absolute	2.095 ± 0.019	2.137 ± 0.016
Relative	4.44 ± 0.10	5.09 ± 0.14**
L. Kidney		
Absolute	1.500 ± 0.025	1.917 ± 0.056**[b]
Relative	3.17 ± 0.06	4.54 ± 0.08**[b]
R. Kidney		
Absolute	1.489 ± 0.019	1.937 ± 0.119**
Relative	3.15 ± 0.05	4.55 ± 0.24**
Liver		
Absolute	15.705 ± 0.341	17.211 ± 0.512*
Relative	33.06 ± 0.40	40.50 ± 0.60**

* 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=18

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 Evaluation of 3,4-Dihydrocoumarin[a]

	Vehicle Control	600 mg/kg
n	10	10
Necropsy body wt	543 ± 10	472 ± 7**
Brain		
Absolute	2.030 ± 0.021	1.990 ± 0.031
Relative	3.75 ± 0.07	4.223 ± 0.09**
L. Kidney		
Absolute	1.760 ± 0.065	2.240 ± 0.045**
Relative	3.24 ± 0.09	4.74 ± 0.07**
R. Kidney		
Absolute	1.660 ± 0.037	2.160 ± 0.043**
Relative	3.06 ± 0.05	4.58 ± 0.08**
Liver		
Absolute	17.840 ± 0.497	20.070 ± 0.502**
Relative	32.81 ± 0.41	42.46 ± 0.59**

** 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 G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Male				
n	9	10	10	10
Necropsy body wt	507 ± 8	536 ± 13	507 ± 13	478 ± 15
Brain				
Absolute	2.067 ± 0.041	2.050 ± 0.027	2.010 ± 0.023	2.040 ± 0.031
Relative	4.08 ± 0.07	3.85 ± 0.10	3.99 ± 0.10	4.30 ± 0.14
L. Kidney				
Absolute	1.667 ± 0.037	1.890 ± 0.055**	1.890 ± 0.043**	2.240 ± 0.056**
Relative	3.29 ± 0.05	3.53 ± 0.06*	3.74 ± 0.06**	4.70 ± 0.08**
R. Kidney				
Absolute	1.622 ± 0.040	1.880 ± 0.055*	1.870 ± 0.060*	2.150 ± 0.050**
Relative	3.20 ± 0.08	3.51 ± 0.06	3.69 ± 0.07*	4.50 ± 0.05**
Liver				
Absolute	16.878 ± 0.668	20.100 ± 0.497**	19.450 ± 0.577**	21.150 ± 0.734**
Relative	33.24 ± 0.93	37.59 ± 0.73**	38.39 ± 0.44**	44.17 ± 0.39**
Female				
n	10	9	10	9
Necropsy body wt	293 ± 7	316 ± 11	301 ± 6	274 ± 7
Brain				
Absolute	1.850 ± 0.027	1.878 ± 0.028	1.850 ± 0.027	1.844 ± 0.024
Relative	6.34 ± 0.14	6.00 ± 0.24	6.16 ± 0.15	6.76 ± 0.22
L. Kidney				
Absolute	0.890 ± 0.018	1.011 ± 0.020**	1.050 ± 0.027**	1.156 ± 0.044**
Relative	3.05 ± 0.04	3.23 ± 0.14	3.49 ± 0.10**	4.21 ± 0.10**
R. Kidney				
Absolute	0.860 ± 0.037	0.956 ± 0.018	1.000 ± 0.021**	1.111 ± 0.051**
Relative	2.94 ± 0.09	3.05 ± 0.11	3.33 ± 0.09**	4.04 ± 0.12**
Liver				
Absolute	8.480 ± 0.219	9.811 ± 0.345**	10.090 ± 0.244**	10.011 ± 0.407**
Relative	29.01 ± 0.55	31.07 ± 0.67*	33.50 ± 0.56**	36.40 ± 0.82**

* 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).

TABLE G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg	1,600 mg/kg
Male						
n	9	9	10	10	10	2
Necropsy body wt	24.7 ± 0.7	25.6 ± 0.7	25.4 ± 0.9	24.6 ± 0.7	25.7 ± 0.6	23.0 ± 1.0
Brain						
Absolute	0.411 ± 0.011	0.418 ± 0.006	0.419 ± 0.005	0.420 ± 0.005	0.438 ± 0.022	0.403 ± 0.013
Relative	16.7 ± 0.2	16.4 ± 0.4	16.6 ± 0.5	17.2 ± 0.5	17.1 ± 0.7	17.5 ± 0.2
Heart						
Absolute	0.151 ± 0.009	0.144 ± 0.009	0.163 ± 0.008	0.152 ± 0.006	0.154 ± 0.005	0.134 ± 0.003
Relative	6.08 ± 0.26	5.61 ± 0.24	6.44 ± 0.28	6.21 ± 0.27	5.98 ± 0.12	5.84 ± 0.38
R. Kidney						
Absolute	0.214 ± 0.007	0.219 ± 0.008	0.232 ± 0.010	0.221 ± 0.009	0.212 ± 0.006	0.230 ± 0.009
Relative	8.67 ± 0.11	8.55 ± 0.17	9.11 ± 0.20	9.00 ± 0.26	8.26 ± 0.18	10.00 ± 0.04°
Liver						
Absolute	0.971 ± 0.043	1.019 ± 0.035	1.061 ± 0.050	1.016 ± 0.036	1.082 ± 0.031	1.189 ± 0.063°
Relative	39.3 ± 1.3	39.9 ± 1.0	41.7 ± 1.2	41.3 ± 0.9	42.1 ± 0.8	51.7 ± 0.5°°
Lungs						
Absolute	0.182 ± 0.007	0.180 ± 0.007	0.193 ± 0.010[b]	0.181 ± 0.006	0.187 ± 0.008	0.161 ± 0.010
Relative	7.37 ± 0.26	7.06 ± 0.22	7.54 ± 0.34[b]	7.40 ± 0.29	7.27 ± 0.22	6.97 ± 0.11
R. Testis						
Absolute	0.105 ± 0.005	0.112 ± 0.002	0.110 ± 0.002	0.110 ± 0.002	0.110 ± 0.004	0.112 ± 0.006
Relative	4.28 ± 0.22	4.39 ± 0.08	4.36 ± 0.18	4.48 ± 0.10	4.29 ± 0.14	4.87 ± 0.05
Thymus						
Absolute	0.026 ± 0.002	0.031 ± 0.002	0.032 ± 0.002	0.026 ± 0.002	0.035 ± 0.002°	0.029 ± 0.003
Relative	1.07 ± 0.09	1.21 ± 0.07	1.26 ± 0.09	1.03 ± 0.08	1.38 ± 0.09	1.25 ± 0.16

TABLE G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg	1,600 mg/kg
Female						
n 10	10	10	10	10	5	
Necropsy body wt	20.5 ± 0.4	20.6 ± 0.5	20.5 ± 0.8	20.6 ± 0.5	21.8 ± 0.6	20.6 ± 0.2
Brain						
Absolute	0.439 ± 0.005	0.444 ± 0.008	0.435 ± 0.004	0.440 ± 0.004	0.441 ± 0.008	0.449 ± 0.010
Relative	21.4 ± 0.3	21.7 ± 0.7	21.4 ± 0.7	21.5 ± 0.5	20.3 ± 0.5	21.8 ± 0.7
Heart						
Absolute	0.123 ± 0.003	0.116 ± 0.003	0.118 ± 0.006	0.122 ± 0.005	0.126 ± 0.007	0.128 ± 0.008
Relative	6.02 ± 0.22	5.64 ± 0.19	5.73 ± 0.16	5.90 ± 0.20	5.82 ± 0.33	6.25 ± 0.45
R. Kidney						
Absolute	0.167 ± 0.003	0.161 ± 0.006	0.163 ± 0.008	0.161 ± 0.008	0.174 ± 0.005	0.183 ± 0.003
Relative	8.17 ± 0.17	7.83 ± 0.22	7.92 ± 0.17	7.81 ± 0.37	8.00 ± 0.24	8.89 ± 0.25
Liver						
Absolute	0.932 ± 0.022	0.955 ± 0.032	0.953 ± 0.038	0.988 ± 0.029	1.047 ± 0.023**	1.158 ± 0.014**
Relative	45.5 ± 1.0	46.5 ± 1.5	46.5 ± 0.6	47.9 ± 0.6	48.2 ± 1.1	56.3 ± 1.1**
Lungs						
Absolute	0.187 ± 0.008	0.179 ± 0.009	0.163 ± 0.007	0.170 ± 0.005	0.186 ± 0.011	0.181 ± 0.009
Relative	9.16 ± 0.42	8.73 ± 0.46	7.96 ± 0.27	8.27 ± 0.27	8.53 ± 0.42	8.80 ± 0.49
Thymus						
Absolute	0.038 ± 0.002	0.036 ± 0.002	0.033 ± 0.003	0.038 ± 0.002	0.037 ± 0.003	0.034 ± 0.004
Relative	1.85 ± 0.09	1.74 ± 0.11	1.62 ± 0.11	1.83 ± 0.08	1.70 ± 0.14	1.66 ± 0.21

* 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 G6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Male				
n	10	9	9	10
Necropsy body wt	51.4 ± 1.5	49.5 ± 1.6	50.3 ± 1.7	52.1 ± 1.3
Brain				
Absolute	0.490 ± 0.010	0.500 ± 0.000	0.500 ± 0.000	0.490 ± 0.010
Relative	9.59 ± 0.30	10.18 ± 0.33	10.04 ± 0.38	9.47 ± 0.35
L. Kidney				
Absolute	0.460 ± 0.043	0.422 ± 0.015	0.444 ± 0.018	0.400 ± 0.000
Relative	8.89 ± 0.68	8.59 ± 0.39	8.89 ± 0.37	7.72 ± 0.20
R. Kidney				
Absolute	0.460 ± 0.022	0.411 ± 0.011	0.444 ± 0.024	0.430 ± 0.015
Relative	8.93 ± 0.26	8.35 ± 0.27	8.85 ± 0.38	8.25 ± 0.22
Liver				
Absolute	2.270 ± 0.190	2.367 ± 0.220	2.067 ± 0.167	2.490 ± 0.131
Relative	43.87 ± 3.08	48.57 ± 5.79	40.66 ± 2.10	47.63 ± 1.90
Female				
n	9	10	9	9
Necropsy body wt	49.2 ± 3.3	53.5 ± 1.5	48.4 ± 3.7	44.3 ± 1.1
Brain				
Absolute	0.511 ± 0.011	0.500 ± 0.000	0.511 ± 0.011	0.500 ± 0.000
Relative	10.65 ± 0.52	9.40 ± 0.26	11.06 ± 0.89	11.36 ± 0.31
L. Kidney				
Absolute	0.289 ± 0.020	0.300 ± 0.000	0.289 ± 0.020	0.300 ± 0.000
Relative	5.89 ± 0.23	5.64 ± 0.16	6.02 ± 0.24	6.81 ± 0.19°°
R. Kidney				
Absolute	0.278 ± 0.022	0.300 ± 0.000	0.311 ± 0.020	0.289 ± 0.011
Relative	5.65 ± 0.28	5.64 ± 0.16	6.48 ± 0.20°	6.57 ± 0.33°
Liver				
Absolute	1.688 ± 0.181[b]	1.670 ± 0.056	1.911 ± 0.309	1.933 ± 0.053
Relative	34.55 ± 1.43[b]	31.22 ± 0.69	38.25 ± 3.16	43.71 ± 0.80°°

° 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=8

APPENDIX H
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE H1 Hematology Data for Rats in the 16-Day Gavage Study of 3,4-Dihydrocoumarin 302
TABLE H2 Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin 303
TABLE H3 Hematology and Clinical Chemistry Data for Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin 307
TABLE H4 Hematology and Clinical Chemistry Data for Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin 308
TABLE H5 Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 309
TABLE H6 Hematology Data for Mice in the 16-Day Gavage Study of 3,4-Dihydrocoumarin 311
TABLE H7 Hematology Data for Mice in the 13-Week Gavage Study of 3,4-Dihydrocoumarin 312
TABLE H8 Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin 314

TABLE H1
Hematology Data for Rats in the 16-Day Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	190 mg/kg	375 mg/kg	750 mg/kg	1,500 mg/kg
Male					
n	5	5	3	4	1[b]
Platelets ($10^3/\mu L$)	554.8 ± 28.7	645.6 ± 25.3*	650.3 ± 35.8	577.0 ± 70.7	695.0
Fibrinogen (mg/dL)	171.6 ± 5.8	165.4 ± 5.4	160.0 ± 2.0	161.0 ± 5.4	164.0
APTT (sec)	18.9 ± 2.1	17.1 ± 2.4	20.1 ± 2.4	18.2 ± 2.5	15.7
Thromboplastin time (sec)	12.1 ± 0.2	12.0 ± 0.53	12.8 ± 0.3	12.9 ± 0.3	12.60
Clotting time (min)	1.55 ± 0.05	2.25 ± 0.27	1.75 ± 0.32[c]	1.60 ± 0.26[d]	2.25
Female					
n	5	5	5	5	
Platelets ($10^3/\mu L$)	584.4 ± 21.4	641.8 ± 4.3	517.4 ± 43.8	550.0 ± 57.7	
Fibrinogen (mg/dL)	150.4 ± 3.4	147.8 ± 5.1	158.0 ± 9.2	154.8 ± 2.8	
APTT (sec)	18.5 ± 2.1	17.8 ± 2.6	18.9 ± 0.4	17.3 ± 0.9	
Thromboplastin time (sec)	12.2 ± 0.3	12.1 ± 0.2	12.2 ± 0.1[e]	12.0 ± 0.2[c]	
Clotting time (min)	1.80 ± 0.24	2.20 ± 0.20	1.45 ± 0.09	1.95 ± 0.18	

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error. APTT = activated partial thromboplastin time. No data for females receiving 1,500 mg/kg due to 100% mortality.
[b] No statistics computed due to high mortality
[c] n=4
[d] n=5
[e] n=3

TABLE H2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Male						
Hematology						
n	9	10	10	10	10	8
Hematocrit (%)	42.7 ± 0.6	40.7 ± 0.5*	41.8 ± 0.5	39.9 ± 0.7**	40.4 ± 0.6**	38.6 ± 0.3**
Hemoglobin (g/dL)	17.0 ± 0.3	16.2 ± 0.2*	16.5 ± 0.2	15.7 ± 0.3**	15.9 ± 0.3**	15.3 ± 0.1**
Erythrocytes ($10^6/\mu L$)	8.36 ± 0.11	8.07 ± 0.10	8.27 ± 0.12	7.93 ± 0.14*	7.98 ± 0.12*	7.51 ± 0.07**
Mean cell volume (fL)	51.2 ± 0.2	50.3 ± 0.3	50.7 ± 0.3	50.4 ± 0.2	50.6 ± 0.2	51.3 ± 0.2
Mean cell hemoglobin (pg)	20.3 ± 0.1	20.1 ± 0.1	20.0 ± 0.1	19.9 ± 0.1*	19.9 ± 0.1	20.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	39.8 ± 0.2	39.8 ± 0.2	39.5 ± 0.2	39.4 ± 0.2	39.3 ± 0.2	39.6 ± 0.2
Platelets ($10^3/\mu L$)	584.7 ± 13.5	572.6 ± 9.1	557.0 ± 12.1	551.2 ± 14.4	538.2 ± 9.3**	524.4 ± 16.4**
Leukocytes ($10^3/\mu L$)	8.80 ± 0.53	7.67 ± 0.45	8.19 ± 0.55	7.44 ± 0.51	7.28 ± 0.38	6.83 ± 0.31**
Segmented neutrophils ($10^3/\mu L$)	1.42 ± 0.19	1.17 ± 0.15	1.72 ± 0.18	1.23 ± 0.13	1.36 ± 0.13	1.28 ± 0.09
Lymphocytes ($10^3/\mu L$)	7.01 ± 0.36	6.13 ± 0.40	6.08 ± 0.42	5.93 ± 0.43	5.64 ± 0.31*	5.23 ± 0.28**
Monocytes ($10^3/\mu L$)	0.26 ± 0.03	0.21 ± 0.04	0.22 ± 0.05	0.19 ± 0.03	0.18 ± 0.03	0.24 ± 0.04
Eosinophils ($10^3/\mu L$)	0.09 ± 0.03	0.14 ± 0.03	0.16 ± 0.05	0.09 ± 0.03	0.08 ± 0.02	0.06 ± 0.02
Thromboplastin time (sec)	11.52 ± 0.26	11.36 ± 0.12[b]	10.92 ± 0.24	11.12 ± 0.65*	10.65 ± 0.30*	10.49 ± 0.16**
Clotting time (min)	3.06 ± 0.07	2.95 ± 0.09	2.93 ± 0.05	2.93 ± 0.07	2.98 ± 0.11	3.13 ± 0.17
Clinical Chemistry						
n	9	10	10	10	10	8
Urea nitrogen (mg/dL)	11.9 ± 0.5	11.5 ± 0.6	12.6 ± 0.5	12.6 ± 0.4	13.7 ± 0.8	15.0 ± 0.6**
Creatinine (mg/dL)	0.62 ± 0.04	0.60 ± 0.03	0.57 ± 0.04	0.52 ± 0.03	0.54 ± 0.03	0.46 ± 0.03**
Sodium (mEq/L)	146 ± 0	148 ± 1	146 ± 0	146 ± 0	146 ± 1	145 ± 0
Potassium (mEq/L)	5.5 ± 0.1	5.5 ± 0.1	5.6 ± 0.1	5.8 ± 0.1*	5.8 ± 0.1*	5.6 ± 0.1
Chloride (mEq/L)	105 ± 0	105 ± 0	105 ± 0	105 ± 0	106 ± 0	104 ± 0
Calcium (mg/dL)	10.57 ± 0.05	10.50 ± 0.03	10.49 ± 0.05	10.57 ± 0.05	10.66 ± 0.09	10.75 ± 0.08

TABLE H2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Male (continued)						
Clinical Chemistry (continued)						
n	9	10	10	10	10	8
Phosphorus (mg/dL)	6.5 ± 0.2	6.5 ± 0.1	6.5 ± 0.2	6.3 ± 0.1	6.6 ± 0.2	6.9 ± 0.2
Total protein (g/dL)	6.9 ± 0.1	6.8 ± 0.1	6.9 ± 0.1	6.9 ± 0.1	7.1 ± 0.2	7.1 ± 0.1
Albumin (g/dL)	3.5 ± 0.0	3.5 ± 0.1	3.5 ± 0.0	3.5 ± 0.0	3.6 ± 0.1*	3.7 ± 0.1**
A/G ratio	1.0 ± 0.0	1.1 ± 0.0	1.0 ± 0.0[b]	1.1 ± 0.0	1.1 ± 0.0*	1.1 ± 0.0**
Total bilirubin (mg/dL)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Alanine aminotransferase (IU/L)	47 ± 1	43 ± 2	45 ± 2	40 ± 2	45 ± 2	48 ± 2
Aspartate aminotransferase (IU/L)	65 ± 3	60 ± 2	62 ± 3	58 ± 4*	60 ± 3	55 ± 2*
Lactate dehydrogenase (IU/L)	406 ± 39	354 ± 37	353 ± 34	318 ± 29	269 ± 29*	226 ± 19**
Ornithine carbamoyltransferase (IU/L)	1.4 ± 0.6	1.6 ± 0.5	1.2 ± 0.5[b]	1.6 ± 0.6	2.5 ± 0.7	3.1 ± 0.9
Sorbitol dehydrogenase (IU/L)	14 ± 1	15 ± 1	13 ± 1	14 ± 1	13 ± 1	12 ± 1*
Cholinesterase (IU/L)	996.6 ± 30.5	890.1 ± 16.0*	946.4 ± 13.7	840.2 ± 11.3**	782.7 ± 20.0**	687.9 ± 13.9**
Female						
Hematology						
n	10	10	10	9	10	5
Hematocrit (%)	39.7 ± 0.5	41.3 ± 0.7	41.3 ± 0.4	40.7 ± 0.3	41.0 ± 0.6	38.2 ± 0.8
Hemoglobin (g/dL)	15.4 ± 0.3	16.2 ± 0.3	16.1 ± 0.2	15.9 ± 0.2	15.8 ± 0.3	15.2 ± 0.3
Erythrocytes ($10^6/\mu L$)	7.38 ± 0.10	7.62 ± 0.14	7.59 ± 0.08	7.49 ± 0.04	7.53 ± 0.13	7.19 ± 0.17
Mean cell volume (fL)	53.8 ± 0.5	54.3 ± 0.2	54.4 ± 0.2	54.3 ± 0.2	54.5 ± 0.3	53.2 ± 0.2
Mean cell hemoglobin (pg)	20.9 ± 0.2	21.2 ± 0.1	21.2 ± 0.1	20.3 ± 1.0	21.0 ± 0.1	21.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	38.9 ± 0.2	39.1 ± 0.2	39.1 ± 0.1	39.1 ± 0.4	38.6 ± 0.1	39.8 ± 0.1*
Platelets ($10^3/\mu L$)	683.6 ± 17.2	620.9 ± 16.0*	662.4 ± 13.4	576.8 ± 27.4**	551.1 ± 18.6**	505.6 ± 50.4**
Leukocytes ($10^3/\mu L$)	6.45 ± 0.22	6.20 ± 0.33	7.45 ± 0.50	6.86 ± 0.35	6.67 ± 0.58	5.72 ± 0.45

TABLE H2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Female (continued)						
Hematology (continued)						
Segmented neutrophils ($10^3/\mu L$)	1.15 ± 0.14	0.89 ± 0.11	1.18 ± 0.14	1.01 ± 0.14	1.14 ± 0.15	1.10 ± 0.09
Lymphocytes ($10^3/\mu L$)	5.07 ± 0.19	5.11 ± 0.28	6.03 ± 0.47	5.63 ± 0.25	5.39 ± 0.45	4.45 ± 0.44
Clinical Chemistry						
n	10	10	10	10	10	5
Monocytes ($10^3/\mu L$)	0.19 ± 0.04	0.14 ± 0.02	0.14 ± 0.03	0.15 ± 0.03	0.10 ± 0.03	0.12 ± 0.05
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.07 ± 0.01	0.08 ± 0.03	0.07 ± 0.02	0.04 ± 0.01	0.05 ± 0.03
Thromboplastin time (sec)	10.60 ± 0.27	10.73 ± 0.33	10.43 ± 0.19[b]	10.54 ± 0.29[c]	10.26 ± 0.21	9.52 ± 0.23*
Clotting time (min)	2.88 ± 0.10	2.95 ± 0.09	2.85 ± 0.04	2.80 ± 0.08[d]	2.85 ± 0.08	3.00 ± 0.08
Urea nitrogen (mg/dL)	13.7 ± 0.5	14.6 ± 0.5	13.7 ± 0.6	13.7 ± 0.8	13.7 ± 0.7	13.2 ± 1.0
Creatinine (mg/dL)	0.55 ± 0.03	0.58 ± 0.04	0.57 ± 0.04	0.61 ± 0.05	0.50 ± 0.04	0.48 ± 0.02
Sodium (mEq/L)	145 ± 0	145 ± 1	145 ± 0	146 ± 1	145 ± 1	145 ± 1
Potassium (mEq/L)	5.9 ± 0.2	5.7 ± 0.1	5.6 ± 0.1	5.7 ± 0.2	5.6 ± 0.2	5.6 ± 0.2
Chloride (mEq/L)	106 ± 0	107 ± 0	106 ± 0	106 ± 0	106 ± 1	106 ± 1
Calcium (mg/dL)	10.55 ± 0.08	10.59 ± 0.07	10.58 ± 0.06	10.74 ± 0.09	10.67 ± 0.10	10.98 ± 0.06**
Phosphorus (mg/dL)	6.3 ± 0.1	5.5 ± 0.3	5.9 ± 0.1	6.7 ± 0.5	6.0 ± 0.3	7.3 ± 0.3
Total protein (g/dL)	6.7 ± 0.1	6.9 ± 0.1	6.9 ± 0.1	7.2 ± 0.1**	7.1 ± 0.1**	7.2 ± 0.1**
Albumin (g/dL)	3.3 ± 0.1	3.5 ± 0.0**	3.5 ± 0.1**	3.7 ± 0.1**	3.7 ± 0.1**	3.9 ± 0.1**
A/G ratio	1.0 ± 0.0	1.1 ± 0.0	1.1 ± 0.0	1.0 ± 0.0	1.1 ± 0.0*	1.1 ± 0.0**
Total bilirubin (mg/dL)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Alanine aminotransferase (IU/L)	47 ± 2	44 ± 2	45 ± 3	47 ± 2	45 ± 2	47 ± 3
Aspartate aminotransferase (IU/L)	71 ± 4	64 ± 2	69 ± 4	69 ± 2	64 ± 2	62 ± 2
Lactate dehydrogenase (IU/L)	333 ± 29	269 ± 18	283 ± 33	302 ± 33	263 ± 26	275 ± 41
Ornithine carbamoyltransferase (IU/L)	2.0 ± 0.8	2.5 ± 0.8	2.4 ± 0.6	3.9 ± 1.0	3.3 ± 0.9	2.3 ± 0.7

TABLE H2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	75 mg/kg	150 mg/kg	300 mg/kg	600 mg/kg	1,200 mg/kg
Female (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	5
Sorbitol dehydrogenase (IU/L)	11 ± 1	10 ± 1	11 ± 1	13 ± 1**	15 ± 1**	13 ± 1**
Cholinesterase (IU/L)	2,675.0 ± 182.0	2,971.0 ± 84.0	3,083.0 ± 104.0	2,764.0 ± 117.0	1,814.0 ± 75.0**	1,078.0 ± 33.0**

* 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. A/G ratio = albumin/globulin ratio.
[b] n=9
[c] n=8
[d] n=10

TABLE H3
Hematology and Clinical Chemistry Data for Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin[a]

	Vehicle Control	600 mg/kg
n	19	19
Hematology		
Hematocrit (%)	40.9 ± 0.4	38.9 ± 0.4°°
Hemoglobin (g/dL)	14.6 ± 0.1	13.9 ± 0.1°°
Erythrocytes ($10^6/\mu L$)	8.36 ± 0.09	7.94 ± 0.10°°
Mean cell volume (fL)	49.0 ± 0.2	49.1 ± 0.3
Mean cell hemoglobin (pg)	17.5 ± 0.1	17.5 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.8 ± 0.2	35.8 ± 0.2
Platelets ($10^3/\mu L$)	543.9 ± 15.4	549.8 ± 23.1
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	3.59 ± 0.15	3.61 ± 0.12
Segmented neutrophils ($10^3/\mu L$)	1.09 ± 0.11	1.18 ± 0.08
Lymphocytes ($10^3/\mu L$)	2.40 ± 0.11	2.30 ± 0.10
Atypical lymphocytes ($10^3/\mu L$)	0.01 ± 0.00	0.04 ± 0.01°°
Monocytes ($10^3/\mu L$)	0.01 ± 0.00	0.01 ± 0.00
Eosinophils ($10^3/\mu L$)	0.04 ± 0.01	0.05 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.01
Activated partial thromboplastin time (sec)	22 ± 0	22 ± 0
Thromboplastin time (sec)	14 ± 0	15 ± 0°°
Clinical Chemistry		
Calcium (mg/dL)	11.58 ± 0.14	11.74 ± 0.13
Alkaline phosphatase (IU/L)	187 ± 8	232 ± 12°
Alanine aminotransferase (IU/L)	81 ± 7	108 ± 12°°
Sorbitol dehydrogenase (IU/L)	29 ± 2	32 ± 2
γ-glutamyltransferase (IU/L)	0.0 ± 0.0	0.0 ± 0.0

° 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

TABLE H4
Hematology and Clinical Chemistry Data for Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Gavage Evaluation of 3,4-Dihydrocoumarin[a]

	Vehicle Control	600 mg/kg
Hematology		
n	10	10
Hematocrit (%)	39.5 ± 0.6	37.5 ± 0.5*
Hemoglobin (g/dL)	14.7 ± 0.2	13.7 ± 0.2**
Erythrocytes ($10^6/\mu L$)	8.38 ± 0.13	7.98 ± 0.12*
Mean cell volume (fL)	47.2 ± 0.4	47.1 ± 0.3
Mean cell hemoglobin (pg)	17.6 ± 0.1	17.1 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	37.3 ± 0.3	36.4 ± 0.1*
Platelets ($10^3/\mu L$)	540.7 ± 16.9	530.3 ± 15.6
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0*
Leukocytes ($10^3/\mu L$)	3.30 ± 0.08	3.54 ± 0.22
Segmented neutrophils ($10^3/\mu L$)	1.07 ± 0.08	1.15 ± 0.12
Lymphocytes ($10^3/\mu L$)	1.97 ± 0.11	2.24 ± 0.14
Atypical lymphocytes ($10^3/\mu L$)	0.13 ± 0.03	0.06 ± 0.02
Monocytes ($10^3/\mu L$)	0.01 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.05 ± 0.01	0.01 ± 0.01*
Nucleated erythrocytes ($10^3/\mu L$)	0.03 ± 0.01	0.01 ± 0.01
Activated partial thromboplastin time (sec)	21 ± 0	20 ± 0
Thromboplastin time (sec)	15 ± 0	16 ± 0**
Clinical Chemistry		
n	10	10
Calcium (mg/dL)	11.20 ± 0.13	10.80 ± 0.13
Alkaline phosphatase (IU/L)	175 ± 8	227 ± 5**
Alanine aminotransferase (IU/L)	69 ± 5	51 ± 3**
Sorbitol dehydrogenase (IU/L)	25 ± 2	21 ± 2
γ-glutamyltransferase (IU/L)	0.0 ± 0.0	0.0 ± 0.0

* 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

TABLE H5
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Male				
n	9	10	10	10
Hematology				
Hematocrit (%)	38.9 ± 0.9	39.6 ± 0.4	39.5 ± 0.6	38.3 ± 0.6
Hemoglobin (g/dL)	14.3 ± 0.4	14.6 ± 0.1	14.5 ± 0.1	14.0 ± 0.1°
Erythrocytes ($10^6/\mu L$)	8.44 ± 0.17	8.37 ± 0.12	8.41 ± 0.20	8.08 ± 0.14
Mean cell volume (fL)	46.3 ± 1.6	47.3 ± 0.5	47.4 ± 0.8	47.5 ± 0.7
Mean cell hemoglobin (pg)	17.0 ± 0.7	17.5 ± 0.2	17.3 ± 0.4	17.4 ± 0.3
Mean cell hemoglobin concentration (g/dL)	36.7 ± 0.5	36.9 ± 0.2	36.7 ± 0.4	36.7 ± 0.5
Platelets ($10^3/\mu L$)	640.0 ± 82.4	564.4 ± 6.3	450.9 ± 24.3°°	555.3 ± 13.6
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	3.28 ± 0.22	3.29 ± 0.20	3.34 ± 0.25	3.66 ± 0.21
Segmented neutrophils ($10^3/\mu L$)	1.07 ± 0.06	1.10 ± 0.12	1.09 ± 0.11	1.20 ± 0.12
Lymphocytes ($10^3/\mu L$)	2.04 ± 0.18	2.07 ± 0.14	2.14 ± 0.19	2.32 ± 0.18
Atypical lymphocytes ($10^3/\mu L$)	0.06 ± 0.03	0.03 ± 0.01	0.02 ± 0.01	0.05 ± 0.01
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
Activated partial thromboplastin time (sec)	21 ± 0	20 ± 0	20 ± 1	19 ± 0°°
Thromboplastin time (sec)	14 ± 0	14 ± 0	14 ± 0	14 ± 0
Clinical Chemistry				
Calcium (mg/dL)	11.00 ± 0.00	10.90 ± 0.10	10.80 ± 0.13	10.80 ± 0.13
Alkaline phosphatase (IU/L)	183 ± 10	174 ± 8	186 ± 7	253 ± 8°°
Alanine aminotransferase (IU/L)	64 ± 5	78 ± 8	84 ± 8°	220 ± 47°°
Sorbitol dehydrogenase (IU/L)	22 ± 2	29 ± 2°	26 ± 2°	34 ± 3°°
γ-glutamyltransferase (IU/L)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.7 ± 0.3°°

TABLE H5
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	150 mg/kg	300 mg/kg	600 mg/kg
Female				
n	10	9	10	9
Hematology				
Hematocrit (%)	36.8 ± 0.4	35.9 ± 0.5	36.8 ± 0.3	35.6 ± 0.7
Hemoglobin (g/dL)	14.0 ± 0.1	13.8 ± 0.2	13.9 ± 0.1	13.6 ± 0.2*
Erythrocytes ($10^6/\mu L$)	6.79 ± 0.06	6.76 ± 0.07	6.97 ± 0.08	6.80 ± 0.13
Mean cell volume (fL)	54.3 ± 0.2	53.2 ± 0.6	52.9 ± 0.2**	52.4 ± 0.5**
Mean cell hemoglobin (pg)	20.7 ± 0.2	20.5 ± 0.2	20.0 ± 0.2*	20.1 ± 0.2*
Mean cell hemoglobin concentration (g/dL)	38.2 ± 0.3	38.5 ± 0.4	37.8 ± 0.2	38.3 ± 0.4
Platelets ($10^3/\mu L$)	591.1 ± 18.6	510.8 ± 20.3*	579.2 ± 20.8	561.1 ± 16.4
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	1.42 ± 0.09	1.60 ± 0.11	1.94 ± 0.09**	2.03 ± 0.18**
Segmented neutrophils ($10^3/\mu L$)	0.40 ± 0.04	0.47 ± 0.06	0.49 ± 0.07	0.63 ± 0.09
Lymphocytes ($10^3/\mu L$)	0.96 ± 0.06	1.09 ± 0.07	1.39 ± 0.07**	1.33 ± 0.14**
Atypical lymphocytes ($10^3/\mu L$)	0.01 ± 0.00	0.01 ± 0.00	0.03 ± 0.01*	0.02 ± 0.01
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 ± 0.00	0.02 ± 0.01	0.01 ± 0.00	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.00	0.01 ± 0.01	0.02 ± 0.00	0.02 ± 0.00*
Activated partial thromboplastin time (sec)	18 ± 0	18 ± 0	18 ± 0	18 ± 0
Thromboplastin time (sec)	14 ± 0	14 ± 0	14 ± 0	14 ± 0
Clinical Chemistry				
Calcium (mg/dL)	10.90 ± 0.10	11.11 ± 0.11	10.90 ± 0.10	10.89 ± 0.20
Alkaline phosphatase (IU/L)	169 ± 5	183 ± 6	191 ± 5*	209 ± 14**
Alanine aminotransferase (IU/L)	42 ± 1	50 ± 6	37 ± 2	33 ± 2**
Sorbitol dehydrogenase (IU/L)	15 ± 1	19 ± 2	16 ± 1	15 ± 1
γ-glutamyltransferase (IU/L)	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.2	1.4 ± 0.2**

* 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

TABLE H6
Hematology Data for Mice in the 16-Day Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	140 mg/kg	280 mg/kg	560 mg/kg	1,125 mg/kg
Male					
n	5	5	5	5	5
Platelets ($10^3/\mu L$)	103.2 ± 11.1	180.0 ± 46.5	181.6 ± 45.4	157.4 ± 35.5	121.0 ± 20.9
Clotting time (min)	1.60 ± 0.40	1.70 ± 0.44	1.80 ± 0.24	1.50 ± 0.39	1.45 ± 0.22
Female					
n	5	4	5	5	5
Platelets ($10^3/\mu L$)	136.2 ± 19.0	94.8 ± 16.8	197.4 ± 50.4	156.0 ± 40.7	150.8 ± 27.1
Clotting time (min)	2.20 ± 0.28	2.13 ± 0.43	1.90 ± 0.30	1.75 ± 0.37	2.10 ± 0.23

[a] Mean ± standard error

TABLE H7
Hematology Data for Mice in the 13-Week Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg	1,600 mg/kg
Male						
n	8	7	10	8	10	2
Hematocrit (%)	32.3 ± 0.6	31.3 ± 1.2	33.7 ± 0.5	32.5 ± 0.8	32.5 ± 0.7	31.4 ± 1.1
Hemoglobin (g/dL)	13.6 ± 0.2	13.2 ± 0.5	14.2 ± 0.2	13.8 ± 0.4	13.9 ± 0.3	13.0 ± 0.4
Erythrocytes ($10^6/\mu L$)	6.48 ± 0.11	6.31 ± 0.24	6.72 ± 0.11	6.45 ± 0.13	6.45 ± 0.12	6.26 ± 0.14
Mean cell volume (fL)	49.9 ± 0.2	49.6 ± 0.2	50.2 ± 0.4	50.3 ± 0.4	50.4 ± 0.3	50.5 ± 0.5
Mean cell hemoglobin (pg)	21.0 ± 0.1	21.0 ± 0.2	21.2 ± 0.2	21.4 ± 0.2	21.5 ± 0.2	20.8 ± 0.2
Mean cell hemoglobin concentration (g/dL)	42.2 ± 0.2	42.2 ± 0.2	42.2 ± 0.2	42.5 ± 0.4	42.7 ± 0.5	41.5 ± 0.1
Platelets ($10^3/\mu L$)	532.4 ± 63.0	456.7 ± 94.8	602.7 ± 66.6	538.4 ± 63.1	409.5 ± 48.6	513.5 ± 189.0
Leukocytes ($10^3/\mu L$)	3.48 ± 0.54	4.71 ± 0.85	3.93 ± 0.67	3.01 ± 0.37	4.94 ± 0.42	3.30 ± 0.60
Segmented neutrophils ($10^3/\mu L$)	0.79 ± 0.14	0.91 ± 0.18	1.09 ± 0.30	0.73 ± 0.12	0.82 ± 0.11	0.34 ± 0.07
Lymphocytes ($10^3/\mu L$)	2.56 ± 0.42	3.60 ± 0.66	2.77 ± 0.50	2.22 ± 0.32	3.92 ± 0.32	2.90 ± 0.69
Monocytes ($10^3/\mu L$)	0.09 ± 0.02	0.14 ± 0.03	0.03 ± 0.02	0.04 ± 0.01	0.14 ± 0.04	0.06 ± 0.02
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.07 ± 0.04	0.04 ± 0.02	0.01 ± 0.01	0.06 ± 0.02	0.00 ± 0.00
Thromboplastin time (sec)	10 ± 0[b]	10 ± 0	10 ± 0	10 ± 0[c]	10 ± 0[b]	10 ± 0
Clotting time (min)	3.19 ± 0.15[b]	2.94 ± 0.22[b]	3.20 ± 0.15	3.03 ± 0.07[d]	2.88 ± 0.16	2.63 ± 0.13

TABLE H7
Hematology Data for Mice in the 13-Week Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg	1,600 mg/kg
Female						
n	10	10	10	9	10	5
Hematocrit (%)	33.3 ± 0.7	33.7 ± 0.9	33.9 ± 0.7	34.6 ± 0.5	34.6 ± 0.4	33.8 ± 0.6
Hemoglobin (g/dL)	13.9 ± 0.3	14.0 ± 0.4	14.2 ± 0.3	14.4 ± 0.2	14.5 ± 0.2	14.0 ± 0.3
Erythrocytes ($10^6/\mu L$)	6.53 ± 0.14	6.53 ± 0.19	6.62 ± 0.13	6.75 ± 0.10	6.71 ± 0.08	6.61 ± 0.12
Mean cell volume (fL)	51.1 ± 0.2	51.5 ± 0.3	51.2 ± 0.1	51.3 ± 0.2	51.6 ± 0.3	51.0 ± 0.3
Mean cell hemoglobin (pg)	21.3 ± 0.1	21.5 ± 0.1	21.4 ± 0.1	21.3 ± 0.1	21.6 ± 0.1	21.2 ± 0.2
Mean cell hemoglobin concentration (g/dL)	41.8 ± 0.2	41.6 ± 0.2	42.0 ± 0.2	41.5 ± 0.2	41.8 ± 0.2	41.5 ± 0.4
Platelets ($10^3/\mu L$)	506.6 ± 59.5	510.7 ± 51.0	532.6 ± 43.8	465.2 ± 35.5[d]	423.8 ± 52.8	509.2 ± 43.4
Leukocytes ($10^3/\mu L$)	4.45 ± 0.52	3.91 ± 0.58	4.33 ± 0.61	4.90 ± 0.52	5.45 ± 0.43	4.98 ± 0.81
Segmented neutrophils ($10^3/\mu L$)	0.63 ± 0.09	0.84 ± 0.18	0.97 ± 0.13	0.95 ± 0.13	0.88 ± 0.07	1.01 ± 0.18
Lymphocytes ($10^3/\mu L$)	3.69 ± 0.49	2.93 ± 0.46	3.26 ± 0.49	3.76 ± 0.50	4.33 ± 0.39	3.88 ± 0.69
Monocytes ($10^3/\mu L$)	0.06 ± 0.01	0.07 ± 0.02	0.05 ± 0.03	0.12 ± 0.02	0.13 ± 0.02°	0.06 ± 0.02
Eosinophils ($10^3/\mu L$)	0.07 ± 0.02	0.06 ± 0.03	0.04 ± 0.01	0.06 ± 0.02	0.10 ± 0.03	0.03 ± 0.02
Thromboplastin time (sec)	10 ± 0	10 ± 0	10 ± 0[b]	10 ± 0[d]	10 ± 0[b]	10 ± 0[e]
Clotting time (min)	3.23 ± 0.09	3.20 ± 0.17	3.33 ± 0.18	3.48 ± 0.15[d]	3.08 ± 0.12	3.00 ± 0.08

° Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
a Mean ± standard error
b n=9
c n=6
d n=10
e n=4

TABLE H8
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin[a]

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Male				
Hematology				
n	10	9	8	10
Hematocrit (%)	37.5 ± 1.0	35.6 ± 2.1	39.7 ± 0.5	39.3 ± 0.5
Hemoglobin (g/dL)	13.1 ± 0.3	13.6 ± 0.3	13.6 ± 0.1	13.6 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.08 ± 0.22	7.74 ± 0.36	8.48 ± 0.14	8.36 ± 0.10
Mean cell volume (fL)	46.5 ± 0.6	45.8 ± 0.9	46.9 ± 0.3	46.9 ± 0.5
Mean cell hemoglobin (pg)	16.3 ± 0.3	17.9 ± 1.3	16.0 ± 0.2	16.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.0 ± 0.2	39.8 ± 3.9	34.2 ± 0.3	34.5 ± 0.3
Platelets ($10^3/\mu L$)	821.3 ± 23.1	832.3 ± 39.1	794.3 ± 20.2	796.9 ± 27.7
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0*
Leukocytes ($10^3/\mu L$)	1.00 ± 0.09	1.48 ± 0.22	1.01 ± 0.18	1.22 ± 0.25
Segmented neutrophils ($10^3/\mu L$)	0.24 ± 0.03	0.33 ± 0.05	0.20 ± 0.05	0.28 ± 0.06
Lymphocytes ($10^3/\mu L$)	0.76 ± 0.07	1.14 ± 0.17	0.80 ± 0.13	0.93 ± 0.20
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.00
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
n	8	8	9	10
Alkaline phosphatase (IU/L)	51 ± 3	45 ± 3	50 ± 2	48 ± 1
Alanine aminotransferase (IU/L)	55 ± 11	28 ± 5	28 ± 2	56 ± 12
Sorbitol dehydrogenase (IU/L)	38 ± 2[b]	38 ± 1[c]	37 ± 2	42 ± 1
γ-glutamyltransferase (IU/L)	5.2 ± 2.8[b]	1.0 ± 0.5[c]	0.6 ± 0.6	0.7 ± 0.5

TABLE H8
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of 3,4-Dihydrocoumarin (continued)

	Vehicle Control	200 mg/kg	400 mg/kg	800 mg/kg
Female				
Hematology				
n	9	8	9	8
Hematocrit (%)	38.6 ± 1.0	38.9 ± 1.2	40.0 ± 0.7	38.7 ± 0.5
Hemoglobin (g/dL)	13.8 ± 0.2	13.6 ± 0.3	13.9 ± 0.2	13.7 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.23 ± 0.15	8.16 ± 0.26	8.38 ± 0.11	8.11 ± 0.14
Mean cell volume (fL)	46.9 ± 1.0	47.9 ± 0.2	47.6 ± 0.5	47.6 ± 0.3
Mean cell hemoglobin (pg)	16.8 ± 0.2	16.7 ± 0.2	16.5 ± 0.2	16.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.9 ± 0.5	35.0 ± 0.3	34.7 ± 0.3	35.3 ± 0.2
Platelets ($10^3/\mu L$)	672.9 ± 12.9	604.8 ± 72.5	591.9 ± 65.3	647.0 ± 41.4
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	1.00 ± 0.19	0.75 ± 0.14	1.01 ± 0.14[c]	1.01 ± 0.18
Segmented neutrophils ($10^3/\mu L$)	0.27 ± 0.05	0.17 ± 0.03	0.30 ± 0.11	0.22 ± 0.05
Lymphocytes ($10^3/\mu L$)	0.73 ± 0.14	0.59 ± 0.11	0.81 ± 0.11[c]	0.80 ± 0.14
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
n	9	9	9	9
Alkaline phosphatase (IU/L)	118 ± 21	107 ± 8	128 ± 9	120 ± 12
Alanine aminotransferase (IU/L)	65 ± 14	28 ± 3°	41 ± 2	66 ± 13
Sorbitol dehydrogenase (IU/L)	29 ± 3	22 ± 3	28 ± 3	32 ± 2
γ-glutamyltransferase (IU/L)	6.5 ± 3.5[d]	15.2 ± 7.0	26.4 ± 9.3	24.3 ± 9.8

° Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=10
[c] n=9
[d] n=8

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

PROCUREMENT AND CHARACTERIZATION OF 3,4-DIHYDROCOUMARIN 318
PREPARATION AND ANALYSIS OF DOSE FORMULATIONS 319
FIGURE I1 Infrared Absorption Spectrum of 3,4-Dihydrocoumarin 320
FIGURE I2 Nuclear Magnetic Resonance Spectrum of 3,4-Dihydrocoumarin 321
TABLE I1 Preparation and Storage of Dose Formulations in the Gavage Studies of 3,4-Dihydrocoumarin 322
TABLE I2 Results of Analysis of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of 3,4-Dihydrocoumarin 323
TABLE I3 Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of 3,4-Dihydrocoumarin 324
TABLE I4 Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin 325
TABLE I5 Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin 329

CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS STUDIES

PROCUREMENT AND CHARACTERIZATION OF 3,4-DIHYDROCOUMARIN

3,4-Dihydrocoumarin was obtained from Givaudan Corporation (Clifton, NJ) in two lots (lot 57599 and lot 44981). Lot 57599 was used throughout the 16-day and 13-week studies in rats and mice and lot 44981 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 3,4-dihydrocoumarin studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a colorless liquid, were identified as 3,4-dihydrocoumarin by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra of 3,4-dihydrocoumarin (*Sadtler Standard Spectra*), as shown in Figures I1 and I2.

The purity of lot 57599 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and gas chromatography. Titration was performed by the hydrolysis of lactone with 0.6 N alcoholic potassium hydroxide and back-titration with 1 N sulfuric acid to the phenolphthalein endpoint. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) hexane:ethyl acetate (70:30) and 2) toluene:acetone (90:10). Plates were examined under shortwave (254 nm) ultraviolet light and a spray of 0.5 g potassium permanganate dissolved in 100 mL N sodium hydroxide. Gas chromatographic analysis was performed with a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used: A) 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 and B) 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.

Elemental analyses of lot 57599 for carbon and hydrogen were in agreement with the theoretical values for 3,4-dihydrocoumarin. Karl Fischer water analysis indicated less than 0.05% water. Functional group titration indicated a purity of 99.1 ± 0.4%. TLC by the first system indicated a major spot and one trace impurity, and the second system indicated a major spot and two trace impurities. Gas chromatography using the first system indicated a major peak and five impurities. Two impurities with a total area of 0.06% relative to the major peak area eluted before the major peak, while three impurities eluted after the major peak and had a total area of 0.83% relative to the major peak. System 2 indicated a major peak and seven impurities. Four impurities eluting before the major peak had a total area of 0.22% relative to the major peak, and three impurities eluting after the major peak had a total area of 0.15% relative to the major peak. The overall purity was determined to be approximately 99%.

The purity of lot 44981 was determined by elemental analysis, Karl Fischer water analyses, free acid titration, functional group titration, thin-layer chromatography, and gas chromatography. Free acid titration was performed by dissolving the sample in absolute ethanol and titrating with 0.1 N aqueous potassium hydroxide. Functional group titration was performed as described above except the titration was monitored potentiometrically with a pH/mV electrode filled with saturated potassium chloride. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) hexane:ethyl acetate (70:30) and 2) toluene:acetone (90:10). Plates were examined under shortwave (254 nm) and longwave (366 nm) ultraviolet light and a spray of 0.5% (w/v) potassium permanganate in 1 N sodium hydroxide. Gas chromatographic analysis was performed with a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used: A) 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 and B) 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.

Elemental analyses of lot 44981 for carbon and hydrogen were in agreement with the theoretical values for 3,4-dihydrocoumarin. Karl Fischer water analysis indicated 0.014 ± 0.002% water. Free acid titration indicated 0.0404 ± 0.0008 mEq of acid per g of sample. Functional group titration indicated a purity of 100.6 ± 0.5%. Each TLC system indicated one major spot and one impurity. Gas chromatography using the first system indicated a major peak and two impurities with a total area of 0.5% relative to the major peak area. A major peak and one impurity with an area totaling 0.2% relative to the major peak area were detected with the second system. The overall purity was determined to be greater than 99%.

Stability studies were performed by the analytical chemistry laboratory on lot 57599. Gas chromatography was performed using the system A described for this lot, but with dodecane added as an internal standard and an isothermal temperature program of 170° C. These studies indicated that 3,4-dihydrocoumarin was stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically at the study laboratory with infrared, 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 solutions were prepared by mixing 3,4-dihydrocoumarin and Mazola® corn oil (w/v) to give the required concentrations (Table I1). The dose formulations were stored in the dark at 25° C. Dose formulations were prepared once for the 16-day studies, every 2 weeks during the 13-week studies, and weekly then every 2 weeks in the 2-year studies. Formulations were discarded 21 days after the date of preparation.

Dose formulation stability studies were performed by the analytical chemistry laboratory. Aliquots were extracted with acetonitrile. The extract was diluted with methylene chloride containing decyl alcohol as an internal standard. Gas chromatographic analysis was then performed with the first system described for the bulk purity analyses of lot 44981, but with a carrier gas flow rate of 30 mL/minute, an oven temperature program of 160° C, isothermal, and an internal standard of decyl alcohol. 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.

Periodic analyses of the dose formulations of 3,4-dihydrocoumarin were conducted at the study laboratory and analytical chemistry laboratory using ultraviolet spectroscopy. 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 4 to 10 weeks (Table I4). In the 2-year studies all dose formulations 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 good agreement with the results obtained by the study laboratory (Table I5).

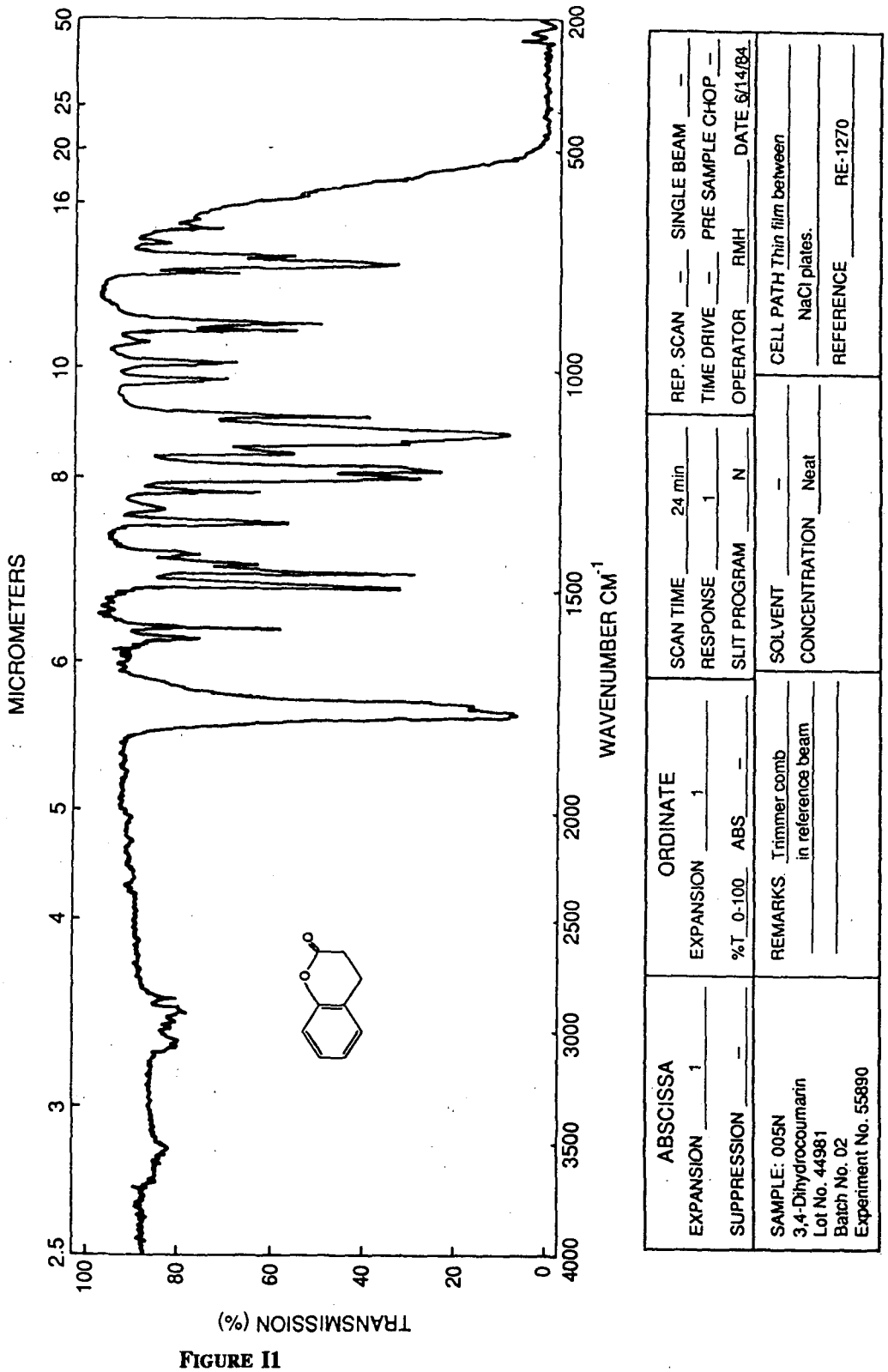

FIGURE I1
Infrared Absorption Spectrum of 3,4-Dihydrocoumarin

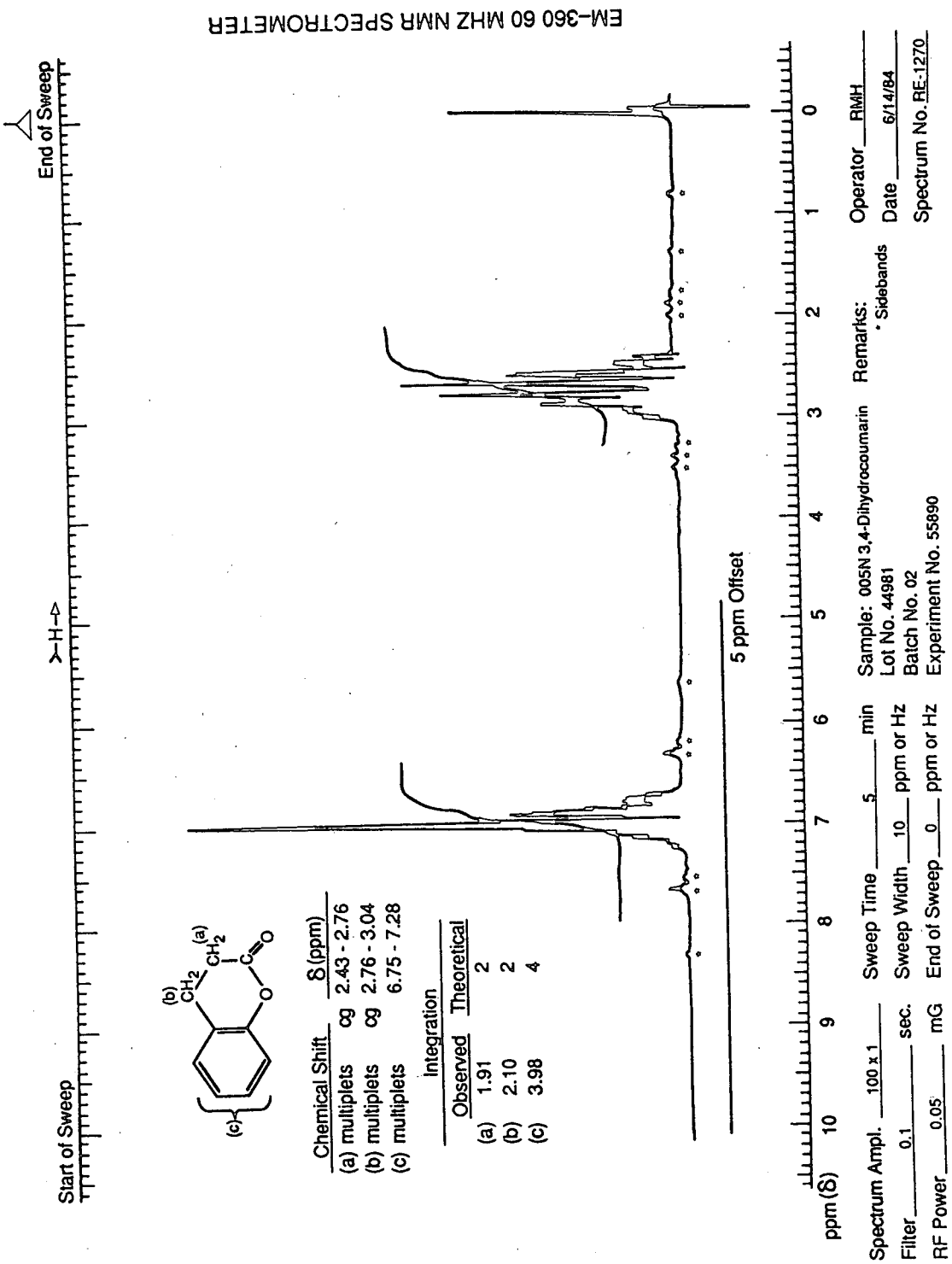

FIGURE I2
Nuclear Magnetic Resonance Spectrum of 3,4-Dihydrocoumarin

TABLE I1
Preparation and Storage of Dose Formulations in the Gavage Studies of 3,4-Dihydrocoumarin

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
3,4-Dihydrocoumarin was mixed with corn oil while being stirred.	Same as 16-day studies	Same as 16-day studies
Chemical Lot Number		
57599	57599	44981
Maximum Storage Time		
14 days	21 days	Same as 13-week studies
Storage Conditions		
Stored at room temperature and protected from light.	Same as 16-day studies	Same as 16-day studies
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 3,4-Dihydrocoumarin

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
Rats[b]				
20 January 1981	16 March 1981	19.0	15.9	−16
		37.5	32.3	−14
		75.0	67.5	−10
		150	119	−21
		300	220	−27
Mice[c]				
20 January 1981	12 March 1981	14.0	12.9	−8
		28.0	25.2	−10
		56.0	52.5	−6
		112.5	100.4	−11
		225	206	−8

[a] Results of duplicate analyses
[b] Mg/mL values: 19.0 mg/mL = 190 mg/kg, 37.5 mg/mL = 375 mg/kg, 75.0 mg/mL = 750 mg/kg, 150 mg/mL = 1,500 mg/kg, and 300 mg/mL = 3,000 mg/kg; dosing volume = 10 mL/kg.
[c] Mg/mL values: 14.0 mg/mL = 140 mg/kg, 28.0 mg/mL = 280 mg/kg, 56.0 mg/mL = 560 mg/kg, 112.5 mg/mL = 1,125 mg/kg, and 225 mg/mL = 2,250 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 3,4-Dihydrocoumarin

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
Rats[b]				
16 April 1981	17 April 1981	7.50	7.60	+1
		7.50	7.37	-2
		15.0	15.3	+2
		15.0	15.1	+1
		30.0	31.8	+6
		30.0	31.7	+6
		60.0	60.9	+2
		60.0	65.8	+10
		120	123	+3
		120	120	0
28 May 1981	3 June 1981	7.50	7.45	-1
		7.50	7.53	0
		15.0	15.6	+4
		15.0	15.1	+1
		30.0	30.7	+2
		30.0	31.2	+4
		60.0	60.8	+1
		60.0	61.8	+3
		120	117	-3
		120	123	+3
Mice[c]				
17 April 1981	21 April 1981	10.0	10.5	+5
		10.0	10.1	+1
		20.0	19.4	-3
		20.0	19.5	-3
		40.0	42.3	+6
		40.0	40.7	+2
		80.0	80.8	+1
		80.0	80.3	0
		160	162	+1
		160	173	+8
29 May 1981	3 June 1981	10.0	9.56	-4
		10.0	9.20	-8
		20.0	19.1	-5
		20.0	18.9	-6
		40.0	38.2	-5
		40.0	38.9	-3
		80.0	78.9	-1
		80.0	80.1	0
		160	173	+8
		160	147	-8

[a] Results of duplicate analyses
[b] Mg/mL values: 7.50 mg/mL = 75 mg/kg, 15.0 mg/mL = 150 mg/kg, 30.0 mg/mL = 300 mg/kg, 60.0 mg/mL = 600 mg/kg, 120 mg/mL = 1,200 mg/kg; dosing volume = 10 mL/kg.
[c] Mg/mL values: 10.0 mg/mL = 100 mg/kg, 20.0 mg/mL = 200 mg/kg, 40.0 mg/mL = 400 mg/kg, 80.0 mg/mL = 800 mg/kg, 160 mg/mL = 1,600 mg/kg; dosing volume = 10 mL/kg.

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
Rats[b]				
28 September 1984	1 October 1984	30.0	29.1	−3
		60.0	59.2	−1
		120	121	+1
2 November 1984	5 November 1984	30.0	30.0	0
		60.0	58.9	−2
		120	129	+8
6 November 1984	13 November 1984[c]	30.0	32.1	+7
		60.0	61.0	+2
		120	119	−1
6 December 1984	7 December 1984	30.0	30.1	0
		60.0	60.1	0
		120	120	0
24 January 1985	25, 26 January 1985	30.0	32.1	+7
		60.0	61.7	+3
		60.0	59.9	0
		120	121	+1
		120	121	+1
28 January 1985	30 January 1985	30.0	29.6	−1
21 March 1985	22 March 1985	30.0	29.2	−3
		30.0	29.2	−3
		60.0	57.2	−5
		60.0	57.6	−4
		120	115	−4
25 March 1985	26 March 1985	120	120	0
4 April 1985	11 April 1985[c]	30.0	29.4	−2
		60.0	58.4	−3
		120	116	−3
30 May 1985	31 May 1985	30.0	29.3	−2
		30.0	29.5	−2
		60.0	61.4	+2
		60.0	60.5	+1
		120	121	+1
		120	121	+1
25 July 1985	26 July 1985	30.0	29.5	−2
		30.0	29.8	−1
		60.0	57.6	−4
		60.0	59.1	−2
		120	117	−3
		120	119	−1

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats (continued)				
19 September 1985	20 September 1985	30.0	28.5	−5
		30.0	28.1	−6
		60.0	59.1	−2
		60.0	59.5	−1
		120	123	+3
		120	124	+3
	9 October 1985[c]	60.0	59.4	−1
		120	120	0
31 October 1985	1-4 November 1985	30.0	30.7	+2
		30.0	30.3	+1
		60.0	64.1	+7
		60.0	64.4	+7
		120	121	+1
		120	122	+2
	20 November 1985[c]	30.0	29.2	−3
		60.0	58.1	−3
		120	122	+2
9 January 1986	10 January 1986	30.0	30.0	0
		30.0	29.6	−1
		60.0	59.9	0
		60.0	59.1	−2
		120	120	0
		120	121	+1
6 March 1986	7 March 1986	30.0	32.8	+9
		30.0	33.3	+11
		60.0	60.0	0
		60.0	59.1	−2
		120	117	−3
		120	119	−1
10 March 1986	13 March 1986	30.0	30.3	+1
1 May 1986	2 May 1986	30.0	31.0	+3
		30.0	30.4	+1
		60.0	61.3	+2
		60.0	61.4	+2
		120	125	+4
		120	125	+4
	20 May 1986[c]	30.0	32.1	+7
		60.0	60.2	0
		120	119	−1

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats (continued)				
26 June 1986	27 June 1986	30.0	29.6	−1
		30.0	28.5	−5
		60.0	58.8	−2
		60.0	58.7	−2
		120	116	−3
		120	117	−3
3 September 1986	4 September 1986	30.0	29.2	−3
		60.0	61.7	+3
		60.0	58.4	−3
		120	119	−1
Mice[d]				
13 December 1984	14 December 1984	20.0	19.7	−2
		40.0	39.7	−1
		80.0	80.8	+1
28 December 1984	3 January 1985	20.0	19.5	−3
		40.0	38.4	−4
		80.0	78.9	−1
7 February 1985	10 February 1985	20.0	19.3	−4
		40.0	39.5	−1
		80.0	81.9	+2
	26 February 1985[c]	20.0	20.5	+3
		40.0	40.2	+1
		80.0	80.8	+1
4 April 1985	5 April 1985	20.0	19.8	−1
		40.0	39.1	−2
		80.0	76.7	−4
30 May 1985	31 May 1985	20.0	19.8	−1
		40.0	40.6	+2
		80.0	81.3	+2
	18 June 1985[c]	20.0	20.2	+1
		40.0	40.2	+1
		80.0	80.2	0
25 July 1985	26 July 1985	20.0	19.6	−2
		40.0	39.3	−2
		80.0	76.9	−4
19 September 1985	20 September 1985	20.0	19.7	−2
		40.0	41.6	+4
		80.0	80.9	+1

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Mice (continued)				
31 October 1985	1-4 November 1985	20.0	20.9	+5
		40.0	39.6	-1
		80.0	83.0	+4
	20 November 1985[c]	20.0	19.3	-4
		40.0	38.1	-5
		80.0	79.1	-1
9 January 1986	10 January 1986	20.0	19.7	-2
		40.0	39.3	-2
		80.0	79.0	-1
6 March 1986	7 March 1986	20.0	20.8	+4
		40.0	39.2	-2
		80.0	80.1	0
1 May 1986	2 May 1986	20.0	20.6	+3
		40.0	42.5	+6
		80.0	82.1	+3
	20 May 1986[c]	20.0	21.3	+7
		40.0	40.9	+2
		80.0	82.2	+3
26 June 1986	27 June 1986	20.0	19.6	-2
		40.0	37.7	-6
		80.0	78.3	-2
3 September 1986	4 September 1986	20.0	20.5	+3
		40.0	38.7	-3
		80.0	80.3	0
16 October 1986	17 October 1986	20.0	20.4	+2
		40.0	40.2	+1
		80.0	78.6	-2
	4 November 1986[c]	20.0	20.3	+2
		40.0	40.4	+1
		80.0	79.0	-1
24 November 1986	26 November 1986	20.0	20.2	+1
		40.0	40.0	0
		80.0	78.7	-2

[a] Results of duplicate analyses
[b] Mg/mL values: 30.0 mg/mL = 150 mg/kg, 60.0 mg/mL = 300 mg/kg, and 120 mg/mL = 600 mg/kg; dose volume = 5 mL/kg.
[c] Animal room samples
[d] Mg/mL values: 20.0 mg/mL = 200 mg/kg, 40.0 mg/mL = 400 mg/kg, and 80.0 mg/mL = 800 mg/kg; dose 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 3,4-Dihydrocoumarin

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
Rats			
28 September 1984	120	121	111 ± 2
25 July 1985	60.0	57.6	58.1 ± 0.2
26 June 1986	120	117	120 ± 1
Mice			
7 February 1985	20.0	19.3	19.6 ± 0.2
9 January 1986	80.0	79.0	78.1 ± 0.2

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

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 332
TABLE J2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 332
TABLE J3 Nutrient Composition of NIH-07 Rat and Mouse Ration 333
TABLE J4 Contaminant Levels in NIH-07 Rat and Mouse Ration 334

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)	22.15 ± 0.48	21.1 – 23.1	27
Crude fat (% by weight)	5.64 ± 0.42	4.7 – 6.4	27
Crude fiber (% by weight)	3.47 ± 0.46	2.7 – 5.4	27
Ash (% by weight)	6.46 ± 0.25	6.1 – 7.0	27
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)	8,426 ± 2,660	4,700 – 15,000	27
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)	20.52 ± 1.67	17.0 – 23.0	27
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 (%)	1.13 ± 0.10	0.95 – 1.41	27
Phosphorus (%)	0.92 ± 0.05	0.73 – 0.99	27
Potassium (%)	0.883 ± 0.078	0.772 – 0.971	6
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.313 ± 0.390	0.258 – 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151 – 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208 – 0.420	8
Iron (ppm)	360.5 ± 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)	0.72 ± 0.22	0.18 – 1.07	27
Cadmium (ppm)	<0.1		27
Lead (ppm)	0.48 ± 0.27	0.05 – 1.32	27
Mercury (ppm)	<0.05		27
Selenium (ppm)	0.35 ± 0.08	0.17 – 0.48	27
Aflatoxins (ppb)	<5.0		27
Nitrate nitrogen (ppm)[bc]	16.95 ± 6.93	2.80 – 41.0	27
Nitrite nitrogen (ppm)[b]	0.40 ± 0.70	<0.10 – 2.60	27
BHA (ppm)[d]	2.51 ± 1.01	<2.00 – 5.00	27
BHT (ppm)[d]	1.67 ± 0.96	<1.00 – 4.00	27
Aerobic plate count (CFU/g)[e]	36,251 ± 40,816	770 – 130,000	27
Coliform (MPN/g)[f]	14.48 ± 45.74	<3.00 – 240	27
E. coli (MPN/g)[g]	5.81 ± 7.94	<3.00 – 43.0	26
E. coli (MPN/g)[h]	3.04 ± 0.20	<3.00 – 4.00	27
Total nitrosoamines (ppb)[i]	7.93 ± 3.22	3.80 – 16.0	27
N-Nitrosodimethylamine (ppb)[i]	6.79 ± 3.06	2.80 – 15.0	27
N-Nitrosopyrrolidine (ppb)[i]	1.14 ± 0.53	<1.00 – 3.40	27
Pesticides			
α-BHC[j]	<0.01		27
β-BHC	<0.02		27
γ-BHC	<0.01		27
δ-BHC	<0.01		27
Heptachlor	<0.01		27
Aldrin	<0.01		27
Heptachlor epoxide	<0.01		27
DDE	<0.01		27
DDD	<0.01		27
DDT	<0.01		27
HCB	<0.01		27
Mirex	<0.01		27
Methoxychlor	<0.05		27
Dieldrin	<0.01		27
Endrin	<0.01		27
Telodrin	<0.01		27
Chlordane	<0.05		27
Toxaphene	<0.1		27
Estimated PCBs	<0.2		27
Ronnel	<0.01		27
Ethion	<0.02		27
Trithion	<0.05		27
Diazinon	<0.1		27
Methyl parathion	<0.02		27
Ethyl parathion	<0.02		27
Malathion[k]	0.22 ± 0.62	0.05 – 3.20	27
Endosulfan 1	<0.01		27
Endosulfan 2	<0.01		27
Endosulfan sulfate	<0.03		27

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Includes one large value of 1.32 ppm obtained from the lot milled on 10 December 1984.
[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] Ten 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

METHODS 338
TABLE K1 Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin 339

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 studies, 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
ELISA	
Mycoplasma arthritidis	6, 12, 18, and 24 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, 18, and 24 months
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

Mice

During the 2-year study, 15 B6C3F$_1$ mice of each sex were maintained with the study animals to serve as sentinel animals. At 7, 12, and 18 months into the studies, blood was drawn from five mice of each sex. Analyses were also conducted on 3 males at 5 months. 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
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	5, 7, 12, and 18 months
ELISA	
M. arthritidis	5, 7, 12, 18, and 24 months
M. pulmonis	5, 7, 12, 18, and 24 months
PVM	5, 7, 12, 18, and 24 months
Sendai	5, 7, 12, 18, and 24 months
MHV (mouse hepatitis virus)	5, 7, 12, 18, and 24 months
Ectromelia virus	5, 7, 12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	5, 7, 12, 18, and 24 months
Reovirus 3	5, 7, 12, 18, and 24 months
Mouse adenoma virus	5, 7, 12, 18, and 24 months
Hemagglutination Inhibition	
K (papovavirus)	5, 7, 12, 18, and 24 months
Polyoma virus	5, 7, 12, 18, and 24 months
MVM (minute virus of mice)	5, 7, 12, 18, and 24 months
Immunofluorescent Assay	
EDIM (Epizootic diarrhea of infant mice)	5, 7, 12, 18, and 24 months
LCM (Lymphocytic choriomeningitis virus)	24 months

Results of serology testing for rats and mice are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Gavage Studies of 3,4-Dihydrocoumarin

	Interval (months)	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	9/9	PVM
	24 months	10/10	PVM
Mice	5 months	0/3	None positive
	7 months	0/10	None positive
	12 months	0/10	None positive
	18 months	0/10	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

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	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
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

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