NTP

National Toxicology Program

U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of

Elmiron®
(CAS No. 37319-17-8)
in F344/N Rats and $B6C3F_1$ Mice
(Gavage Studies)

NTP TR 512

MAY 2004

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF ELMIRON®

(CAS NO. 37319-17-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

May 2004

NTP TR 512

NIH Publication No. 04-4446

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 and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Perspectives (EHP) http://ehp.niehs.nih.gov (866-541-3841 or 919-653-2590). In addition, printed copies of these reports are available from EHP as supplies last. A listing of all the NTP Technical Reports printed since 1982 appears at the end of this Technical Report.

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CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

K.M. Abdo, Ph.D., Study Scientist
A. Nyska, D.V.M., Study Pathologist
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
R.A. Herbert, D.V.M., Ph.D.
R.R. Maronpot, D.V.M.
D.L. Morgan, Ph.D.
D.P. Orzech, M.S.
S.D. Peddada, Ph.D.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S., ILS, Inc.

Microbiological Associates, Inc.

Conducted 2-week studies and evaluated pathology findings

M.L. Wenk, Ph.D., Principal Investigator
L.L. Pippin, D.V.M.

Battelle Columbus Operations

Conducted 3-month and 2-year studies and evaluated pathology findings

M.R. Hejtmancik, Ph.D., Principal Investigator
S.L. Grumbein, D.V.M., Ph.D.
M.J. Ryan, D.V.M., Ph.D.
A.W. Singer, D.V.M.

Experimental Pathology Laboratories, Inc.

Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
A.E. Brix, D.V.M., Ph.D.
G. Willson, B.V.M. & S.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group

Evaluated slides and prepared pathology report on rats (March 8, 2001)

J.B. Nold, D.V.M., Ph.D., Chairperson
Pathology Associates International
A.E. Brix, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
G.P. Flake, M.D.
National Toxicology Program
B.F. Hamilton, D.V.M., Ph.D.
GlaxoSmithKline
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
P.B. Little, D.V.M., M.S., Ph.D.
Pathology Associates International
A. Nyska, D.V.M.
National Toxicology Program
G. Pearse, B.V.M. & S.
National Toxicology Program
M.J. Ryan, D.V.M., Ph.D.
Battelle Columbus Operations
L. Tomlison, D.V.M., Observer
North Carolina State University
G. Willson, B.V.M. & S.
Experimental Pathology Laboratories, Inc.

Evaluated slides and prepared pathology report on mice (January 18, 2001)

J.B. Nold, D.V.M., Ph.D., Chairperson
Pathology Associates International
A.E. Brix, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
G.P. Flake, M.D.
National Toxicology Program
S.L. Grumbein, D.V.M., Ph.D.
Battelle Toxicology Northwest
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
P.B. Little, M.S., D.V.M., Ph.D.
Pathology Associates International
A. Nyska, D.V.M.
National Toxicology Program
G. Pearse, B.V.M. & S.
National Toxicology Program
G. Willson, B.V.M. & S., Observer
Experimental Pathology Laboratories, Inc.
D. Wolf, D.V.M., Ph.D.
Environmental Protection Agency

Analytical Sciences, Inc.
Provided statistical analyses

P.W. Crockett, Ph.D., Principal Investigator
L.J. Betz, M.S.
K.P. McGowan, M.B.A.
J.T. Scott, M.S.

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
M.P. Barker, B.A.
P.H. Carver, B.A.
P.A. Gideon, B.A.
L.M. Harper, B.S.
D.C. Serbus, Ph.D.

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SUMMARY

Background

Elmiron® is used as a drug for the relief of urinary bladder pain associated with interstitial cystitis. We studied the effects of Elmiron® on male and female rats and mice to identify potential toxic or cancer-related hazards to humans.

Methods

We dissolved Elmiron® in deionized water and gave it to groups of male and female rats and mice by depositing it directly into their stomachs through a tube, 5 days a week for 2 years. Each study had four groups of 50 animals; three groups received different doses of Elmiron® and the fourth group, the controls, received only water. Tissues from more than 40 sites were examined for every animal.

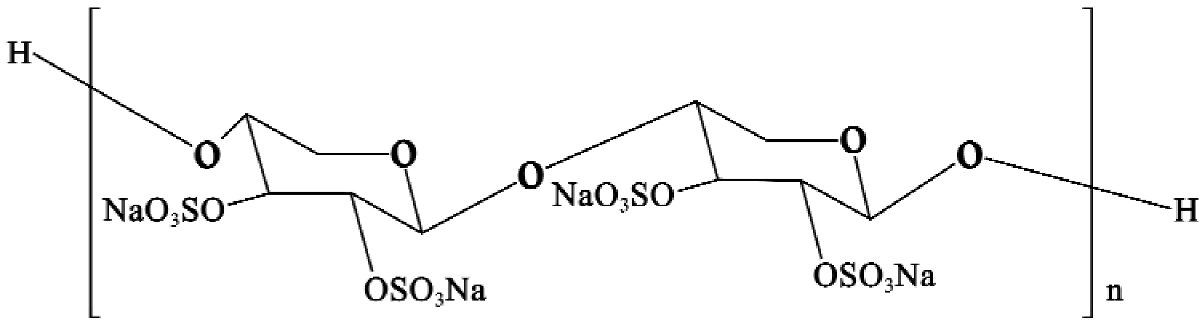
Results

Elmiron® had no effect on the body weight or survival of male or female rats and did not result in any increase in tumors. Male and female mice receiving the highest daily dose of Elmiron® (500 milligrams of Elmiron® per kilogram of body weight) had more liver tumors than did the other groups of mice. Elmiron® caused inflammation of the rectum in male and female rats and mice at the highest dose.

Conclusions

We conclude that Elmiron® did not cause cancer in male or female rats. Elmiron® caused liver tumors (hemangiosarcomas) in male and female mice. An increase in malignant lymphomas in female mice might have been related to Elmiron®.

ABSTRACT



ELMIRON®

CAS No. 37319-17-8

Chemical Formula: $H\text{-}[C_{10}H_{12}O_5(OSO_3Na)_4]_n\text{-}H$ (where n=2 to 12) Molecular Weight: 1,500 to 5,000

Synonyms: PZ68; pentosan polysulfate sodium; sodium xylan polysulfate; xylan hydrogen sulfate, sodium salt
Trade names: Cartrophen, Fibrase, Fibrezym, Hémoclor, SP-54, Thrombocid

Elmiron®, a white powder, is the sodium salt of pentosan polysulfate, a semisynthetic sulfated polyanion composed of β-D-xylopyranose residues with biological properties similar to heparin. Elmiron® is used in the United States for the relief of urinary bladder pain associated with interstitial cystitis. Because of its stimulating effect on fibrinolysis, Elmiron® has been used clinically in the treatment and prevention of thrombotic disorders. The United States Food and Drug Administration nominated Elmiron® for toxicology and carcinogenicity testing by the National Toxicology Program because of its orphan drug status. Male and female F344/N rats and B6C3F$_1$ mice received Elmiron®, which met product specifications provided by the manufacturer, in deionized water by gavage for 2 weeks, 3 months, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium,* rat and mouse bone marrow cells, and mouse peripheral blood erythrocytes.

2-Week Study in Rats

Groups of five male and five female rats were administered 0, 33, 111, 333, 1,000, or 3,000 mg Elmiron®/kg body weight in deionized water by gavage, 5 days per week, for 16 days. Elmiron® administration had no effect on survival or body weight gain. Activated partial thromboplastin time was significantly increased in 3,000 mg/kg rats. Liver weights of 3,000 mg/kg rats were significantly greater than those of the vehicle controls. Hepatocellular cytoplasmic vacuolization occurred in all 3,000 mg/kg females.

2-Week Study in Mice

Groups of five male and five female mice were administered Elmiron® in deionized water by gavage at doses of 0, 33, 111, 333, 1,000, or 3,000 mg/kg, 5 days per week, for 16 days. All mice survived to the end of the study. Mean body weight gains of male mice administered 333 mg/kg or greater were significantly greater than that of the vehicle control group. Liver weights of 1,000 and 3,000 mg/kg males were significantly increased.

3-Month Study in Rats

Groups of 10 male and 10 female rats were administered Elmiron® in deionized water by gavage at doses of 0, 63,

125, 250, 500, or 1,000 mg/kg, 5 days per week, for 14 weeks. No deaths were attributed to administration of Elmiron®. Mean body weights of 125 mg/kg males were less than those of vehicle controls and the mean body weights of all dosed groups of females were greater. Hematology results indicated that Elmiron®, at the doses selected, induced a minimal erythron decrease and leukocyte and platelet count increases that may have been secondarily related to the inflammatory lesions observed in various tissues of rats. Liver and spleen weights of males administered 250 mg/kg or greater were significantly increased. Liver weights of all dosed groups of females and kidney, lung, and spleen weights of 1,000 mg/kg females were significantly increased. Histiocytic cellular infiltration, chronic active inflammation, and ulcers of the rectum occurred in most 500 and 1,000 mg/kg rats. Administration of Elmiron® was associated with the presence of vacuolated histiocytes in the mandibular and mesenteric lymph nodes, lung, kidney, and liver of male and female rats. Histochemical investigations of the vacuolated histiocytes indicated the presence of neutral and acidic mucins and lipid material within the vacuoles. Transmission electron microscopy identified these vacuoles as lysosomal structures that exhibited a variety of contents.

3-Month Study in Mice

Groups of 10 male and 10 female mice were administered Elmiron® in deionized water by gavage at doses of 0, 63, 125, 250, 500, or 1,000 mg/kg, 5 days per week, for 14 weeks. One 250 mg/kg female mouse was sacrificed moribund on day 84; all other mice survived to the end of the study. Mean body weights of dosed groups were similar to those of the vehicle control groups. Hematology results indicated that Elmiron®, at the doses selected, induced a minimal erythron decrease and leukocyte and platelet count increases that may have been secondarily related to the inflammatory lesions observed in various tissues of mice. Liver weights of 500 mg/kg males and 1,000 mg/kg males and females and spleen weights of 1,000 mg/kg males were significantly increased. Histiocytic cellular infiltration and chronic active inflammation of the rectum occurred in most 1,000 mg/kg mice. Administration of Elmiron® was associated with the presence of vacuolated histiocytes in the mandibular and mesenteric lymph nodes, liver, and spleen of males and females. Histochemical investigations of the vacuolated histiocytes indicated the presence of neutral and acidic mucins within the vacuoles. Transmission electron microscopy identified these vacuoles as lysosomal structures that exhibited a variety of contents.

2-Year Study in Rats

Groups of 50 males and 50 females were administered Elmiron® in deionized water by gavage at doses of 0, 14, 42, or 126 mg/kg to males and 0, 28, 84, or 252 mg/kg to females, 5 days per week, for 104 or 105 weeks. Survival of all dosed groups of rats was similar to that of the vehicle control groups. Mean body weights of all dosed groups were similar to those of the vehicle controls throughout the 2-year study.

Microscopically, myxomatous changes were present in the rectum of 56% of 126 mg/kg males and 83% of 252 mg/kg females. The incidences of chronic active focal alveolar inflammation of the lung were increased in all dosed groups. The incidences of histiocytic cellular infiltration of the mesenteric lymph nodes were increased in 42 and 126 mg/kg males and in 84 and 252 mg/kg females, and lymphohistiocytic hyperplasia was present in the spleen of 126 mg/kg males and 252 mg/kg females.

2-Year Study in Mice

Groups of 50 males and 50 females were administered Elmiron® in deionized water by gavage at doses of 0, 56, 168, or 504 mg/kg, 5 days per week, for 104 or 105 weeks. Survival of all dosed groups of mice was similar to that of the vehicle control groups. Mean body weights of males were similar to those of vehicle controls. Mean body weights of 504 mg/kg females were progressively less than those of the vehicle controls during the second year of the study.

Increased incidences of hemangiosarcomas of the liver and hepatocellular neoplasms were observed in male and female mice. The incidences of hemangiosarcomas in the 504 mg/kg groups exceeded the historical control ranges for males and females; both the trend and the incidence in the 504 mg/kg groups were significant for males. Hemangiosarcomas in males and females were attributed to Elmiron® administration. The incidence of hepatocellular adenoma in 504 mg/kg females was significantly increased and exceeded the historical control range; the trends for hepatocellular adenoma and for hepatocellular adenoma or carcinoma (combined) were also significant in females and were attributed to Elmiron® administration. There was also a marginal increase in the incidences of hepatocellular neoplasms in male mice, which may have been associated with Elmiron® administration.

Malignant lymphomas occurred with a positive trend in female mice; the incidence in the 504 mg/kg group was also significantly increased and matched the upper limit of the historical control range. These malignant lymphomas may have been associated with Elmiron® administration.

Nonneoplastic lesions related to the administration of Elmiron® occurred in the liver, rectum, mesenteric lymph node, and spleen of 504 mg/kg mice and to a lesser extent in 168 mg/kg mice. These lesions were similar to those observed in the 3-month study.

Genetic Toxicology

Elmiron® was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535 with or without induced hamster or rat liver S9 enzymes. No increases in the frequency of micronucleated polychromatic erythrocytes were seen in bone marrow cells of rats or mice administered Elmiron® by gavage three times at 24-hour intervals. No significant alterations in the frequency of micronucleated normochromatic erythrocytes were seen in peripheral blood samples from male or female mice administered Elmiron® for 3 months by gavage.

Conclusions

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of Elmiron® in male F344/N rats administered 14, 42, or 126 mg/kg or in female F344/N rats administered 28, 84, or 252 mg/kg. There was *some evidence of carcinogenic activity* of Elmiron® in male $B6C3F_1$ mice based on increased incidences of liver hemangiosarcoma. The increased incidences of hepatocellular neoplasms in male mice may have been related to Elmiron® administration. There was *some evidence of carcinogenic activity* of Elmiron® in female $B6C3F_1$ mice based on the increased incidences of liver hemangiosarcoma and hepatocellular neoplasms. The increased incidences of malignant lymphomas in female mice may have been related to Elmiron® administration.

Elmiron® administration caused increased incidences of nonneoplastic lesions (presence of vacuolated histiocytes) of the rectum, lung, mesenteric lymph node, and spleen (males) in rats and of the liver, rectum, mesenteric lymph node, and spleen in mice.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Elmiron®

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses in deionized water by gavage	0, 14, 42, or 126 mg/kg	0, 28, 84, or 252 mg/kg	0, 56, 168, or 504 mg/kg	0, 56, 168, or 504 mg/kg
Body weights	Dosed groups similar to the vehicle control group	Dosed groups similar to the vehicle control group	Dosed groups similar to the vehicle control group	504 mg/kg group less than the vehicle control group
Survival rates	26/50, 29/50, 25/50, 28/50	30/50, 31/50, 28/50, 27/50	39/50, 40/50, 38/50, 30/50	37/50, 38/50, 37/50, 34/50
Nonneoplastic effects	Large intestine, rectum: myxomatous change (0/48, 1/48, 3/49, 25/45) infiltration cellular, histiocyte (0/48, 0/48, 0/49, 4/45) Lung: alveolus, inflammation, chronic active, focal (0/50, 6/50, 11/50, 14/50) Lymph node, mesenteric: infiltration cellular, histiocyte (1/50, 1/50, 18/50, 39/49) Spleen: lymphohistiocytic hyperplasia (2/50, 2/50, 2/50, 8/50)	Large intestine, rectum: myxomatous change (0/46, 1/43, 12/44, 35/42) infiltration cellular, histiocyte (0/46, 0/43, 0/44, 18/42) Lung: alveolus, inflammation, chronic active, focal (2/50, 25/50, 27/50, 34/50) Lymph node, mesenteric: infiltration cellular, histiocyte (0/50, 3/50, 27/50, 42/49)	Liver: inflammation, chronic (11/50, 15/50, 23/50, 33/50) Large intestine, rectum: inflammation, chronic active (0/49, 0/47, 1/46, 8/44); necrosis (0/49, 0/47, 0/46, 5/44); metaplasia, squamous (0/49, 0/47, 0/46, 5/44); infiltration cellular, histiocyte (0/49, 0/47, 0/46, 6/44); myxomatous change (0/49, 0/47, 0/46, 13/44) Lymph node, mesenteric: infiltration cellular, histiocyte (0/48, 15/46, 34/45, 37/41) Spleen: infiltration cellular, histiocyte (0/49, 1/50, 1/49, 23/49)	Liver: clear cell focus (0/50, 4/49, 1/50, 21/49) Large intestine, rectum: inflammation, chronic active (0/45, 0/45, 2/44, 32/46); necrosis (0/45, 0/45, 1/44, 24/46); metaplasia, squamous (0/45, 0/45, 1/44, 26/46); infiltration cellular, histiocyte (0/45, 0/45, 2/44, 10/46); myxomatous change (0/45, 3/45, 21/44, 31/46) Lymph node, mesenteric: infiltration cellular, histiocyte (0/47, 23/44, 35/42, 25/45) Spleen: infiltration cellular, histiocyte (0/47, 3/48, 12/47, 28/46)
Neoplastic effects	None	None	Liver: hemangiosarcoma (2/50, 0/50, 4/50, 9/50)	Liver: hemangiosarcoma (1/50, 1/49, 1/50, 4/49); hepatocellular adenoma (7/50, 5/49, 4/50, 15/49); hepatocellular adenoma or carcinoma (10/50, 8/49, 9/50, 18/49)
Equivocal findings	None	None	Liver: hepatocellular adenoma or carcinoma (23/50, 23/50, 26/50, 31/50)	All Organs: malignant lymphoma (7/50, 8/50, 6/50, 16/50)
Level of evidence of carcinogenic activity	No evidence	No evidence	Some evidence	Some evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9
Micronucleated erythrocytes	
Rat bone marrow *in vivo:*	Negative
Mouse bone marrow *in vivo:*	Negative
Mouse peripheral blood *in vivo:*	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as “were also related” to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as “may have been” related to chemical exposure.

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 Elmiron® on September 5, 2002, 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 the 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.

Norman R. Drinkwater, Ph.D., Chairperson
McArdle Laboratory for Cancer Research
University of Wisconsin-Madison
Madison, WI

Kim Boekelheide, M.D., Ph.D.
Division of Biology and Medicine
Department of Pathology and Laboratory Medicine
Brown University
Providence, RI

Michael R. Elwell, D.V.M., Ph.D.
Pfizer, Inc.
Groton, CT

Shuk-Mei Ho, Ph.D., Principal Reviewer
Department of Surgery, Division of Urology
University of Massachusetts Medical School
Worcester, MA

James E. Klaunig, Ph.D., Principal Reviewer
Division of Toxicology
Department of Pharmacology and Toxicology
Indiana University School of Medicine
Indianapolis, IN

Walter W. Piegorsch, Ph.D.
Department of Statistics
University of South Carolina
Columbia, SC

Stephen M. Roberts, Ph.D., Principal Reviewer
Department of Physiological Sciences
College of Veterinary Medicine
University of Florida
Gainesville, FL

Richard D. Storer, M.P.H., Ph.D.
Department of Genetic and Cellular Toxicology
Merck Research Laboratories
West Point, PA

Mary Anna Thrall, D.V.M.
Department of Pathology
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, CO

Mary Vore, Ph.D.
Graduate Center for Toxicology
University of Kentucky
Lexington, KY

Cheryl Lyn Walker, Ph.D.
M.D. Anderson Cancer Center
The University of Texas
Smithville, TX

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On September 5, 2002, the draft Technical Report on the toxicology and carcinogenesis studies of Elmiron® received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of Elmiron® by describing the therapeutic uses and mechanisms of the drug, the design and dose selection for the gavage studies, the survival and body weight effects, and the compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year gavage studies were *no evidence of carcinogenic activity* of Elmiron® in male F344/N rats administered 14, 42, or 126 mg/kg or in female F344/N rats administered 28, 84, or 252 mg/kg and *some evidence of carcinogenic activity* of Elmiron® in male and female $B6C3F_1$ mice. The increased incidences of malignant lymphomas may have been related to Elmiron® administration.

Dr. Klaunig, the first principal reviewer, asked if the occurrence of hemangiosarcomas in male mice might have been related to changes in hemosiderin, hemolysis, or to macrophages. He also asked if there was any relationship between the hemangiosarcomas and lysosomal storage malfunction. He noted that the liver neoplasms in female mice were predominantly adenomas.

Dr. Ho, the second principal reviewer, asked for clarification of the interpretive conclusion for the lymphomas in female mice.

Dr. Roberts, the third principal reviewer, asked if the strength of evidence of the hemangiosarcomas in female mice contributed to the call of *some evidence*.

Dr. Abdo replied that neither hemolysis nor hemosiderin deposition were observed. Dr. A. Nyska, NIEHS, said that while some inflammation was seen in the livers of mice, it was not of sufficient severity to contribute to tumor formation. He noted that other sulfated polysaccharides that induced a similar type of histiocytic infiltration induced tumors in the large intestine, an effect not seen in the present study. Explaining the rationale for the conclusions, Dr. J.K. Haseman, NIEHS, noted that hemangiosarcomas are very uncommon tumors in female mice, and their association with chemical administration was supported by a similar effect in the males. The lymphomas, where the incidences were also of borderline statistical significance with a highly variable background rate, were considered *equivocal evidence* in part because no corresponding increase was seen in the males. Dr. J.R. Hailey, NIEHS, added that these rapidly developing tumors did not spread to other organs any more in the exposed animals than in the control groups.

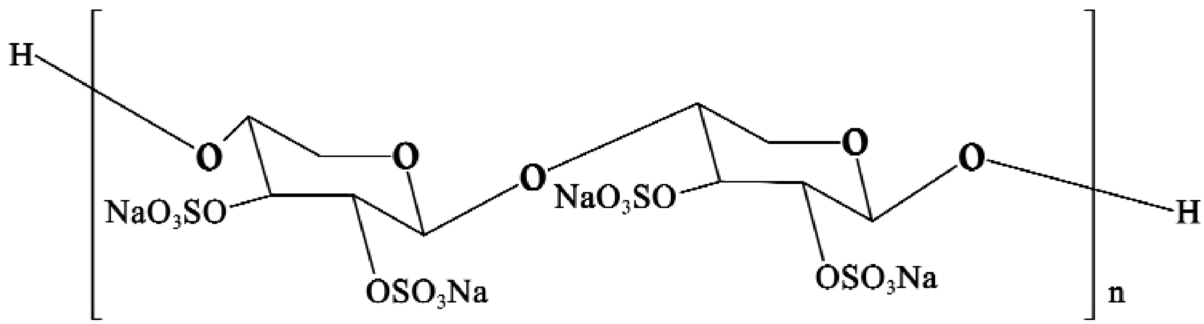
Dr. Elwell noted that the few hemangiomas were not included with hemangiosarcomas for analysis, though in some other studies these tumors were pooled. Dr. Nyska replied that the three hemangiosarcomas observed in the top dose group of female mice occurred in organs other than the liver, so in this case combining them for analysis may not have been appropriate. Dr. Hailey added that in studies in which vascular tumors increased, the vast majority were hemangiosarcomas.

Dr. Piegorsch suggested that the statistical significance of the lymphomas in female mice might warrant a stronger conclusion than "may have been related". Dr. Boekelheide questioned whether the contribution of the hepatocellular neoplasms to the conclusion for male mice was weakened by most of the neoplasms being adenomas. Dr. J.R. Bucher, NIEHS, suggested that terminology consistent with previous reports would be "hepatocellular neoplasms, predominantly adenomas" and that, of the effects in female mice, the hemangiosarcomas were the most significant biologically.

Dr. Roberts moved that the conclusions be accepted as written, and Dr. Klaunig seconded the motion. Dr. Piegorsch argued for inclusion of the malignant lymphomas into the *some evidence* conclusion for female mice. Dr. Bucher observed that lymphomas historically had a highly variable incidence, and Dr. Hailey described some other NTP studies in which similar incidences of lymphomas were judged *equivocal evidence* or *no evidence*. He added that the site of origin (spleen) of the lymphomas in this study was not unusual.

Dr. Piegorsch offered an amendment that the lymphomas be included in the list of neoplasms supporting the conclusion of some evidence for female mice. Dr. Ho seconded the motion, which failed by a vote of seven to three. Dr. Roberts offered an amendment that the hepatocellular neoplasms be listed before the hemangiosarcomas in the female mouse conclusion. The amendment failed for lack of a second. The original motion was then approved unanimously with 10 votes.

INTRODUCTION



ELMIRON®

CAS No. 37319-17-8

Chemical Formula: $H\text{-}[C_{10}H_{12}O_5(OSO_3Na)_4]_n\text{-}H$ (where n=2 to 12) Molecular Weight: 1,500 to 5,000

Synonyms: PZ68; pentosan polysulfate sodium; sodium xylan polysulfate; xylan hydrogen sulfate, sodium salt
Trade names: Cartrophen, Fibrase, Fibrezym, Hémoclor, SP-54, Thrombocid

Chemical and Physical Properties

Elmiron®, a white powder, is the sodium salt of pentosan polysulfate, a semisynthetic sulfated polyanion composed of β-D-xylopyranose residues with properties similar to heparin. It is slightly hygroscopic, with a solubility in water of 1 to 10. The pH of a 10% solution in water is 6.0 (*Merck Index*, 1996).

Production, Use, and Human Exposure

Elmiron® (pentosan polysulfate sodium) is prepared by reaction of xylan with sulfonic acid in pyridine to give a pyridine salt. This salt is treated with an aqueous solution of chlorine dioxide to yield a white precipitate. An aqueous solution of this precipitate is reacted with 5 N sulfuric acid and hydrogen peroxide. The reaction mixture is neutralized with 5 N sodium hydroxide, bleached with chlorine dioxide, and dialyzed until a negative test for sulfate ion is obtained on the outside water. The dialyzate is then concentrated to yield the solid sodium xylan polysulfate, which is purified by crystallization from an ethanol-acetone mixture. Elmiron® is used for the treatment of thrombosis and hyperlipidemia in Argentina, France, Great Britain, Italy, Mexico, Portugal, and South Africa (Tardy-Poncet *et al.*, 1994). In the United States, it has been approved by the Food and Drug Administration (FDA) for the relief of urinary bladder pain associated with interstitial cystitis (Alza, 1998). The recommended dosage for urinary bladder pain is 300 mg taken orally in 100 mg capsules three times daily. Because of its stimulating effect on fibrinolysis, Elmiron® has been used clinically in the treatment and prevention of thrombotic disorders (Joffe, 1976; Vinazzer, 1984).

Human exposure to Elmiron® in the United States occurs primarily in the treatment of interstitial cystitis. An estimated 450,000 people in the United States suffer from interstitial cystitis (Alza, 1998). No exposure guidelines have been recommended by The American Conference of Governmental Industrial Hygienists, the National Institute for Occupational Safety and Health, or the Occupational Safety and Health Administration.

Absorption, Distribution, Metabolism and Excretion

Experimental Animals

Radiolabeled (tritium) pentosan polysulfate (5 mg/kg) was administered orally or intravenously to Sprague-Dawley rats (number and sex not reported) (Dencker *et al.*, 1985). The rats were terminated at selected post-exposure time periods (4 hours after intravenous and 1 hour after oral administration) and subjected to autoradiography. Radioactivity was distributed extensively in the whole animal with notable amounts in connective tissue and lesser amounts in bone and cartilage. Detection of radioactivity in the upper intestine suggested some hepatic excretion. The most notable observation was the high concentration of activity in the urine and the preferential localization of activity corresponding to the lining of the urinary tract (pelvis, ureter, and bladder). The distribution after oral administration was similar to that observed for intravenous administration, but the activity was lower.

Pentosan polysulfate (labeled and unlabeled) was administered intravenously to groups of two or three New Zealand White rabbits at doses of 6.3 to 12,656 µg/kg (Cadroy *et al.*, 1987). The disappearance of radioactivity from the plasma was triphasic. The half-lives of the alpha phase (distribution) and gamma phase (residual radioactivity) were 1.8 to 6.8 and 189 to 309 minutes, respectively, and were not dose dependent; similarly, the volume of distribution was not dose dependent. The half-life of the beta phase (disappearance) was dose dependent and was 15.1 to 18.6 minutes at 6.3 to 316 µg/kg and was 17.8 to 31.8 minutes at 632 to 6,328 µg/kg. The half-life was 41.5 minutes at 12,656 µg/kg. The clearance of pentosan polysulfate was reduced with increasing dose, suggesting a progressive saturation of a clearance mechanism.

Humans

Only parenteral routes of administration were used in human studies. Studies using iodine radiolabeled Elmiron® and heparin radiotracer techniques were developed for use in toxicokinetic studies (MacGregor *et al.*, 1984); the use of ^{35}S- and ^{3}H-Elmiron® was problematic because of the loss of the label from extensive metabolism and the difficulty of recovering a sufficient amount of labeled material for counting. These radiolabeled materials are usually administered with unlabeled Elmiron® in chemical disposition studies in which a competitive binding assay for sulfated polysaccharides is used to measure the concentration of Elmiron® in biological fluids.

Five healthy volunteers (four male and one female) were administered subcutaneous injections of 75 mg Elmiron®; plasma concentrations were measured with a competitive binding assay (CBA) that used ^{125}I-heparin as the tracer (Dawes *et al.*, 1986). The absorption was variable, with an area under the curve of 6.7 to 12 µg/hour per mL of plasma. Maximal plasma concentrations were achieved after 2 to 3 hours and were 1.3 to 3.1 µg/mL. Clearance from plasma was almost complete after 7 hours. The recovery of Elmiron® from the urine ranged from 2.9 to 4.1 percent, and the correlation coefficient between the excretion rate (µg/hour) and plasma concentration for the five subjects was 0.69. Activated partial thromboplastin time (APTT) determinations and antifactor Xa clotting assays were used in conjunction with the CBA. The results of the APTT determinations were consistent with those of the CBA. Antifactor Xa activity was detected in plasma even after the clearance of Elmiron®, indicated by the CBA and APTT.

Elmiron® was administered to two male and one female volunteers at weekly intervals, and a CBA was used to measure the clearance of Elmiron® from plasma (MacGregor *et al.*, 1985). When administered intravenously, the mean half-lives in plasma were 7, 21, and 55 minutes at 1, 10, and 100 mg, respectively. Elmiron® could not be detected in plasma after the intravenous administration of 0.1 mg. Following subcutaneous administration of 100 mg, plasma levels peaked at 120 minutes. Elmiron® was completely cleared from the plasma at 480 minutes postinjection.

The organ distribution and catabolism of Elmiron® were examined in five healthy volunteers (MacGregor *et al.*, 1984). Three subjects were injected intravenously with 0.1, 1, or 7 mg Elmiron® (unlabeled) containing an iodinated derivative (^{123}I-Elmiron®). A volunteer was administered the intravenous tracer alone and then the tracer plus 50 mg Elmiron® at 3-week intervals. A fifth volunteer was injected subcutaneously with 50 mg Elmiron® containing the radioactive tracer. Clearance of radioactivity was biphasic. The half-life of radioactivity in the blood was 13 to 18 minutes after the intravenous doses of 0.1, 1, and 7 mg ^{123}I-Elmiron® and 45 minutes after the 50 mg subcutaneous dose. Ninety percent of the radioactivity was removed from the blood within 80 minutes of intravenous injection and within 240 minutes of subcutaneous injection. The remainder of the radioactivity was removed in a second phase within 24 to 96 hours. Initially, the clearance of the drug from the blood and plasma was similar, but the radioactivity in plasma decreased more rapidly than in whole blood due to the progressive association of the tracer with the packed cell fraction. Following subcutaneous injection, radioactivity was detected in the blood within 5 minutes and peaked at 80 minutes. Radioactivity was detected in the urine within 1 hour following intravenous administration. During the 24 hours following administration by either route, the average recovery in the urine was 31% and did not appear to be dose-related.

The metabolic fate of Elmiron® was also examined using a combination of gel filtration and Polybrene binding techniques (MacGregor *et al.*, 1984). Following intravenous injection, Elmiron® was rapidly cleared from the plasma but returned later in desulfated form. Removal appeared to be slower when the tracer was injected subcutaneously with 50 mg Elmiron® than when used in conjunction with lower intravenous doses. The authors speculated that the most likely sites of desulfation were the liver and spleen, which are rich sources of sulfatases. Analysis of postinjection urine samples showed the presence of not only sulfated Elmiron® but also desulfated macromolecular and depolymerized Elmiron®. The metabolic fate appeared to be similar with either route of administration.

Photographic images obtained at 5-minute intervals 7.5 to 47.5 minutes after an intravenous injection of 1 mg Elmiron® with radiotracer into one human subject demonstrated progressive uptake by the liver and spleen (MacGregor *et al.*, 1984). After 50 minutes, 60% of the dose was associated with the liver and 7.5% with the spleen. After 3 hours, a profile scan showed that 60% of the radioactivity was found in the liver and spleen and 13% in the bladder. After 43 hours, 37% of the radioactivity was retained in the liver and spleen. Over an 18-hour postinjection period, the urine contained 37% of the radioactivity. Stool samples collected 18 and 42 hours postinjection contained 0.13% and 0.07% of the radioactivity, respectively.

Pharmacology

Elmiron® has significant anticoagulant properties in humans and animals. A single dose of the drug produced a significant increase in plasminogen activator activity for 3 to 6 hours when administered orally (500 mg) or subcutaneously (50 mg) to six healthy male volunteers (Marsh *et al.*, 1985). It reduced thrombin generation, impaired the generation of chromogenic antifactor Xa, and increased levels of lipoprotein lipase and euglobulin clot lysis (Fischer *et al.*, 1982). Following intravenous injection of 40 mg pentosan polysulfate (the free acid of Elmiron®) to three healthy humans, a significant prolongation of prothrombin clotting time occurred (Scully *et al.*, 1983). Subcutaneous or intravenous injection of pentosan polysulfate to healthy volunteers increased fibrinolysis without evoking the release of tissue-type plasminogen activator (Sie *et al.*, 1985). Pentosan polysulfate produced a dose-dependent anticoagulant effect following intramuscular or subcutaneous administration (25, 50, 75, 100, or 150 mg) to eight healthy volunteers (Thebault *et al.*, 1985).

Elmiron® has been used in Europe after surgery to retard or prevent the formation of deep vein thrombosis. One study showed a 36% reduction in the incidence of deep vein thrombosis in patients undergoing Elmiron® therapy following surgery (Joffe, 1976). Side effects have included thrombocytopenia (Follea *et al.*, 1985; Gouault-Heilmann *et al.*, 1985) and gastrointestinal disturbances including dyspepsia and diarrhea (Fritjofsson *et al*., 1987; Wedren, 1987). These effects occurred after oral doses of 200 mg Elmiron® given twice daily for up to 6 months.

The anticoagulant properties of Elmiron® have been evaluated in rats and rabbits when controlled subdermal damage was used to induce bleeding. Intravenous doses of 2.6 and 9.2 anti-factor Xa units/kg body weight were used to inhibit thrombus formation by 50% and to enhance bleeding by 300%, respectively (Hobbelen *et al.*, 1985). An increase in fibrinolysis occurred in groups of four to eight female Sprague-Dawley rats administered 2, 4, 6, or 10 mg Elmiron®/kg body weight by subcutaneous injection, 6 mg/kg by intramuscular injection, or 10 mg/kg by intravenous injection.

The effect of Elmiron® on microvascular hemostasis and platelet activity *in vivo* was examined in the ear and mesenteric microcirculation of the rabbit. Groups of six male and six female New Zealand White rabbits were given intravenous doses of 0, 0.5, 1, 2, or 5 mg/kg (Esquivel *et al.*, 1982). The primary hemostatic plug formation time (PHT) and the total hemostatic plug formation time (THT) were determined in venules and arterioles. Dose-related increases in PHT and THT in venules and arterioles (highest doses only) were observed with a concurrent decrease in platelet activity.

Following an intravenous injection of 0.5 mg/kg Elmiron®, induced occluding thrombi decreased from 80% in controls to 0% in treated male and female rabbits (strain and number not specified) (Bjorck *et al.*, 1984). Rabbits (sex, strain, and number not specified) administered 12 or 24 mg/kg Elmiron® intravenously showed a 19- or 25-fold increase, respectively, in blood loss following ear piercing (Fernandez *et al.*, 1986).

Toxicity

Experimental Animals

After a review of the available literature, no information regarding the acute toxic or lethal effects of Elmiron® was found. Animal studies have been limited and directed more towards the evaluation of the anticoagulant effects and toxicokinetics.

The potential reproductive toxicity of Elmiron® in Sprague-Dawley rats was assessed in a continuous breeding protocol (NTP, 1997). In rats (20 per sex), gavage administration of up to 1,000 mg/kg did not affect reproductive performance. No breeding, fertility, or necropsy endpoints related to reproduction were altered by the drug. No differences were noted in epididymal sperm morphology, epididymal sperm density, sperm motility, testicular spermatid head counts, percentage of normal sperm, or estrous cyclicity.

Elmiron® is known to be chondroprotective *in vitro* by increasing rat collagenase activity (Nethery *et al.*, 1992). The drug has been shown to slow the degradation of cartilage occurring in animal models with osteoarthritis and to promote the repair of damaged cartilage (Ghosh, 1988, 1999; Hutadilok *et al.*, 1988).

Humans

As in rats, Nethery *et al.* (1992) showed that Elmiron® increases human collagenase activity. Patients with advanced cancer who received 180, 270, 400, 600, or 800 mg/m^2 Elmiron® orally twice daily developed moderate to severe proctitis and diarrhea within 1 to 2 months of treatment at all doses tested. These effects were reversed upon cessation of treatment (Marshall *et al.*, 1997).

Elmiron® has also been reported to increase the number of circulating T-cells in migraine patients with low basophil and T-cell counts (Thonnard-Newman and Bigelow, 1988). In addition, it has inhibitory effects on human immunodeficiency virus replication (Baba *et al.*, 1988). When tested on viruses grown in human peripheral mononuclear cells (PMNC), Elmiron® was found to be nontoxic. At doses greater than 1 µg, the drug had a proliferative effect on uninfected and a protective effect on infected PMNC, and it enhanced virus production at low concentrations (Anand *et al.*, 1990).

Pentosan polysulfate (free acid) did not cross the placenta during the middle trimester of pregnancy following intravenous administration of 50 mg to eight pregnant women (Forestier *et al.*, 1986); a control group consisted of untreated pregnant women. Comparison of the maternal results of hemostasis prior to and 30 minutes following Elmiron® injection indicated an increase in APTT, an impairment in factor Xa generation, and a decrease in factor V level. In contrast, no changes in these parameters occurred in fetal plasma.

Carcinogenicity

Experimental Animals

No information on the carcinogenicity of Elmiron® in animals was found in a review of the literature. Furthermore, no information was available on the chronic toxicity or carcinogenicity of chemicals structurally similar to this drug. However, Elmiron® was reported to block the growth of subcutaneously administered human tumor zenografts in nude mice and angiogenesis induced by Kaposi's sarcoma-derived fibroblast growth factor. Subcutaneous growth of tumors from human tumor cell lines in athymic nude mice was inhibited in a dose-dependent fashion after daily intraperitoneal injections of the drug (Lippman and Wellstein, 1992).

Humans

No epidemiology studies of Elmiron® were found in a review of the literature.

Genetic Toxicity

No published mutagenicity data for Elmiron® were identified in a search of the literature.

Study Rationale

The FDA nominated Elmiron® for toxicity and carcinogenicity testing by the NTP because of its orphan drug status. Under the Investigational New Drug Procedure, Elmiron® is approved for use in the United States for the treatment of interstitial cystitis (inflammation of the bladder). Consequently, there is the potential for long-term exposure of individuals undergoing therapy. Prechronic and chronic studies in rats and mice were recommended due to the lack of adequate toxicity and carcinogenicity data.

MATERIALS AND METHODS

Procurement and Characterization of Elmiron®

Elmiron® was obtained from Baker Norton Pharmaceuticals (Miami, FL) in three lots. Identity and purity analyses were conducted by the analytical chemistry laboratory (Research Triangle Institute, Research Triangle Park, NC) and by the 3-month and 2-year study laboratory (Appendix I). Reports on analyses performed in support of the Elmiron® studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white powder, was identified as Elmiron® by the analytical chemistry laboratory using molecular weight, refractive index, pH, optical rotation, and sulfur content (determined by Galbraith Laboratories, Knoxville, TN) and by the study laboratory with infrared spectroscopy. Molecular weight was determined using gel permeation high-performance liquid chromatography (HPLC). Sulfur content was determined by elemental analysis. The observed molecular weights, refractive indices, pH values, and optical rotations were consistent with literature values (*Merck Index*, 1996). The infrared spectra were consistent with the structure of Elmiron®. The sulfur contents of all lots were greater than 15%, consistent with manufacturer specifications. Because all measured parameters were in general agreement with manufacturer specifications, the three lots of chemical were presumed to consist largely, if not wholly, of sulfated xylan.

Purity analysis of this test article was not typical because the characteristics of the material were defined by manufacturing specifications. Therefore, chromatographic analyses were conducted to ensure that the molecular weight profile remained within the manufacturer's specifications over the course of the studies.

Characterization of all three Elmiron® lots was conducted by the analytical chemistry laboratory using Karl Fischer titration and HPLC. For lot 30018-01, Karl Fischer titration indicated 6.88% ± 0.94% water. HPLC indicated a major peak, one lesser peak with an area of 13% of the total area, and three minor impurities with areas of 0.2% or less. For lot R50996-08, Karl Fischer titration indicated 4.06% ± 0.83% water. HPLC indicated a major peak only. For lot R60819-10, Karl Fischer titration indicated 3.37% ± 0.17% water. HPLC indicated a major peak and one impurity peak accounting for 10.4% of the total peak area by one system and a major peak and two impurity peaks with areas of 11.3% and 0.7% of the total peak area by a second system.

Stability data provided by the manufacturer showed no degradation of the bulk chemical when stored at 80° C for 48 hours. All lots of the bulk chemical were stored in amber glass containers with Teflon®-lined lids at room temperature, protected from light. Stability of the bulk chemical was monitored by the study laboratory during the 3-month and 2-year studies using HPLC. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

Dose formulations were prepared once (2-week studies) or every 4 weeks (3-month and 2-year studies) by mixing Elmiron® with deionized water (Table I2). Formulations were stored refrigerated in glass bottles for up to 4 weeks (2-week studies) or 35 days.

Stability studies of a 2.53 mg/mL dose formulation were conducted by the analytical chemistry laboratory using HPLC. Stability was confirmed for 35 days for dose formulations stored in polypropylene vials at temperatures up to 28° C or for 3 hours under simulated animal room conditions.

During the 2-week studies, the dose formulations and animal room samples were analyzed once by the analytical chemistry laboratory using HPLC (Table I3). All 10 dose formulations and all animal room samples were within 10% of the target concentrations. During the 3-month and 2-year studies, the dose formulations were analyzed periodically by the study laboratory using HPLC; animal room samples were also analyzed. During the 3-month studies, all 18 dose formulations and all animal room samples were within 10% of the target concentrations (Table I4). During the 2-year studies, all 66 dose formulations and all animal room samples were within 10% of the target concentrations (Table I5).

2-Week Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were 5 weeks old. Animals were quarantined for 11 (rats) or 12 (mice) days and were 6 (rats) or 7 (mice) weeks old on the first day of the studies. Groups of five male and five female rats and mice were administered 0, 33, 111, 333, 1,000, or 3,000 mg Elmiron®/kg body weight in deionized water by gavage, 5 days per week for 16 days. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage; male mice were housed individually. The animals were weighed and clinical findings were recorded initially, on day 8, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

For evaluation of activated partial thromboplastin time (APTT) at the end of the 2-week study, rats were anesthetized with Metofane™ (Pitman-Moore, Inc., Mundelein, IL), and blood was collected by cardiac puncture. Samples were placed in tubes containing sodium citrate anticoagulant, rocked by hand, and shipped over ice to PCL Clinical Laboratory. Measurements were performed on an RA-4 coagulation analyzer (Organon Teknika, Boxtel, Netherlands).

Necropsies were performed on all rats and mice. The heart, right kidney, liver, lung, spleen, right testis, and thymus were weighed. Histopathologic examinations were performed on vehicle control rats and mice, 1,000 mg/kg female rats (liver only), and 3,000 mg/kg rats and mice. Table 1 lists the tissues and organs examined.

3-Month Studies

The 3-month studies were conducted to evaluate the cumulative toxic effects of repeated exposure to Elmiron® and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were 3 or 4 weeks old. Rats were quarantined for 11 (males) or 12 (females) days and were 5 or 6 weeks old on the first day of the study. Mice were quarantined for 13 (males) or 14 (females) days and were 6 weeks old on the first day of the study. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Approximately 1 month after the studies began and at study termination, serologic analyses were performed on five male and five female sentinel rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female core study rats and mice and groups of 20 male and 20 female clinical pathology study rats were administered Elmiron® in deionized water by gavage at doses of 0, 63, 125, 250, 500, or 1,000 mg/kg, 5 days per week, for 14 weeks. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage; male mice were housed individually. Clinical findings were recorded weekly for rats and mice. The animals were weighed initially, on day 8, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

On days 4 and 23, clinical pathology study rats were anesthetized with a carbon dioxide/oxygen mixture. On day 4, blood was collected from the posterior vena cava or aorta of 10 males and 10 females for APTT determinations; these rats were then discarded. On days 4 and 23, blood was drawn from the retroorbital sinus of the remaining clinical pathology study rats for hematology and clinical chemistry analyses; on day 23, blood was drawn from these rats for APTT determinations as described for day 4. At study termination, blood was drawn, as previously described, from core study rats for hematology, clinical chemistry, and APTT analyses and from core study mice for hematology analyses. Blood samples were collected into tubes containing sodium citrate for APTT analyses or tubes containing potassium EDTA for hematology; the tubes were inverted by hand. Samples for clinical chemistry analyses were placed in microcollection serum separator tubes and centrifuged. For APTT analyses, citrated plasma was mixed with platelet factor 3, silica, and excess calcium ion; the time from reagent mixing to clot formation was measured. Erythrocyte, platelet, and leukocyte counts, hematocrit values, hemoglobin concentration, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were determined using the Cell-Dyn® 3500 hematology analyzer (Abbott Laboratories, Abbott Park, IL). Clinical chemistry analyses were performed using the Hitachi 704® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN). Reagents were supplied by Abbott Laboratories (Abbott Park, IL) (hematology), Boehringer Mannheim (Indianapolis, IN) (clinical chemistry), or Sigma (St. Louis, MO) (clinical chemistry and APTT). Leukocyte differentials, nucleated erythrocyte counts, and morphological evaluation of blood cells were determined by light microscopy of blood smears stained with modified Wright-Giemsa using a Hema-Tek® slide stainer (Miles Laboratory, Ames Division, Elkhart, IN). Parameters measured are listed in Table 1.

At the end of the 3-month studies, samples were collected for sperm motility and vaginal cytology evaluations on vehicle control and 250, 500, and 1,000 mg/kg core study rats and mice. The parameters evaluated are listed in Table 1. For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

Necropsies were performed on all core study animals. The heart, right kidney, liver, lung, spleen, right testis, and thymus of core study rats and mice were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on all vehicle controls, animals in the lower dose groups that died early, and 1,000 mg/kg core study rats and mice. For all remaining core study groups, tissues were examined to the no-observed effect level. Table 1 lists the tissues and organs routinely examined.

Histiocytic Vacuolation Assessment

Histochemical Investigation

Additional sections of the rectum, liver, mandibular and mesenteric lymph nodes, lung (rats), and spleen (mice) from three male rats and two male mice administered 1,000 mg/kg during the 3-month studies were taken. Slides from these tissues were stained with periodic acid-Schiff (PAS), Alcian Blue (AB), and oil red-O (ORO) to identify material in vacuolated macrophages that were observed in these tissues when stained with hematoxylin and eosin. PAS stains mucin and AB (pH 2.5) stains weakly acidic sulfated mucosubstances, hyaluronic acid, and sialomucins.

Electron Microscopic Investigation

All tissues from the 3-month studies were immersion-fixed in 10% neutral buffered formalin and either embedded in paraffin blocks for light microscopic examination or left in formalin and sealed in plastic bags. Tissues that exhibited significant histiocyte infiltration by light microscopy were retrieved from stored wet tissues, trimmed into approximately 1-mm cubes, and placed in McDowell-Trump electron microscopy fixative (McDowell and Trump, 1976). Tissues from three male rats and two male mice administered 1,000 mg/kg were selected for the electron microscopy tissue evaluation. The lung of all three rats was examined. The rectum of two rats and the mesenteric lymph node of one of these two rats were also examined. The lung and mesenteric lymph node of one mouse and the mandibular lymph node of the other mouse were examined. The selected tissues were processed in Spurr's resin for ultrastructural examination; 1-µ sections were cut, stained with toluidine blue, and examined at selected representative areas for further electron microscopy processing. Thin sections (approximately 90 nm) were cut, mounted on 200-mesh copper grids, stained with 5% methanolic uranyl acetate and Reynold's lead citrate, and examined on a Zeiss 900 transmission electron microscope (Carl Zeiss, Inc., Thornwood, NY). Electron microscopic exposures were taken of selected representative ultrastructural findings and developed into transmission electron micrographs for evaluation.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats and mice were administered Elmiron® in deionized water at doses of 0, 14, 42, or 126 mg/kg (male rats); 0, 28, 84, or 252 mg/kg (female rats); or 0, 56, 168, or 504 mg/kg (mice), 5 days per week, for 104 to 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. Rats were quarantined for 13 (males) or 14 (females) days and were 6 weeks old on the first day of the study. Mice were quarantined for 12 (males) or 11 (females) days and were 6 weeks old on the first day of the study. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Male rats were housed two or three per cage, and female rats and mice were housed five per cage; male mice were housed individually. Feed and water were available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed initially and body weights and clinical findings were recorded every 4 weeks.

Complete necropsies and microscopic examinations were performed on all surviving rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the lung, mesenteric lymph node, rectum, spleen, and urinary bladder of male and female rats; the mammary gland and mediastinal lymph node of female rats; the adrenal gland, liver, mesenteric lymph node, mesentery (fat), rectum, spleen, and urinary bladder of male and female mice; the gallbladder and nose of male mice; and the kidney and pituitary gland of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson 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 PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), 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 decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

Table 1
Experimental Design and Materials and Methods in the Gavage Studies of Elmiron®

2-Week Studies	3-Month Studies	2-Year Studies
Study Laboratory		
Microbiological Associates, Inc. (Bethesda, MD)	Battelle Columbus Operations (Columbus, OH)	Battelle Columbus Operations (Columbus, OH)
Strain and Species		
F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice
Animal Source		
Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies		
Rats: 11 days Mice: 12 days	Rats: 11 (males) or 12 (females) days Mice: 13 (males) or 14 (females) days	Rats: 13 (males) or 14 (females) days Mice: 12 (males) or 11 (females) days
Average Age When Studies Began		
Rats: 6 weeks Mice: 7 weeks	Rats: 5 or 6 weeks Mice: 6 weeks	6 weeks
Date of First Dose		
Rats: April 3, 1995 Mice: April 4, 1995	Rats: March 25 (males) or 26 (females), 1996 Mice: March 27 (males) or 28 (females), 1996	Rats: June 25 (males) or 26 (females), 1997 Mice: June 30 (females) or July 1 (males), 1997
Duration of Dosing		
5 days/week for 16 days	5 days/week for 14 weeks	5 days/week for 104 to 105 weeks
Date of Last Dose		
Rats: April 18, 1995 Mice: April 19, 1995	Rats: June 25 (males) or 26 (females), 1996 Mice: June 27 (males) or 28 (females), 1996	Rats: June 22 (males) or 24 (females), 1999 Mice: June 28 (females) or 30 (males), 1999
Necropsy Dates		
Rats: April 19, 1995 Mice: April 20, 1995	Rats: June 25 (males) or 26 (females), 1996 Mice: June 27 (males) or 28 (females), 1996	Rats: June 21-23 (males) or 23-25 (females), 1999 Mice: June 30 to July 1, 1999 (males) or June 28-29, 1999 (females)
Average Age at Necropsy		
9 weeks	Rats: 18 or 19 weeks Mice: 19 weeks	Rats: 110 to 111 weeks Mice: 110 weeks
Size of Study Groups		
5 males and 5 females	Rats: Core study - 10 males and 10 females Clinical pathology study - 20 males and 20 females Mice: 10 males and 10 females	50 males and 50 females
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 2-week studies	Same as 2-week studies

Table 1
Experimental Design and Materials and Methods in the Gavage Studies of Elmiron®

2-Week Studies	3-Month Studies	2-Year Studies
Animals per Cage		
Rats: 5 Mice: 1 (males) or 5 (females)	Rats: 5 Mice: 1 (males) or 5 (females)	Rats: 2 or 3 (males) or 5 (females) Mice: 1 (males) or 5 (females)
Method of Animal Identification		
Tail tattoo	Tail tattoo	Tail tattoo
Diet		
NTP-2000 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly	Same as 2-week studies	Same as 2-week studies except diet was irradiated
Water		
Tap water (Washington Suburban Sanitary Commission Potomac Plant) via automatic watering system, available *ad libitum*	Tap water (City of Columbus municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Tap water (City of Columbus municipal supply) via automatic watering system, available *ad libitum*
Cages		
Polycarbonate, changed twice weekly or once weekly (male mice)	Polycarbonate (Lab Products, Maywood, NJ), changed twice weekly or once weekly (male mice) and rotated once every 2 weeks	Same as 3-month studies
Bedding		
Heat treated Sani-Chips® (P.J. Murphy Forest Products, Montville, NJ), changed twice weekly or once weekly (male mice)	Heat treated Sani-Chips® hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed twice weekly or once weekly (male mice)	Irradiated Sani-Chips® hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed twice weekly or once weekly (male mice)
Cage Filters		
DuPont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH), changed once every 2 weeks	Same as 2-week studies	Same as 2-week studies
Racks		
Stainless steel, drawer-type (Lab Products, Inc., Maywood, NJ), changed and rotated every 2 weeks	Same as 2-week studies	Same as 2-week studies
Animal Room Environment		
Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour
Doses		
0, 33, 111, 333, 1,000, or 3,000 mg/kg in deionized water by gavage [dosing volume 5 mL/kg (rats) or 10 mL/kg (mice)]	0, 63, 125, 250, 500, or 1,000 mg/kg in deionized water by gavage [dosing volume 5 mL/kg (rats) or 10 mL/kg (mice)]	Rats: 0, 14, 42, or 126 mg/kg (males) or 0, 28, 84, or 252 mg/kg (females) in deionized water by gavage (dosing volume 5 mL/kg) Mice: 0, 56, 168, or 504 mg/kg in deionized water by gavage (dosing volume 10 mL/kg)

Table 1
Experimental Design and Materials and Methods in the Gavage Studies of Elmiron®

2-Week Studies	3-Month Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice daily; animals were weighed and clinical findings were recorded initially, on day 8, and at the end of the studies.	Observed twice daily; core study animals were weighed initially, on day 8, weekly, and at the end of the studies; clinical findings were recorded weekly beginning on day 2 until the end of the studies.	Observed twice daily; animals were weighed initially and body weights and clinical findings were recorded every 4 weeks beginning on day 29.
Method of Sacrifice		
Anesthetization with Metofane™ followed by exsanguination by cardiac puncture (rats) or via the abdominal aorta (mice)	Carbon dioxide asphyxiation	Same as 3-month studies
Necropsy		
Necropsies were performed on all animals. Organs weighed were the heart, right kidney, liver, lung, spleen, right testis, and thymus.	Necropsies were performed on all core study animals. Organs weighed were the heart, right kidney, liver, lung, spleen, right testis, and thymus.	Necropsies were performed on all animals.
Clinical Pathology		
Blood was collected by cardiac puncture from all rats at the end of the study for activated partial thromboplastin time measurements.	Blood was collected from the posterior vena cava, aorta, or retroorbital sinus of clinical pathology study rats on days 4 and 23 and from core study animals at the end of the studies for hematology and clinical chemistry (rats). ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte count and differentials; and activated partial thromboplastin time (rats) ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids	None

Table 1
Experimental Design and Materials and Methods in the Gavage Studies of Elmiron®

2-Week Studies	3-Month Studies	2-Year Studies
Histopathology		
Histopathology was performed on vehicle control and 3,000 mg/kg rats and mice. In addition to gross lesions, the forestomach, large intestine (colon and rectum), kidney, liver, and urinary bladder were examined. In addition, the liver of 1,000 mg/kg female rats was examined.	Complete histopathology was performed on vehicle control and 1,000 mg/kg core study rats and mice and animals in the lower dose groups that died early. In addition to gross lesions and tissues masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymus and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. For all remaining core study groups, tissues were examined to a no-observed effect level. In addition, selected sections of the liver, lung, mandibular and mesenteric lymph nodes, rectum, and spleen (mice only) from three male rats and two male mice administered 1,000 mg/kg were taken for histochemical and/or electron microscopic evaluation. Slides prepared for histochemical evaluation were stained with periodic acid-Schiff, Alcian Blue, and oil red-O to identify material in vacuolated macrophages that were observed in these tissues when stained with hematoxylin and eosin.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissues masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymus and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Motility and Vaginal Cytology		
None	At the end of the studies, sperm samples were collected from core study male animals in the vehicle control, 250, 500, and 1,000 mg/kg groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from females in the vehicle control, 250, 500, and 1,000 mg/kg groups for vaginal cytology evaluations. The percentage of time spent in the various estrous cycle stages and estrous cycle length were evaluated.	None

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A4, B1, B4, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1-P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

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 historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal 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-related 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-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across doses.

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The NTP historical database for studies that use the NTP-2000 diet contains all 16 studies (15 for male rats) completed up to the present. Based on the extensive NTP historical database established for the NIH-07 diet, route of administration was not considered to be a significant variable for spontaneous neoplasms for the vast majority of sites. Thus, in general, the historical database will include studies with various routes of administration. For certain types of neoplasms where variations have been observed depending on route of administration, only studies with similar routes of administration will be used for comparison.

Quality Assurance Methods

The 3-month and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. 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, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of Elmiron® was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium,* micronucleated erythrocytes in rat and mouse bone marrow, and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity/mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms.

DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However, these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

2-WEEK STUDY

All rats survived to the end of the study (Table 2). Final mean body weights and body weight gains were similar among dosed and vehicle control groups. There were no clinical findings attributed to Elmiron® administration.

A significant increase in activated partial thromboplastin time was observed in 3,000 mg/kg rats (Table F1). Liver weights of 3,000 mg/kg rats were significantly greater than those of the vehicle controls (Table G1). The incidences of minimal to mild hepatocellular cytoplasmic vacuolization were significantly increased in 3,000 mg/kg female rats (vehicle control, 0/5; 33 mg/kg, 0/0; 111 mg/kg, 0/0; 333 mg/kg, 0/0; 1,000 mg/kg, 0/5; 3,000 mg/kg, 5/5). The vacuoles were clear, discrete, round, variably sized, and located in the cytoplasm of hepatocytes located in the periportal areas. They most likely represented fat.

Dose Selection Rationale: Based on the increased incidences of hepatocellular cytoplasmic vacuolization and increased activated partial thromboplastin time in the 3,000 mg/kg groups, the highest Elmiron® dose selected for the 3-month study in rats was 1,000 mg/kg.

TABLE 2
Survival and Body Weights of Rats in the 2-Week Gavage Study of Elmiron®

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	122 ± 6	204 ± 8	82 ± 3	
33	5/5	121 ± 5	200 ± 7	79 ± 2	98
111	5/5	121 ± 7	204 ± 8	83 ± 4	100
333	5/5	121 ± 8	204 ± 13	84 ± 5	100
1,000	5/5	122 ± 6	207 ± 7	85 ± 1	101
3,000	5/5	121 ± 8	204 ± 9	83 ± 2	100
Female					
0	5/5	101 ± 3	144 ± 2	43 ± 1	
33	5/5	98 ± 5	135 ± 2	37 ± 3	94
111	5/5	99 ± 3	143 ± 4	44 ± 3	99
333	5/5	96 ± 4	134 ± 1	38 ± 4	93
1,000	5/5	98 ± 3	137 ± 3	39 ± 4	95
3,000	5/5	97 ± 5	135 ± 6	38 ± 2	94

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test.

3-Month Study

Four male rats died due to dosing accidents; all other rats survived to the end of the study (Table 3). Final mean body weights of 125 and 500 mg/kg males and body weight gains of 125 mg/kg males were significantly less than those of the vehicle controls. Final mean body weights and body weight gains of dosed groups of females were greater than those of the vehicle controls. There were no clinical findings related to Elmiron® administration.

Table 3
Survival and Body Weights of Rats in the 3-Month Gavage Study of Elmiron®

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	103 ± 1	341 ± 5	239 ± 5	
63	9/10[c]	104 ± 1	342 ± 6	239 ± 7	100
125	10/10	102 ± 1	309 ± 6**	208 ± 5**	91
250	10/10	103 ± 1	330 ± 6	227 ± 5	97
500	9/10[d]	101 ± 2	320 ± 5*	219 ± 5	94
1,000	8/10[e]	103 ± 1	337 ± 8	234 ± 8	99
Female					
0	10/10	94 ± 1	173 ± 5	79 ± 4	
63	10/10	95 ± 1	193 ± 3**	98 ± 3**	111
125	10/10	94 ± 1	196 ± 4**	101 ± 4**	113
250	10/10	94 ± 2	195 ± 3**	101 ± 3**	113
500	10/10	94 ± 1	183 ± 2	89 ± 2	106
1,000	10/10	94 ± 1	192 ± 4**	98 ± 4**	111

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 9
[d] Week of death: 5
[e] Week of death: 1, 5

Hematology and clinical chemistry data are listed in Tables 4 and F2. On day 4, a minimal increase in the erythron, evidenced by minimal increases in erythrocyte counts, hemoglobin concentrations, or hematocrit values, occurred in various dosed groups of females. This increase was transient and, by day 23, erythron values for females had returned to vehicle control levels. At study termination, erythron values were minimally decreased in 500 mg/kg males and in 1,000 mg/kg males and females. In 1,000 mg/kg rats, the erythron values were decreased by 8% or less compared to vehicle control values and were accompanied by no changes in the erythrocyte indices or reticulocyte counts. On day 23 and at study termination, platelet counts were minimally increased in 1,000 mg/kg males and females; the mechanism was unknown but may reflect an increased production or altered peripheral distribution.

At all time points, increased leukocyte counts occurred in dosed males and females. The leukocytosis occurred primarily in 1,000 mg/kg males and females and in 500 mg/kg females and was characterized by increased lymphocyte counts. Increased segmented neutrophil counts also occurred in 500 and 1,000 mg/kg females at study termination. The mechanism for the leukocytosis in this study was unknown. There was evidence,

TABLE 4
Selected Hematology Data for Rats in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
n						
Day 4	10	10	9	10	10	10
Day 23	10	9	10	10	8	10
Week 14	10	8	10	10	9	8
Hematocrit (%)						
Day 4	38.5 ± 0.7	37.9 ± 0.5	38.2 ± 0.6	38.3 ± 0.5	38.2 ± 0.5	37.4 ± 0.5
Day 23	45.2 ± 0.5	45.0 ± 0.6	44.4 ± 0.6	44.1 ± 0.6	42.7 ± 0.5*	45.4 ± 0.7
Week 14	46.7 ± 0.3	46.0 ± 0.7	46.6 ± 0.5	45.7 ± 0.3	45.0 ± 0.5*	44.3 ± 0.7**
Hemoglobin (g/dL)						
Day 4	12.4 ± 0.2	12.2 ± 0.2	12.3 ± 0.2	12.3 ± 0.2	12.3 ± 0.1	12.0 ± 0.1
Day 23	15.0 ± 0.2	15.0 ± 0.2	14.6 ± 0.2	14.7 ± 0.2	14.2 ± 0.2*	15.1 ± 0.2
Week 14	15.4 ± 0.1	15.3 ± 0.2	15.4 ± 0.2	15.1 ± 0.1	14.7 ± 0.1**	14.3 ± 0.2**
Erythrocytes (10^6/µL)						
Day 4	6.45 ± 0.16	6.34 ± 0.09	6.37 ± 0.16	6.46 ± 0.11	6.43 ± 0.11	6.30 ± 0.08
Day 23	7.64 ± 0.09	7.67 ± 0.12	7.44 ± 0.13	7.45 ± 0.11	7.22 ± 0.07	7.67 ± 0.12
Week 14	8.71 ± 0.07	8.60 ± 0.13	8.67 ± 0.10	8.51 ± 0.06	8.42 ± 0.09*	8.28 ± 0.13**
Platelets (10^3/µL)						
Day 4	831.1 ± 38.5	887.2 ± 25.5	915.7 ± 30.6	881.4 ± 17.1	903.4 ± 25.8	886.5 ± 21.21
Day 23	797.6 ± 49.9	867.6 ± 49.8	920.0 ± 18.9	941.3 ± 9.9**	928.6 ± 90.1**	970.8 ± 39.8**
Week 14	644.1 ± 12.1	671.8 ± 11.8	729.8 ± 9.4**	775.7 ± 26.8**	799.1 ± 18.4**	778.5 ± 31.9**
Leukocytes (10^3/µL)						
Day 4	6.77 ± 0.31	7.16 ± 0.18	7.78 ± 0.63	7.51 ± 0.47	8.10 ± 0.29**	9.59 ± 0.43**
Day 23	10.27 ± 0.81	9.09 ± 0.80	9.81 ± 0.53	10.27 ± 0.65	11.78 ± 0.63	13.21 ± 1.11*
Week 14	11.31 ± 0.59	11.38 ± 1.02	11.73 ± 0.67	10.86 ± 0.73	12.19 ± 1.46	15.38 ± 0.84*
Lymphocytes (10^3/µL)						
Day 4	5.66 ± 0.29	5.67 ± 0.15	6.20 ± 0.59	6.18 ± 0.45	6.41 ± 0.17*	7.83 ± 0.38**
Day 23	8.59 ± 0.76	7.53 ± 0.75	7.87 ± 0.47	8.53 ± 0.57	10.07 ± 0.70	11.26 ± 0.99
Week 14	9.27 ± 0.64	9.10 ± 0.85	8.84 ± 0.53	8.42 ± 0.58	9.70 ± 1.18	12.30 ± 0.75
Segmented neutrophils (10^3/µL)						
Day 4	0.80 ± 0.06	1.17 ± 0.06*	1.06 ± 0.12	0.93 ± 0.07	1.33 ± 0.15**	1.21 ± 0.18
Day 23	1.24 ± 0.08	1.09 ± 0.11	1.47 ± 0.11	1.26 ± 0.18	1.25 ± 0.09	1.39 ± 0.15
Week 14	1.83 ± 0.20	1.97 ± 0.29	2.56 ± 0.19	2.14 ± 0.19	2.12 ± 0.50	2.67 ± 0.30

Table 4
Selected Hematology Data for Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Female						
n						
Day 4	10	10	9	9	10	10
Day 23	9	10	9	8	10	10
Week 14	8	9	8	9	10	10
Hematocrit (%)						
Day 4	39.2 ± 0.4	41.4 ± 0.2**	40.9 ± 0.3*	40.0 ± 0.3	40.6 ± 0.5	41.2 ± 0.3**
Day 23	46.5 ± 0.7	46.0 ± 0.5	45.6 ± 0.5	44.7 ± 0.6	45.0 ± 0.6	44.6 ± 0.4
Week 14	45.7 ± 0.5	44.5 ± 0.6*	45.8 ± 0.6	44.4 ± 0.4	45.3 ± 0.6	42.2 ± 0.5**
Hemoglobin (g/dL)						
Day 4	12.8 ± 0.1	13.4 ± 0.1**	13.3 ± 0.1	13.0 ± 0.1	13.3 ± 0.2	13.3 ± 0.2**
Day 23	15.3 ± 0.2	15.2 ± 0.1	15.1 ± 0.2	14.8 ± 0.2	14.9 ± 0.2	14.8 ± 0.2
Week 14	15.2 ± 0.1	14.9 ± 0.1	15.3 ± 0.2	14.8 ± 0.1	15.0 ± 0.2	14.0 ± 0.2**
Erythrocytes ($10^6/\mu L$)						
Day 4	6.66 ± 0.10	6.99 ± 0.03	6.90 ± 0.08	6.82 ± 0.08	6.94 ± 0.09	7.04 ± 0.06**
Day 23	7.86 ± 0.13	7.77 ± 0.10	7.65 ± 0.10	7.47 ± 0.11*	7.54 ± 0.11	7.48 ± 0.10*
Week 14	8.17 ± 0.08	7.93 ± 0.09*	8.21 ± 0.09	7.90 ± 0.06	8.05 ± 0.10	7.48 ± 0.08**
Platelets ($10^3/\mu L$)						
Day 4	771.3 ± 33.7	830.1 ± 14.0	790.9 ± 45.2	824.6 ± 11.8[b]	814.5 ± 43.8	752.7 ± 25.2
Day 23	834.4 ± 21.0	834.8 ± 19.5	834.7 ± 20.6	846.4 ± 31.3	841.3 ± 19.6	958.2 ± 23.1**
Week 14	698.8 ± 25.2	681.2 ± 22.7	688.0 ± 21.2	718.4 ± 23.0	775.4 ± 26.1*	869.1 ± 14.3**
Leukocytes ($10^3/\mu L$)						
Day 4	7.83 ± 0.32	8.30 ± 0.46	8.96 ± 0.28*	9.21 ± 0.29*	10.49 ± 0.36**	12.08 ± 0.70**
Day 23	9.00 ± 0.90	9.60 ± 0.50	10.90 ± 0.66	10.05 ± 0.30	11.17 ± 0.65*	13.55 ± 1.00**
Week 14	10.23 ± 0.49	10.27 ± 0.62	11.71 ± 0.82	10.96 ± 1.07	12.88 ± 1.28*	17.27 ± 1.09**[c]
Lymphocytes ($10^3/\mu L$)						
Day 4	6.28 ± 0.25	6.98 ± 0.42	7.55 ± 0.29*	7.87 ± 0.33**	8.78 ± 0.39**	10.23 ± 0.70**
Day 23	7.08 ± 0.68	8.03 ± 0.44	8.96 ± 0.56	8.33 ± 0.24	9.15 ± 0.38*	11.30 ± 0.87**
Week 14	8.03 ± 0.42	7.66 ± 0.51	9.19 ± 0.61	8.63 ± 0.88	9.89 ± 0.98*	12.39 ± 1.02**[c]
Segmented neutrophils ($10^3/\mu L$)						
Day 4	1.06 ± 0.07	0.96 ± 0.06	0.95 ± 0.07	0.95 ± 0.07	1.29 ± 0.16	1.21 ± 0.07
Day 23	1.35 ± 0.27	1.16 ± 0.10	1.32 ± 0.10	1.30 ± 0.20	1.58 ± 0.29	1.79 ± 0.20
Week 14	1.74 ± 0.12	2.07 ± 0.18	2.05 ± 0.18	1.96 ± 0.23	2.46 ± 0.29*	4.08 ± 0.41**[c]

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=9

however, of a treatment-related chronic inflammatory process in the large intestine, liver, and lung and of lymphoid hyperplasia in the spleen; these changes may have been related to the increases in the circulating leukocyte counts in dosed rats.

Serum alanine aminotransferase activity was decreased in various male and female dosed groups at all time points. The significance of this change was unknown, but could be related to some alteration in liver metabolism or enzyme inhibition. Alkaline phosphatase activity, a marker of cholestasis, was decreased in various male and all female dosed groups on day 23 and at study termination; bile acid concentrations, another marker of cholestasis, were unaffected. While the mechanism for the decreased alkaline phosphatase activity was unknown, it has been suggested that decreased serum activity might be related to decreased feed intake (Travlos *et al.*, 1996). Based on the body weight data, however, there was no indication of an altered nutritional status in this study. Other changes in clinical chemistry results were sporadic and were not considered toxicologically relevant.

Liver and spleen weights of males administered 250 mg/kg or greater were significantly increased (Tables 5 and G2). Liver weights of all dosed groups of females and kidney, lung, and spleen weights of 1,000 mg/kg females were significantly greater than those of the vehicle controls. There were no significant differences in sperm motility or vaginal cytology parameters between dosed and vehicle control rats (Tables H1 and H2).

No gross lesions were observed that could be attributed to exposure to Elmiron®. Microscopically, exposure of

Table 5
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
n	10	9	10	10	9	8
Necropsy body wt	351 ± 5	363 ± 6	347 ± 6	356 ± 7	333 ± 5	351 ± 8
Liver						
Absolute	12.5 ± 0.3	12.9 ± 0.4	12.3 ± 0.3	13.9 ± 0.3*	13.5 ± 0.3*	15.9 ± 0.7**
Relative	35.5 ± 0.8	35.5 ± 0.5	35.5 ± 0.8	39.1 ± 0.5**	40.5 ± 0.5**	45.2 ± 1.2**
Spleen						
Absolute	0.67 ± 0.0	0.72 ± 0.0	0.72 ± 0.0	0.75 ± 0.0**	0.75 ± 0.0**	0.89 ± 0.0**
Relative	1.89 ± 0.0	1.99 ± 0.0	2.06 ± 0.0*	2.11 ± 0.0**	2.26 ± 0.1**	2.54 ± 0.1**
Female						
n	10	10	10	10	10	10
Necropsy body wt	191 ± 4	197 ± 3	204 ± 5*	198 ± 4	191 ± 3	195 ± 4
R. Kidney						
Absolute	0.60 ± 0.0	0.60 ± 0.0	0.62 ± 0.0	0.60 ± 0.0	0.60 ± 0.0	0.65 ± 0.0*
Relative	3.12 ± 0.1	3.04 ± 0.0	3.03 ± 0.1	3.04 ± 0.0	3.15 ± 0.1	3.35 ± 0.1*
Liver						
Absolute	5.93 ± 0.1	6.68 ± 0.1**	7.02 ± 0.2**	6.93 ± 0.1**	7.01 ± 0.1**	8.90 ± 0.2**
Relative	31.1 ± 0.5	33.9 ± 0.5**	34.5 ± 0.6**	35.01 ± 0.6**	36.7 ± 0.8**	45.7 ± 0.6**
Lung						
Absolute	1.06 ± 0.0	1.11 ± 0.0	1.22 ± 0.0*	1.15 ± 0.0*	1.16 ± 0.0*	1.24 ± 0.0**
Relative	5.56 ± 0.2	5.66 ± 0.2	6.00 ± 0.1	5.79 ± 0.2	6.07 ± 0.2	6.34 ± 0.2**
Spleen						
Absolute	0.51 ± 0.0	0.51 ± 0.0	0.53 ± 0.0	0.55 ± 0.0	0.55 ± 0.0	0.62 ± 0.0**
Relative	2.68 ± 0.1	2.61 ± 0.1	2.60 ± 0.1	2.75 ± 0.1	2.90 ± 0.1	3.17 ± 0.0**

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

rats to Elmiron® was associated with nonneoplastic lesions of the rectum, mandibular and mesenteric lymph nodes, lung, kidney, and liver (Table 6).

The incidences of histiocytic cellular infiltration, chronic active inflammation, and chronic ulcers of the rectum were significantly increased in 500 and 1,000 mg/kg males and females; histiocytic cellular infiltration and chronic active inflammation were also significantly increased in 250 mg/kg males. The incidences and severities of histiocytic cellular infiltration generally increased with increasing dose, and this minimal to mild lesion was characterized by aggregates of foamy macrophages within the lamina propria that filled and distended the lamina propria and resulted in disorganization and distortion of the mucosal crypts. The macrophages were large with abundant foamy cytoplasm due to the presence of numerous intracytoplasmic, variably sized, clear vacuoles. The lamina propria appeared expanded with a faint bluish tinged acellular material (myxomatous change). This material stained negatively with a periodic acid-Schiff (PAS) reaction and positively with an Alcian Blue (AB) stain. AB stains sulfated mucopolysaccharide-like substances such as normal ground substance in the interstitium. Elmiron® is a sulfated polyanion and thus the myxomatous change may have been the test material or some form of the test material that accumulated in the lamina propria. Chronic active inflammation was characterized by lymphocytes and neutrophils in the lamina propria, mucosa, and/or lumen of the rectum. Ulceration consisted of focal denudation of the epithelial lining. These areas usually had an inflammatory base, and some of the mucosal areas appeared to be healing from a previous ulceration. This was characterized by an attenuated epithelium covering the surface of the lamina propria associated with loss of the crypts of the mucosa. The no-observed-effect level (NOEL) for rectal lesions was 63 mg/kg in males;

TABLE 6
Incidences of Selected Nonneoplastic Lesions in Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
Intestine Large, Rectum[a]	10	10	10	10	10	9
Infiltration Cellular, Histiocyte[b]	0	0	3 (1.0)[c]	7** (1.1)	9** (1.6)	8** (2.0)
Inflammation, Chronic Active	0	0	2 (1.0)	7** (1.0)	8** (1.1)	8** (1.8)
Ulcer, Chronic	0	0	1 (1.0)	3 (1.0)	7** (1.0)	7** (1.4)
Lymph Node, Mandibular	10	1	10	10	10	10
Infiltration Cellular, Histiocyte	0	0	0	3 (1.0)	8** (1.1)	7** (1.3)
Lymph Node, Mesenteric	10	1	10	10	10	9
Infiltration Cellular, Histiocyte	0	0	0	6** (1.0)	8** (1.4)	8** (1.8)
Lung	10	10	10	10	10	10
Alveolus, Infiltration Cellular, Histiocyte	0	2 (1.0)	5* (1.0)	6** (1.2)	10** (1.1)	8** (1.3)
Interstitium, Inflammation, Chronic	0	0	0	0	1 (1.0)	3 (1.0)
Kidney	10	1	0	0	10	9
Renal Tubule, Vacuolization Cytoplasmic	0	0			0	8** (1.0)
Liver	10	2	2	10	10	10
Midzonal, Vacuolization Cytoplasmic	0	1 (1.0)	0	0	4* (1.0)	8** (1.6)
Inflammation, Granulomatous	0	0	0	0	4* (1.0)	6** (1.2)

Table 6
Incidences of Selected Nonneoplastic Lesions in Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Female						
Intestine Large, Rectum	10	10	10	10	10	10
Infiltration Cellular, Histiocyte	0	2 (1.0)	1 (1.0)	2 (1.0)	10** (1.5)	10** (2.0)
Inflammation, Chronic Active	0	0	0	0	9** (1.0)	10** (1.4)
Ulcer, Chronic	0	0	0	0	6** (1.0)	8** (1.0)
Lymph Node, Mandibular	10	1	2	10	10	10
Infiltration Cellular, Histiocyte	0	1 (1.0)	2 (1.0)	3 (1.0)	3 (1.0)	10** (1.2)
Lymph Node, Mesenteric	10	2	5	7	10	10
Infiltration Cellular, Histiocyte	0	2 (1.0)	5** (1.2)	7** (1.0)	7** (1.0)	10** (1.1)
Lung	10	10	10	10	10	10
Alveolus, Infiltration Cellular, Histiocyte	0	7** (1.0)	5* (1.0)	6** (1.0)	7** (1.0)	9** (1.3)
Interstitium, Inflammation, Chronic	0	1 (1.0)	0	1 (1.0)	3 (1.0)	6** (1.0)
Kidney	10	0	0	0	10	10
Renal Tubule, Vacuolization Cytoplasmic	0				0	10** (1.0)
Liver	10	10	10	10	10	10
Midzonal, Vacuolization Cytoplasmic	0	0	0	0	0	7** (1.0)
Inflammation, Granulomatous	9 (1.2)	10 (1.0)	10 (1.0)	10 (1.0)	9 (1.2)	10 (1.3)

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

a NOEL was not determined for females because rectal lesions were observed in all dosed groups of females.

Minimal to mild histiocytic cellular infiltration of the mandibular and mesenteric lymph nodes occurred in all dosed groups of rats except 63 and 125 mg/kg males. Incidences of this lesion in the lymph nodes were generally significantly increased in males dosed with 250 mg/kg or greater. In females, incidences of histiocytic infiltration increased in a dose-related manner; the increase was significant in the mandibular lymph node of 1,000 mg/kg females and in the mesenteric lymph node of 125 mg/kg or greater females. Histiocytic infiltration consisted of large macrophages with foamy cytoplasm filled with variably sized, clear vacuoles; the macrophages were located in the subcapsular or medullary sinuses (Plates 1 and 2). The NOEL for lymph node lesions was 125 mg/kg in males; a NOEL was not determined for females because these lesions were observed in all dosed groups. It is likely that with systemic lymphatic circulation, Elmiron®-induced vacuolated macrophages would be present to some degree in other lymph nodes; however, other lymph nodes are not routinely examined microscopically.

Incidences of minimal focal or multifocal alveolar histiocytic infiltration of the lungs were significantly increased in all dosed groups of rats except 63 mg/kg males (Plate 3). A NOEL for this lesion was not determined for either sex because the lesion was observed in all dosed groups of rats. The incidence of minimal chronic interstitial inflammation in the lungs was significantly increased in 1,000 mg/kg females and was characterized by fibrosis of the alveolar wall, infiltration of the interstitium with lymphocytes and macrophages, and the flattening of the alveolar epithelial cells.

Incidences of minimal tubule epithelial cytoplasmic vacuolation of the kidney were significantly increased in 1,000 mg/kg rats. The renal tubule epithelial vacuolation was located in the outer cortex, particularly the subcapsular region, and it was characterized by one to several small clear vacuoles in the cytoplasm. The NOEL for renal tubule epithelial cytoplasmic vacuolation was 500 mg/kg in males and females.

Incidences of minimal midzonal hepatocytic cytoplasmic vacuolization were significantly increased in 500 mg/kg males and 1,000 mg/kg males and females. The vacuoles were clear and variably sized and stained positively with oil red-O (ORO) stain, which is consistent with fatty change. In some rats, this change consisted of cytoplasmic clear areas, which is characteristic of glycogen infiltration. The NOEL for this lesion was 500 mg/kg for females. Incidences of minimal multifocal granulomatous inflammation of the liver were significantly increased in 500 and 1,000 mg/kg males. These inflammatory foci were characterized by aggregation of histiocytes mixed with mononuclear cells (Plates 4 and 5).

Histiocytic Vacuolation Assessment

Histochemical Investigation: In order to identify the nature of the histiocytic cytoplasmic vacuolation seen in different organs, samples of the rectum, liver, mesenteric and mandibular lymph nodes, and lungs were taken from three male 1,000 mg/kg rats. The samples were stained with AB for acidic sulfated mucopolysaccharides, hyaluronic acid, and sialomucin; with PAS for neutral mucopolysaccharides; and with ORO for neutral lipids.

Vacuolated cells (histiocytes) containing PAS-positive material were noted in the lamina propria of the rectum, mesenteric and mandibular lymph nodes, liver, and lungs. The accumulated material within the vacuolated cells was AB positive only in the rectum and lungs. The grade of staining for PAS and AB varied in intensity and was marked in the lungs and minimal to mild in the rectum, liver, and lymph nodes. The accumulated material within the vacuolated cells was ORO positive only in the lungs. The positive staining with ORO indicates the presence of a lipid component in the vacuoles and may represent membranous structures associated with production of surfactant.

The results indicate that the vacuolated cells accumulated mucins, which are hexosamine-containing polysaccharides covalently bound to varying amounts of protein. The positive staining for both neutral and acidic mucins in the same cells indicates that the vacuolated cells contained a mixture of different types of mucin.

Electron Microscopic Evaluation: The purpose of this study was to gain information about the ultrastructural characteristics of the histiocyte infiltrates observed in rats administered Elmiron®. Rectal, lung, and lymph node samples that exhibited significant histiocyte infiltration by light microscopy were selected from three male 1,000 mg/kg rats.

Many macrophages were evident within the lamina propria of the rectum examined ultrastructurally (Plate 6). These macrophages had voluminous cytoplasm, which was distended with numerous variably sized lysosomes. Some lysosomes were clear or had scant profiles of membranous material, but most were filled with concentric lamellae of electron dense material, consistent with myelin figures. Other cells in the lamina propria were those normally present in this tissue, and included eosinophils, occasional neutrophils, fibroblasts, and lymphoid cells. The interstitium contained multiple small bundles of collagen. In one sample, the lamina propria had distended, clear, interstitial spaces. These spaces may represent edema, fixation artifact, or possibly areas of absorbed and then dissolved test material. Thus, this may correlate with areas of myxomatous change, described by light microscopy in the rectum of affected animals.

Many of the alveolar macrophages in the lung exhibited unusual lysosomal changes from numerous linear crystalline structures to clear vacuoles containing concentric lamellar bodies. These electron-dense structures were membrane bound and were single or multiple within lysosomes. Some macrophages contained more lysosomal crystals than others, and in some lysosomes, phagocytized material other than the linear crystals was also present. A few linear crystals within macrophage lysosomes were also identified. Some of these linear crystals appeared to have a lucent core. A lung from a different rat exhibited numerous large alveolar macrophages with cytoplasm that was distended with rounded lysosomes. These lysosomes appeared clear or contained electron-lucent material as well as fragments of material and myelin figures similar to those seen in the lamina propria of the rectum.

The vacuolated macrophages (histiocytes) were evident in the subcapsular sinuses of the lymph nodes and were interspersed with lymphocytes (Plate 7). Some macrophages were engorged with lysosomes containing concentric lamellar bodies (myelin figures) similar to those seen in the rectum. Other macrophage lysosomes were mostly clear and contained only fragments of myelin figures. Additionally, many macrophages contained electron-dense residual bodies. Occasionally, lysosomes with linear crystalline inclusions were seen in the macrophages of lymph nodes.

Dose Selection Rationale: Survival and body weights were not adversely affected by treatment; however, higher dose groups had significant histological alterations in the rectum. The rectal mucosal architecture was altered by the cellular infiltrates, and many of the ulcers had some degree of scarring. These changes were not observed at 2 weeks and, therefore, appeared to progress with time. The incidence and severity also progressed with increasing dose concentration. Although the changes were not severe at the end of 3 months, there was concern that in a 2-year study, these lesions might become more severe with an adverse affect on the host. Therefore, doses for the 2-year study were selected at which the incidences of rectal lesions were not significant (0, 14, 42, and 126 mg/kg for males and 0, 28, 84, and 252 mg/kg for females).

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 7 and in the Kaplan-Meier survival curves (Figure 1). Survival of all dosed groups was similar to that of the vehicle controls.

Body Weights and Clinical Findings

Mean body weights of all dosed groups were similar to those of the vehicle controls throughout the 2-year study (Tables 8 and 9; Figure 2). There were no clinical findings related to Elmiron® administration.

Gross Observations

Chemical-related tan, gray, or white foci, and tan, pale, or mottled discoloration occurred in the lung. These correlated histologically with chronic active inflammation and were increased in all dosed groups of males and females.

Table 7
Survival of Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	2	2	0	5
Moribund	15	10	17	12
Natural deaths	7	9	8	5
Animals surviving to study termination	26	29	25	28
Percent probability of survival at end of study[b]	54	61	50	63
Mean survival (days)[c]	667	665	664	645
Survival analysis[d]	P=0.621N	P=0.659N	P=0.604	P=0.563N
	Vehicle Control	**28 mg/kg**	**84 mg/kg**	**252 mg/kg**
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	1	1	2	6
Moribund	6	8	11	11
Natural deaths	13	10	9	6
Animals surviving to study termination	30	31	28	27[e]
Percent probability of survival at end of study	61	63	59	62
Mean survival (days)	672	678	667	640
Survival analysis	P=1.000N	P=0.940N	P=0.953	P=1.000N

[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 vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dose group is indicated by **N**.
[e] Includes one animal that died during the last week of the study

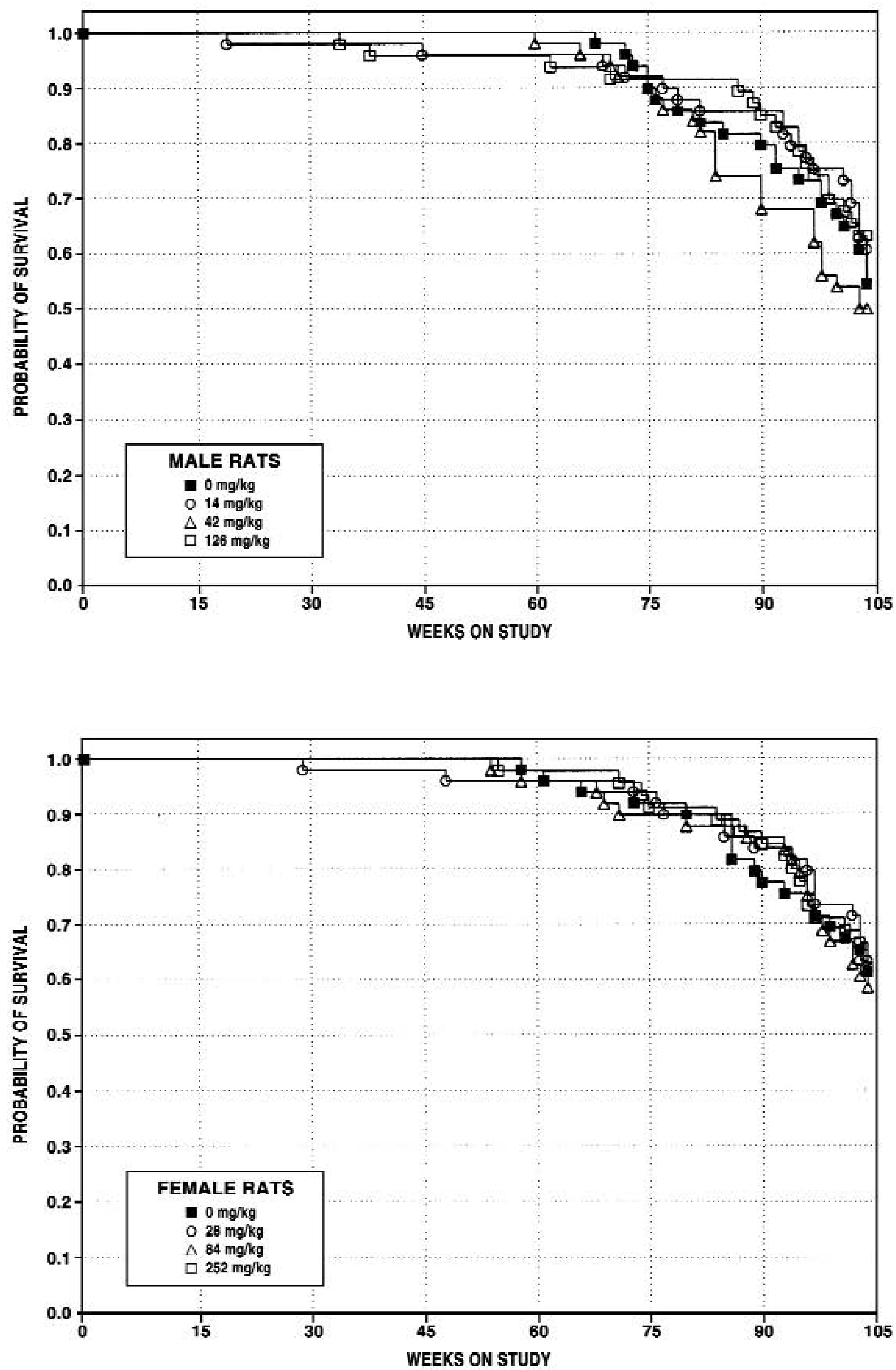


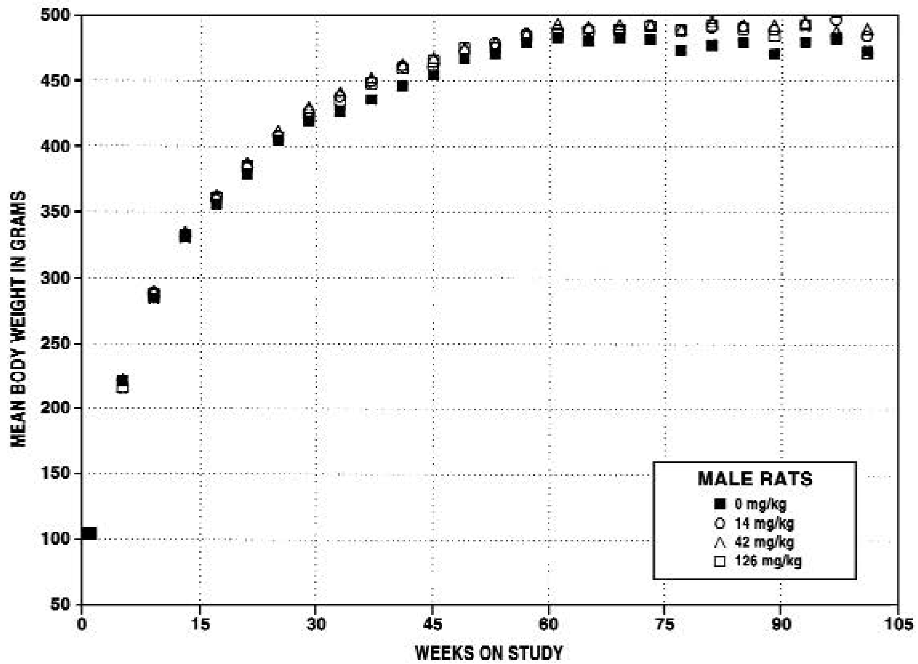
FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Elmiron® by Gavage for 2 Years

Table 8
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Elmiron®

Weeks	Vehicle Control		14 mg/kg			42 mg/kg			126 mg/kg		
on Study	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	105	50	105	100	50	105	100	50	104	99	50
5	221	50	222	100	50	222	100	50	216	98	50
9	284	50	289	102	50	290	102	50	287	101	50
13	331	50	331	100	50	336	101	50	332	100	50
17	356	49	360	101	50	363	102	50	361	101	50
21	379	49	384	101	49	388	102	50	385	102	49
25	404	49	408	101	49	412	102	50	407	101	48
29	419	49	427	102	49	430	103	50	423	101	48
33	426	49	438	103	48	441	103	50	435	102	48
37	436	49	450	103	48	453	104	50	448	103	47
41	446	49	462	104	48	462	104	50	459	103	46
45	454	49	461	101	48	468	103	50	466	103	46
49	467	49	473	101	47	475	102	50	475	102	46
53	471	49	479	102	47	479	102	50	475	101	45
57	479	49	487	102	47	487	102	50	484	101	45
61	484	49	490	101	47	494	102	49	486	101	45
65	480	49	490	102	47	492	102	49	489	102	44
69	484	48	489	101	47	493	102	48	490	101	43
73	482	46	493	102	45	493	102	46	492	102	42
77	474	43	490	103	44	490	103	43	489	103	42
81	478	42	491	103	43	496	104	42	493	103	42
85	480	40	492	103	41	493	103	37	490	102	42
89	471	39	489	104	41	492	105	37	485	103	41
93	480	36	494	103	39	495	103	34	493	103	38
97	483	35	497	103	37	488	101	34	483	100	35
101	473	32	484	102	36	490	104	27	471	100	32
Mean for weeks											
1-13	235		237	101		238	101		235	100	
14-52	421		429	102		432	103		429	102	
53-101	478		490	103		491	103		486	102	

Table 9
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Elmiron®

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	28 mg/kg Av. Wt. (g)	28 mg/kg Wt. (% of controls)	28 mg/kg No. of Survivors	84 mg/kg Av. Wt. (g)	84 mg/kg Wt. (% of controls)	84 mg/kg No. of Survivors	252 mg/kg Av. Wt. (g)	252 mg/kg Wt. (% of controls)	252 mg/kg No. of Survivors
1	93	50	93	100	50	94	100	50	93	100	50
5	147	50	146	100	50	148	100	50	146	100	50
9	173	50	170	98	50	173	100	50	172	99	50
13	186	50	179	96	50	186	100	50	184	99	50
17	195	50	191	98	50	193	99	49	192	99	49
21	200	50	201	100	50	199	100	49	199	99	48
25	212	50	210	99	50	209	98	49	208	98	48
29	217	49	215	99	49	215	99	49	217	100	48
33	227	49	220	97	49	220	97	49	219	97	47
37	234	49	224	96	49	227	97	49	225	96	47
41	240	49	236	98	49	236	98	49	231	96	46
45	245	49	237	97	49	241	98	49	238	97	46
49	255	49	248	97	48	251	99	49	248	97	45
53	259	49	250	97	48	258	100	49	255	99	45
57	269	49	260	97	48	268	100	48	266	99	44
61	276	48	268	97	48	275	100	47	274	99	44
65	282	47	277	98	48	286	102	47	282	100	44
69	292	46	284	97	47	291	100	46	288	99	44
73	294	46	290	99	47	297	101	44	292	99	43
77	299	45	292	98	45	297	99	44	292	98	41
81	305	44	298	98	44	307	101	42	296	97	41
85	308	44	304	99	43	309	101	42	299	97	40
89	315	40	307	98	42	311	99	41	303	96	39
93	314	38	310	99	41	311	99	41	303	97	38
97	327	36	317	97	39	316	97	35	312	95	33
101	320	34	314	98	36	316	99	32	310	97	31
Mean for weeks											
1-13	150		147	98		150	100		149	99	
14-52	225		220	98		221	98		220	98	
53-101	297		290	98		296	100		290	98	



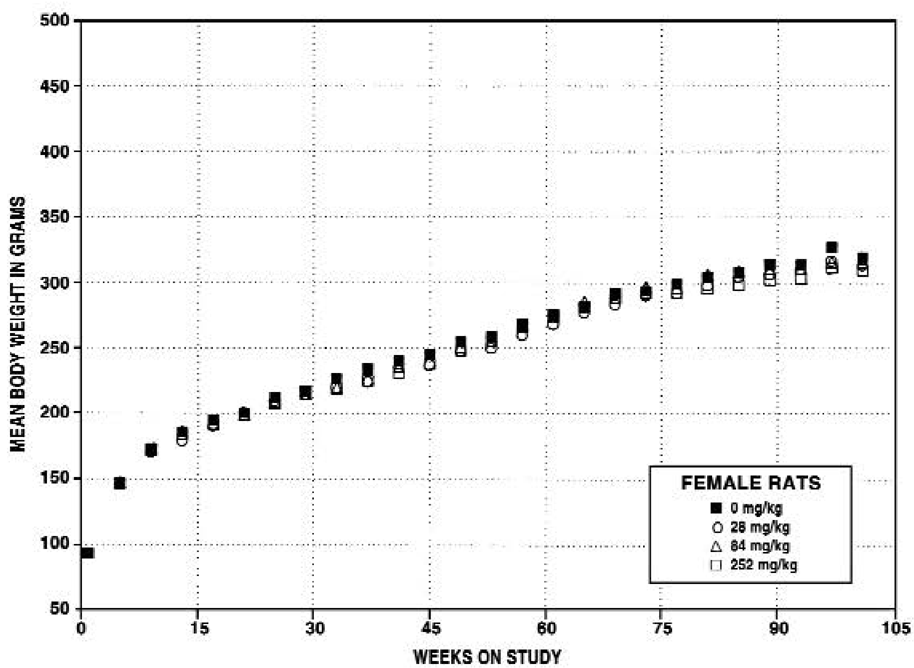


FIGURE 2
Growth Curves for Male and Female Rats Administered Elmiron® by Gavage for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the rectum, lung, mesenteric lymph node, spleen, and mammary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats.

Rectum: Incidences of minimal rectal myxomatous change were significantly increased in 126 mg/kg males and 84 and 252 mg/kg females (Tables 10, A4, and B4). This change was characterized by an acellular expansion of the lamina propria. The accumulated myxomatous material did not have the bluish tint of the similarly described lesion in mice. Minimal rectal histiocytic cellular infiltration occurred in 126 mg/kg males, and the incidence was significantly increased in 252 mg/kg females. The histiocytic infiltrates were composed of randomly distributed vacuolated macrophages within the lamina propria. The incidence of minimal chronic inflammation was increased in 126 mg/kg males, and sporadic incidences of minimal to mild acute focal or chronic inflammation occurred in 84 and 252 mg/kg females. Mild rectal erosion occurred in two 42 mg/kg and two 126 mg/kg male rats. Minimal rectal ulceration was observed in one 126 mg/kg male rat.

Lung: The incidences of minimal to mild chronic active focal to multifocal alveolar inflammation were significantly increased in all dosed groups of males and females, and the severity increased with increasing dose (Tables 10, A4, and B4). Chronic active inflammation was typically focal to multifocal, affecting one to many alveoli, and was characterized by vacuolated histiocytes and eosinophilic material in the alveoli, loss of epithelial cells, infiltration of a scant number of neutrophils, interstitial fibrosis, alveolar epithelialization (proliferation considered to be secondary to the chronic inflammation), and presence of cholesterol clefts. These focal lesions were usually subpleural.

Mesenteric Lymph Node: Incidences of minimal histiocytic cellular infiltration were significantly increased in 42 and 126 mg/kg males and 84 and 252 mg/kg females (Tables 10, A4, and B4). These clear, vacuolated histiocytes were common in the subcapsular spaces. Although other lymph nodes were not examined, it is likely that they too may contain Elmiron®-induced vacuolated macrophages.

Spleen: Increased incidences of lymphohistiocytic hyperplasia were noted in 126 mg/kg males and 252 mg/kg females (Tables 10, A4, and B4). Lymphohistiocytic hyperplasia was mild to moderate in severity and ranged from approximately 0.85 to 13.0 mm in cross-sectional dimension. The lesions were round, well demarcated, expansile, and composed of a sheet of mature lymphocytes interspersed with aggregates of pale-stained histiocytes (Plates 8 and 9). The histiocytes contained pale, finely granular cytoplasm and were not considered to represent the same change as the vacuolated histiocytes seen in the mesenteric lymph node and in the rectum. This lesion is uncommon in untreated control F344/N rats and may represent an exaggerated granulomatous inflammation or immune response (Stefanski, *et al.* 1990).

Mammary Gland: The incidence of fibroadenoma was significantly increased in 84 mg/kg females (vehicle control, 15/50; 28 mg/kg, 23/50; 84 mg/kg, 24/50; 252 mg/kg, 21/50; Table B3) but was within the historical range in controls (all routes) given NTP-2000 diet [437/959 (44% ± 12%), range 28%-72%]. The incidence of adenolipoma, fibroadenoma, adenoma, or carcinoma (combined) was significantly increased in 252 mg/kg females (16/50, 24/50, 24/50, 24/50; Table B3); this combined incidence was within the historical control range [459/959 (47% ± 13%), range 28%-74%]. In both instances, the incidence in the concurrent control group is at the lower end of the historical control range. Because of the unusually low incidence in the concurrent control group, the lack of a dose relationship, and because the incidences were within the historical control ranges, these neoplasms were not considered to be related to Elmiron® administration.

Table 10
Incidences of Selected Nonneoplastic Lesions in Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Male				
Large Intestine, Rectum[a]	48	48	49	45
Myxomatous Change[b]	0	1 (2.0)[c]	3 (1.3)	25** (1.0)
Infiltration Cellular, Histiocyte	0	0	0	4 (1.0)
Inflammation, Chronic	1 (2.0)	0	1 (3.0)	5 (1.8)
Erosion	0	0	2 (2.5)	2 (2.0)
Ulcer	0	0	0	1 (1.0)
Lung	50	50	50	50
Alveolus, Inflammation, Chronic Active, Focal	0	6* (1.0)	11** (1.4)	14** (1.6)
Lymph Node, Mesenteric	50	50	50	49
Infiltration Cellular, Histiocyte	1 (2.0)	1 (2.0)	18** (1.2)	39** (1.5)
Spleen	50	50	50	50
Hyperplasia, Lymphohistiocytic	2 (2.0)	2 (2.0)	2 (2.0)	8* (2.8)
	Vehicle Control	**28 mg/kg**	**84 mg/kg**	**252 mg/kg**
Female				
Large Intestine, Rectum	46	43	44	42
Myxomatous Change	0	1 (1.0)	12** (1.1)	35** (1.1)
Infiltration Cellular, Histiocyte	0	0	0	18** (1.2)
Inflammation, Acute, Focal	0	0	0	1 (2.0)
Inflammation, Chronic	0	0	1 (2.0)	1 (1.0)
Lung	50	50	50	50
Alveolus, Inflammation, Chronic Active, Focal	2 (1.0)	25** (1.3)	27** (1.6)	34** (2.1)
Lymph Node, Mesenteric	50	50	50	49
Infiltration Cellular, Histiocyte	0	3 (1.3)	27** (1.3)	42** (1.5)
Spleen	50	50	50	50
Hyperplasia, Lymphohistiocytic	0	1 (2.0)	2 (2.5)	4 (3.3)

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
** P≤0.01
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Mice

2-Week Study

All mice survived to the end of the study (Table 11). Mean body weight gains of male mice given 333 mg/kg or greater were significantly greater than that of the vehicle controls. There were no clinical findings attributed to Elmiron® administration. Liver weights of 1,000 and 3,000 mg/kg males were significantly greater than those of the vehicle controls (Table G3). Mild focal ulceration and histiocytic accumulation of the rectum was observed in one 3,000 mg/kg female mouse.

Dose Selection Rationale: Due to the presence of ulceration in the 3,000 mg/kg female and the potential progressive nature of this lesion, 1,000 mg/kg was selected as the high dose for the 3-month study of Elmiron®.

Table 11
Survival and Body Weights of Mice in the 2-Week Gavage Study of Elmiron®

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	23.8 ± 0.4	25.4 ± 0.4	1.6 ± 0.1	
33	5/5	23.9 ± 0.6	25.9 ± 0.3	2.0 ± 0.3	102
111	5/5	24.1 ± 0.9	26.1 ± 0.8	2.0 ± 0.2	103
333	5/5	23.8 ± 0.6	26.3 ± 0.6	2.5 ± 0.2*	103
1,000	5/5	23.9 ± 0.5	26.2 ± 0.6	2.4 ± 0.2*	103
3,000	5/5	23.4 ± 0.3	25.9 ± 0.2	2.5 ± 0.2**	102
Female					
0	5/5	20.0 ± 0.5	22.6 ± 0.6	2.6 ± 0.5	
33	5/5	20.5 ± 0.6	21.6 ± 0.5	1.1 ± 0.3	96
111	5/5	19.3 ± 0.5	21.5 ± 0.6	2.2 ± 0.3	95
333	5/5	19.7 ± 0.7	21.8 ± 0.6	2.1 ± 0.2	97
1,000	5/5	19.5 ± 0.8	22.5 ± 0.8	3.0 ± 0.1	100
3,000	5/5	19.3 ± 0.6	22.6 ± 0.4	3.3 ± 0.4	100

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
a Number of animals surviving at 2 weeks/number initially in group
b Weights and weight changes are given as mean ± standard error.

3-Month Study

One 250 mg/kg female mouse was sacrificed moribund on day 84 due to an ovarian mass that was confirmed to be a teratoma; all other mice survived to the end of the study (Table 12). Final mean body weights and body weight gains of dosed groups were similar to those of the vehicle controls. There were no clinical findings related to Elmiron® administration.

Table 12
Survival and Body Weights of Mice in the 3-Month Gavage Study of Elmiron®

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	23.1 ± 0.4	34.1 ± 0.8	11.0 ± 0.6	
63	10/10	23.1 ± 0.3	34.2 ± 0.7	11.1 ± 0.5	100
125	10/10	22.6 ± 0.5	34.4 ± 0.9	11.8 ± 0.9	101
250	10/10	22.9 ± 0.3	33.9 ± 0.9	11.0 ± 0.8	99
500	10/10	23.5 ± 0.2	36.4 ± 1.0	13.0 ± 0.9	107
1,000	10/10	22.4 ± 0.4	34.3 ± 0.8	11.9 ± 1.0	101
Female					
0	10/10	18.3 ± 0.3	27.7 ± 0.8	9.5 ± 0.7	
63	10/10	18.4 ± 0.3	26.8 ± 0.9	8.4 ± 0.6	97
125	10/10	18.3 ± 0.2	29.0 ± 0.8	10.7 ± 0.6	105
250	9/10[c]	18.5 ± 0.3	28.0 ± 0.7	9.4 ± 0.5	101
500	10/10	18.7 ± 0.3	26.9 ± 0.8	8.3 ± 0.7	97
1,000	10/10	18.3 ± 0.3	28.9 ± 0.7	10.6 ± 0.6	104

[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the vehicle control group are not significant by Dunnett's test.
[c] Week of death: 12

Hematology data are listed in Tables 13 and F3. Hematological changes in mice were similar to those in rats. There was evidence of decreased hematocrit values, hemoglobin concentrations, and erythrocyte counts and increases in platelet and leukocyte counts. The decrease in the erythron was minimal and primarily affected 500 and 1,000 mg/kg males and females. There was also a minimal decrease in the mean cell volume and mean cell hemoglobin values, suggesting that the decreased erythron may have been related to altered erythrocyte production, possibly as a result of the inflammation observed histologically and/or to a minor blood loss associated with the rectal lesions. The increased leukocyte count was characterized by increased lymphocyte counts and may be consistent with the inflammation and histiocytic infiltration observed histologically. Platelet counts were increased in 1,000 mg/kg males and females; the mechanism was unknown but may reflect an increased production or altered peripheral distribution. No other hematological changes were considered to be treatment related.

TABLE 13
Selected Hematology Data for Mice in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
n	10	10	10	10	10	10
Hematocrit (%)	49.8 ± 0.8	49.6 ± 1.2	49.2 ± 0.3	48.2 ± 0.5	47.3 ± 0.6*	47.1 ± 0.5**
Hemoglobin (g/dL)	16.5 ± 0.3	16.5 ± 0.4	16.3 ± 0.2	16.0 ± 0.2	15.7 ± 0.2*	15.9 ± 0.1*
Erythrocytes (10^6/µL)	10.63 ± 0.19	10.68 ± 0.30	10.62 ± 0.08	10.44 ± 0.12	10.30 ± 0.13	10.62 ± 0.13
Mean cell volume (fL)	46.9 ± 0.2	46.6 ± 0.2	46.2 ± 0.1**	46.2 ± 0.1**	45.9 ± 0.1**	44.4 ± 0.2**
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.5 ± 0.1	15.3 ± 0.1	15.4 ± 0.1	15.3 ± 0.0*	14.9 ± 0.1**
Platelets (10^3/µL)	721.4 ± 54.0	757.0 ± 54.0	756.6 ± 25.4	794.7 ± 21.0	876.7 ± 38.8*	970.3 ± 39.8**
Leukocytes (10^3/µL)	4.82 ± 0.29	6.29 ± 0.51*	6.02 ± 0.21*	6.23 ± 0.34*	5.80 ± 0.53*	8.36 ± 0.50**
Lymphocytes (10^3/µL)	4.07 ± 0.24	5.34 ± 0.41*	5.05 ± 0.20*	5.32 ± 0.30**	5.01 ± 0.42*	7.44 ± 0.40**
Segmented neutrophils (10^3/µL)	0.62 ± 0.05	0.69 ± 0.10	0.78 ± 0.12	0.79 ± 0.12	0.63 ± 0.11	0.76 ± 0.12
Female						
n	10	10	9	9	10	10
Hematocrit (%)	48.0 ± 0.7	46.5 ± 0.5*	45.4 ± 0.6**	45.7 ± 0.6**	44.1 ± 0.4**	43.6 ± 0.4**
Hemoglobin (g/dL)	16.1 ± 0.3	15.7 ± 0.2	15.3 ± 0.2*	15.3 ± 0.2**	15.0 ± 0.1**	14.8 ± 0.2**
Erythrocytes (10^6/µL)	10.18 ± 0.16	9.92 ± 0.10*	9.64 ± 0.12**	9.83 ± 0.12*	9.58 ± 0.09**	9.77 ± 0.11**
Mean cell volume (fL)	47.2 ± 0.2	46.9 ± 0.1*	47.0 ± 0.1	46.5 ± 0.2**	46.1 ± 0.2**	44.6 ± 0.2**
Mean cell hemoglobin (pg)	15.8 ± 0.1	15.9 ± 0.1	15.8 ± 0.1	15.6 ± 0.1*	15.6 ± 0.1	15.1 ± 0.1**
Platelets (10^3/µL)	608.9 ± 35.7	666.3 ± 38.4	743.4 ± 27.7*	724.7 ± 23.1*	771.3 ± 30.7**	871.1 ± 33.3**
Leukocytes (10^3/µL)	4.77 ± 0.28	5.62 ± 0.36	5.31 ± 0.27	6.08 ± 0.54	6.11 ± 0.27**	8.33 ± 0.57**
Lymphocytes (10^3/µL)	3.93 ± 0.24	4.50 ± 0.28	4.22 ± 0.15	4.97 ± 0.54	5.15 ± 0.26**	7.28 ± 0.54**
Segmented neutrophils (10^3/µL)	0.69 ± 0.08	0.99 ± 0.16	0.93 ± 0.14	0.91 ± 0.15	0.74 ± 0.07	0.88 ± 0.10

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.

Liver weights of 500 mg/kg males and 1,000 mg/kg males and females were significantly greater than those of the vehicle controls (Tables 14 and G4). Spleen weights of 1,000 mg/kg males were significantly increased. There were no significant differences in sperm motility or vaginal cytology parameters between dosed and vehicle control mice (Tables H3 and H4).

No gross lesions were observed that could be attributed to exposure to Elmiron®. Microscopically, exposure of mice to Elmiron® was associated with nonneoplastic lesions of the rectum, mandibular and mesenteric lymph nodes, liver, and spleen (Table 15).

The incidences of minimal to mild histiocytic cellular infiltration of the rectum were significantly increased in 1,000 mg/kg mice. The incidences and severities of this lesion were generally dose-related, and this lesion was characterized by aggregates of foamy macrophages within the lamina propria which filled and distended the

Table 14
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
n	10	10	10	10	10	10
Necropsy body wt	35.6 ± 1.1	35.7 ± 0.8	36.1 ± 1.0	35.5 ± 0.7	37.6 ± 1.0	35.3 ± 0.8
Liver						
Absolute	1.493 ± 0.065	1.495 ± 0.036	1.573 ± 0.051	1.545 ± 0.034	1.714 ± 0.047**	1.831 ± 0.046**
Relative	41.9 ± 0.9	41.8 ± 0.5	43.6 ± 0.5	43.5 ± 0.8	45.6 ± 0.5**	51.9 ± 0.9**
Spleen						
Absolute	0.071 ± 0.002	0.073 ± 0.002	0.079 ± 0.003	0.073 ± 0.001	0.074 ± 0.002	0.083 ± 0.002**
Relative	2.003 ± 0.047	2.047 ± 0.051	2.194 ± 0.061	2.061 ± 0.035	1.986 ± 0.040	2.370 ± 0.081**
Female						
n	10	10	10	9	10	10
Necropsy body wt	27.9 ± 0.8	27.9 ± 1.0	29.9 ± 0.9	28.0 ± 0.5	27.4 ± 0.8	29.3 ± 0.8
Liver						
Absolute	1.218 ± 0.030	1.226 ± 0.030	1.298 ± 0.037	1.325 ± 0.033	1.297 ± 0.038	1.591 ± 0.076**
Relative	43.7 ± 0.8	44.2 ± 0.8	43.5 ± 0.5	47.4 ± 1.1*	47.5 ± 0.7*	54.3 ± 1.9**

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

Table 15
Incidences of Selected Nonneoplastic Lesions in Mice in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
Intestine Large, Rectum[a]	10	10	10	10	10	10
Infiltration Cellular, Histiocyte[b]	0	0	0	3 (1.0)[c]	3 (1.7)	10** (2.6)
Inflammation, Chronic Active	0	0	0	0	0	8** (1.3)
Ulcer	0	0	0	0	0	2 (1.5)
Lymph Node, Mandibular	10	10	10	10	10	10
Infiltration Cellular, Histiocyte	0	1 (1.0)	3 (1.0)	9** (1.1)	10** (1.1)	8** (1.5)
Lymph Node, Mesenteric	10	10	10	10	10	10
Infiltration Cellular, Histiocyte	0	0	4* (1.0)	10** (1.3)	10** (1.1)	10** (1.4)
Liver	10	2	0	10	10	10
Vacuolization Cytoplasmic	0	0		0	4* (1.0)	9** (1.2)
Inflammation	5 (1.0)	2 (1.0)		7 (1.0)	6 (1.0)	10* (1.5)
Spleen	10	0	0	0	10	10
Infiltration Cellular, Histiocyte	0				0	9** (1.0)
Female						
Intestine Large, Rectum	10	10	10	10	10	10
Infiltration Cellular, Histiocyte	0	0	0	0	3 (2.0)	10** (2.6)
Inflammation, Chronic Active	0	0	0	0	1 (1.0)	7** (1.1)
Lymph Node, Mandibular	10	10	10	9	10	9
Infiltration Cellular, Histiocyte	0	0	2 (1.5)	7** (1.1)	9** (1.3)	9** (2.1)
Lymph Node, Mesenteric	10	10	10	10	10	10
Infiltration Cellular, Histiocyte	0	0	1 (1.0)	10** (1.2)	10** (1.7)	10** (1.6)
Liver	10	5	5	8	10	10
Vacuolization Cytoplasmic	0	0	0	0	0	2 (1.0)
Inflammation	8 (1.0)	5 (1.0)	5 (1.0)	7 (1.0)	7 (1.1)	9 (1.3)
Spleen	10	0	0	10	10	10
Infiltration Cellular, Histiocyte	0			0	4* (1.0)	10** (1.0)

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

lamina propria and resulted in disorganization and distortion of the mucosal crypts. The macrophages were large with abundant foamy cytoplasm due to the presence of numerous intracytoplasmic, variably sized, clear vacuoles. The lamina propria appeared expanded with a faint bluish tinged acellular material (myxomatous change).

The incidences of minimal chronic active inflammation of the rectum were significantly increased in 1,000 mg/kg mice; this lesion also occurred in 500 mg/kg females. The chronic active inflammation was characterized by lymphocytes and neutrophils in the lamina propria, mucosa, and/or lumen of the rectum. Minimal ulceration occurred in 1,000 mg/kg males and consisted of focal denudation of the epithelial lining. These areas were usually small with an inflammatory base, and some of the mucosal areas appeared to be healing from a previous ulceration. This was characterized by an attenuated epithelium covering the surface of the lamina propria associated with loss of the crypts of the mucosa.

Incidences of minimal histiocytic infiltration of the mandibular and mesenteric lymph nodes were generally significantly increased in males dosed with 125 mg/kg or greater and in 250 mg/kg or greater females. Histiocytic infiltration consisted of large macrophages with foamy cytoplasm filled with variably sized clear vacuoles; the macrophages were located in the subcapsular and/or medullary sinuses. Although other lymph nodes were not examined, it is likely that they too may contain Elmiron®-induced vacuolated macrophages.

Incidences of minimal centrilobular hepatocellular cytoplasmic vacuolization were significantly increased in 500 and 1,000 mg/kg male mice. This lesion was also observed in 1,000 mg/kg female mice. The vacuolization was characterized by the presence of clear, spherical vacuoles in the cytoplasm of hepatocytes, which are consistent with the presence of fat. Minimal inflammation of the liver was generally observed in vehicle control and dosed groups of mice and was significantly increased in 1,000 mg/kg males. Severity of the inflammation was slightly increased in the 1,000 mg/kg groups, and the lesion comprised macrophages, monocytes, lymphocytes, and neutrophils scattered throughout the parenchyma.

Incidences of minimal histiocytic infiltration of the spleen were significantly increased in 1,000 mg/kg males and females and 500 mg/kg females. Histiocytic infiltration was characterized by macrophages with foamy cytoplasm filled with one to several clear vacuoles. The histiocytes were located in the red pulp and as a mantle in the white pulp.

Histiocytic Vacuolation Assessment

Histochemical Evaluation: In order to identify the nature of the histiocytic cytoplasmic vacuolation seen in different organs, samples of the spleen, rectum, liver, and mesenteric and mandibular lymph nodes were taken from two 1,000 mg/kg male mice and stained as described for 3-month rats.

Occasional vacuolated cells (histiocytes) containing PAS-positive cytoplasmic material were observed in the mesenteric lymph node and spleen. In the spleen only, the vacuolated cells also contained AB-positive material.

The results indicate that the vacuolated cells accumulated mucins, which are hexosamine-containing polysaccharides covalently bound to varying amounts of protein. The positive staining for both neutral and acidic mucins in the same cells indicates that the vacuolated cells contained a mixture of different types of mucin.

Electron Microscopic Evaluation: The purpose of this study was to gain information about the ultrastructural characteristics of the histiocyte infiltrates observed in mice administered Elmiron®. Lung and lymph node samples that exhibited significant histiocyte infiltration by light microscopy were selected from two 1,000 mg/kg male mice. The results indicated that the vacuolated macrophages had lysosomal changes similar to those described in rats.

Dose Selection Rationale: Survival and body weights were not adversely affected by treatment; however, mice exposed to 1,000 mg/kg had significant histological alterations in the rectum. The rectal mucosal architecture was altered by the cellular infiltrates, and ulcers were present in two males. These changes were not observed at 2 weeks and, therefore, appeared to progress with time. The incidence and severity also progressed with increasing dose concentration. Although the changes were not severe at the end of 3 months, there was concern that in a 2-year study, these lesions might become more severe with an adverse affect on the host. Therefore, doses for the 2-year study were selected at which the incidences of rectal lesions were not significant (0, 56, 168, and 504 mg/kg).

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 16 and in the Kaplan-Meier survival curves (Figure 3). Life table analysis showed a slight dose-related negative trend in the survival of males; however, pairwise comparison showed that survival of all dosed groups was similar to that of the vehicle controls.

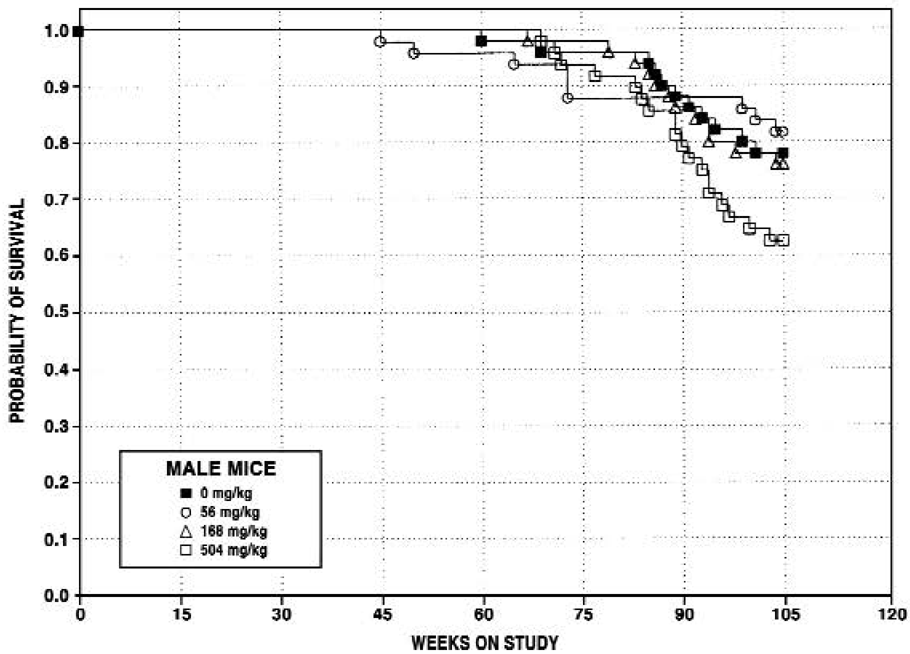
Body Weights and Clinical Findings

Mean body weights of male mice were similar to those of the vehicle controls throughout the 2-year study (Figure 4; Tables 17 and 18). Mean body weights of 504 mg/kg females were progressively less than those of the vehicle controls during the second year of the study; this group lost weight after week 65. Mean body weights of 56 and 168 mg/kg females were generally less than those of the vehicle controls during the last 4 months of the study. There were no clinical findings related to Elmiron® administration.

Table 16
Survival of Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	1	0	2
Moribund	7	4	4	3
Natural deaths	4	5	8	15
Animals surviving to study termination	39	40	38	30
Percent probability of survival at end of study[b]	78	82	76	63
Mean survival (days)[c]	702	679	702	658
Survival analysis[d]	P=0.038	P=0.860N	P=0.974	P=0.140
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	1	1	0	0
Moribund	4	5	3	7
Natural deaths	8	6	10	9
Animals surviving to study termination	37	38[e]	37	34
Percent probability of survival at end of study	76	78	74	68
Mean survival (days)	692	689	695	699
Survival analysis	P=0.359	P=0.962N	P=0.968	P=0.544

[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 vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A lower mortality in a dose group is indicated by **N**.
[e] Includes one animal that died during the last week of the study



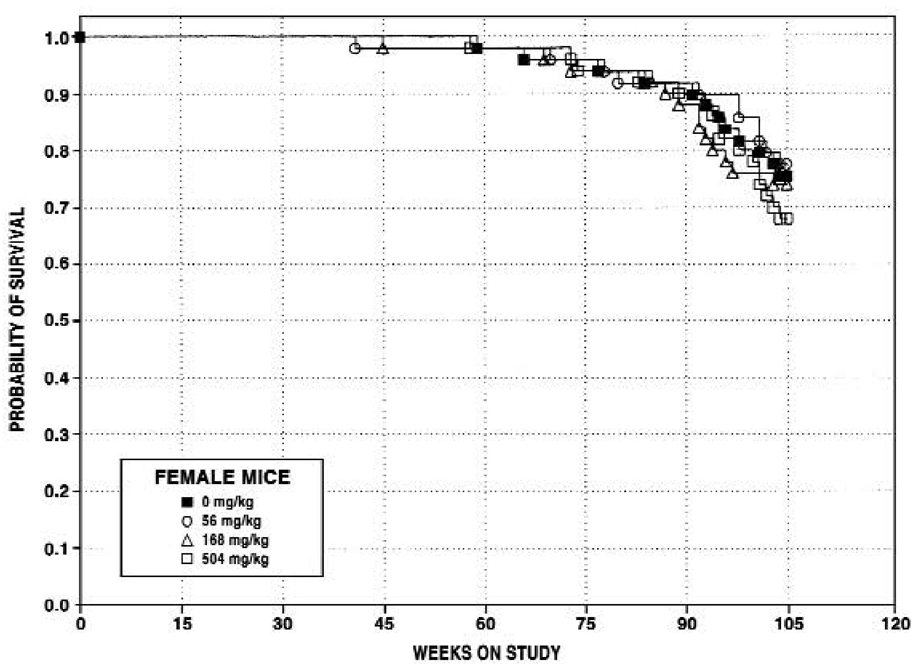


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Elmiron® by Gavage for 2 Years

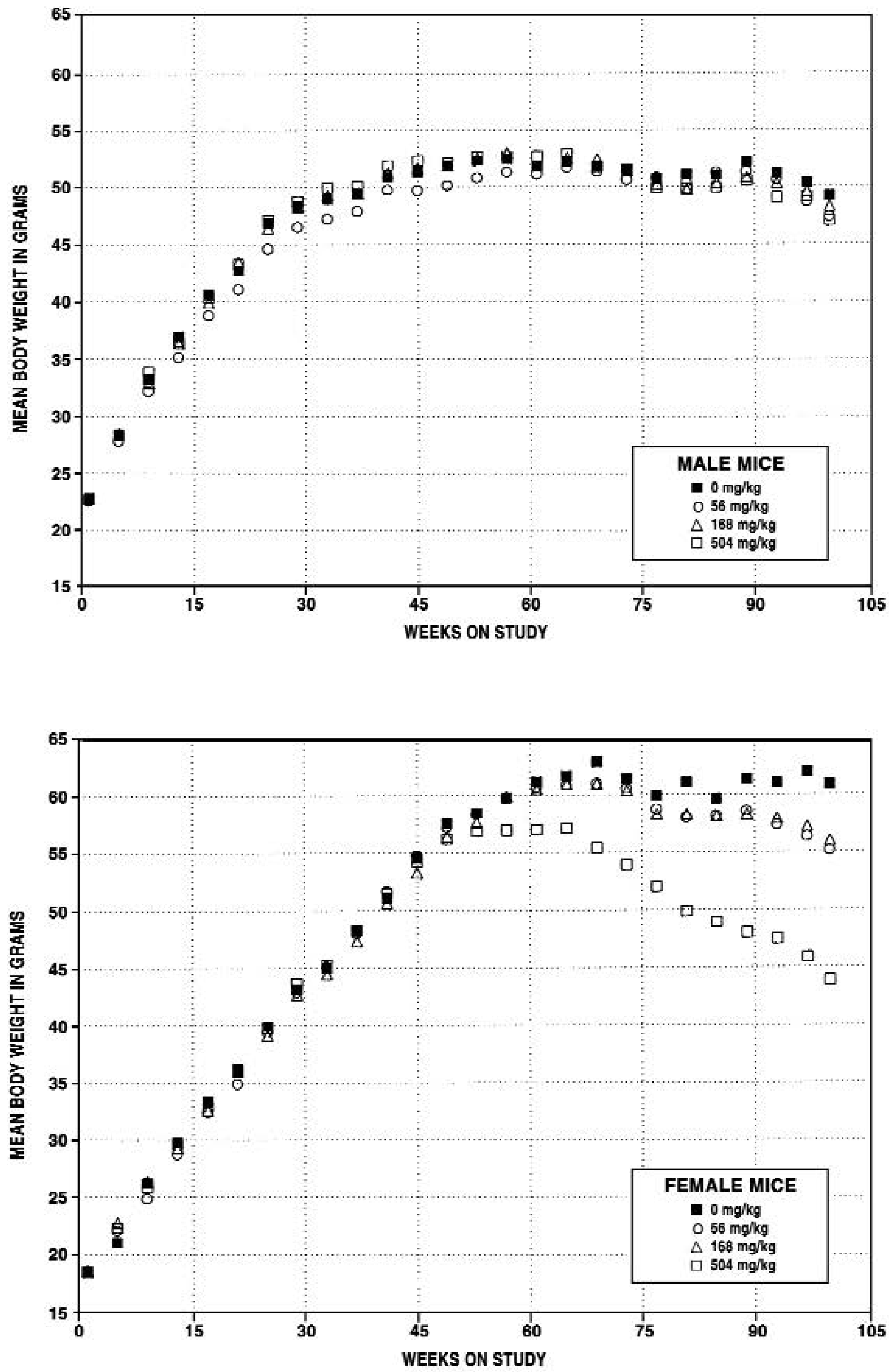


FIGURE 4
Growth Curves for Male and Female Mice Administered Elmiron® by Gavage for 2 Years

Table 17
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Elmiron®

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	56 mg/kg Av. Wt. (g)	56 mg/kg Wt. (% of controls)	56 mg/kg No. of Survivors	168 mg/kg Av. Wt. (g)	168 mg/kg Wt. (% of controls)	168 mg/kg No. of Survivors	504 mg/kg Av. Wt. (g)	504 mg/kg Wt. (% of controls)	504 mg/kg No. of Survivors
1	22.8	50	22.5	99	50	22.8	100	50	22.7	100	50
5	28.3	50	27.8	98	49	28.5	101	50	28.4	100	48
9	33.3	50	32.2	97	49	32.9	99	50	33.9	102	48
13	37.0	50	35.2	95	49	36.4	98	50	36.5	99	48
17	40.6	50	38.8	96	49	39.9	98	50	40.4	100	48
21	42.7	50	41.1	96	49	43.5	102	50	43.3	101	48
25	46.9	50	44.7	95	49	46.5	99	50	47.1	100	48
29	48.4	50	46.6	96	49	48.2	100	50	48.7	101	48
33	49.0	50	47.3	97	49	49.3	101	50	49.9	102	48
37	49.4	50	47.9	97	49	49.4	100	50	50.0	101	48
41	50.9	50	49.8	98	49	51.3	101	50	51.9	102	48
45	51.3	50	49.7	97	49	51.7	101	50	52.3	102	48
49	51.9	50	50.1	97	48	51.9	100	50	52.1	100	48
53	52.3	50	50.8	97	47	52.6	101	50	52.7	101	48
57	52.5	50	51.3	98	47	53.0	101	50	52.7	100	48
61	51.9	49	51.1	99	47	51.8	100	50	52.7	102	48
65	52.3	49	51.7	99	47	52.6	101	50	52.9	101	48
69	51.9	49	51.4	99	46	52.4	101	49	51.8	100	48
73	51.5	48	50.6	98	46	51.4	100	49	51.6	100	45
77	50.7	48	50.8	100	43	50.2	99	49	49.9	98	45
81	51.1	48	50.4	99	43	49.8	98	48	49.9	98	44
85	51.0	48	51.3	101	43	50.3	99	47	49.9	98	42
89	52.2	45	51.3	98	43	50.8	97	44	50.5	97	40
93	51.2	43	50.6	99	43	50.3	98	42	49.0	96	37
97	50.4	41	48.7	97	43	49.5	98	40	49.1	97	33
100	49.2	40	47.4	96	42	48.3	98	39	47.1	96	31
Mean for weeks											
1-13	30.4		29.4	97		30.2	99		30.4	100	
14-52	47.9		46.2	96		47.9	100		48.4	101	
53-100	51.4		50.6	98		51.0	99		50.8	99	

Table 18
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Elmiron®

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	56 mg/kg Av. Wt. (g)	56 mg/kg Wt. (% of controls)	56 mg/kg No. of Survivors	168 mg/kg Av. Wt. (g)	168 mg/kg Wt. (% of controls)	168 mg/kg No. of Survivors	504 mg/kg Av. Wt. (g)	504 mg/kg Wt. (% of controls)	504 mg/kg No. of Survivors
1	18.5	50	18.4	100	50	18.6	101	50	18.5	100	50
5	21.0	50	22.0	105	49	22.7	108	50	22.3	106	50
9	26.2	50	24.9	95	49	26.4	101	50	25.9	99	50
13	29.8	50	28.7	96	49	29.3	98	50	29.6	99	50
17	33.4	50	32.4	97	49	32.6	98	50	32.9	99	50
21	36.2	50	34.9	96	49	36.1	100	50	36.2	100	50
25	39.9	50	39.4	99	49	39.1	98	50	39.7	100	50
29	43.1	49	42.9	100	49	42.7	99	50	43.7	101	50
33	45.0	49	45.2	100	49	44.5	99	50	45.3	101	50
37	48.2	49	48.0	100	49	47.3	98	50	48.3	100	50
41	51.1	49	51.7	101	48	50.7	99	50	51.5	101	50
45	54.6	49	54.8	100	48	53.3	98	50	54.3	100	50
49	57.6	49	57.2	99	48	56.5	98	49	56.2	98	50
53	58.5	49	58.4	100	48	57.7	99	49	56.9	97	50
57	59.8	49	59.8	100	48	59.9	100	49	57.0	95	50
61	61.2	48	60.7	99	48	60.5	99	49	57.0	93	49
65	61.7	48	60.9	99	48	61.0	99	49	57.1	93	49
69	62.9	47	61.0	97	48	61.0	97	49	55.4	88	49
73	61.4	47	60.6	99	47	60.4	98	48	53.9	88	49
77	59.9	47	58.8	98	47	58.3	97	47	52.0	87	47
81	61.1	46	58.1	95	45	58.3	95	47	49.9	82	47
85	59.7	45	58.2	98	45	58.2	98	46	49.0	82	46
89	61.4	45	58.6	95	45	58.3	95	45	48.0	78	46
93	61.0	44	57.4	94	44	57.9	95	42	47.5	78	44
97	62.0	41	56.4	91	44	57.2	92	39	45.9	74	41
100	60.9	40	55.2	91	42	56.0	92	38	43.9	72	40
Mean for weeks											
1-13	23.9		23.5	98		24.3	102		24.1	101	
14-52	45.5		45.2	99		44.8	98		45.3	100	
53-100	60.9		58.8	97		58.8	97		51.8	85	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of malignant lymphoma and histiocytic sarcoma and neoplasms and nonneoplastic lesions of the liver, rectum, mesenteric lymph node, spleen, and adrenal gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: The incidences of hemangiosarcoma occurred with a positive trend in male mice, and the incidence in the 504 mg/kg group was significantly increased (Tables 19 and C3). The incidences of this lesion in 168 and 504 mg/kg males and 504 mg/kg females exceeded the historical ranges in controls (all routes) given NTP-2000 diet (Tables 19, C4, and D4a). Hemangiosarcomas were characterized by pleomorphic, proliferative endothelial cells which formed irregular vascular spaces. A hyaline perivascular or interstitial material often surrounded the neoplastic vascular spaces. Large areas of hemorrhage, thrombosis, and necrosis sometimes occurred within the lesions (Plates 10 and 11).

Table 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Clear Cell Focus[a]	21	23	19	15
Basophilic Focus	14	10	5*	10
Eosinophilic Focus	13	11	9	12
Inflammation Chronic	11 (1.1)[b]	15 (1.1)	23** (1.0)	33** (1.3)
Hemangiosarcoma[c]				
Overall rate[d]	2/50 (4%)	0/50 (0%)	4/50 (8%)	9/50 (18%)
Adjusted rate[e]	4.4%	0.0%	8.8%	21.2%
Terminal rate[f]	1/39 (3%)	0/40 (0%)	4/38 (11%)	5/30 (17%)
First incidence (days)	646	—[h]	730 (T)	539
Poly-3 test[g]	P<0.001	P=0.246N	P=0.332	P=0.017
Hepatocellular Adenoma, Multiple	9	3	5	10
Hepatocellular Adenoma (includes multiple)	19	15	15	20
Hepatocellular Carcinoma, Multiple	4	1	4	2
Hepatocellular Carcinoma (includes multiple)	11	13	15	13
Hepatocellular Adenoma or Carcinoma[i]				
Overall rate	23/50 (46%)	23/50 (46%)	26/50 (52%)	31/50 (62%)
Adjusted rate	48.0%	50.2%	53.0%	66.6%
Terminal rate	18/39 (46%)	19/40 (48%)	16/38 (42%)	18/30 (60%)
First incidence (days)	420	455	548	483
Poly-3 test	P=0.031	P=0.498	P=0.386	P=0.049

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Female				
Number Examined Microscopically	50	49	50	49
Clear Cell Focus	0	4	1	21**
Basophilic Focus	5	6	8	12*
Eosinophilic Focus	10	6	7	15
Inflammation Chronic	40 (1.0)	37 (1.1)	40 (1.1)	38 (1.7)
Hemangiosarcoma[j]				
Overall rate	1/50 (2%)	1/49 (2%)	1/50 (2%)	4/49 (8%)
Adjusted rate	2.2%	2.2%	2.2%	8.9%
Terminal rate	1/37 (3%)	1/38 (3%)	1/37 (3%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)	645
Poly-3 test	P=0.056	P=0.760N	P=0.760	P=0.177
Hepatocellular Adenoma, Multiple	1	2	2	6
Hepatocellular Adenoma (includes multiple)[k]				
Overall rate	7/50 (14%)	5/49 (10%)	4/50 (8%)	15/49 (31%)
Adjusted rate	15.4%	11.1%	8.9%	32.8%
Terminal rate	6/37 (16%)	5/38 (13%)	3/37 (8%)	11/34 (32%)
First incidence (days)	536	729 (T)	647	517
Poly-3 test	P=0.003	P=0.388N	P=0.267N	P=0.042
Hepatocellular Carcinoma	3	3	5	3
Hepatocellular Adenoma or Carcinoma[l]				
Overall rate	10/50 (20%)	8/49 (16%)	9/50 (18%)	18/49 (37%)
Adjusted rate	21.9%	17.8%	20.0%	39.1%
Terminal rate	8/37 (22%)	7/38 (18%)	8/37 (22%)	11/34 (32%)
First incidence (days)	536	722	647	517
Poly-3 test	P=0.010	P=0.411N	P=0.514N	P=0.057

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
** $P \leq 0.01$
(T) Terminal sacrifice
a Number of animals with lesion
b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
c Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 24/959 (2.6% ± 1.4%), range 0%-4%
d Number of animals with neoplasm per number of animals examined microscopically
e Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
f Observed incidence at terminal kill
g Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparison between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by **N**.
h Not applicable; no neoplasms in animal group
i Historical incidence: 441/959 (48.4% ± 12.9%), range 26%-72%
j Historical incidence: 6/954 (0.7% ± 1.4%), range 0%-4%
k Historical incidence: 144/954 (15.9% ± 6.1%), range 7%-28%
l Historical incidence: 203/954 (22.6% ± 9.1%), range 9%-40%

The incidences of hepatocellular adenoma or carcinoma (combined) occurred with a positive trend in male mice. The incidence in 504 mg/kg males was significantly increased but was within the historical range in controls given NTP-2000 diet (Tables 19, C3, and C4). The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends in female mice (Tables 19 and D3). The incidence of hepatocellular adenoma in 504 mg/kg females was significantly increased and exceeded the historical range in controls given NTP-2000 diet (Tables 19 and D4b). A diagnosis of hepatocellular carcinoma was made when some or all of the following were present: variable growth pattern (solid, trabecular, or glandular), increased numbers of mitotic figures, cytoplasmic inclusions, cellular atypia, and nuclear pleomorphism, irregular borders with invasion and compression, and metastasis. Hepatocellular adenomas show distinct compression, but cellular and nuclear morphology and hepatic cord arrangement are more uniform. The hepatic plates within adenomas intersect the surrounding normal parenchyma at sharp angles.

The incidences of altered hepatocellular foci were increased in 504 mg/kg females; in this group, the incidence of eosinophilic focus was slightly increased, and the incidences of clear cell and basophilic foci were significantly increased (Tables 19, C5, and D5). Altered hepatocellular foci may be classified as basophilic, eosinophilic, clear cell, or mixed. They may be mildly compressive but lack distinct borders and retain alignment of hepatic cords with adjacent parenchyma. Clear cell focus was the most common variant of foci diagnosed in these mice. The increased incidence of clear cell focus in 504 mg/kg females was considered to be Elmiron® related. It is not clear if the eosinophilic and basophilic foci are Elmiron® related.

The incidences of minimal chronic inflammation of the liver were increased in 168 and 504 mg/kg males (Tables 19 and C5). In females, the incidences of chronic inflammation were similar among the vehicle control and dosed groups, but the severity was increased in the 504 mg/kg group (Tables 19 and D5). Chronic inflammation included a spectrum of morphological changes, including microgranulomas (clusters of macrophages, occasional neutrophils, and individual cell necrosis), mononuclear cell (primarily lymphocytic) infiltrates in the periportal areas and along larger blood vessels, pigmented macrophages, and increased cellularity of hepatic sinusoids.

Sporadic hemangiosarcomas were diagnosed as primary neoplasms in several other tissues in mice, including the bone marrow, spleen, heart, mesenteric lymph node, ovary, skin, mesentery, urinary bladder, preputial gland, and testis (Tables 20, C1, and D1). However, the incidences of hemangiosarcoma in these extrahepatic sites were low and did not appear to be related to Elmiron® administration. For several mice, extrahepatic hemangiosarcomas occurred concomitantly with hepatic hemangiosarcomas and were possibly metastatic sites. Three 504 mg/kg males with hepatic hemangiosarcomas had extrahepatic hemangiosarcomas involving the spleen, heart, bone marrow, and mesenteric lymph node. Individual 56 and 504 mg/kg female mice with hepatic hemangiosarcomas each had extrahepatic hemangiosarcomas involving the bone marrow and the mesentery, respectively. Three 504 mg/kg females had a single incidence of hemangioma.

TABLE 20
Incidences of Hemangioma and Hemangiosarcoma in Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Male				
Number Necropsied	50	50	50	50
Hemangiosarcoma, Liver[a]	2	0	4	9*
Hemangiosarcoma, Bone Marrow	2	0	2	1
Hemangiosarcoma, Spleen	0	0	1	2
Hemangiosarcoma, Heart	0	0	0	1
Hemangiosarcoma, Lymph Node, Mesenteric	0	0	0	1
Hemangiosarcoma, Urinary Bladder	0	0	1	0
Hemangiosarcoma, Preputial Gland	1	0	0	0
Hemangiosarcoma, Testis	1	0	0	0
Hemangiosarcoma, (All Organs)[b]				
Overall rate[c]	6/50 (12%)	0/50 (0%)	7/50 (14%)	9/50 (18%)
Adjusted rate[d]	13.0%	0.0%	15.2%	21.2%
Terminal rate[e]	4/39 (10%)	0/40 (0%)	5/38 (13%)	5/30 (17%)
First incidence (days)	590	—[f]	653	539
Poly-3 test[g]	P=0.026	P=0.018N	P=0.493	P=0.227
Female				
Number Necropsied	50	50	50	50
Hemangiosarcoma, Liver	1	1	1	4
Hemangiosarcoma, Bone Marrow	0	1	0	0
Hemangiosarcoma, Spleen	0	1	0	0
Hemangioma, Ovary	0	0	0	2
Hemangiosarcoma, Ovary	0	0	1	0
Hemangioma, Skin, Subcutaneous	0	0	0	1
Hemangiosarcoma, Skin, Subcutaneous	0	0	1	0
Hemangiosarcoma, Mesentery	0	0	0	1
Hemangioma, (All Organs)[h]				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	6.6%
Terminal rate	0/37 (0%)	0/38 (0%)	0/37 (0%)	2/34 (6%)
First incidence (days)	—	—	—	660
Poly-3 test	P=0.008	—[i]	—	P=0.121
Hemangiosarcoma, (All Organs)[j]				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted rate	2.2%	2.2%	6.6%	8.8%
Terminal rate	1/37 (3%)	1/38 (3%)	2/37 (5%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	509	645
Poly-3 test	P=0.093	P=0.759N	P=0.309	P=0.184

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 50/959 (5.5% ± 3.7%), range 0%-14%
[c] Number of animals with neoplasm per number of animals examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Not applicable; no neoplasms in animal group
[g] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparison between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by **N**.
[h] Historical incidence: 15/959 (1.5% ± 1.8%), range 0%-5%
[i] Value of statistic cannot be computed.
[j] Historical incidence: 22/959 (2.6% ± 2.4%), range 0%-8%

Malignant Lymphoma: The incidence of malignant lymphoma was significantly increased in 504 mg/kg females, and the overall rate was at the upper end of the historical control range (Tables 21, D3, and D4c). Malignant lymphoma in the $B6C3F_1$ mouse generally originates in a primary lymphoid organ (particularly the spleen) and, as it progresses, it spreads and involves other organs. The organ distribution was similar between the vehicle control and dosed groups. Similar increased incidences were not observed in males; however, in NTP studies, increased incidences of malignant lymphoma have commonly occurred in only one sex of the $B6C3F_1$ mouse. It is not clear if the increased incidence in 504 mg/kg females is related to Elmiron® administration.

Histiocytic Sarcoma: Although the incidences of histiocytic sarcoma in dosed females were not significantly increased (vehicle control, 0/50; 56 mg/kg, 4/50; 168 mg/kg, 1/50; 504 mg/kg, 3/50; Table D3), the incidence in the 56 mg/kg group slightly exceeded the historical range in controls given NTP-2000 diet [11/959 (1.1% ± 1.6%), range 0%-6%]. Because this neoplasm was significantly increased only in the lowest dosed group, this response was not considered to be related to Elmiron® administration.

Rectum: The incidences of minimal to mild chronic active inflammation, necrosis, squamous metaplasia, histiocytic cellular infiltration, and myxomatous change were significantly increased in 504 mg/kg mice (Tables 22, C5, and D5). The lesions appeared to be more common and severe in females. A significantly increased incidence of minimal myxomatous change also occurred in 168 mg/kg females.

Chronic active inflammation was characterized by an infiltrate of macrophages, lymphocytes, neutrophils, and plasma cells in the lamina propria and/or submucosa. Necrosis and squamous metaplasia were associated with the chronic active inflammation (Plates 12 to 16).

TABLE 21
Incidences of Malignant Lymphoma in Female Mice in the 2-year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Malignant Lymphoma[a]				
Overall rate[b]	7/50 (14%)	8/50 (16%)	6/50 (12%)	16/50 (32%)
Adjusted rate[c]	15.6%	17.1%	13.1%	34.9%
Terminal rate[d]	6/37 (16%)	5/38 (13%)	3/37 (8%)	14/34 (41%)
First incidence (days)	723	281	509	621
Poly-3 test[e]	P=0.006	P=0.537	P=0.482N	P=0.028

[a] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 148/959 (14.5% ± 6.8%), range 6%-32%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparison between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by **N**.

Histiocytic cell infiltration consisted of infiltrates of vacuolated macrophages within the lamina propria and submucosa. Similar vacuolated macrophages were seen in the mesenteric lymph node and spleen of dosed animals. Occasional vacuolated cells were also seen in the inner layer of the tunica muscularis and associated with Auerbach's plexuses. It was not entirely clear if these cells represented the same population of vacuolated macrophages or if they were other types of vacuolated cells. However, since there was no evidence that other types of cells accumulated intracytoplasmic vacuolation in other affected organs, the vacuolated cells may be macrophages.

Myxomatous change consisted of expanded, bluish tinged acellular material in the lamina propria. This material stained negatively with a PAS reaction, but stained positively with an AB stain. AB stains sulfated mucopolysaccharide-like substances such as normal ground substance in the interstitium. Because Elmiron® is a sulfated polyanion, the myxomatous change may be the test material, or some form of the test material, which is accumulated in the lamina propria. Myxomatous change was not a prominent morphological feature in animals with chronic active inflammation of the rectum and was not diagnosed in most of these animals. It is

Table 22
Incidences of Selected Nonneoplastic Lesions in Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Male				
Intestine Large, Rectum[a]	49	47	46	44
Inflammation, Chronic Active[b]	0	0	1 (1.0)[c]	8** (2.0)
Necrosis	0	0	0	5* (2.0)
Metaplasia, Squamous	0	0	0	5* (1.6)
Infiltration Cellular, Histiocyte	0	0	0	6** (1.0)
Myxomatous Change	0	0	0	13** (1.4)
Lymph Node, Mesenteric	48	46	45	41
Infiltration Cellular, Histiocyte	0	15** (1.3)	34** (2.1)	37** (2.0)
Spleen	49	50	49	49
Infiltration Cellular, Histiocyte	0	1 (1.0)	1 (1.0)	23** (1.0)
Female				
Intestine Large, Rectum	45	45	44	46
Inflammation, Chronic Active	0	0	2 (2.5)	32** (2.1)
Necrosis	0	0	1 (4.0)	24** (2.0)
Metaplasia, Squamous	0	0	1 (2.0)	26** (2.0)
Infiltration Cellular, Histiocyte	0	0	2 (1.0)	10** (1.0)
Myxomatous Change	0	3 (1.0)	21** (1.1)	31** (1.7)
Lymph Node, Mesenteric	47	44	42	45
Infiltration Cellular, Histiocyte	0	23** (1.2)	35** (1.9)	25** (2.0)
Spleen	47	48	47	46
Infiltration Cellular, Histiocyte	0	3 (1.0)	12** (1.0)	28** (1.0)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

believed, however, that the myxomatous change was probably present, masked by the more prominent inflammatory response.

Mesenteric Lymph Node: Incidences of histiocytic cellular infiltration of the mesenteric lymph node in all dosed groups of males and females were significantly increased (Tables 22, C5, and D5). In males, the incidence and severity of histiocytic infiltration increased with increasing dose. In females, the lesion was similar in severity and incidence in the 168 and 504 mg/kg groups. Mice administered 56 mg/kg had reduced incidences and severities of histiocytic infiltration compared to those of the 504 mg/kg groups. Histiocytic cellular infiltration consisted of infiltration of vacuolated macrophages, whose cytoplasm was distended by one to many variably sized clear vacuoles. The vacuolated macrophages were most easily recognized in the subcapsular spaces of the lymph nodes.

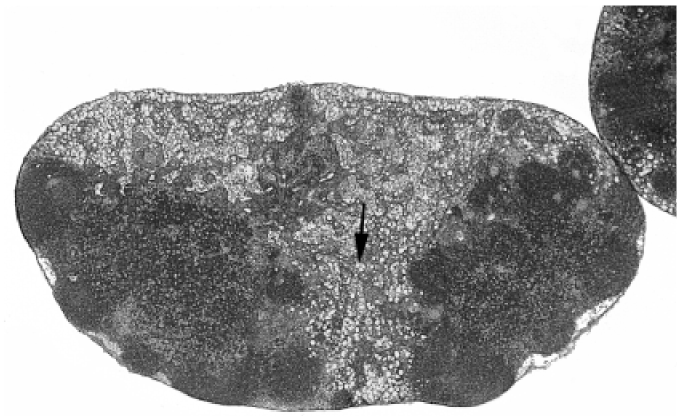
Histiocytic infiltration was seen in mandibular lymph nodes of three 504 mg/kg females (Table D5), although the severity was less than that in the mesenteric lymph nodes. Mandibular lymph nodes were not specifically examined for this lesion in all animals. It is likely that, with systemic lymphatic circulation, Elmiron®-induced vacuolated macrophages would be present to some degree in other lymph nodes.

Spleen: The incidences of minimal histiocytic cellular infiltration of the spleen in 504 mg/kg males and in 168 and 504 mg/kg females (Tables 22, C5, and D5) were significantly greater than those in the vehicle controls. These vacuolated cells, consistent with macrophages, were similar to the histiocytes described in the mesenteric lymph nodes. These cells were not numerous (generally less than 20 in an entire spleen), and they were present at the periphery of the white pulp and within the red pulp. Because this finding occurred only in dosed mice, it is believed that these vacuolated cells are similar to the vacuolated macrophages seen in the lymph nodes.

Adrenal Gland: The incidence of adrenal cortical hypertrophy was significantly increased in 504 mg/kg females (vehicle control, 1/49; 56 mg/kg, 3/49; 168 mg/kg, 3/49; 504 mg/kg, 12/48; Table D5). The severity of this lesion was increased in 504 mg/kg males (1.8, 1.4, 1.4, 1.9) and females (1.0, 1.0, 1.0, 1.7) compared to the other dosed groups. Hypertrophy of the adrenal cortex was characterized as focal areas of hypertrophied cells of the zona fasciculata. These foci were sometimes mildly expansile but still retained some cord-like orientation with the adrenal capsular zone. Adrenal cortical hypertrophy is differentiated from cortical hyperplasia by the lack of cellular proliferation, as evidenced by increased numbers of cells or dividing cells (mitoses). Adrenal cortical hypertrophy is a common background finding in mice and is not considered a proliferative lesion. An increase in adrenal cortical hypertrophy did not occur in 504 mg/kg males; the incidence of this lesion was significantly decreased in 504 mg/kg males.

Genetic Toxicology

Elmiron®, tested over a concentration range of 100 to 10,000 µg/plate, was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 with or without induced rat or hamster liver S9 (Table E1). No consistent increase in the frequency of micronucleated polychromatic erythrocytes (PCEs) was seen in bone marrow cells of rats (Table E2) or mice (Table E3) administered 156.25 to 2,500 mg Elmiron®/kg body weight by gavage three times at 24-hour intervals. In the rat study, an initial trial yielded a weakly positive result (trend P value=0.019), but a second trial gave clearly negative results, and Elmiron® was judged to be negative overall in the rat and mouse bone marrow micronucleus tests. No increase in the frequency of micronucleated normochromatic erythrocytes was seen in male or female $B6C3F_1$ mice administered a daily dose of 63, 125, 250, 500, or 1,000 mg/kg Elmiron® by gavage for 3 months (Table E4). There were slight decreases in the percentages of PCEs in the circulating blood of 500 and 1,000 mg/kg mice, but the decreases were not significant.



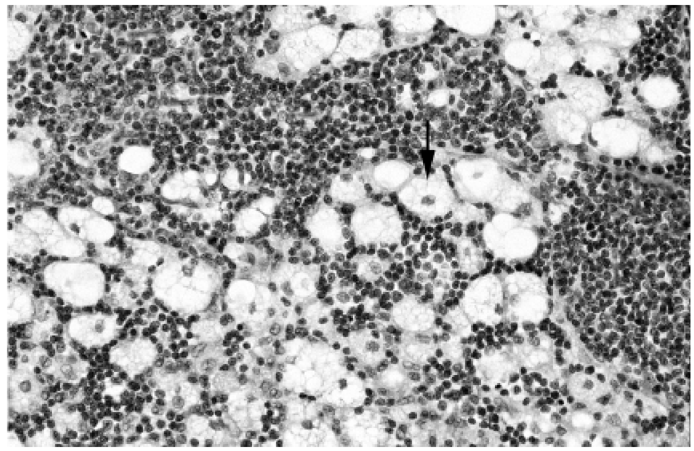


Plate 1
Presence of histiocytes in the subcapsular and/or medullary sinuses (arrow) in the mesenteric lymph node of a male F344/N rat administered 1,000 mg/kg Elmiron® by gavage for 3 months. H&E; 8x

Plate 2
Higher magnification of Plate 1. Note the presence of vacuolated histiocytes (arrow) adjacent to normal lymphoid medullary cord. H&E; 80x

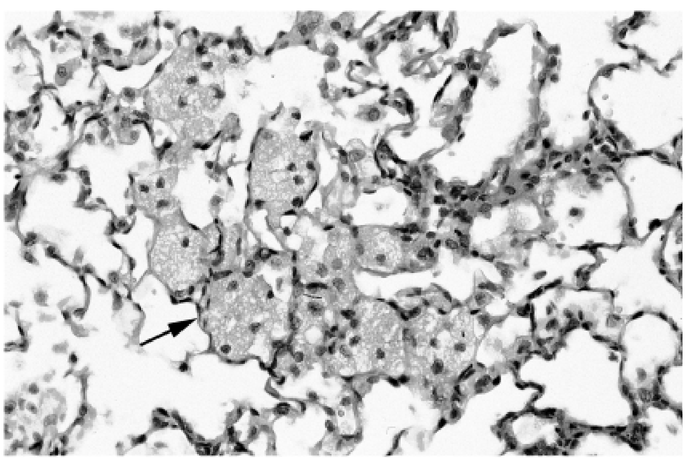


Plate 3
Alveolar histiocytic infiltration (arrow) associated with minimal chronic interstitial inflammation in the lung of a male F344/N rat administered 1,000 mg/kg Elmiron® by gavage for 3 months. H&E; 80x

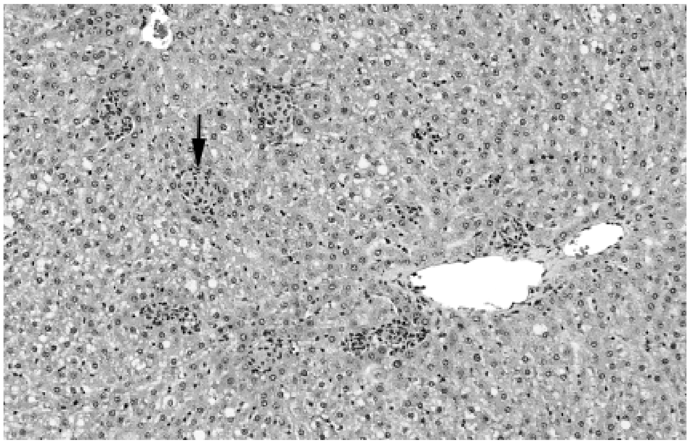


Plate 4
Multifocal granulomatous inflammation (arrow) in the liver of a male F344/N rat administered 1,000 mg/kg Elmiron® by gavage for 3 months. H&E; 33x

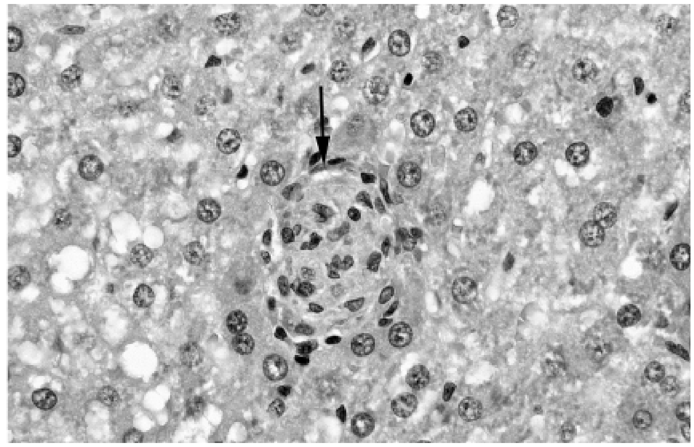


Plate 5
Higher magnification of Plate 4. Note the histiocytes (arrow) composing the granulomatous reaction. H&E

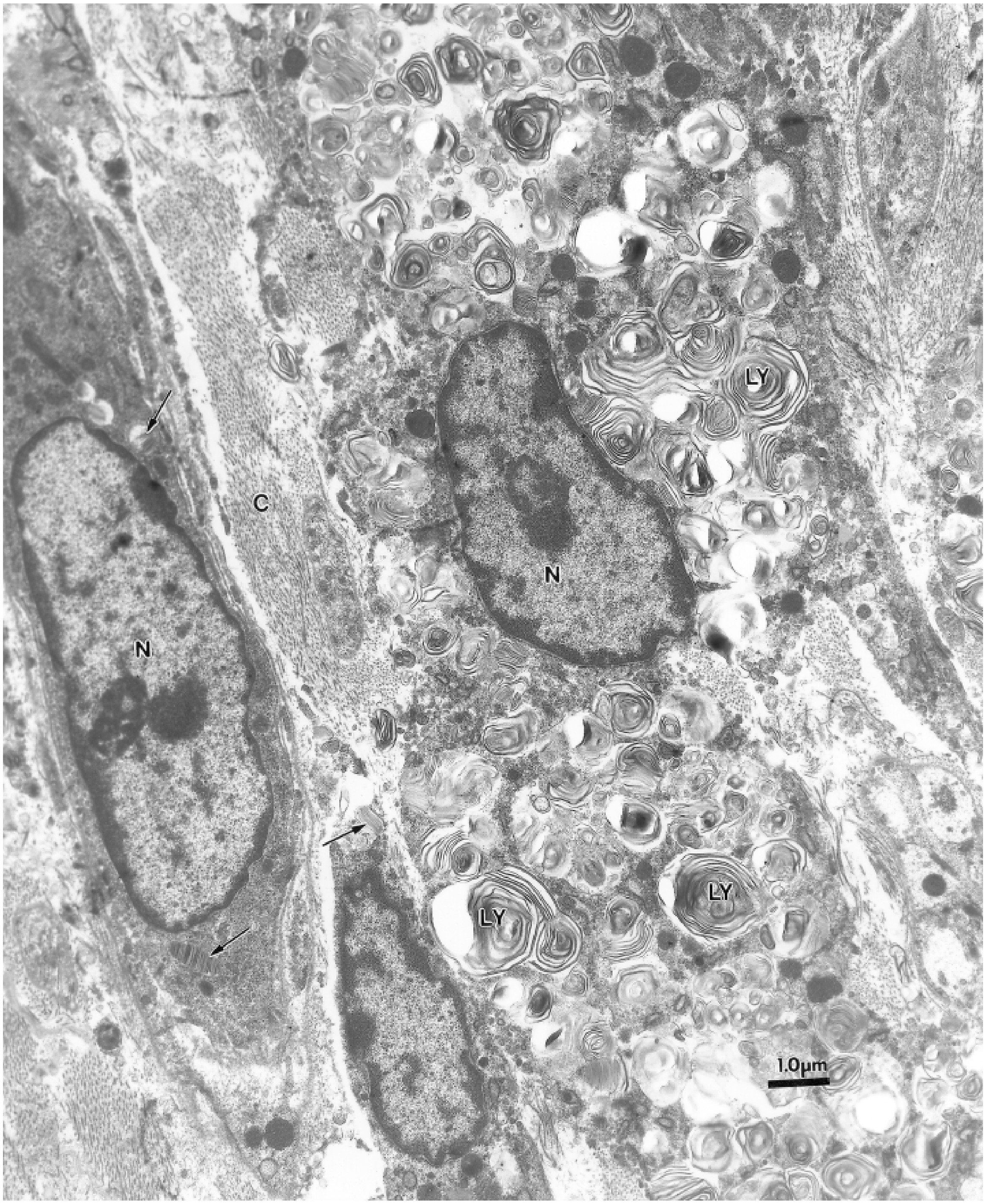


Plate 6

The cytoplasm of this macrophage within the lamina propria from the rectum of a male rat administered 1,000 mg/kg Elmiron® by gavage for 3 months contains numerous lysosomes filled with concentric lamellar material, myelin figures. The two cells along the left exhibit small lysosomes with lamellar material (arrows). These may be macrophages, which recently migrated into the lamina propria, and are just beginning to accumulate the lysosomal material. C=Collagen; LY=Lysosome; N=Nucleus. 10,900×

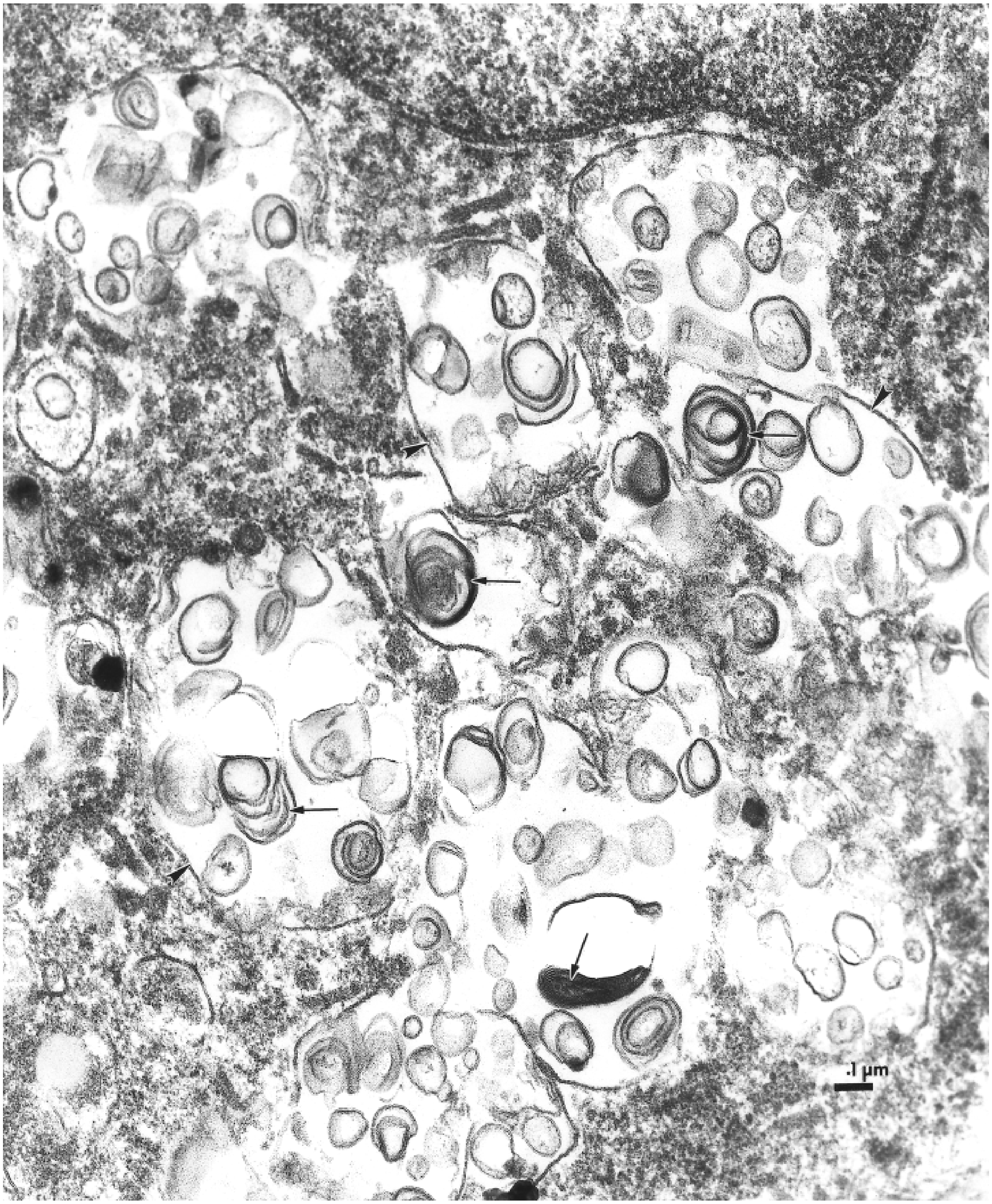


Plate 7
Mesenteric lymph node from a male rat administered 1,000 mg/kg Elmiron® by gavage for 3 months showing lysosomes within a macrophage distended with myelin figures. The small arrows illustrate some of the myelin figures. The arrowheads indicate the single layer membrane of the lysosomes. 71,700x

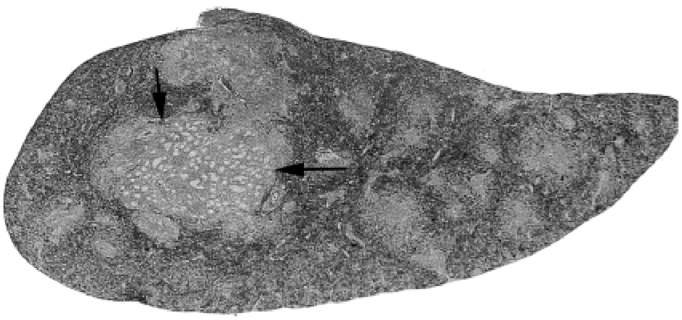


Plate 8
Well-demarcated nodule of lymphohistiocytic hyperplasia (arrows) in the spleen of a male F344/N rat administered 126 mg/kg Elmiron® by gavage for 2 years. H&E; 3.3×

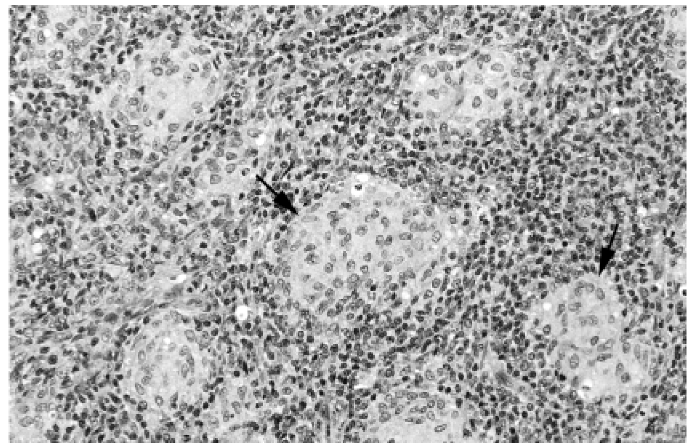


Plate 9
Lymphohistiocytic hyperplasia in the spleen of a male F344/N rat administered 126 mg/kg Elmiron® by gavage for 2 years (arrows). The nodule is composed of a sheet of mature lymphocytes interspersed with aggregates of macrophages. H&E; 66×

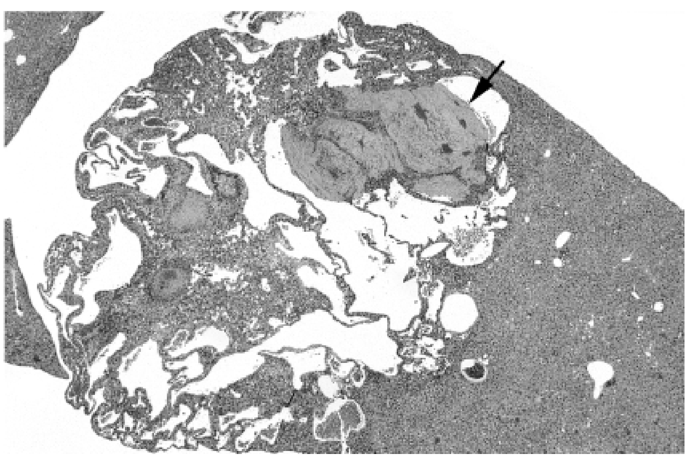


Plate 10
Hemangiosarcoma in the liver of a male B6C3F$_1$ mouse administered 504 mg/kg Elmiron® by gavage for 2 years. Some of the vascular spaces contain thrombi (arrow). H&E; 5×

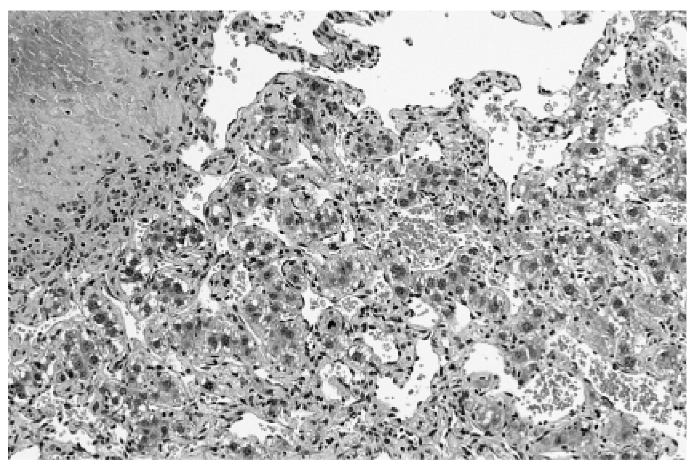


Plate 11
Hemangiosarcoma in the liver of a male B6C3F$_1$ mouse administered 504 mg/kg Elmiron® by gavage for 2 years. The irregular vascular spaces are lined by pleomorphic endothelial cells. H&E; 40×

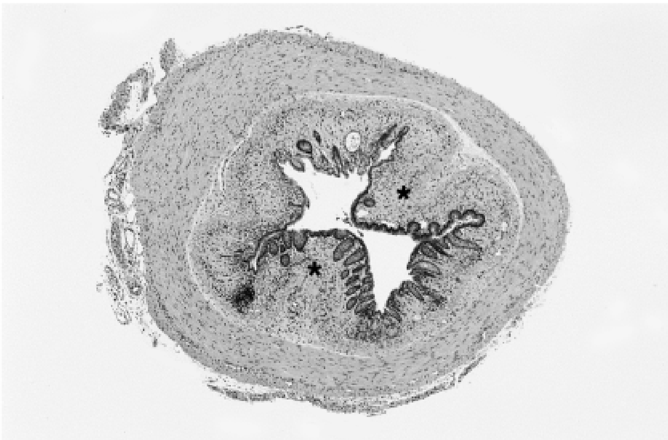


Plate 12
Low magnification of cross section of the rectum of a female $B6C3F_1$ mouse administered 504 mg/kg Elmiron® per day for 2 years. Note the thickened lamina propria (asterisks). Compare to Plate 13. H&E; 8×

Plate 13
The rectum of a control male $B6C3F_1$ mouse from the 2-year Elmiron® study. Note the normal thickness of the lamina propria (asterisks). Compare to Plate 12. H&E; 8×

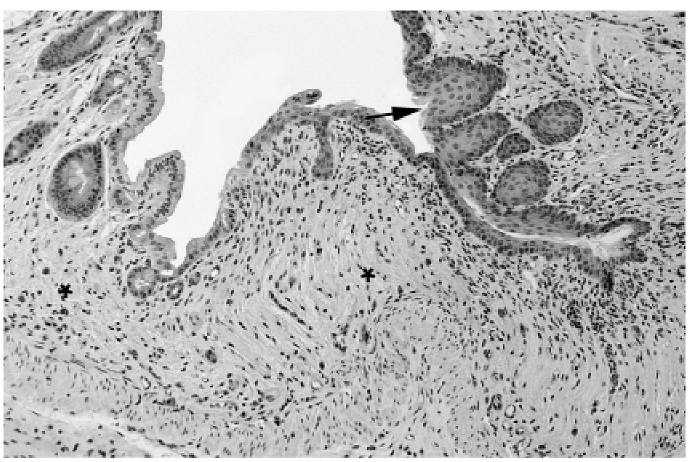


Plate 14
Chronic inflammation and myxomatous change (asterisks) of the lamina propria and squamous metaplasia (dark arrow) of the mucosa in the rectum of a female $B6C3F_1$ mouse administered 504 mg/kg Elmiron® by gavage for 2 years. Compare to Plate 15. H&E; 33×

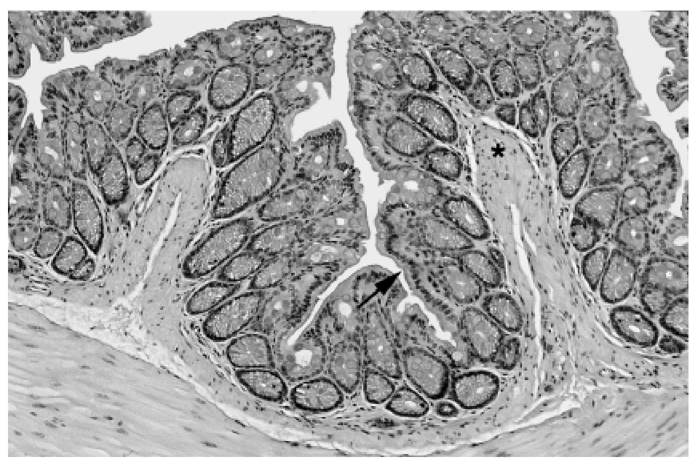


Plate 15
Columnar epithelium (arrow) and many goblet cells are present in the lining epithelium and crypts, and dense collagenous tissue (asterisk) present in the lamina propria in the rectum of a control male $B6C3F_1$ mouse from the 2-year Elmiron® study. Compare to Plate 14. H&E; 33×

Plate 16

Squamous metaplasia (arrows) of the mucosa and chronic inflammation of the lamina propria in the rectum of a female $B6C3F_1$ mouse administered 504 mg/kg Elmiron® by gavage for 2 years. H&E; 33×

DISCUSSION AND CONCLUSIONS

Elmiron®, a highly sulfated, semisynthetic pentose polysaccharide with properties similar to heparin, is used in the United States for the relief of urinary bladder pain associated with interstitial cystitis. Because of its orphan drug status, the FDA nominated this drug for testing by the National Toxicology Program. Elmiron® was evaluated for toxicity and carcinogenicity in 2-week, 3-month, and 2-year gavage studies in F344/N rats and B6C3F$_1$ mice.

On a body weight basis, the doses used in the NTP studies were greater than that used for humans by 20- to 700-fold for rats and mice in the 2-week studies, 15- to 233-fold for rats and mice in the 3-month studies, and 3.3- to 29-fold for male rats, 15- to 58-fold for female rats, and 10- to 117-fold for male and female mice in the 2-year studies.

In the 2-week studies, Elmiron®-related increases occurred in the liver weights of 3,000 mg/kg male and female rats and 1,000 and 3,000 mg/kg male mice. There was a slight but significant increase in activated partial thromboplastin time (APTT) in 3,000 mg/kg rats. This increase is consistent with that observed by Hobbelen *et al.* (1985) and suggests a decrease in clotting efficiency. Hepatocellular cytoplasmic vacuolization occurred in all female rats administered 3,000 mg/kg.

Sites of toxicity for Elmiron® in the 3-month studies were the rectum, mesenteric and mandibular lymph nodes, liver, lung (rats), kidney (rats), and spleen (mice). Elmiron®-related increases in lung (female rats), liver, kidney (female rats), and spleen (male mice) weights in the 3-month studies correlated with increased macrophage infiltration, vacuolization, and inflammation in these organs. It is possible that the increased liver and spleen weights could be attributed in part to induction of sulfatases. These enzymes are necessary for the metabolism of this highly sulfated drug. The liver and spleen appear to be the likely sites of phase I metabolism of Elmiron®, because earlier distribution and metabolism studies (MacGregor *et al.*, 1984) found the drug and/or its metabolites in these two organs. However, histochemical and electron microscopic evaluation of these organs from the current studies revealed that Elmiron® resulted in a condition resembling a lysosomal storage disorder characterized by accumulation of mucin and lipid-like materials. This may also have contributed to the increase in organ weights.

The increased leukocyte counts observed in rats and mice administered Elmiron® were considered related to the inflammatory lesions seen in the rectum and the liver. The decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts seen in dosed mice may have been caused by loss of blood related to rectal lesions. The slight increase in APTT observed in rats was consistent with the anticoagulant properties of this drug. However, the increase observed in this study was less than that observed by Hobbelen *et al.* (1985). This difference was probably due to differences between oral and subcutaneous routes of administration and to the fact that Elmiron® is poorly absorbed by the oral route.

Several Elmiron®-related lesions were observed in rats and mice in the 3-month studies. The principal lesions were rectal ulceration and histiocytic cellular infiltration in several organs. Ulcer of the rectum occurred in over 50% of rats dosed with 500 or 1,000 mg/kg. Histiocytic cellular infiltration occurred in the rectum and mandibular and mesenteric lymph nodes of rats and mice, lung of rats, and spleen of mice in most dosed groups. Additional lesions observed in dosed animals included inflammation of the rectum, liver, and lung (rats), and cytoplasmic vacuolization of the liver and kidney (rats).

In the 3-month studies, multiple organ histiocytic infiltration characterized by the accumulation of foamy macrophages was the main feature of Elmiron® administration in rats and mice. The histochemical investigation indicated that the vacuolated cells accumulated mucins, hexosamine containing polysaccharides covalently bound to varying amounts of protein. Positive staining for both neutral and acidic mucins in the same cells indicated that the vacuolated cells contained a mixture of different types of mucin. The positive reaction for oil red-O staining in the lungs indicated the presence of a lipid component in the vacuoles suggested to represent membranous structures associated with the production of surfactants. Electron microscopic examination of the vacuolated cells revealed cytoplasmic, membrane-bound structures, morphologically typical for diagnosis of a lysosomal storage disorder.

Lysosomes are key components of the intracellular digestive tract. They contain a battery of hydrolyte enzymes (Cotran *et al.*, 1999). An inherited or drug-induced deficiency or inhibited function of one or more of these enzymes results in disturbed digestion of intracellular organelles. This leads to accumulation of undigested material (e.g., phospholipids) and concurrent development of concentric lamellar bodies, which can cause a lysosomal storage disorder. Electron microscopic examination of the Elmiron®-induced vacuolated cells revealed cytoplasmic, membrane-bound structures (including concentric lamellar bodies), which are morphologically indicative of lysosomal storage disorder.

In inherited lysosomal storage disease in humans, there is a deficiency in, or malfunction of, one of the enzymes participating in the breakdown of complex, large macromolecules that may be derived from the metabolic turnover of intracellular organelles or acquired extracellularly (Cotran *et al.*, 1999). The lysosomes become sufficiently large and numerous to cause interference with normal cellular functions and lead to the disorder. Because cells of the mononuclear system possess numerous lysosomes, organs rich in phagocytic cells, such as the spleen and liver, are frequently enlarged in several types of lysosomal storage disorders. The chemical structure and the amount of substrate found in a particular cell type determine the ultrastructural appearance of the lysosomal storage disorder (Castagnaro *et al.*, 1987). The enzymatic dysfunctions are divided into categories based on the biochemical nature of the accumulated metabolite, such as glycogenoses, mucopolysaccharidoses, and mucolipidoses. According to Prasad *et al.* (1996), the different morphological aspects observed in a particular lysosomal storage disorder may vary in appearance, depending on the storing cell type, because some enzymes are involved in the catabolism of more than one substrate. For example, in a certain glycoproteinosis, one cell type may accumulate oligosaccharides and another cell type will store glycolipid (Prasad *et al.*, 1996).

The prominent lysosomal changes seen in rats and mice treated with Elmiron® suggest a drug-induced storage disorder morphologically similar to types reported in the literature (Ruben *et al.*, 1989, 1991; Kacew *et al.*, 1997). For example, cationic amphiphilic drugs (CADs) are known to induce phospholipidosis in experimental animals. This group includes a wide variety of pharmacological agents that share a common physicochemical structure, a hydrophobic ring bearing a hydrophilic side chain with a charged cationic amine group (Halliwell, 1997). The range of ultrastructural morphological features of CAD-induced phospholipidosis includes the presence of electron-lucent vacuoles; concentric, intravesicular lamellar bodies; clear cytoplasmic vacuoles with flocculent, peripheral, electron-dense structures; and crystalline, electron-dense bodies (Ruben *et al.*, 1989; Kacew *et al.*, 1997). It has been suggested that the various morphological aspects induced by the CADs are bi-directional processes between states of liquification and coacervation, resulting in heterogeneity of the morphologic alterations (Kacew *et al.*, 1997). As the vacuoles become progressively larger with time, they apparently accumulate electron-lucent material. Progressive vacuolar coalescence and accumulation of electron-lucent material result in cellular enlargement. The CAD disobutamide was found to induce a lysosomal storage disorder in the rat and dog in which smooth muscle cells, epithelial cells, macrophages, fibroblasts, capillary endothelia, cardiac myocytes, hepatocytes, and ocular uveal cells were involved in cytoplasmic vacuolation (Ruben *et al.*, 1989). Various investigations have demonstrated that the primary site for drug induced phospholipidosis is the lysosomal fraction (Kacew *et al.*, 1997).

Several mechanisms for drug-induced phospholipidosis have been suggested (Halliwell, 1997). One involves binding of the drug to phospholipids and, as a consequence, the formation of a new substrate, the substrate-drug complex, that is less susceptible to phospholipases associated with decreased catabolism. Therefore, degradation is impaired. Another possibility is that the drug binds to enzymes resulting in reduced phospholipid degradation. Alternatively, the drug may bind to the plasma membrane or intracellular membranes of acidic vesicles, mitochondria, endoplasmic reticulum, or the nucleus, with subsequent disruption of membrane synthesis, recycling, turnover, or trafficking.

The chemical structure of Elmiron® differs from that of CADs. In addition, only one type of cell, the macrophage, is apparently involved in the Elmiron®-induced accumulation disorder. Despite the uniqueness of Elmiron®, however, the mechanism for the disorder is likely similar to that described for CADs (Kacew *et al.*,

1997) in which myelin figures develop from hydration of lipid material (Ghadially, 1997). The cytoplasmic, membrane-bound structures within macrophages are lysosomes containing membranous material of cellular origin and, perhaps, remnants of phagocytized Elmiron®. In an *in vitro* study, cytoplasm of lavaged alveolar macrophages from Sprague-Dawley rats exposed for 24 hours to 1, 10, or 100 mg/mL Elmiron® stained positively in a dose-related fashion with Alcian Blue (AB). Lavaged macrophages incubated similarly without Elmiron® were AB negative (Appendix L). Positive staining with AB is indicative of the presence of acidic sulfated mucopolysaccharides, hyaluronic acid, and sialomucin. The accumulation of this material was associated with cellular enlargement. Because histochemical and *in vitro* studies showed that the accumulated materials were mucoid and lipoid in nature, the apparent storage disorder induced by Elmiron® was considered to be a mucolipidosis.

Limited published information is available on the absorption, distribution, metabolism, or elimination of Elmiron® in animals. A comparative intravenous (50 mg) and oral (1,500 mg) bioavailability study of Elmiron® using healthy young male volunteers was conducted (Faaij *et al.*, 1999). In the absence of specific assays to measure Elmiron® in blood, indirect methods (measurement of prolongation of APTT and increases in antifactor Xa and hepatic triglyceride lipase activities) were used. It was demonstrated that intravenous administration of Elmiron® changed the pharmacodynamic parameters in an expected way, comparable to other heparin-like compounds. On the other hand, oral administration of Elmiron® resulted in insignificant effects, indicating low bioavailability even with a high oral dose. It was postulated that Elmiron® is poorly absorbed after oral administration or experiences extensive presystemic breakdown. Danielson *et al.* (1990) demonstrated the poor oral absorption of Elmiron® in healthy volunteers, comparing oral (400 mg) and intravenous (40 mg) bioavailability of Elmiron®. Results indicated that oral bioavailability was less than 1% after a single dose.

The current studies, using oral dosing of Elmiron®, resulted in histiocytosis of the rectum, lymph nodes, lung, and spleen. The greatest abundance of vacuolated histiocytes was found within rectal tissue and mesenteric lymph nodes, suggesting that the focally disrupted rectal mucosal barrier served as the port of entry for Elmiron® or its metabolites. The rectal lamina propria appeared expanded with a faint, bluish-tinged, acellular material indicative of a myxomatous change. This material stained positively with AB, which highlights sulfated mucopolysaccharide-like compounds such as normal ground substance in the interstitium. The myxomatous change observed in the rectum may indicate accumulation of the test material or some form of the test material in the lamina propria. It is likely that material was phagocytized by the macrophages and accumulated in lysosomes filled with myelin figures. These macrophages then circulated to other tissues (lymph nodes, spleen, and lung) via lymphatics or blood.

The localization of Elmiron®-induced lesions (ulceration and inflammation) in the rectum may have been the result of exposure of this tissue to high concentrations of the drug. This suggestion was based on the fact that the orally administered drug is poorly absorbed from the gastrointestinal tract and the fact that the primary physiological function of the rectum is the reabsorption of water. Interestingly, inflammation and ulceration of the rectum were described following a clinical trial in cancer patients orally treated with 180, 270, or 400 mg/m^2 three times daily (Marshall *et al.*, 1997). The ulcers were time and dose dependent. Rectal ulcers were not observed in intravenous and subcutaneous Elmiron® trials. The authors suggested that the pathogenesis of the ulceration could be due to the removal of sulfur from the mucosa by Elmiron®. Normally, a high concentration of sulfur-containing side chains is required in the mucus secreted by the rectum to serve as an effective mucosal barrier. Another suggested mechanism is related to the binding of unabsorbed Elmiron® to mucosal β-fibroblastic growth factor, depriving the local tissues of a potential protectant and/or repair stimulant (Marshall *et al.*, 1997). Dietary administration of other sulfated polysaccharides such as degraded carrageenan, amylopectin sulfate, and dextran sulfate sodium to F344 rats produced similar rectal lesions as those seen with Elmiron® (Oohashi, *et al.*, 1981; Ishioka *et al.*, 1985, 1987).

In the 3-month studies, the renal tubule epithelial cytoplasmic vacuolization observed in 1,000 mg/kg rats and the hepatocytic vacuolization seen in rats and mice administered the higher doses were considered to be degenerative changes rather than indicative of a lysosomal storage disorder. The presence of hepatic inflammation in 500 and 1,000 mg/kg male rats and the increased severity of hepatic inflammation in 1,000 mg/kg male and female mice were characterized by aggregation of histiocytes mixed with other inflammatory cells. As the histiocytes did not have vacuolated cytoplasm, the change in the liver was not considered to be of the same nature as that involving the infiltrated macrophages described in the rectum, lymph nodes, spleen, and lungs.

It is recognized that histiocytic infiltrates are normally seen in lymph nodes, but the unique feature in these studies was the frequency and strikingly clear vacuolization of the macrophages. Cytoplasm of lymph node macrophages is typically eosinophilic and finely granular or lightly pigmented, either brown or gray. The prominent clear vacuoles in the Elmiron®-treated animals suggest significant accumulation of some material. The material may be phagocytized myxomatous material from the rectal lamina propria and may be Elmiron®.

In the 3-month studies, some histiocytic infiltration was seen in mandibular lymph nodes, although the severity was less than that seen in mesenteric lymph nodes. It is likely that, with systemic lymphatic circulation, Elmiron®-induced vacuolated macrophages would be present to some degree in all lymph nodes. An ultrastructural characteristic of all the specimens examined was the presence of macrophages with numerous to excessive numbers of lysosomes in the cytoplasm. These lysosomes contained several types of material, most typically concentric lamellar bodies consistent with myelin figures. Other lysosomes were mostly clear, suggesting that some or most of the lysosomal contents were lost in routine fixative and processing solutions, or that the material itself was electron lucent. Some lysosomes also contained dense granular material, lipid, or linear crystalline structures. The linear crystals were most prominent in the alveolar macrophages of one mouse lung examined, but occasional linear crystals were also seen in lymph node macrophages.

The concentric lamellar bodies (myelin figures) with lysosomes (myelinosomes) are consistent with accumulated phospholipid (i.e., phospholipidosis) (Ghadially, 1997). Drug-induced phospholipidoses have been extensively studied, predominantly with cationic lipophilic drugs (Ruben *et al.*, 1989, 1991, 1993; Lullmann-Rauch *et al.*, 1995; Kacew *et al.*, 1997). In drug-induced phospholipidosis it is believed that the myelin figures form because the drugs bind to intracellular lipids and lipids within membranes, especially phospholipids. Lysosomes ingest the bound materials, and because of their altered physicochemical properties, cannot digest or otherwise metabolize them. Hence, the material accumulates within lysosomes. It is also hypothesized that the drugs may selectively inhibit lysosomal enzymes, preventing normal lysosomal function. In some recognized drug-induced phospholipidoses, the accumulation of myelinosomes occurs within multiple tissues in the body, although the lung and alveolar macrophages are among the most common tissues involved.

In summary, 1,000 mg/kg rats and mice exhibited histiocytic infiltrates in the rectum, lymph nodes, spleen (mice), and lung (rats) following 3 months of gavage administration of Elmiron®. These histiocytes were foamy macrophages with prominent clear cytoplasmic vacuoles. Histochemical investigation of the vacuolated histiocytes indicated the presence of neutral and acidic mucins and lipid material in the vacuoles. Transmission electron microscopy showed these vacuoles to be lysosomes that exhibited a variety of contents. These findings suggest that Elmiron® was phagocytized in the rectal lamina propria and transported via the lymphatics and blood to different organs, yielding an Elmiron®-induced phospholipidosis.

Elmiron® administration appeared to induce a unique lysosomal storage disorder. The main feature of this drug-induced abnormality was the presence in multiple organs of vacuolated macrophages, which apparently were the only cell type accumulating in these vacuoles. The cytoplasm of these macrophages contained numerous lysosomes that exhibited clear vacuoles or were filled with concentric lamellae of electron-dense material (Plates 6 and 7). In other investigations, we noted that cultures of lung macrophages exposed to Elmiron® became distended and accumulated AB positive material, which was probably Elmiron®. In conclusion, we suggest that overloading of the tissue histiocytes with Elmiron® interferes with the regular activity of the lysosomal enzymes, which leads to the accumulation of undigested membranous structures.

In the 2-year rat study, there were no Elmiron®-related increases in the incidences of neoplasms at any site. The doses selected for use in this study are considered adequate for assessing the carcinogenicity of this drug as indicated by the increased incidence of chemical-related nonneoplastic lesions. Elmiron®-induced nonneoplastic lesions observed in rats were similar to those observed in the 3-month study. They included histiocytic infiltration of the rectum, mesenteric lymph node, and spleen; myxomatous change of the rectum; and lung inflammation. The lack of a carcinogenic effect of Elmiron® contrasts with other sulfated polysaccharides such as degraded carrageenan, amylopectin sulfate, and dextran sulfate sodium. These three sulfated polysaccharides when administered at 5% to 10% in the diet caused a significant increase in colorectal tumors in F344 rats (Oohashi, *et al.*, 1981; Ishioka *et al.*, 1985, and 1987). The lack of carcinogenic activity of Elmiron® as compared to these sulfated polysaccharides may partially be accounted for by differences in the method of administration (gavage versus dietary), dose size, degree of sulfation (75% to 80% versus 18% to 40%) and sugar moiety (pentose versus hexose).

In the 2-year mouse study, increased incidences of liver hemangiosarcoma in male and female mice were related to Elmiron® administration. Elmiron® exposure was associated with a positive trend in hemangiosarcomas in male mice, and the incidence in the 504 mg/kg group was significantly increased. The incidences in the 168 and 504 mg/kg males and the 504 mg/kg females exceeded the historical ranges in controls. The hemangiosarcomas were morphologically similar to spontaneously occurring hemangiosarcomas, consisting of pleomorphic, proliferative endothelial cells which formed irregular vascular spaces.

Sporadic hemangiosarcomas were diagnosed as primary neoplasms in several other tissues in mice, including the bone marrow, spleen, heart, mesenteric lymph node, ovary, skin, mesentery, urinary bladder, preputial gland, and testis (Table 20). However, the incidences of hemangiosarcomas in these extrahepatic sites were low and did not appear to be related to Elmiron® administration. For several animals, extrahepatic hemangiosarcomas occurred concomitantly with hepatic hemangiosarcomas and were possibly metastatic sites. In animals with hemangiosarcomas at more than one site, the site of origin could not be determined by histologic evaluation. Three 504 mg/kg males with hepatic hemangiosarcomas had extrahepatic hemangiosarcomas that involved the spleen (two animals), heart (one animal), bone marrow (one animal), and mesenteric lymph node (one animal). Two females with hepatic hemangiosarcomas had extrahepatic hemangiosarcomas that involved the bone marrow (one animal) and the mesentery (one animal).

Hemangiosarcoma is a malignant neoplasm of the vascular endothelium. Spontaneous hemangiosarcomas occur in 3.0% of male $B6C3F_1$ mice and 3.6% of female $B6C3F_1$ mice. Hemangiosarcomas may occur at a variety of sites; however, the liver and spleen are the most common sites for male $B6C3F_1$ mice, and the spleen and subcutis are the most common sites for female $B6C3F_1$ mice. A retrospective study of chemically induced vascular tumors (Chandra, S.A., Hardisty, J.F., Seely, J.C., Haseman, J.K., and Maronpot, R.R., unpublished) listed 20 NTP studies in which there were chemical-related increased incidences of vascular neoplasms in the $B6C3F_1$ mouse. In the vast majority of these studies, the increased incidence occurred most commonly at a specific site and less commonly at two or three specific sites. In general, the vasculature as a whole is not affected, but rather the vasculature within a specific organ or tissue is affected. The most common site of chemically induced vascular neoplasms in the $B6C3F_1$ mouse in NTP studies is in the liver.

In this Technical Report, the incidences of hemangiosarcoma at individual sites as well as the incidences at all sites combined are presented in the Results. Only the incidences in the liver are statistically significant and/or outside of historical control ranges. The incidences of hemangioma are also included in the Results section; however, combined analyses of hemangioma and hemangiosarcoma were not included. Unlike the liver and kidney, for example, where there is evidence of a morphologic and biologic continuum between benign and malignant neoplasms, the link between hemangioma and hemangiosarcoma is not nearly as strong. Also, the vast majority of NTP studies with chemical-related increases in vasculature neoplasms have involved hemangiosarcomas without an increase in hemangiomas.

While the increased incidence of hemangiosarcoma in the liver of 504 mg/kg male mice is statistically significant, that in the females is not. However, spontaneous hemangiosarcoma of the liver is much less common in the female $B6C3F_1$ mouse, occurring in only 6 out of 954 (0.6%) females fed the NTP-2000 diet. The incidences in historical control animals fed NIH-07 diet are similar to that observed with the NTP-2000 diet regardless of route of administration. The incidence in 504 mg/kg female mice (4 out of 50) also exceeds the historical control range for all routes using NIH-07 diet.

The incidences of hepatocellular adenoma or carcinoma (combined) occurred with positive trends in male and female mice. The incidence of adenoma in 504 mg/kg females was significantly increased and exceeded the historical control ranges. Also, six female mice in the

504 mg/kg group had multiple adenomas, compared with only one in the vehicle controls. These neoplasms were considered related to Elmiron® administration. In male mice the separate incidences of hepatocellular adenomas and carcinomas were not significantly increased and there was no increase in neoplasm multiplicity. Therefore, it is uncertain if the marginal increase in the incidences of hepatocellular neoplasms in male mice was associated with Elmiron® administration. Hepatocellular adenomas were observed in humans with glycogen storage disorder type I and hepatocellular carcinomas were observed in type III subjects (Alshak *et al.*, 1994; Haagsma *et al.*, 1997; Siciliano *et al.*, 2000). Type I is caused by a decrease or difficiency in glucose-6-phosphatase in liver cells. Type III disorder is an autosomal recessive disorder characterized by a deficiency of glycogen debranching enzyme.

Malignant lymphomas occurred with a positive trend in female mice; the incidence in the 504 mg/kg group was also significantly increased and matched the upper limit of the historical control ranges. These malignant lymphomas may have been associated with Elmiron® administration.

Because the data from the three NTP micronucleus studies reported in Appendix E were obtained from gavage studies, the negative results in these tests may not accurately reflect the potential for Elmiron® to induce chromosomal damage in erythrocytic stem cells in the bone marrow. Due to the low absorption and distribution of Elmiron® after oral dosing, bone marrow stem cells may not have been exposed to the chemical. The database of NTP studies listed 23 chemicals that produced an increase in liver hemangiosarcoma. Except for 2-butoxyethanol, chloroprene, and now Elmiron®, the chemicals were mutagenic in *Salmonella* tests, suggesting that some compounds may induce liver tumors by mechanism(s) other than direct reaction with DNA.

Several sulfated hexosans were reported to be nonmutagenic in *Salmonella* but were tumorgenic in the F344 rats, resulting in an increase colorectal tumors (Oohashi *et al.*, 1981; Ishioka *et al.*, 1987). The authors speculated that these chemicals may act as tumor promoters or initiators. These sulfated hexosans may also be considered physical carcinogens because of their deposition in the foamy macrophages of the local colorectal mucosa. Whether Elmiron® (a pentosan sulfate) acts by similar mechanisms in inducing liver tumors is not known.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of Elmiron® in male F344/N rats administered 14, 42, or 126 mg/kg or in female F344/N rats administered 28, 84, or 252 mg/kg. There was *some evidence of carcinogenic activity* of Elmiron® in male B6C3F$_1$ mice based on increased incidences of liver hemangiosarcoma. The increased incidences of hepatocellular neoplasms in male mice may have been related to Elmiron® administration. There was *some evidence of carcinogenic activity* of Elmiron® in female B6C3F$_1$ mice based on the increased incidences of liver hemangiosarcoma and hepatocellular neoplasms. The increased incidences of malignant lymphomas in female mice may have been related to Elmiron® administration.

Elmiron® administration caused increased incidences of nonneoplastic lesions (presence of vacuolated histiocytes) of the rectum, lung, mesenteric lymph node, and spleen (males) in rats and of the liver, rectum, mesenteric lymph node, and spleen in mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®[a]

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	2	2		5
Moribund	15	10	17	12
Natural deaths	7	9	8	5
Survivors				
Terminal sacrifice	26	29	25	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Intestine large, rectum	(48)	(48)	(49)	(45)
Histiocytic sarcoma			1 (2%)	
Polyp adenomatous	1 (2%)	1 (2%)	1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Mesentery	(9)	(11)	(9)	(13)
Schwannoma malignant		1 (9%)		
Pancreas	(50)	(50)	(50)	(50)
Acinus, adenoma			1 (2%)	
Acinus, carcinoma		1 (2%)		
Salivary glands	(50)	(50)	(49)	(50)
Schwannoma malignant	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)			
Tongue		(1)		
Squamous cell papilloma		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)		3 (6%)	1 (2%)
Pheochromocytoma benign	6 (12%)	6 (12%)	2 (4%)	8 (16%)
Bilateral, pheochromocytoma benign	1 (2%)	1 (2%)	1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Carcinoma		1 (2%)		
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	19 (38%)	18 (36%)	18 (36%)	13 (26%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma	1 (2%)			

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, salivary glands			1 (2%)	
Bilateral, C-cell, adenoma	1 (2%)	1 (2%)		
Bilateral, C-cell, carcinoma	1 (2%)			
Bilateral, follicle, carcinoma		1 (2%)		
C-cell, adenoma	5 (10%)	7 (14%)	8 (16%)	6 (12%)
C-cell, adenoma, multiple	2 (4%)			1 (2%)
C-cell, carcinoma	1 (2%)	1 (2%)		1 (2%)
Follicle, adenoma		1 (2%)	1 (2%)	3 (6%)
Follicle, carcinoma	2 (4%)			1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Carcinoma	1 (2%)			
Prostate	(50)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Seminal vesicle	(50)	(50)	(50)	(49)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	35 (70%)	37 (74%)	37 (74%)	35 (70%)
Interstitial cell, adenoma	9 (18%)	6 (12%)	6 (12%)	5 (10%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(11)	(17)	(10)	(13)
Deep cervical, carcinoma, metastatic, thyroid gland	1 (9%)			1 (8%)
Mediastinal, carcinoma, metastatic, thyroid gland	1 (9%)			
Lymph node, mandibular	(5)	(5)	(9)	(2)
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Spleen	(50)	(50)	(50)	(50)
Thymus	(45)	(44)	(43)	(43)
Integumentary System				
Mammary gland	(49)	(49)	(50)	(48)
Adenoma	1 (2%)			
Fibroadenoma	2 (4%)	1 (2%)	3 (6%)	5 (10%)
Fibroma	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Keratoacanthoma	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Squamous cell carcinoma		1 (2%)	1 (2%)	
Squamous cell papilloma	1 (2%)			
Sebaceous gland, adenoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Sebaceous gland, carcinoma			1 (2%)	1 (2%)

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Integumentary System (continued)				
Skin (continued)	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
Vertebra, chordoma	1 (2%)			
Skeletal muscle			(1)	(2)
Histiocytic sarcoma			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant				1 (2%)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)			1 (2%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			
Carcinoma, metastatic, thyroid gland	1 (2%)	1 (2%)		1 (2%)
Chordoma, metastatic, bone	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Schwannoma malignant, metastatic, salivary glands		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Respiratory epithelium, adenoma		1 (2%)		
Trachea	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, salivary glands			1 (2%)	
Special Senses System				
None				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Ureter	(1)			
Urinary bladder	(50)	(50)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	15 (30%)	16 (32%)	12 (24%)	16 (32%)
Mesothelioma malignant	2 (4%)		2 (4%)	4 (8%)

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	48	50	45
Total primary neoplasms	124	117	110	113
Total animals with benign neoplasms	49	47	49	45
Total benign neoplasms	93	90	88	84
Total animals with malignant neoplasms	29	25	22	25
Total malignant neoplasms	31	27	22	29
Total animals with metastatic neoplasms	4	2	1	1
Total metastatic neoplasms	6	2	2	2

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[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 Elmiron®: Vehicle Control

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

+: 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 Elmiron®: Vehicle Control

Number of Days on Study	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	
Carcass ID Number	007	024	025	042	045	046	048	049	002	005	006	008	010	012	021	022	028	032	036	047	026	034	035	037	044	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous													X													1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+					+	+							+			9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																								X		1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant									X																	1
Pheochromocytoma benign									X		X		X							X						6
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X					X	X	X	X			X		X	X	X	X		X			X		19
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																	X									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
Bilateral, C-cell, carcinoma																										1
C-cell, adenoma						X						X			X		X									5
C-cell, adenoma, multiple								X												X						2
C-cell, carcinoma																										1
Follicle, carcinoma								X											X							2
General Body System																										
Tissue NOS																	+									1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

Number of Days on Study	111	475	503	505	519	519	526	547	573	589	600	630	640	640	661	685	686	699	707	717	721	724	724	724	727
Carcass ID Number	033	039	038	003	019	050	014	001	040	009	023	017	011	043	013	018	031	027	029	041	016	015	020	030	004
Genital System																									
Coagulating gland																		+							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma		X																							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X						X	X		X	X		X	X			X	X		X	X	X	X	X
Interstitial cell, adenoma					X	X	X			X			X												
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+	+		+								+	+		+	+	
Deep cervical, carcinoma, metastatic, thyroid gland												X													
Mediastinal, carcinoma, metastatic, thyroid gland												X													
Lymph node, mandibular	+	M	M	M	+	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	+	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma			X		X																				
Fibroma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																									
Squamous cell papilloma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma															X										
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, chordoma																			X						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland														X											

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

Number of Days on Study	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	
Carcass ID Number	007	024	025	042	045	046	048	049	002	005	006	008	010	012	021	022	028	032	036	047	026	034	035	037	044	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X		35
Interstitial cell, adenoma								X		X	X														X	9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+			+		+					+											11
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Mediastinal, carcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular	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	5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X															1
Fibroadenoma																										2
Fibroma								X																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																						X				1
Keratoacanthoma	X													X												2
Squamous cell papilloma																			X							1
Sebaceous gland, adenoma						X																				1
Subcutaneous tissue, fibroma														X												1
Subcutaneous tissue, fibrosarcoma															X											2
Subcutaneous tissue, lipoma											X															1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, chordoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

	1	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
Number of Days on Study	1	7	0	0	1	1	2	4	7	8	0	3	4	4	6	8	8	9	0	1	2	2	2	2	2
	1	5	3	5	9	9	6	7	3	9	0	0	0	0	1	5	6	9	7	7	1	4	4	4	7
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	3	3	3	0	1	5	1	0	4	0	2	1	1	4	1	1	3	2	2	4	1	1	2	3	0
	3	9	8	3	9	0	4	1	0	9	3	7	1	3	3	8	1	7	9	1	6	5	0	0	4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																X									
Carcinoma, metastatic, thyroid gland												X													
Chordoma, metastatic, bone																			X						
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter													+												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X	X	X			X		X					X		X	X	X	
Mesothelioma malignant																		X			X				

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

Number of Days on Study	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	
Carcass ID Number	007	024	025	042	045	046	048	049	002	005	006	008	010	012	021	022	028	032	036	047	026	034	035	037	044	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma			X																							1
Alveolar/bronchiolar carcinoma, multiple																										1
Carcinoma, metastatic, thyroid gland																										1
Chordoma, metastatic, bone																										1
Pheochromocytoma malignant, metastatic, adrenal medulla									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X				X	X			X				X	15
Mesothelioma malignant																										2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 14 mg/kg

Number of Days on Study	131	223	313	478	503	533	551	574	577	645	645	654	668	674	705	713	713	715	717	719	724	727	727	727	727
Carcass ID Number	079	061	071	055	093	058	084	062	098	056	090	054	067	100	080	086	095	099	060	057	092	064	066	073	077
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Polyp adenomatous																									
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery															+	+	+				+				
Schwannoma malignant																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant											X			X											
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																+									
Squamous cell papilloma																X									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma																							X		
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X		X						X			X		X			X	X			X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
Bilateral, follicle, carcinoma							X																		
C-cell, adenoma										X													X		
C-cell, carcinoma												X													
Follicle, adenoma																									
General Body System																									
None																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 14 mg/kg

Number of Days on Study	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	
Carcass ID Number	082	083	085	091	059	063	065	068	069	070	072	074	076	078	081	087	088	089	097	051	052	053	075	094	096	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous							X																			1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+							+								+			+		+	+	+		11
Schwannoma malignant																						X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, carcinoma						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										2
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X	X						X		X	X							X			6
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X				X		X		X	X			X	X							X	18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma					X																					1
Bilateral, follicle, carcinoma																										1
C-cell, adenoma													X		X				X	X					X	7
C-cell, carcinoma																										1
Follicle, adenoma																						X				1
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 14 mg/kg

Number of Days on Study	131	233	313	478	503	533	551	574	577	645	645	654	668	674	705	713	713	715	717	719	724	727	727	727	727
Carcass ID Number	079	061	071	055	093	058	084	062	098	056	090	054	067	100	080	086	095	099	060	057	092	064	066	073	077
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X	X		X	X		X	X	X	X		X		X	X	X	X	X	X
Interstitial cell, adenoma					X	X			X			X													
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+			+				+	+	+	+			+	+	+			+				
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma													X												
Squamous cell carcinoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma									X																
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Carcinoma, metastatic, thyroid gland							X																		
Schwannoma malignant, metastatic, salivary glands														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 14 mg/kg

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	7	7	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	9	9	9	9	9	9	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	8	8	8	9	5	6	6	6	6	7	7	7	7	7	8	8	8	8	9	5	5	5	7	9	9	Tissues/
	2	3	5	1	9	3	5	8	9	0	2	4	6	8	1	7	8	9	7	1	2	3	5	4	6	Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	37
Interstitial cell, adenoma						X														X						6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+				+				+				+	+	+							17
Lymph node, mandibular	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	+	5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																							X			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma											X			X												3
Squamous cell carcinoma														X												1
Sebaceous gland, adenoma																	X									1
Subcutaneous tissue, fibroma																									X	1
Subcutaneous tissue, fibrosarcoma		X				X																				2
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, lipoma										X																1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, thyroid gland																										1
Schwannoma malignant, metastatic, salivary glands																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 14 mg/kg

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

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 14 mg/kg

Number of Days on Study	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	
Carcass ID Number	082	083	085	091	059	063	065	068	069	070	072	074	076	078	081	087	088	089	097	051	052	053	075	094	096	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X											X		X								X	16

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 42 mg/kg

Number of Days on Study	419	462	484	492	521	526	533	561	574	582	582	586	587	630	630	630	674	674	679	685	686	686	695	716	717
Carcass ID Number	130	120	114	118	148	128	143	124	127	102	134	119	140	104	125	149	112	123	132	146	106	113	109	116	142
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Polyp adenomatous				X																					
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Mesentery			+				+								+					+	+	+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Schwannoma malignant														X											
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant	X																				X				
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Parathyroid gland	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X						X				X		X						X	X		X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, salivary glands														X											
C-cell, adenoma											X									X					
Follicle, adenoma																									
General Body System																									
Peritoneum			+																						

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 42 mg/kg

Number of Days on Study	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	729	729	
Carcass ID Number	101	107	108	110	111	115	126	129	135	136	137	138	139	141	144	103	105	117	121	131	145	147	150	122	133	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Polyp adenomatous																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery										+										+				+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																		X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant		X																								3
Pheochromocytoma benign											X									X						2
Bilateral, pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X			X			X		X							X			X	X		18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, salivary glands																										1
C-cell, adenoma						X		X			X				X									X	X	8
Follicle, adenoma		X																								1
General Body System																										
Peritoneum																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 42 mg/kg

Number of Days on Study	419	462	484	492	521	526	533	561	574	582	582	586	587	630	630	630	674	674	679	685	686	686	695	716	717
Carcass ID Number	130	120	114	118	148	128	143	124	127	102	134	119	140	104	125	149	112	123	132	146	106	113	109	116	142
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X		X		X		X	X	X			X	X		X	X	X	X					X
Interstitial cell, adenoma						X		X					X			X						X		X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+	+					+		+				+			
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma									X																
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																X				X			X		
Squamous cell carcinoma																									
Sebaceous gland, adenoma																									
Sebaceous gland, carcinoma															X										
Subcutaneous tissue, fibroma																	X								
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Histiocytic sarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Histiocytic sarcoma							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, salivary glands														X											

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 42 mg/kg

Number of Days on Study	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	729	729	
Carcass ID Number	1001	1007	1008	1010	1011	1015	1026	1029	1035	1036	1037	1038	1039	1041	1044	1003	1005	1017	1021	1031	1045	1047	1050	1023	1033	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	37
Interstitial cell, adenoma																										6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node											+		+					+		+	+					10
Lymph node, mandibular	M	M	+	+	+	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	9
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma									X											X						3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										3
Squamous cell carcinoma																					X					1
Sebaceous gland, adenoma												X														1
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibroma			X													X										3
Subcutaneous tissue, fibrosarcoma																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Histiocytic sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, salivary glands																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 42 mg/kg

Number of Days on Study	419	462	484	492	521	526	533	561	574	582	582	586	587	630	630	630	674	674	679	685	686	686	695	716	717
Carcass ID Number	130	120	114	118	148	128	143	124	127	102	134	119	140	104	125	149	112	123	132	146	106	113	109	116	142
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Leukemia mononuclear						X				X	X					X		X				X		X	X
Mesothelioma malignant																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 42 mg/kg

Number of Days on Study	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	729	729	
Carcass ID Number	101	107	108	110	111	115	126	129	135	136	137	138	139	141	144	103	105	117	121	131	145	147	150	122	133	Total Tissues/ Tumors
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear	X					X										X				X						12
Mesothelioma malignant				X						X																2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 126 mg/kg

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

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 126 mg/kg

Number of Days on Study	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	
Carcass ID Number	163	168	181	187	191	192	193	196	199	200	155	156	165	166	167	173	177	182	183	188	194	160	179	189	190	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+	+	+		+							+	+		+								13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant								X																		1
Pheochromocytoma benign				X						X		X		X							X			X		8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma												X	X				X			X	X	X		X		13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X					X					X				6
C-cell, adenoma, multiple																X										1
C-cell, carcinoma																								X		1
Follicle, adenoma																					X	X				3
Follicle, carcinoma									X																	1
General Body System																										
None																										
Genital System																										
Coagulating gland																				+						1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X				X		X	35
Interstitial cell, adenoma																		X			X	X				5

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 126 mg/kg

Number of Days on Study	120	161	237	261	352	433	456	484	604	622	629	640	660	661	669	679	689	691	707	708	709	720	727	727	727
Carcass ID Number	1171	1175	1186	1185	1153	1164	1195	1180	1198	1152	1151	1162	1197	1178	1169	1184	1170	1157	1159	1174	1172	1176	1154	1158	1161
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+														+					+	+	+	
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																		X							
Sebaceous gland, adenoma																X			X						
Sebaceous gland, carcinoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma														X											
Skeletal muscle			+		+																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																	X								
Respiratory System																									
Larynx							+																		
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 126 mg/kg

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	7	7	7	7	7	7	7	7	7	7	8	8	8	8	8	8	8	8	8	8	8	9	9	9	9	
	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	6	6	8	8	9	9	9	9	9	0	5	5	6	6	6	7	7	8	8	8	9	6	7	8	9	Tissues/
	3	8	1	7	1	2	3	6	9	0	5	6	5	6	7	3	7	2	3	8	4	0	9	9	0	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+									+		+				+			+			+		+	+	13
Deep cervical, carcinoma, metastatic, thyroid gland																								X		1
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma	X				X										X										X	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Sebaceous gland, adenoma																										2
Sebaceous gland, carcinoma					X																					1
Subcutaneous tissue, fibroma					X																					1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Larynx																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		2
Alveolar/bronchiolar carcinoma																									X	1
Carcinoma, metastatic, thyroid gland																								X		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye					+																					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																				+						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 126 mg/kg

	1	1	2	2	3	4	4	4	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
Number of Days on Study	2	6	3	6	5	3	5	8	0	2	2	4	6	6	6	7	8	9	0	0	0	2	2	2	2
	0	1	7	1	2	3	6	4	4	2	9	0	0	1	9	9	9	1	7	8	9	0	7	7	7
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	7	7	8	8	5	6	9	8	9	5	5	6	9	7	6	8	7	5	5	7	7	7	5	5	6
	1	5	6	5	3	4	5	0	8	2	1	2	7	8	9	4	0	7	9	4	2	6	4	8	1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X		X		X	X	X	X	X					X	
Mesothelioma malignant									X	X															X

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Elmiron®: 126 mg/kg

Number of Days on Study	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	
Carcass ID Number	163	168	181	187	191	192	193	196	199	200	155	156	165	166	167	173	177	182	183	188	194	160	179	189	190	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X							X		X		X		X	X		X							16
Mesothelioma malignant														X												4

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	7/50 (14%)	7/50 (14%)	3/50 (6%)	8/50 (16%)
Adjusted rate[b]	16.8%	16.7%	7.5%	19.9%
Terminal rate[c]	4/26 (15%)	6/29 (21%)	3/25 (12%)	7/28 (25%)
First incidence (days)	640	713	727 (T)	660
Poly-3 test[d]	P=0.383	P=0.608N	P=0.172N	P=0.473
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.4%	0.0%	7.3%	2.5%
Terminal rate	1/26 (4%)	0/29 (0%)	1/25 (4%)	1/28 (4%)
First incidence (days)	727 (T)	—[e]	419	727 (T)
Poly-3 test	P=0.544	P=0.497N	P=0.301	P=0.755
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall	7/50 (14%)	7/50 (14%)	6/50 (12%)	9/50 (18%)
Adjusted rate	16.8%	16.7%	14.7%	22.3%
Terminal rate	4/26 (15%)	6/29 (21%)	4/25 (16%)	8/28 (29%)
First incidence (days)	640	713	419	660
Poly-3 test	P=0.276	P=0.608N	P=0.514N	P=0.363
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	4.8%	2.4%	2.5%	7.5%
Terminal rate	1/26 (4%)	0/29 (0%)	0/25 (0%)	3/28 (11%)
First incidence (days)	685	577	686	727 (T)
Poly-3 test	P=0.266	P=0.491N	P=0.511N	P=0.485
Mammary Gland: Fibroadenoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted rate	4.7%	2.4%	7.4%	12.5%
Terminal rate	0/26 (0%)	1/29 (3%)	2/25 (8%)	5/28 (18%)
First incidence (days)	503	727 (T)	574	727 (T)
Poly-3 test	P=0.063	P=0.505N	P=0.477	P=0.191
Mammary Gland: Fibroma, Fibroadenoma, or Adenoma				
Overall rate	4/50 (8%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted rate	9.4%	2.4%	7.4%	12.5%
Terminal rate	2/26 (8%)	1/29 (3%)	2/25 (8%)	5/28 (18%)
First incidence (days)	503	727 (T)	574	727 (T)
Poly-3 test	P=0.189	P=0.182N	P=0.528N	P=0.462
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	19/50 (38%)	18/50 (36%)	18/50 (36%)	13/50 (26%)
Adjusted rate	42.6%	40.3%	42.4%	31.7%
Terminal rate	12/26 (46%)	10/29 (35%)	11/25 (44%)	8/28 (29%)
First incidence (days)	503	313	462	629
Poly-3 test	P=0.170N	P=0.499N	P=0.580N	P=0.203N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	20/50 (40%)	18/50 (36%)	18/50 (36%)	13/50 (26%)
Adjusted rate	44.5%	40.3%	42.4%	31.7%
Terminal rate	12/26 (46%)	10/29 (35%)	11/25 (44%)	8/28 (29%)
First incidence (days)	503	313	462	629
Poly-3 test	P=0.141N	P=0.425N	P=0.506N	P=0.155N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Skin: Keratoacanthoma				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.9%	7.1%	7.4%	2.5%
Terminal rate	2/26 (8%)	2/29 (7%)	0/25 (0%)	0/28 (0%)
First incidence (days)	727 (T)	668	630	691
Poly-3 test	P=0.319N	P=0.510	P=0.492	P=0.509N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	3/50 (6%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate	7.3%	7.1%	7.4%	2.5%
Terminal rate	3/26 (12%)	2/29 (7%)	0/25 (0%)	0/28 (0%)
First incidence (days)	727 (T)	668	630	691
Poly-3 test	P=0.228N	P=0.653N	P=0.655	P=0.314N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted rate	7.3%	7.1%	9.9%	2.5%
Terminal rate	3/26 (12%)	2/29 (7%)	1/25 (4%)	0/28 (0%)
First incidence (days)	727 (T)	668	630	691
Poly-3 test	P=0.233N	P=0.653N	P=0.491	P=0.314N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted rate	9.7%	7.1%	9.9%	2.5%
Terminal rate	4/26 (15%)	2/29 (7%)	1/25 (4%)	0/28 (0%)
First incidence (days)	727 (T)	668	630	691
Poly-3 test	P=0.165N	P=0.488N	P=0.635	P=0.185N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.4%	2.4%	7.5%	2.5%
Terminal rate	1/26 (4%)	1/29 (3%)	2/25 (8%)	1/28 (4%)
First incidence (days)	727 (T)	727 (T)	674	727 (T)
Poly-3 test	P=0.633N	P=0.757N	P=0.295	P=0.755
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rate	7.2%	7.2%	10.0%	5.0%
Terminal rate	2/26 (8%)	3/29 (10%)	3/25 (12%)	1/28 (4%)
First incidence (days)	661	727 (T)	674	661
Poly-3 test	P=0.418N	P=0.658N	P=0.482	P=0.513N
Skin (Sebaceous Gland): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.4%	2.4%	5.0%	7.4%
Terminal rate	1/26 (4%)	1/29 (3%)	1/25 (4%)	1/28 (4%)
First incidence (days)	727 (T)	727 (T)	630	679
Poly-3 test	P=0.172	P=0.757N	P=0.492	P=0.297
Testes: Adenoma				
Overall rate	44/50 (88%)	43/50 (86%)	43/50 (86%)	40/50 (80%)
Adjusted rate	93.0%	92.9%	91.5%	90.0%
Terminal rate	26/26 (100%)	28/29 (97%)	24/25 (96%)	26/28 (93%)
First incidence (days)	475	503	484	433
Poly-3 test	P=0.346N	P=0.658N	P=0.550N	P=0.435N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/50 (0%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.4%	2.5%	7.5%
Terminal rate	0/26 (0%)	1/29 (3%)	1/25 (4%)	2/28 (7%)
First incidence (days)	—	727 (T)	727 (T)	707
Poly-3 test	P=0.059	P=0.503	P=0.493	P=0.113
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted rate	4.9%	4.7%	2.5%	10.0%
Terminal rate	2/26 (8%)	1/29 (3%)	1/25 (4%)	3/28 (11%)
First incidence (days)	727 (T)	551	727 (T)	707
Poly-3 test	P=0.184	P=0.683N	P=0.511N	P=0.324
Thyroid Gland (C-cell): Adenoma				
Overall rate	8/50 (16%)	8/50 (16%)	8/50 (16%)	7/50 (14%)
Adjusted rate	18.9%	19.0%	19.7%	17.4%
Terminal rate	6/26 (23%)	7/29 (24%)	6/25 (24%)	5/28 (18%)
First incidence (days)	519	645	582	689
Poly-3 test	P=0.486N	P=0.607	P=0.573	P=0.543N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	10/50 (20%)	9/50 (18%)	8/50 (16%)	8/50 (16%)
Adjusted rate	23.2%	21.2%	19.7%	19.9%
Terminal rate	6/26 (23%)	7/29 (24%)	6/25 (24%)	6/28 (21%)
First incidence (days)	519	645	582	689
Poly-3 test	P=0.440N	P=0.516N	P=0.454N	P=0.462N
All Organs: Benign or Malignant Mesothelioma				
Overall rate	2/50 (4%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate	4.8%	0.0%	5.0%	9.8%
Terminal rate	0/26 (0%)	0/29 (0%)	2/25 (8%)	2/28 (7%)
First incidence (days)	699	—	727 (T)	604
Poly-3 test	P=0.084	P=0.234N	P=0.682	P=0.331
All Organs: Mononuclear Cell Leukemia				
Overall rate	15/50 (30%)	16/50 (32%)	12/50 (24%)	16/50 (32%)
Adjusted rate	34.1%	35.5%	28.4%	38.0%
Terminal rate	5/26 (19%)	4/29 (14%)	4/25 (16%)	8/28 (29%)
First incidence (days)	519	313	526	484
Poly-3 test	P=0.401	P=0.532	P=0.368N	P=0.438
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	47/50 (94%)	49/50 (98%)	45/50 (90%)
Adjusted rate	100.0%	97.9%	99.6%	99.5%
Terminal rate	26/26 (100%)	29/29 (100%)	25/25 (100%)	28/28 (100%)
First incidence (days)	475	313	462	433
Poly-3 test	P=0.721N	P=0.500N	P=1.000N	P=1.000N
All Organs: Malignant Neoplasms				
Overall rate	29/50 (58%)	25/50 (50%)	22/50 (44%)	25/50 (50%)
Adjusted rate	63.1%	53.6%	49.4%	57.9%
Terminal rate	11/26 (42%)	9/29 (31%)	9/25 (36%)	14/28 (50%)
First incidence (days)	475	313	419	484
Poly-3 test	P=0.499N	P=0.237N	P=0.129N	P=0.388N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	48/50 (96%)	50/50 (100%)	45/50 (90%)
Adjusted rate	100.0%	99.9%	100.0%	99.5%
Terminal rate	26/26 (100%)	29/29 (100%)	25/25 (100%)	28/28 (100%)
First incidence (days)	475	313	419	433
Poly-3 test	P=1.000N	P=1.000N	P=1.000	P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pituitary gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparison between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Elmiron®[a]

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	2	2		5
Moribund	15	10	17	12
Natural deaths	7	9	8	5
Survivors				
Terminal sacrifice	26	29	25	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Muscularis, periesophageal tissue, inflammation, chronic		1 (2%)		
Periesophageal tissue, hemorrhage	1 (2%)			1 (2%)
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	4 (8%)	1 (2%)		3 (6%)
Intestine large, rectum	(48)	(48)	(49)	(45)
Erosion			2 (4%)	2 (4%)
Infiltration cellular, histiocyte				4 (9%)
Inflammation, chronic	1 (2%)		1 (2%)	5 (11%)
Myxomatous change		1 (2%)	3 (6%)	25 (56%)
Parasite metazoan	5 (10%)	8 (17%)	4 (8%)	3 (7%)
Ulcer				1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Epithelium, cyst		1 (2%)		
Epithelium, necrosis		1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)
Inflammation, chronic, focal			1 (2%)	
Peyer's patch, hyperplasia		1 (2%)		
Intestine small, ileum	(50)	(50)	(50)	(50)
Parasite metazoan			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Basophilic focus	27 (54%)	27 (54%)	22 (44%)	19 (38%)
Clear cell focus	18 (36%)	22 (44%)	23 (46%)	16 (32%)
Eosinophilic focus	9 (18%)	12 (24%)	5 (10%)	4 (8%)
Fatty change, focal			1 (2%)	
Fibrosis, focal		1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	5 (10%)	5 (10%)	7 (14%)	9 (18%)
Inflammation, granulomatous	30 (60%)	26 (52%)	32 (64%)	27 (54%)
Mixed cell focus	8 (16%)	17 (34%)	13 (26%)	11 (22%)
Necrosis, focal	1 (2%)			
Artery, hyperplasia, focal		1 (2%)		
Bile duct, hyperplasia	44 (88%)	41 (82%)	32 (64%)	39 (78%)
Centrilobular, degeneration	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Centrilobular, fatty change			1 (2%)	1 (2%)
Centrilobular, necrosis	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Mesentery	(9)	(11)	(9)	(13)
Accessory spleen				1 (8%)
Hemorrhage				1 (8%)
Fat, inflammation, granulomatous				2 (15%)
Fat, necrosis	7 (78%)	10 (91%)	9 (100%)	8 (62%)

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

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Fibrosis		1 (2%)		
Acinus, atrophy	12 (24%)	14 (28%)	14 (28%)	16 (32%)
Acinus, hyperplasia, focal		2 (4%)	1 (2%)	
Duct, necrosis			1 (2%)	
Salivary glands	(50)	(50)	(49)	(50)
Duct, parotid gland, sublingual gland, mineralization			1 (2%)	
Parotid gland, atrophy, focal	1 (2%)		1 (2%)	
Sublingual gland, atrophy, focal			1 (2%)	
Sublingual gland, hypertrophy, focal	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema		1 (2%)		
Hyperplasia, focal, squamous			2 (4%)	1 (2%)
Inflammation, acute		1 (2%)		
Inflammation, chronic			1 (2%)	
Mineralization	1 (2%)			
Ulcer	1 (2%)	2 (4%)	4 (8%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Mineralization	2 (4%)		1 (2%)	1 (2%)
Ulcer	1 (2%)	3 (6%)	5 (10%)	2 (4%)
Epithelium, hyperplasia, focal	1 (2%)		2 (4%)	1 (2%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, mineralization	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Atrium, inflammation, chronic			1 (2%)	
Atrium, thrombosis	2 (4%)	4 (8%)		1 (2%)
Myocardium, degeneration	41 (82%)	41 (82%)	42 (84%)	41 (82%)
Myocardium, necrosis, focal		1 (2%)		
Vein, thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia				1 (2%)
Hyperplasia, diffuse	1 (2%)			
Hyperplasia, focal	14 (28%)	16 (32%)	17 (34%)	17 (34%)
Necrosis, acute			1 (2%)	
Necrosis, focal		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(50)
Fibrosis			3 (6%)	
Hyperplasia, diffuse	2 (4%)			
Hyperplasia, focal	10 (20%)	17 (34%)	12 (24%)	13 (26%)
Necrosis, acute	1 (2%)			
Necrosis, focal			1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Parathyroid gland	(46)	(44)	(45)	(47)
Cyst, multiple	1 (2%)			

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		1 (2%)
Cyst	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Hyperplasia				2 (4%)
Necrosis, focal				1 (2%)
Pars distalis, hyperplasia, focal	12 (24%)	12 (24%)	17 (34%)	9 (18%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	31 (62%)	36 (72%)	40 (80%)	35 (70%)
Follicle, cyst			1 (2%)	
Follicle, hyperplasia				1 (2%)
General Body System				
Peritoneum			(1)	
Inflammation, chronic			1 (100%)	
Genital System				
Coagulating gland	(1)			(1)
Inflammation, chronic				1 (100%)
Epididymis	(50)	(50)	(50)	(50)
Fibrosis				1 (2%)
Granuloma sperm	1 (2%)		1 (2%)	1 (2%)
Inflammation, acute				1 (2%)
Preputial gland	(50)	(50)	(50)	(50)
Cyst			3 (6%)	2 (4%)
Hyperplasia	1 (2%)	2 (4%)		
Inflammation, chronic	35 (70%)	44 (88%)	42 (84%)	37 (74%)
Inflammation, suppurative	1 (2%)		2 (4%)	1 (2%)
Prostate, NOS	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)			
Hyperplasia, focal			1 (2%)	
Inflammation, acute	1 (2%)			
Inflammation, chronic active	18 (36%)	16 (32%)	19 (38%)	18 (37%)
Seminal vesicle	(50)	(50)	(50)	(49)
Atrophy	1 (2%)	1 (2%)		
Fibrosis		1 (2%)	1 (2%)	
Hyperplasia	4 (8%)		2 (4%)	2 (4%)
Testes	(50)	(50)	(50)	(50)
Cyst			2 (4%)	
Artery, necrosis			1 (2%)	
Germinal epithelium, atrophy	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Interstitial cell, hyperplasia	5 (10%)		1 (2%)	2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis	2 (4%)	1 (2%)		1 (2%)
Infiltration cellular, lymphocyte	1 (2%)			
Infiltration cellular, histiocyte	1 (2%)			

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Hematopoietic System (continued)				
Lymph node	(11)	(17)	(10)	(13)
Deep cervical, angiectasis				1 (8%)
Deep cervical, hyperplasia, lymphoid	1 (9%)			
Mediastinal, angiectasis				1 (8%)
Mediastinal, ectasia		2 (12%)	2 (20%)	1 (8%)
Mediastinal, hemorrhage	2 (18%)			1 (8%)
Mediastinal, hyperplasia, lymphoid	2 (18%)	7 (41%)	2 (20%)	1 (8%)
Mediastinal, hyperplasia, plasma cell				1 (8%)
Mediastinal, infiltration cellular, histiocyte			1 (10%)	
Pancreatic, ectasia		1 (6%)		
Pancreatic, hemorrhage		1 (6%)		
Renal, ectasia			1 (10%)	
Renal, infiltration cellular, plasma cell			1 (10%)	
Lymph node, mandibular	(5)	(5)	(9)	(2)
Ectasia			1 (11%)	1 (50%)
Infiltration cellular, plasma cell	1 (20%)			
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Ectasia		2 (4%)	2 (4%)	
Fibrosis		1 (2%)		
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)	1 (2%)	18 (36%)	39 (80%)
Inflammation, granulomatous				3 (6%)
Necrosis, lymphoid		1 (2%)		
Endothelial cell, hyperplasia		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Fibrosis, focal		2 (4%)		1 (2%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	3 (6%)	4 (8%)
Hyperplasia, lymphohistiocytic	2 (4%)	2 (4%)	2 (4%)	8 (16%)
Necrosis, focal		1 (2%)		
Capsule, fibrosis, focal	1 (2%)			1 (2%)
Lymphoid follicle, atrophy	20 (40%)	25 (50%)	29 (58%)	25 (50%)
Lymphoid follicle, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Lymphoid follicle, necrosis	1 (2%)			
Integumentary System				
Mammary gland	(49)	(49)	(50)	(48)
Hyperplasia	25 (51%)	37 (76%)	31 (62%)	17 (35%)
Duct, dilatation	12 (24%)	24 (49%)	27 (54%)	15 (31%)
Duct, dilatation, diffuse		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Metaplasia, osseous		1 (2%)		
Epidermis, cyst, squamous	1 (2%)			
Epidermis, epidermis, cyst	1 (2%)			
Sebaceous gland, hyperplasia, focal				1 (2%)

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cyst	2 (4%)			
Femur, hyperostosis	1 (2%)			
Skeletal muscle			(1)	(2)
Hemorrhage				1 (50%)
Inflammation, acute				1 (50%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hydrocephalus	8 (16%)	7 (14%)	9 (18%)	6 (12%)
Cerebrum, degeneration, focal			1 (2%)	
Hippocampus, cerebrum, degeneration		1 (2%)		
Hypothalamus, compression	6 (12%)	2 (4%)	5 (10%)	4 (8%)
Medulla, degeneration, focal			1 (2%)	
Respiratory System				
Larynx				(1)
Hemorrhage				1 (100%)
Lung	(50)	(50)	(50)	(50)
Emphysema, focal		1 (2%)		
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Infiltration cellular, histiocyte				1 (2%)
Metaplasia, osseous		3 (6%)		
Myxomatous change				1 (2%)
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia	6 (12%)			1 (2%)
Alveolar epithelium, hyperplasia, focal	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Alveolar epithelium, metaplasia, squamous				2 (4%)
Alveolus, emphysema, focal		1 (2%)		1 (2%)
Alveolus, inflammation, acute	1 (2%)	1 (2%)		2 (4%)
Alveolus, inflammation, chronic active, focal		6 (12%)	11 (22%)	14 (28%)
Artery, thrombosis				1 (2%)
Interstitium, fibrosis, focal				1 (2%)
Interstitium, alveolus, inflammation				1 (2%)
Mediastinum, inflammation, chronic		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Foreign body	1 (2%)			
Inflammation, chronic	9 (18%)	7 (14%)	8 (16%)	9 (18%)
Thrombosis				1 (2%)
Ulcer	2 (4%)	1 (2%)		
Trachea	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, chronic	1 (2%)			4 (8%)
Ulcer				1 (2%)
Epithelium, metaplasia, squamous	1 (2%)			1 (2%)
Special Senses System				
Eye		(1)		(1)
Cataract		1 (100%)		1 (100%)

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	14 mg/kg	42 mg/kg	126 mg/kg
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Glomerulosclerosis		1 (2%)		
Hemorrhage			1 (2%)	
Hydronephrosis	2 (4%)			
Infarct	2 (4%)		2 (4%)	
Nephropathy	40 (80%)	42 (84%)	41 (82%)	37 (74%)
Artery, thrombosis	1 (2%)			
Pelvis, inflammation, suppurative			1 (2%)	
Renal tubule, necrosis, focal	2 (4%)	1 (2%)	2 (4%)	
Renal tubule, pigmentation, lipofuscin		1 (2%)	3 (6%)	
Vein, inflammation, chronic	1 (2%)			
Urethra				(1)
Inflammation, suppurative				1 (100%)
Urinary bladder	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)		
Inflammation, acute	1 (2%)			
Mineralization	1 (2%)			
Ulcer	2 (4%)			

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

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Elmiron®[a]

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1	2	6
Moribund	6	8	11	11
Natural deaths	13	10	9	6
Survivors				
Died last week of study				1
Terminal sacrifice	30	31	28	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(46)	(43)	(44)	(42)
Leiomyosarcoma, metastatic, vagina			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Fibrous histiocytoma			1 (2%)	
Hepatocellular carcinoma	1 (2%)			
Leiomyosarcoma, metastatic, uterus	1 (2%)			
Mesentery	(8)	(4)	(6)	(9)
Liposarcoma	1 (13%)			
Pancreas	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	2 (4%)	1 (2%)		3 (6%)
Bilateral, pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma		1 (2%)	2 (4%)	
Parathyroid gland	(46)	(44)	(46)	(45)
Adenoma	1 (2%)			
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	21 (42%)	21 (42%)	26 (52%)	19 (38%)
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma			1 (2%)	
C-cell, adenoma	11 (22%)	7 (14%)	9 (18%)	9 (18%)
C-cell, adenoma, multiple		1 (2%)		
Follicle, carcinoma	1 (2%)			1 (2%)
General Body System				
None				

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Adenoma	3 (6%)			4 (8%)
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor malignant		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Adenocarcinoma			1 (2%)	
Leiomyoma				1 (2%)
Leiomyosarcoma	1 (2%)			
Polyp stromal	7 (14%)	8 (16%)	7 (14%)	5 (10%)
Sarcoma stromal			1 (2%)	
Endometrium, polyp stromal				1 (2%)
Endometrium, sarcoma stromal				1 (2%)
Vagina			(2)	(2)
Leiomyosarcoma			1 (50%)	1 (50%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(7)	(19)	(14)	(13)
Lymph node, mandibular	(3)	(8)	(3)	(2)
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Spleen	(50)	(50)	(50)	(50)
Thymus	(45)	(41)	(46)	(41)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenolipoma				1 (2%)
Adenoma			1 (2%)	1 (2%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Fibroadenoma	11 (22%)	21 (42%)	16 (32%)	17 (34%)
Fibroadenoma, multiple	4 (8%)	2 (4%)	8 (16%)	4 (8%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Keratoacanthoma			1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)		2 (4%)	
Subcutaneous tissue, fibrous histiocytoma			1 (2%)	
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)		
Musculoskeletal System				
Skeletal muscle			(1)	
Leiomyosarcoma, metastatic, vagina			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Oligodendroglioma malignant				1 (2%)

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma		1 (2%)		
Fibrous histiocytoma			1 (2%)	
Leiomyosarcoma, metastatic, uterus	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland	(1)			
Adenoma	1 (100%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Adenolipoma				1 (2%)
Leukemia mononuclear	7 (14%)	14 (28%)	8 (16%)	10 (20%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	45	44	40
Total primary neoplasms	79	80	90	82
Total animals with benign neoplasms	37	41	41	35
Total benign neoplasms	66	63	74	65
Total animals with malignant neoplasms	12	17	14	15
Total malignant neoplasms	13	17	16	17
Total animals with metastatic neoplasms	2		1	
Total metastatic neoplasms	3		2	

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

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

Number of Days on Study	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	208	209	210	216	217	222	226	235	243	245	247	249	213	214	215	219	221	224	225	227	228	236	240	242	248	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Leiomyosarcoma, metastatic, uterus																										1
Mesentery		+				+	+					+				+									+	8
Liposarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									X	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue		+																								1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign										X																2
Bilateral, pheochromocytoma malignant								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Adenoma		X																								1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X		X				X	X							X			X			X	X	21
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X				X	X							X	X				X		X						11
Follicle, carcinoma																						X				1
General Body System																										
None																										

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

Number of Days on Study	191	406	427	462	509	559	596	596	600	601	621	629	651	673	678	690	707	719	722	726	728	728	729	729	729
Carcass ID Number	230	220	238	250	244	231	206	212	201	246	233	223	211	234	239	237	241	218	229	203	207	232	202	204	205
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma		X																							
Polyp stromal											X	X												X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																			+	+					
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Fibroadenoma											X				X	X					X			X	
Fibroadenoma, multiple													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Subcutaneous tissue, fibroma														X											
Subcutaneous tissue, lipoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus		X																							
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

Number of Days on Study	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	208	209	210	216	217	222	226	235	243	245	247	249	213	214	215	219	221	224	225	227	228	236	240	242	248	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X			X															3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal	X				X					X					X											7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+		+				+		+								+						7
Lymph node, mandibular	M	M	M	M	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma			X					X					X			X					X				X	11
Fibroadenoma, multiple		X										X												X		4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma														X												1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Pheochromocytoma malignant, metastatic, adrenal medulla								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland																					+					1
Adenoma																					X					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

	1	4	4	4	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7
Number of Days on Study	9	0	2	6	0	5	9	9	0	0	2	2	5	7	7	9	0	1	2	2	2	2	2	2	2
	1	6	7	2	9	9	6	6	0	1	1	9	1	3	8	0	7	9	2	6	8	8	9	9	9
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	3	2	3	5	4	3	0	1	0	4	3	2	1	3	3	3	4	1	2	0	0	3	0	0	0
	0	0	8	0	4	1	6	2	1	6	3	3	1	4	9	7	1	8	9	3	7	2	2	4	5
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X				X	X								X				

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: Vehicle Control

Number of Days on Study	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	208	209	210	216	217	222	226	235	243	245	247	249	213	214	215	219	221	224	225	227	228	236	240	242	248	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X									X									7

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 28 mg/kg

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

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 28 mg/kg

Number of Days on Study	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	294	252	253	256	259	262	263	267	274	278	281	282	286	291	296	251	270	271	272	275	277	279	280	297	300	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+																			4
Oral mucosa																		+								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Parathyroid gland	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X		X	X	X	X		X	X	X							X	X			X		21
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X				X									X					X				7
C-cell, adenoma, multiple										X																1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant											X															1
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal								X			X			X							X			X		8

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 28 mg/kg

Number of Days on Study	1	3	4	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	9	3	7	1	2	3	8	9	2	5	7	7	7	7	1	1	1	1	1	2	2	2	2	2	2
	7	3	4	0	6	9	9	4	2	3	0	7	8	8	4	5	6	6	9	8	8	8	8	8	8
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	9	6	9	8	8	6	6	9	6	8	5	9	8	9	5	6	6	8	9	5	5	6	7	7	8
	2	9	0	7	9	6	8	5	1	4	8	8	3	9	4	5	0	8	3	5	7	4	3	6	5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+		+					+	+	+	+	+				+		
Lymph node, mandibular	M	M	M	M	+	M	+	M	+	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma														X											
Fibroadenoma			X						X		X		X				X	X			X	X			
Fibroadenoma, multiple												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye										+									+			+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X	X					X	X			X						

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 28 mg/kg

Number of Days on Study	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	294	252	253	256	259	262	263	267	274	278	281	282	286	291	296	251	270	271	272	275	277	279	280	297	300	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+	+	+			+	+		+		+	+				+	+							19
Lymph node, mandibular	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	8
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma	X	X	X		X			X		X	X	X	X		X		X		X						X	21
Fibroadenoma, multiple									X																	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lipoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X					X				X			X	X									14

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 84 mg/kg

Number of Days on Study	111	375	405	474	483	491	545	559	614	645	653	664	667	667	673	678	685	691	711	713	715	723	728	728	728
Carcass ID Number	322	308	332	309	313	301	329	320	324	330	326	333	306	341	315	327	303	314	334	339	336	319	302	304	310
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, vagina					X																				
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma														X											
Mesentery					+		+	+							+					+					
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X				X		X		X		X	X		X	X	X	X	X	X	X	X
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma															X		X				X	X	X		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp stromal								X				X								X			X		
Sarcoma stromal								X																	
Vagina					+									+											
Leiomyosarcoma					X																				

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 84 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	312	316	317	318	325	328	337	338	331	343	344	345	347	348	349	305	307	311	321	323	335	340	342	346	350	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Leiomyosarcoma, metastatic, vagina																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Mesentery																					+					6
Oral mucosa														+												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X									X													2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X						X			X				X	X					26
Pars intermedia, adenoma																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma												X														1
C-cell, adenoma						X				X	X				X											9
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															1
Polyp stromal		X	X			X																				7
Sarcoma stromal																										1
Vagina																										2
Leiomyosarcoma																										1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 84 mg/kg

Number of Days on Study	111	375	405	474	483	491	545	559	614	645	653	664	667	667	673	678	685	691	711	713	715	723	728	728	728
Carcass ID Number	322	308	332	309	313	301	329	320	324	330	326	333	306	341	315	327	303	314	334	339	336	319	302	304	310
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+			+	+		+					+				+			
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Fibroadenoma															X	X				X	X		X		
Fibroadenoma, multiple				X													X		X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma																						X			
Subcutaneous tissue, fibrous histiocytoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Leiomyosarcoma, metastatic, vagina					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																	X								
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X				X	X	X	X					X							

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 84 mg/kg

Number of Days on Study	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	312	316	317	318	325	328	337	338	331	343	344	345	347	348	349	305	307	311	321	323	335	340	342	346	350	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+					+				+				+	+					+		+			14
Lymph node, mandibular	+	M	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Carcinoma		X																								1
Fibroadenoma		X	X			X			X		X		X	X				X	X			X			X	16
Fibroadenoma, multiple	X															X				X			X	X		8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																			X							1
Subcutaneous tissue, fibroma										X																2
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Leiomyosarcoma, metastatic, vagina																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																				X	8

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 252 mg/kg

Number of Days on Study	111	139	216	273	329	379	495	518	525	588	603	624	651	656	660	667	672	678	680	706	720	723	727	728	728
Carcass ID Number	354	389	355	385	368	390	379	399	371	383	373	365	356	395	388	400	357	384	386	364	397	398	360	353	358
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	A	+	+	A	A	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+		+		+													+	+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X	X						X	X	X	X			X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X		X				X				X	X	
Follicle, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Polyp stromal														X											
Endometrium, polyp stromal																									
Endometrium, sarcoma stromal													X												
Vagina															+						+				
Leiomyosarcoma																					X				

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 252 mg/kg

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	
	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Total
Carcass ID Number	5	6	6	7	7	9	9	5	6	7	7	8	8	9	9	5	6	6	6	7	7	7	8	8	9	Tissues/
	9	1	6	5	7	2	6	1	9	2	8	1	7	1	3	2	2	3	7	0	4	6	0	2	4	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+															+	+								9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X				X													3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X						X		X	X				X	X		X		X	X		19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X	X	X														X					9
Follicle, carcinoma			X																							1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X											X						X			4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																				X						1
Polyp stromal		X	X										X					X								5
Endometrium, polyp stromal																							X			1
Endometrium, sarcoma stromal																										1
Vagina																										2
Leiomyosarcoma																										1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Elmiron®: 252 mg/kg

Number of Days on Study	111	139	216	273	329	379	495	518	525	588	603	624	651	656	660	667	672	678	680	706	720	723	727	728	728
Carcass ID Number	354	389	355	385	368	390	379	399	371	383	373	365	356	395	388	400	357	384	386	364	397	398	360	353	358
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+	+						+	+									
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	M	+	M	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenolipoma										X															
Adenoma																									X
Carcinoma																		X							
Fibroadenoma										X			X			X	X			X		X			X
Fibroadenoma, multiple																					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant						X																			
Peripheral nerve																+									
Spinal cord																+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenolipoma										X															
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 Elmiron®: 252 mg/kg

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	
	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Total
	5	6	6	7	7	9	9	5	6	7	7	8	8	9	9	5	6	6	6	7	7	7	8	8	9	Tissues/
	9	1	6	5	7	2	6	1	9	2	8	1	7	1	3	2	2	3	7	0	4	6	0	2	4	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+							+	+	+		+	+			+							+			13
Lymph node, mandibular	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
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenolipoma																										1
Adenoma																										1
Carcinoma																			X					X		3
Fibroadenoma	X	X				X			X		X	X	X		X					X			X			17
Fibroadenoma, multiple														X		X		X								4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+																			+			3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenolipoma																										1
Leukemia mononuclear			X																							10

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

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/50 (4%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate[b]	4.8%	2.3%	0.0%	7.6%
Terminal rate[c]	1/30 (3%)	1/31 (3%)	0/28 (0%)	2/27 (7%)
First incidence (days)	722	728 (T)	—[d]	727
Poly-3 test[e]	P=0.238	P=0.492N	P=0.240N	P=0.470
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	7.2%	2.3%	0.0%	7.6%
Terminal rate	2/30 (7%)	1/31 (3%)	0/28 (0%)	2/27 (7%)
First incidence (days)	722	728 (T)	—	727
Poly-3 test	P=0.378	P=0.297N	P=0.120N	P=0.633
Clitoral Gland: Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	4/49 (8%)
Adjusted rate	7.1%	0.0%	0.0%	10.4%
Terminal rate	2/30 (7%)	0/31 (0%)	0/28 (0%)	3/26 (12%)
First incidence (days)	601	—	—	706
Poly-3 test	P=0.108	P=0.116N	P=0.122N	P=0.446
Mammary Gland: Fibroadenoma				
Overall rate	15/50 (30%)	23/50 (46%)	24/50 (48%)[f]	21/50 (42%)[f, g]
Adjusted rate	34.9%	51.5%	55.9%	51.6%
Terminal rate	11/30 (37%)	16/31 (52%)	17/28 (61%)	14/27 (52%)
First incidence (days)	621	474	474	588
Poly-3 test	P=0.186	P=0.085	P=0.036	P=0.088
Mammary Gland: Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.4%	2.3%	2.4%	7.6%
Terminal rate	0/30 (0%)	0/31 (0%)	1/28 (4%)	2/27 (7%)
First incidence (days)	707	678	728 (T)	678
Poly-3 test	P=0.140	P=0.755N	P=0.758	P=0.283
Mammary Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.4%	2/3%	4.8%	10.1%
Terminal rate	0/30 (0%)	0/31 (0%)	2/28 (7%)	3/27 (11%)
First incidence (days)	707	678	728 (T)	678
Poly-3 test	P=0.061	P=0.755N	P=0.495	P=0.159
Mammary Gland: Adenolipoma, Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	16/50 (32%)	24/50 (48%)	24/50 (48%)	24/50 (48%)
Adjusted rate	37.2%	53.5%	55.9%	58.7%
Terminal rate	11/30 (37%)	16/31 (52%)	17/28 (61%)	16/27 (59%)
First incidence (days)	621	474	474	588
Poly-3 test	P=0.077	P=0.089	P=0.058	P=0.034
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	21/50 (42%)	21/50 (42%)	26/50 (52%)	19/50 (38%)
Adjusted rate	46.7%	47.5%	58.4%	46.0%
Terminal rate	9/30 (30%)	16/31 (52%)	14/28 (50%)	11/27 (41%)
First incidence (days)	462	526	474	525
Poly-3 test	P=0.510N	P=0.555	P=0.181	P=0.564N

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Skin (Subcutaneous Tissue): Fibroma or Fibrous Histiocytoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.4%	0.0%	7.2%	0.0%
Terminal rate	0/30 (0%)	0/31 (0%)	1/28 (4%)	0/27 (0%)
First incidence (days)	673	—	667	—
Poly-3 test	P=0.478N	P=0.497N	P=0.301	P=0.514N
Thyroid Gland (C-cell): Adenoma				
Overall rate	11/50 (22%)	8/50 (16%)	10/50 (20%)	9/50 (18%)
Adjusted rate	26.1%	18.6%	23.9%	22.5%
Terminal rate	9/30 (30%)	6/31 (19%)	6/28 (21%)	5/27 (19%)
First incidence (days)	673	715	673	651
Poly-3 test	P=0.536N	P=0.285N	P=0.507N	P=0.451N
Uterus: Stromal Polyp				
Overall rate	7/50 (14%)	8/50 (16%)	7/50 (14%)	6/50 (12%)
Adjusted rate	16.4%	18.6%	16.6%	15.2%
Terminal rate	5/30 (17%)	6/31 (19%)	4/28 (14%)	5/27 (19%)
First incidence (days)	621	716	559	656
Poly-3 test	P=0.453N	P=0.506	P=0.608	P=0.558N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	7/50 (14%)	8/50 (16%)	7/50 (14%)	7/50 (14%)
Adjusted rate	16.4%	18.6%	16.6%	17.6%
Terminal rate	5/30 (17%)	6/31 (19%)	4/28 (14%)	5/27 (19%)
First incidence (days)	621	716	559	651
Poly-3 test	P=0.554	P=0.506	P=0.608	P=0.561
All Organs: Mononuclear Cell Leukemia				
Overall rate	7/50 (14%)	14/50 (28%)	8/50 (16%)	10/50 (20%)
Adjusted rate	16.3%	30.9%	18.5%	23.8%
Terminal rate	4/30 (13%)	6/31 (19%)	2/28 (7%)	2/27 (7%)
First incidence (days)	596	510	491	495
Poly-3 test	P=0.493	P=0.084	P=0.506	P=0.275
All Organs: Benign Neoplasms				
Overall rate	37/50 (74%)	41/50 (82%)	41/50 (82%)	35/50 (70%)
Adjusted rate	80.1%	88.9%	90.1%	83.0%
Terminal rate	22/30 (73%)	28/31 (90%)	26/28 (93%)	22/27 (82%)
First incidence (days)	462	474	474	525
Poly-3 test	P=0.532N	P=0.176	P=0.132	P=0.471
All Organs: Malignant Neoplasms				
Overall rate	12/50 (24%)	17/50 (34%)	14/50 (28%)	15/50 (30%)
Adjusted rate	27.0%	37.4%	31.1%	34.8%
Terminal rate	6/30 (20%)	8/31 (26%)	4/28 (14%)	4/27 (15%)
First incidence (days)	406	510	483	379
Poly-3 rate	P=0.398	P=0.202	P=0.422	P=0.288

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

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	45/50 (90%)	44/50 (88%)	40/50 (80%)
Adjusted rate	88.3%	94.7%	94.2%	88.5%
Terminal rate	25/30 (83%)	29/31 (94%)	26/28 (93%)	22/27 (82%)
First incidence (days)	406	474	474	379
Poly-3 rate	P=0.396N	P=0.218	P=0.251	P=0.616

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Not applicable; no neoplasms in animal group
[e] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparison between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[f] One incidence of adenoma occurred in an animal that also had a fibroadenoma.
[g] One incidence of adenolipoma occurred in an animal that also had a fibroadenoma.

Table B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Elmiron®[a]

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1	2	6
Moribund	6	8	11	11
Natural deaths	13	10	9	6
Survivors				
Died last week of study				1
Terminal sacrifice	30	31	28	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Muscularis, inflammation, chronic				1 (2%)
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	2 (4%)	3 (6%)	3 (6%)	3 (6%)
Intestine large, rectum	(46)	(43)	(44)	(42)
Infiltration cellular, histiocyte				18 (43%)
Inflammation, acute, focal				1 (2%)
Inflammation, chronic			1 (2%)	1 (2%)
Myxomatous change		1 (2%)	12 (27%)	35 (83%)
Parasite metazoan	2 (4%)	3 (7%)	1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Intestine small, ileum	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis			2 (4%)	1 (2%)
Basophilic focus	39 (78%)	35 (70%)	40 (80%)	34 (68%)
Clear cell focus	8 (16%)	4 (8%)	8 (16%)	6 (12%)
Eosinophilic focus	12 (24%)	12 (24%)	14 (28%)	10 (20%)
Fibrosis, focal			1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	8 (16%)	11 (22%)	14 (28%)
Inflammation, granulomatous	36 (72%)	31 (62%)	37 (74%)	39 (78%)
Mixed cell focus	19 (38%)	12 (24%)	10 (20%)	9 (18%)
Necrosis, focal				1 (2%)
Regeneration		1 (2%)	1 (2%)	
Tension lipidosis			1 (2%)	
Bile duct, hyperplasia	13 (26%)	14 (28%)	11 (22%)	14 (28%)
Bile duct, inflammation			1 (2%)	
Centrilobular, fatty change	1 (2%)	2 (4%)		
Mesentery	(8)	(4)	(6)	(9)
Fat, necrosis	7 (88%)	4 (100%)	6 (100%)	9 (100%)
Oral mucosa		(1)	(1)	
Cyst			1 (100%)	
Pharyngeal, hyperplasia, squamous		1 (100%)		
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy	7 (14%)	12 (24%)	11 (22%)	8 (16%)
Acinus, hyperplasia, focal	1 (2%)	1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Parotid gland, atrophy, diffuse				1 (2%)
Parotid gland, atrophy, focal	2 (4%)	1 (2%)		
Parotid gland, hyperplasia, focal	1 (2%)			

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

Table B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Inflammation, acute			1 (2%)	
Inflammation, chronic, focal				1 (2%)
Epithelium, hyperplasia, squamous				1 (2%)
Epithelium, inflammation, focal, suppurative				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Inflammation, chronic, focal				1 (2%)
Mineralization		1 (2%)		1 (2%)
Pigmentation, hemosiderin				1 (2%)
Ulcer			1 (2%)	3 (6%)
Epithelium, ectasia		1 (2%)		
Tongue	(1)			
Epithelium, hyperplasia, focal, squamous	1 (100%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, inflammation, chronic			1 (2%)	1 (2%)
Heart	(50)	(50)	(50)	(50)
Artery, hyperplasia, focal				1 (2%)
Atrium, thrombosis		1 (2%)		
Myocardium, degeneration	38 (76%)	30 (60%)	31 (62%)	34 (68%)
Myocardium, inflammation, chronic, focal	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia, focal	20 (40%)	17 (34%)	17 (34%)	19 (38%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia, focal	5 (10%)	2 (4%)	4 (8%)	4 (8%)
Necrosis				1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Cyst	20 (40%)	21 (42%)	18 (36%)	22 (44%)
Hemorrhage	1 (2%)			
Pars distalis, hyperplasia, focal	16 (32%)	15 (30%)	10 (20%)	13 (26%)
Pars distalis, mineralization				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	1 (2%)
C-cell, hyperplasia	33 (66%)	38 (76%)	34 (68%)	31 (62%)
Follicle, hyperplasia			2 (4%)	
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Cyst	4 (8%)	4 (8%)	4 (8%)	3 (6%)
Fibrosis	1 (2%)			
Hyperplasia	1 (2%)			
Hyperplasia, focal	5 (10%)	3 (6%)	2 (4%)	3 (6%)

Table B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Genital System (continued)				
Clitoral gland (continued)	(50)	(50)	(50)	(49)
Inflammation, chronic	7 (14%)	10 (20%)	11 (22%)	8 (16%)
Inflammation, suppurative	1 (2%)		1 (2%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Cyst	4 (8%)	5 (10%)	7 (14%)	5 (10%)
Inflammation, granulomatous				1 (2%)
Oviduct		(1)		
Cyst		1 (100%)		
Uterus	(50)	(50)	(50)	(50)
Inflammation, suppurative				1 (2%)
Ulcer		1 (2%)		
Cervix, endometrium, hyperplasia				1 (2%)
Endometrium, hyperplasia, cystic	4 (8%)	5 (10%)	3 (6%)	6 (12%)
Endometrium, inflammation, chronic			1 (2%)	
Vagina			(2)	(2)
Hyperplasia			1 (50%)	
Infiltration cellular, polymorphonuclear				1 (50%)
Epithelium, vacuolization cytoplasmic				1 (50%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis		1 (2%)	1 (2%)	
Lymph node	(7)	(19)	(14)	(13)
Deep cervical, hemorrhage				1 (8%)
Deep cervical, hyperplasia, lymphoid		1 (5%)		1 (8%)
Deep cervical, infiltration cellular, histiocyte	1 (14%)			
Mediastinal, congestion				1 (8%)
Mediastinal, ectasia		2 (11%)	3 (21%)	1 (8%)
Mediastinal, hemorrhage		3 (16%)	2 (14%)	3 (23%)
Mediastinal, hyperplasia, lymphoid	2 (29%)	3 (16%)	3 (21%)	6 (46%)
Mediastinal, infiltration cellular, mast cell				1 (8%)
Mediastinal, infiltration cellular, plasma cell	1 (14%)			1 (8%)
Mediastinal, infiltration cellular, histiocyte	1 (14%)		4 (29%)	
Mediastinal, necrosis, lymphoid		1 (5%)		
Pancreatic, infiltration cellular, histiocyte				1 (8%)
Pancreatic, pigmentation, hemosiderin				1 (8%)
Lymph node, mandibular	(3)	(8)	(3)	(2)
Infiltration cellular, histiocyte		1 (13%)		
Necrosis, lymphoid		1 (13%)		
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Ectasia				1 (2%)
Hyperplasia, lymphoid			2 (4%)	2 (4%)
Infiltration cellular, histiocyte		3 (6%)	27 (54%)	42 (86%)
Spleen	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	6 (12%)	2 (4%)	4 (8%)	5 (10%)
Hemorrhage			1 (2%)	
Hyperplasia, lymphohistiocytic		1 (2%)	2 (4%)	4 (8%)
Necrosis, focal	1 (2%)			
Lymphoid follicle, atrophy	35 (70%)	32 (64%)	31 (62%)	28 (56%)
Lymphoid follicle, hyperplasia				1 (2%)
Thymus	(45)	(41)	(46)	(41)
Epithelial cell, hyperplasia	1 (2%)			

Table B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)			
Hyperplasia, focal	7 (14%)	3 (6%)	3 (6%)	2 (4%)
Duct, dilatation	29 (58%)	15 (30%)	20 (40%)	23 (46%)
Skin	(50)	(50)	(50)	(50)
Ulcer				1 (2%)
Subcutaneous tissue, pigmentation, hemosiderin		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hydrocephalus	8 (16%)	6 (12%)	8 (16%)	10 (20%)
Cerebrum, degeneration, focal			1 (2%)	
Cerebrum, gliosis, focal			1 (2%)	
Cerebrum, necrosis, focal	1 (2%)			
Hypothalamus, compression	5 (10%)	3 (6%)	5 (10%)	8 (16%)
Medulla, compression		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	5 (10%)	3 (6%)	1 (2%)	
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Infiltration cellular, histiocyte			1 (2%)	
Inflammation, chronic active, focal			1 (2%)	
Inflammation, granulomatous, multifocal	1 (2%)			
Metaplasia, osseous	2 (4%)		1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)			
Alveolar epithelium, hyperplasia, focal	3 (6%)	4 (8%)	5 (10%)	3 (6%)
Alveolus, emphysema, focal	1 (2%)			
Alveolus, inflammation, acute		1 (2%)		1 (2%)
Alveolus, inflammation, chronic active, focal	2 (4%)	25 (50%)	27 (54%)	34 (68%)
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic	6 (12%)	3 (6%)	7 (14%)	5 (10%)
Trachea	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Inflammation, chronic		1 (2%)		
Peritracheal tissue, hemorrhage		1 (2%)		
Special Senses System				
Eye		(3)	(1)	(3)
Cataract		1 (33%)	1 (100%)	2 (67%)
Degeneration		2 (67%)		
Cornea, fibrosis				1 (33%)

Table B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	28 mg/kg	84 mg/kg	252 mg/kg
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct	2 (4%)			1 (2%)
Inflammation, focal, suppurative		1 (2%)		
Nephropathy	16 (32%)	13 (26%)	11 (22%)	16 (32%)
Pelvis, inflammation, suppurative			1 (2%)	
Renal tubule, cyst		1 (2%)		
Renal tubule, necrosis				1 (2%)
Renal tubule, pigmentation, lipofuscin			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)

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

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Elmiron®[a]

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1		2
Moribund	7	4	4	3
Natural deaths	4	5	8	15
Survivors				
Terminal sacrifice	39	40	38	30
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(47)	(47)	(42)
Sarcoma, metastatic, liver	1 (2%)			
Intestine large, cecum	(49)	(47)	(46)	(39)
Carcinoma			1 (2%)	
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Intestine small, duodenum	(47)	(47)	(44)	(40)
Carcinoma			1 (2%)	
Polyp adenomatous				1 (3%)
Intestine small, jejunum	(47)	(47)	(44)	(38)
Carcinoma	4 (9%)	1 (2%)		
Polyp adenomatous		1 (2%)		
Sarcoma, metastatic, liver	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)		4 (8%)	9 (18%)
Hepatoblastoma	1 (2%)	1 (2%)		
Hepatocellular carcinoma	7 (14%)	12 (24%)	11 (22%)	11 (22%)
Hepatocellular carcinoma, multiple	4 (8%)	1 (2%)	4 (8%)	2 (4%)
Hepatocellular adenoma	10 (20%)	12 (24%)	10 (20%)	10 (20%)
Hepatocellular adenoma, multiple	9 (18%)	3 (6%)	5 (10%)	10 (20%)
Histiocytic sarcoma	1 (2%)			2 (4%)
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Mesentery	(10)	(4)	(20)	(10)
Sarcoma			1 (5%)	
Pancreas	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)			
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Stomach, forestomach	(49)	(50)	(50)	(50)
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma			2 (4%)	
Stomach, glandular	(49)	(49)	(48)	(46)
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Sarcoma, metastatic, liver	1 (2%)			
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Sarcoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Adenoma			1 (2%)	
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Subcapsular, adenoma	2 (4%)			
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma benign			1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma			2 (4%)	
Pituitary gland	(47)	(48)	(49)	(48)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(48)	(49)	(50)	(49)
C-cell, carcinoma		1 (2%)		
Follicular cell, adenoma				1 (2%)
General Body System				
Peritoneum		(1)		
Mast cell tumor malignant, metastatic, bone marrow		1 (100%)		
Genital System				
Preputial gland	(49)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(49)
Sarcoma, metastatic, liver	1 (2%)			
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Testes	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Interstitial cell, adenoma		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemangiosarcoma	2 (4%)		2 (4%)	1 (2%)
Histiocytic sarcoma				2 (4%)
Mast cell tumor malignant		1 (2%)		
Sarcoma			1 (2%)	
Lymph node	(1)	(1)	(1)	(1)
Mediastinal, mast cell tumor malignant, metastatic, bone marrow		1 (100%)		
Lymph node, mandibular	(28)	(29)	(30)	(30)
Mast cell tumor malignant, metastatic, bone marrow		1 (3%)		

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(46)	(45)	(41)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, mesentery			1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Spleen	(49)	(50)	(49)	(49)
Hemangiosarcoma			1 (2%)	2 (4%)
Histiocytic sarcoma				1 (2%)
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Integumentary System				
Skin	(49)	(50)	(50)	(50)
Keratoacanthoma			1 (2%)	
Subcutaneous tissue, fibrous histiocytoma				1 (2%)
Subcutaneous tissue, melanoma malignant		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Chondroma	1 (2%)			
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Skeletal muscle		(2)		(1)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (100%)
Mast cell tumor malignant, metastatic, bone marrow		1 (50%)		
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (50%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	9 (18%)	3 (6%)	8 (16%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	4 (8%)	3 (6%)	5 (10%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	7 (14%)	3 (6%)	10 (20%)	5 (10%)
Histiocytic sarcoma	1 (2%)			
Mediastinum, mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Nose	(50)	(50)	(50)	(47)
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Pleura				(1)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (100%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Special Senses System				
Harderian gland	(49)	(48)	(49)	(48)
Adenoma	6 (12%)	9 (19%)	4 (8%)	6 (13%)
Carcinoma			1 (2%)	2 (4%)
Bilateral, adenoma			1 (2%)	
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Urinary bladder	(50)	(49)	(49)	(49)
Hemangiosarcoma			1 (2%)	
Transitional epithelium, papilloma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			3 (6%)
Lymphoma malignant	3 (6%)	1 (2%)	2 (4%)	4 (8%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	38	32	41	42
Total primary neoplasms	69	52	71	75
Total animals with benign neoplasms	29	24	29	27
Total benign neoplasms	38	29	36	34
Total animals with malignant neoplasms	24	20	27	30
Total malignant neoplasms	31	23	35	41
Total animals with metastatic neoplasms	8	5	11	6
Total metastatic neoplasms	12	25	12	8

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

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

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

+: 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 Elmiron®: Vehicle Control

Number of Days on Study	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	050	001	002	005	007	009	010	011	014	018	021	023	024	027	028	030	031	032	033	034	035	040	042	048	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, liver																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										4
Sarcoma, metastatic, liver																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatoblastoma											X															1
Hepatocellular carcinoma	X				X				X																	7
Hepatocellular carcinoma, multiple																							X			4
Hepatocellular adenoma								X							X		X		X							10
Hepatocellular adenoma, multiple	X	X			X											X					X		X			9
Histiocytic sarcoma																										1
Mesentery			+		+	+							+	+	+			+			+					10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, liver																										1
Tooth		+	+		+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma										X						X										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Thyroid gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										

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

Number of Days on Study	420	477	590	599	606	620	632	646	664	690	702	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	003	020	015	038	012	046	045	022	036	017	044	004	006	008	013	016	019	025	026	029	037	039	041	043	047
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Hemangiosarcoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, liver										X															
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X														X								
Lymph node																									
Lymph node, mandibular	M	M	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	M	+	+	M	+	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	M	+	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X												X	X						X		
Alveolar/bronchiolar adenoma, multiple									X																
Alveolar/bronchiolar carcinoma					X									X											
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver			X	X		X													X						X
Histiocytic sarcoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	050	001	002	005	007	009	010	011	014	018	021	023	024	027	028	030	031	032	033	034	035	040	042	048	049	Total Tissues/ Tumors
Genital System																										
Coagulating gland																								+		1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma								X																		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, liver																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Lymph node											+															1
Lymph node, mandibular	M	M	+	M	M	+	+	+	M	+	+	+	+	M	+	+	M	+	+	M	M	+	M	M	+	28
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	40
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondroma												X														1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X					X								X							X				X	9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma		X															X									4
Alveolar/bronchiolar carcinoma, multiple						X																				1
Hepatocellular carcinoma, metastatic, liver	X								X																	7
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

Number of Days on Study	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	050	001	002	005	007	009	010	011	014	018	021	023	024	027	028	030	031	032	033	034	035	040	042	048	049	Total Tissues/ Tumors
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X	X				X										X					6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant				X							X															3

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	011	311	346	455	508	508	508	688	707	728	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	077	098	073	080	071	086	099	083	096	063	051	052	053	059	060	061	062	064	065	070	074	075	081	082	085
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Intestine large, colon	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Intestine small, duodenum	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp adenomatous																									
Intestine small, ileum	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma			X																						
Hepatocellular carcinoma							X	X	X											X					
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma				X									X		X	X		X					X		
Hepatocellular adenoma, multiple																			X						
Mast cell tumor malignant, metastatic, bone marrow																									
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Mesentery								+																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Squamous cell carcinoma		X																							
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Tooth										+	+	+	+	+	+	+		+		+	+		+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	089	090	091	092	094	095	097	100	054	055	056	057	058	066	067	068	069	072	076	078	079	084	087	088	093	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	M	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	I	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mast cell tumor malignant, metastatic, bone marrow				X																						1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																									X	1
Polyp adenomatous																				X						1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																										1
Hepatocellular carcinoma	X													X	X		X		X	X		X			X	12
Hepatocellular carcinoma, multiple												X														1
Hepatocellular adenoma													X	X						X	X	X			X	12
Hepatocellular adenoma, multiple							X										X									3
Mast cell tumor malignant, metastatic, bone marrow				X																						1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Mesentery									+	+			+													4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow				X																						1
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mast cell tumor malignant, metastatic, bone marrow				X																						1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Tooth	+					+	+	+	+		+		+		+	+					+	+	+	+	+	27
Cardiovascular System																										
Blood vessel						+																				1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	011	311	346	455	508	508	508	688	707	728	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	077	098	073	080	071	086	099	083	096	063	051	052	053	059	060	061	062	064	065	070	074	075	081	082	085
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma																									
General Body System																									
Peritoneum																									
Mast cell tumor malignant, metastatic, bone marrow																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									
Lymph node																									
Mediastinal, mast cell tumor Malignant, metastatic, bone marrow																									
Lymph node, mandibular	+	M	M	+	M	+	+	+	M	M	+	M	M	M	+	M	M	+	M	M	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Thymus	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	I	M	+	+	+	+	M

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731
Carcass ID Number	089	090	091	092	094	095	097	100	054	055	056	057	058
Endocrine System													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow				X									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	M	+	+	M	+	+
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma	X												
General Body System													
Peritoneum				+									
Mast cell tumor malignant, metastatic, bone marrow				X									
Genital System													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach													
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma													
Hematopoietic System													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant				X									
Lymph node				+									
Mediastinal, mast cell tumor Malignant, metastatic, bone marrow				X									
Lymph node, mandibular	+	+	+	+	+	M	M	M	+	+	+	M	+
Mast cell tumor malignant, metastatic, bone marrow				X									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M
Squamous cell carcinoma, metastatic, stomach, forestomach													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow				X									
Squamous cell carcinoma, metastatic, stomach, forestomach													
Thymus	+	+	+	M	+	+	I	M	+	+	+	M	M

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	066	067	068	069	072	076	078	079	084	087	088	093	Total Tissues/ Tumors
Endocrine System													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	42
Pituitary gland	+	+	+	+	+	I	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, carcinoma													1
General Body System													
Peritoneum													1
Mast cell tumor malignant, metastatic, bone marrow													1
Genital System													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	I	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach													1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma	X												1
Hematopoietic System													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant													1
Lymph node													1
Mediastinal, mast cell tumor Malignant, metastatic, bone marrow													1
Lymph node, mandibular	+	M	+	M	+	+	M	M	M	+	+	+	29
Mast cell tumor malignant, metastatic, bone marrow													1
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	46
Squamous cell carcinoma, metastatic, stomach, forestomach													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow													1
Squamous cell carcinoma, metastatic, stomach, forestomach													1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	39

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	0	3	3	4	5	5	5	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	1	1	4	5	0	0	0	8	0	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	1	1	6	5	8	8	8	8	7	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	9	7	8	7	8	9	8	9	6	5	5	5	5	6	6	6	6	6	7	7	7	8	8	8
	7	8	3	0	1	6	9	3	6	3	1	2	3	9	0	1	2	4	5	0	4	5	1	2	5
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, melanoma malignant																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Skeletal muscle		+																							
Mast cell tumor malignant, metastatic, bone marrow																									
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X					X	X								
Alveolar/bronchiolar carcinoma											X							X							
Hepatocellular carcinoma, metastatic, liver									X																
Mediastinum, mast cell tumor Malignant, metastatic, bone marrow																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X		X							X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach		X																							
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant													X												

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	089	090	091	092	094	095	097	100	054	055	056	057	058	066	067	068	069	072	076	078	079	084	087	088	093	Total Tissues/ Tumors
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, melanoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow				X																						1
Skeletal muscle				+																						2
Mast cell tumor malignant, metastatic, bone marrow				X																						1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										3
Alveolar/bronchiolar carcinoma	X																									3
Hepatocellular carcinoma, metastatic, liver																			X						X	3
Mediastinum, mast cell tumor Malignant, metastatic, bone marrow				X																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye											+															1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	48
Adenoma						X					X	X			X						X			X		9
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	465	548	581	592	597	611	620	641	653	653	680	725	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	126	104	110	119	139	123	149	133	108	141	137	150	109	112	113	114	115	116	124	125	128	130	131	132	134
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	A	A	+	A	M	+	+	A	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Intestine large, colon	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	A	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X														
Intestine small, duodenum	A	+	A	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, jejunum	A	+	A	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Hepatocellular carcinoma		X						X	X	X		X								X					
Hepatocellular carcinoma, multiple			X	X		X																			
Hepatocellular adenoma					X									X		X									
Hepatocellular adenoma, multiple				X			X																X		
Mesentery							+				+			+	+	+	+	+			+		+		
Sarcoma							X																		
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X														X				
Stomach, glandular	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth										+	+		+	+	+	+	+	+	+		+		+		+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver												X													
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Parathyroid gland	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	135	138	140	144	146	147	101	102	103	105	106	107	111	117	118	120	121	122	127	129	136	142	143	145	148	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	I	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma														X												1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X	X			X																			4
Hepatocellular carcinoma														X	X		X	X		X						11
Hepatocellular carcinoma, multiple					X																					4
Hepatocellular adenoma		X	X	X										X	X		X								X	10
Hepatocellular adenoma, multiple												X									X					5
Mesentery	+	+				+		+	+	+	+				+						+		+	+		20
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+		+	+	+	+	+	+	+	+	+			+			+		+	+	+	+		30
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																							X			2
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	M	M	M	+	+	M	M	+	I	+	+	M	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	465	548	581	592	597	611	620	641	653	653	680	725	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	126	104	110	119	139	123	149	133	108	141	137	150	109	112	113	114	115	116	124	125	128	130	131	132	134
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X	X															
Sarcoma																									
Lymph node																									
Lymph node, mandibular	M	M	+	M	+	+	M	M	+	M	M	M	+	+	+	+	+	M	M	+	M	M	+	+	+
Lymph node, mesenteric	+	+	A	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery							X																		
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X										X		X			X				X			
Alveolar/bronchiolar carcinoma							X									X			X						
Hepatocellular carcinoma, metastatic, liver			X	X		X		X				X								X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+								
Harderian gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X		X					X			
Carcinoma																									
Bilateral, adenoma																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	3	3	4	4	4	4	0	0	0	0	0	0	1	1	1	2	2	2	2	2	3	4	4	4	4	Tissues/
	5	8	0	4	6	7	1	2	3	5	6	7	1	7	8	0	1	2	7	9	6	2	3	5	8	Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										2
Sarcoma													X													1
Lymph node															+											1
Lymph node, mandibular	+	M	+	+	+	+	M	M	+	+	+	+	+	M	M	+	+	+	M	M	M	+	+	+	+	30
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Sarcoma, metastatic, mesentery																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma					X																					1
Thymus	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	M	+	M	+	+	+	+	+	M	M	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	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X				X	X														8
Alveolar/bronchiolar carcinoma		X							X																	5
Hepatocellular carcinoma, metastatic, liver					X									X				X		X						10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																									+	2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X														4
Carcinoma																									X	1
Bilateral, adenoma								X																		1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	465	548	581	592	597	611	620	641	653	653	680	725	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	126	104	110	119	139	123	149	133	108	141	137	150	109	112	113	114	115	116	124	125	128	130	131	132	134
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Transitional epithelium, papilloma																								X	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	135	138	140	144	146	147	101	102	103	105	106	107	111	117	118	120	121	122	127	129	136	142	143	145	148	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant															X			X								2

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	011	017	483	492	498	539	576	584	590	617	621	626	631	646	657	658	668	676	695	721	730	730	730	730	730
Carcass ID Number	190	157	162	176	182	171	165	200	167	160	154	163	188	158	155	159	178	151	191	179	153	161	164	170	172
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	A	+	A	+	+	+	A	A	M	+	A	A	A	M	A	A	+	M	+	+	+	+
Intestine large, colon	+	A	+	+	+	A	+	+	+	A	+	+	A	+	A	A	+	A	A	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	A	A	+	+	A	+	A	A	+	+	+	+	+	+
Intestine large, cecum	+	A	A	A	+	A	+	+	+	A	A	+	A	+	A	A	+	A	A	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	A	+	+	+	A	A	+	A	+	A	A	+	A	A	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	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	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X					X	X		X							X				
Hepatocellular carcinoma			X	X	X			X	X						X	X									
Hepatocellular carcinoma, multiple										X							X								
Hepatocellular adenoma			X								X														
Hepatocellular adenoma, multiple							X						X					X			X		X		
Histiocytic sarcoma																			X	X					
Mesentery													+								+				+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Tooth											+					+				+		+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X														
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number	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	Total
	7	7	8	8	8	9	9	9	9	9	9	5	5	6	6	6	7	7	8	8	8	8	8	9	9	Tissues/
	3	7	0	4	5	2	4	5	7	8	9	2	6	6	8	9	4	5	1	3	6	7	9	3	6	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	34
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Polyp adenomatous													X													1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X											X	X						X	9
Hepatocellular carcinoma																X			X	X		X				11
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma			X					X	X				X				X					X	X		X	10
Hepatocellular adenoma, multiple	X			X			X				X										X					10
Histiocytic sarcoma																										2
Mesentery								+				+	+		+						+		+	+		10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Tooth		+	+		+	+	+	+	+	+	+			+				+			+	+	+	+	+	23
Cardiovascular System																										
Blood vessel															+											1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	I	+	+	+	+	+	M	+	+	+	+	+	M	I	+	+	+	+	M	+	+	+	+	M	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars intermedia, adenoma							X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	0	0	4	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	1	1	8	9	9	3	7	8	9	1	2	2	3	4	5	5	6	7	9	2	3	3	3	3	3
	1	7	3	2	8	9	6	4	0	7	1	6	1	6	7	8	8	6	5	1	0	0	0	0	0
Carcass ID Number	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	9	5	6	7	8	7	6	0	6	6	5	6	8	5	5	5	7	5	9	7	5	6	6	7	7
	0	7	2	6	2	1	5	0	7	0	4	3	8	8	5	9	8	1	1	9	3	1	4	0	2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma														X					X						
Lymph node																									
Lymph node, mandibular	+	+	+	+	M	M	M	+	M	+	+	+	+	M	M	M	M	+	+	+	+	+	+	M	M
Lymph node, mesenteric	+	A	+	A	+	+	+	+	+	+	A	+	A	+	A	A	+	A	A	M	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Histiocytic sarcoma																			X						
Thymus	+	+	+	+	M	M	+	M	M	M	+	+	+	M	+	M	+	M	M	M	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																	+								
Alveolar/bronchiolar carcinoma, metastatic, lung																	X								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland								X																	
Spinal cord																									+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X	X	X	X									
Alveolar/bronchiolar carcinoma																	X	X							
Hepatocellular carcinoma, metastatic, liver				X					X						X		X								
Nose	+	A	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	A	+	+	+	+	+	+
Pleura																	+								
Alveolar/bronchiolar carcinoma, metastatic, lung																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	0	0	0	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	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	7	7	8	8	8	9	9	9	9	9	9	5	5	6	6	6	7	7	8	8	8	8	8	9	9	Tissues/
	3	7	0	4	5	2	4	5	7	8	9	2	6	6	8	9	4	5	1	3	6	7	9	3	6	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								1
Histiocytic sarcoma																										2
Lymph node						+																				1
Lymph node, mandibular	+	+	M	+	+	+	+	M	M	+	+	M	+	+	+	M	+	+	+	M	M	M	M	+	M	30
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Hemangiosarcoma																			X							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																		X								2
Histiocytic sarcoma																										1
Thymus	M	M	+	+	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	33
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma									X																	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																5
Alveolar/bronchiolar carcinoma							X										X									4
Hepatocellular carcinoma, metastatic, liver																						X				5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pleura																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	011	017	483	492	498	539	576	584	590	617	621	626	631	646	657	658	668	676	695	721	730	730	730	730	730
Carcass ID Number	190	157	162	176	182	171	165	200	167	160	154	163	188	158	155	159	178	151	191	179	153	161	164	170	172
Special Senses System																									
Eye								+																	
Harderian gland	+	+	+	+	+	+	+	+	M	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Adenoma						X				X								X				X			
Carcinoma								X																	
Zymbal's gland	+																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X					X	X					
Lymphoma malignant																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	173	177	180	184	185	192	194	195	197	198	199	152	156	166	168	169	174	175	181	183	186	187	189	193	196	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma										X							X									6
Carcinoma							X																			2
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Lymphoma malignant		X			X	X					X															4

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	6/50 (12%)	9/50 (18%)	5/50 (10%)	6/50 (12%)
Adjusted rate[b]	13.1%	20.3%	11.0%	14.3%
Terminal rate[c]	5/39 (13%)	7/40 (18%)	5/38 (13%)	3/30 (10%)
First incidence (days)	606	688	730 (T)	539
Poly-3 test[d]	P=0.480N	P=0.261	P=0.510N	P=0.557
Harderian Gland: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	9/50 (18%)	6/50 (12%)	8/50 (16%)
Adjusted rate	13.1%	20.3%	13.2%	18.8%
Terminal rate	5/39 (13%)	7/40 (18%)	6/38 (16%)	4/30 (13%)
First incidence (days)	606	688	730 (T)	539
Poly-3 test	P=0.398	P=0.261	P=0.611	P=0.327
Small Intestine (Jejunum): Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	8.7%	2.3%	0.0%	0.0%
Terminal rate	3/39 (8%)	1/40 (3%)	0/38 (0%)	0/30 (0%)
First incidence (days)	590	730 (T)	—[e]	—
Poly-3 test	P=0.056N	P=0.191N	P=0.062N	P=0.077N
Small Intestine (Duodenum or Jejunum): Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	8.7%	2.3%	2.2%	0.0%
Terminal rate	3/39 (8%)	1/40 (3%)	1/38 (3%)	0/30 (0%)
First incidence (days)	590	730 (T)	730 (T)	—
Poly-3 test	P=0.074N	P=0.191N	P=0.183N	P=0.077N
Liver: Hemangiosarcoma				
Overall rate	2/50 (4%)	0/50 (0%)	4/50 (8%)	9/50 (18)%
Adjusted rate	4.4%	0.0%	8.8%	21.2%
Terminal rate	1/39 (3%)	0/40 (0%)	4/38 (11%)	5/30 (17%)
First incidence (days)	646	—	730 (T)	539
Poly-3 test	P=0.001	P=0.246N	P=0.332	P=0.017
Liver: Hepatocellular Adenoma				
Overall rate	19/50 (38%)	15/50 (30%)	15/50 (30%)	20/50 (40%)
Adjusted rate	40.0%	33.4%	32.1%	46.5%
Terminal rate	15/39 (39%)	14/40 (35%)	12/38 (32%)	15/30 (50%)
First incidence (days)	420	455	592	483
Poly-3 test	P=0.195	P=0.328N	P=0.280N	P=0.342
Liver: Hepatocellular Carcinoma				
Overall rate	11/50 (22%)	13/50 (26%)	15/50 (30%)	13/50 (26%)
Adjusted rate	23.5%	28.8%	31.1%	28.8%
Terminal rate	8/39 (21%)	10/40 (25%)	7/38 (18%)	4/30 (13%)
First incidence (days)	590	508	548	483
Poly-3 test	P=0.407	P=0.365	P=0.273	P=0.365
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	23/50 (46%)	23/50 (46%)	26/50 (52%)	31/50 (62%)
Adjusted rate	48.0%	50.2%	53.0%	66.6%
Terminal rate	18/39 (46%)	19/40 (48%)	16/38 (42%)	18/30 (60%)
First incidence (days)	420	455	548	483
Poly-3 test	P=0.031	P=0.498	P=0.386	P=0.049

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	12/50 (24%)	14/50 (28%)	15/50 (30%)	13/50 (26%)
Adjusted rate	25.6%	30.4%	31.1%	28.8%
Terminal rate	9/39 (23%)	10/40 (25%)	7/38 (18%)	4/30 (13%)
First incidence (days)	590	346	548	483
Poly-3 test	P=0.498	P=0.387	P=0.357	P=0.455
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	24/50 (48%)	24/50 (48%)	26/50 (52%)	31/50 (62%)
Adjusted rate	50.1%	51.3%	53.0%	66.6%
Terminal rate	19/39 (49%)	19/40 (48%)	16/38 (42%)	18/30 (60%)
First incidence	420	346	548	483
Poly-3 test	P=0.047	P=0.533	P=0.467	P=0.074
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	10/50 (20%)	3/50 (6%)	8/50 (16%)	5/50 (10%)
Adjusted rate	21.6%	6.8%	17.5%	11.9%
Terminal rate	8/39 (21%)	3/40 (8%)	7/38 (18%)	1/30 (3%)
First incidence (days)	599	730 (T)	581	631
Poly-3 test	P=0.331N	P=0.042N	P=0.405N	P=0.175N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adjusted rate	10.9%	6.8%	10.9%	9.7%
Terminal rate	4/39 (10%)	3/40 (8%)	4/38 (11%)	2/30 (7%)
First incidence (days)	606	730 (T)	620	668
Poly-3 test	P=0.559	P=0.379N	P=0.627	P=0.567N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	14/50 (28%)	5/50 (10%)	13/50 (26%)	9/50 (18%)
Adjusted rate	30.0%	11.3%	28.1%	21.2%
Terminal rate	11/39 (28%)	5/40 (13%)	11/38 (29%)	3/30 (10%)
First incidence (days)	599	730 (T)	581	631
Poly-3 test	P=0.466N	P=0.025N	P=0.512N	P=0.239N
All Organs: Hemangiosarcoma				
Overall rate	6/50 (12%)	0/50 (0%)	7/50 (14%)	9/50 (18%)
Adjusted rate	13.0%	0.0%	15.2%	21.2%
Terminal rate	4/39 (10%)	0/40 (0%)	5/38 (13%)	5/30 (17%)
First incidence (days)	590	—	653	539
Poly-3 test	P=0.026	P=0.018N	P=0.493	P=0.227
All Organs: Benign Neoplasms				
Overall rate	29/50 (58%)	24/50 (48%)	29/50 (58%)	27/50 (54%)
Adjusted rate	60.6%	53.2%	61.1%	60.2%
Terminal rate	24/39 (62%)	21/40 (53%)	24/38 (63%)	17/30 (57%)
First incidence (days)	420	455	581	483
Poly-3 test	P=0.450	P=0.305N	P=0.562	P=0.569N
All Organs: Malignant Neoplasms				
Overall rate	24/50 (48%)	20/50 (40%)	27/50 (54%)	30/50 (60%)
Adjusted rate	50.3%	42.6%	55.3%	63.6%
Terminal rate	18/39 (46%)	15/40 (38%)	17/38 (45%)	14/30 (47%)
First incidence (days)	590	311	548	483
Poly-3 test	P=0.044	P=0.296N	P=0.384	P=0.132

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	38/50 (76%)	32/50 (64%)	41/50 (82%)	42/50 (84%)
Adjusted rate	77.8%	67.1%	83.2%	87.5%
Terminal rate	30/39 (77%)	25/40 (63%)	30/38 (79%)	24/30 (80%)
First incidence (days)	420	311	548	483
Poly-3 test	P=0.039	P=0.168N	P=0.336	P=0.159

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparison between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

Table C4
Historical Incidence of Liver Neoplasms in Control Male B6C3F$_1$ Mice

Study	Incidence in Controls: Hemangiosarcoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]				
Acrylonitrile (gavage)	2/50	23/50	14/50	32/50
trans-Cinnamaldehyde (feed)	0/100	14/100	13/100	26/100
Citral (feed)	2/100	20/100	13/100	28/100
Decalin (inhalation)	1/50	22/50	10/50	28/50
p,p′-Dichlorodiphenyl sulfone (feed)	2/50	6/50	9/50	15/50
Dipropylene glycol (drinking water)	0/50	17/50	14/50	29/50
Elmiron® (gavage)	2/50	19/50	11/50	23/50
2,4-Hexadienal (gavage)	1/50	23/50	8/50	31/50
Indium phosphide (inhalation)	2/50	17/50	11/50	26/50
60-Hz Magnetic fields (whole body exposure)	4/100	30/100	19/100	46/100
Methacrylonitrile (gavage)	1/49	17/49	13/49	24/49
o-Nitrotoluene (feed)	1/60	18/60	12/60	27/60
p-Nitrotoluene (feed)	1/50	14/50	8/50	20/50
Riddelliine (gavage)	2/50	16/50	23/50	36/50
Sodium nitrite (drinking water)	2/50	19/50	9/50	24/50
Vanadium pentoxide (inhalation)	1/50	15/50	14/50	26/50
Overall Historical Incidence in Controls Given NTP-2000 Diet				
Total (%)	24/959 (2.5%)	290/959 (30.2%)	201/959 (21.0%)	441/959 (46.0%)
Mean ± standard deviation	2.6% ± 1.4%	31.9% ± 10.1%	22.1% ± 8.1%	48.4% ± 12.9%
Range	0%-4%	12%-46%	13%-46%	26%-72%

[a] Data as of January 30, 2002

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

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1		2
Moribund	7	4	4	3
Natural deaths	4	5	8	15
Survivors				
Terminal sacrifice	39	40	38	30
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Hyperplasia, squamous	1 (2%)			
Inflammation, acute		1 (2%)		
Inflammation, chronic active	1 (2%)			
Gallbladder	(40)	(38)	(39)	(34)
Cyst		1 (3%)	1 (3%)	
Degeneration, hyaline	3 (8%)	1 (3%)		1 (3%)
Inflammation, chronic active	1 (3%)			
Epithelium, hyperplasia			1 (3%)	
Intestine large, colon	(50)	(47)	(47)	(42)
Necrosis			1 (2%)	
Intestine large, rectum	(49)	(47)	(46)	(44)
Infiltration cellular, histiocyte				6 (14%)
Inflammation, acute			1 (2%)	
Inflammation, chronic active			1 (2%)	8 (18%)
Metaplasia, squamous				5 (11%)
Myxomatous change				13 (30%)
Necrosis				5 (11%)
Intestine large, cecum	(49)	(47)	(46)	(39)
Inflammation, chronic active				2 (5%)
Necrosis				1 (3%)
Intestine small, jejunum	(47)	(47)	(44)	(38)
Hyperplasia, lymphoid				1 (3%)
Mineralization		1 (2%)		
Necrosis		1 (2%)		
Intestine small, ileum	(46)	(47)	(43)	(38)
Inflammation, acute				1 (3%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus	14 (28%)	10 (20%)	5 (10%)	10 (20%)
Clear cell focus	21 (42%)	23 (46%)	19 (38%)	15 (30%)
Eosinophilic focus	13 (26%)	11 (22%)	9 (18%)	12 (24%)
Fatty change	9 (18%)	12 (24%)	8 (16%)	13 (26%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Infarct			1 (2%)	
Inflammation, chronic	11 (22%)	15 (30%)	23 (46%)	33 (66%)
Mineralization	1 (2%)			
Necrosis	2 (4%)	2 (4%)	2 (4%)	5 (10%)
Tension lipidosis	2 (4%)	2 (4%)	2 (4%)	
Vacuolization cytoplasmic, focal	1 (2%)			
Bile duct, cyst	1 (2%)			
Centrilobular, degeneration		1 (2%)	3 (6%)	4 (8%)

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

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Alimentary System (continued)				
Mesentery	(10)	(4)	(20)	(10)
Mineralization	1 (10%)			
Fat, necrosis	10 (100%)	3 (75%)	19 (95%)	10 (100%)
Pancreas	(50)	(50)	(49)	(50)
Atrophy		1 (2%)	1 (2%)	1 (2%)
Cyst			1 (2%)	
Artery, inflammation		1 (2%)		
Stomach, forestomach	(49)	(50)	(50)	(50)
Hyperplasia, squamous	6 (12%)		2 (4%)	3 (6%)
Inflammation, acute	1 (2%)			1 (2%)
Ulcer		1 (2%)		1 (2%)
Stomach, glandular	(49)	(49)	(48)	(46)
Hyperplasia		1 (2%)		
Inflammation, chronic active				1 (2%)
Mineralization				1 (2%)
Necrosis			1 (2%)	1 (2%)
Tooth	(33)	(27)	(30)	(23)
Inflammation, chronic active	6 (18%)	6 (22%)	5 (17%)	6 (26%)
Malformation	29 (88%)	22 (81%)	27 (90%)	20 (87%)
Cardiovascular System				
Blood vessel		(1)		(1)
Angiectasis		1 (100%)		
Thrombosis		1 (100%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	3 (6%)		1 (2%)	2 (4%)
Inflammation, suppurative			1 (2%)	
Mineralization	1 (2%)		1 (2%)	2 (4%)
Artery, inflammation, chronic active			3 (6%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Hyperplasia	5 (10%)	8 (16%)	8 (16%)	13 (27%)
Hypertrophy	27 (54%)	27 (54%)	23 (46%)	15 (31%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia		3 (6%)		1 (2%)
Vacuolization cytoplasmic			1 (2%)	
Pituitary gland	(47)	(48)	(49)	(48)
Pars distalis, hyperplasia			3 (6%)	2 (4%)
Thyroid gland	(48)	(49)	(50)	(49)
Follicular cell, hyperplasia				1 (2%)
General Body System				
None				
Genital System				
Preputial gland	(49)	(50)	(49)	(50)
Ectasia	3 (6%)	3 (6%)	5 (10%)	3 (6%)
Infiltration cellular, histiocyte				1 (2%)
Inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)	3 (6%)

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Genital System (continued)				
Prostate, NOS	(50)	(49)	(50)	(50)
Inflammation, chronic active			1 (2%)	1 (2%)
Inflammation, suppurative		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(49)
Congestion		1 (2%)		
Dilatation			5 (10%)	
Inflammation, chronic active			1 (2%)	2 (4%)
Inflammation, suppurative		1 (2%)		
Testes	(50)	(50)	(49)	(50)
Atrophy	1 (2%)			
Germinal epithelium, degeneration			1 (2%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Angiectasis		1 (2%)		1 (2%)
Lymph node	(1)	(1)	(1)	(1)
Mediastinal, infiltration cellular, histiocyte				1 (100%)
Lymph node, mesenteric	(48)	(46)	(45)	(41)
Angiectasis	3 (6%)		3 (7%)	
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage			1 (2%)	
Infiltration cellular, histiocyte		15 (33%)	34 (76%)	37 (90%)
Spleen	(49)	(50)	(49)	(49)
Amyloid deposition				1 (2%)
Hematopoietic cell proliferation	10 (20%)	8 (16%)	15 (31%)	15 (31%)
Infiltration cellular, mast cell				1 (2%)
Infiltration cellular, histiocyte		1 (2%)	1 (2%)	23 (47%)
Integumentary System				
Skin	(49)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Subcutaneous tissue, edema		1 (2%)		
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Mineralization				1 (2%)
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	7 (14%)	4 (8%)	4 (8%)
Alveolus, infiltration cellular, histiocyte	1 (2%)		1 (2%)	2 (4%)
Mediastinum, hemorrhage				1 (2%)
Mediastinum, inflammation, acute		1 (2%)		1 (2%)

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(47)
Inflammation, suppurative	5 (10%)		11 (22%)	2 (4%)
Polyp, inflammatory	1 (2%)			
Glands, degeneration, hyaline			1 (2%)	
Olfactory epithelium, atrophy		3 (6%)	1 (2%)	
Olfactory epithelium, hyperplasia			1 (2%)	
Olfactory epithelium, metaplasia		3 (6%)	1 (2%)	1 (2%)
Sinus, inflammation, chronic active			1 (2%)	
Trachea	(50)	(50)	(49)	(50)
Mineralization	1 (2%)			
Special Senses System				
Eye		(1)	(2)	(1)
Cornea, inflammation, chronic		1 (100%)	2 (100%)	
Harderian gland	(49)	(48)	(49)	(48)
Atrophy		1 (2%)	1 (2%)	
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute		1 (2%)	2 (4%)	
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Cyst			3 (6%)	1 (2%)
Hydronephrosis			1 (2%)	1 (2%)
Infarct	1 (2%)	3 (6%)	4 (8%)	
Infiltration cellular, mast cell				1 (2%)
Inflammation, suppurative		3 (6%)	3 (6%)	1 (2%)
Metaplasia, osseous	1 (2%)	1 (2%)		
Mineralization	1 (2%)			
Nephropathy	43 (86%)	41 (82%)	47 (94%)	41 (84%)
Papilla, necrosis		1 (2%)		
Renal tubule, hyperplasia			2 (4%)	
Urinary bladder	(50)	(49)	(49)	(49)
Artery, inflammation, chronic active			1 (2%)	
Transitional epithelium, hyperplasia		1 (2%)		

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

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Elmiron®[a]

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1		
Moribund	4	5	3	7
Natural deaths	8	6	10	9
Survivors				
Died last week of study		1		
Terminal sacrifice	37	37	37	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(39)	(40)	(38)	(38)
Sarcoma, metastatic, uterus			1 (3%)	
Intestine large, cecum	(41)	(43)	(44)	(43)
Leiomyoma				1 (2%)
Intestine small, duodenum	(41)	(44)	(42)	(42)
Polyp adenomatous		2 (5%)		1 (2%)
Intestine small, jejunum	(43)	(44)	(42)	(42)
Carcinoma	1 (2%)			
Intestine small, ileum	(42)	(44)	(42)	(42)
Liver	(50)	(49)	(50)	(49)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Hepatocellular carcinoma	3 (6%)	3 (6%)	5 (10%)	3 (6%)
Hepatocellular adenoma	6 (12%)	3 (6%)	2 (4%)	9 (18%)
Hepatocellular adenoma, multiple	1 (2%)	2 (4%)	2 (4%)	6 (12%)
Histiocytic sarcoma		3 (6%)	1 (2%)	2 (4%)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)		2 (4%)	
Sarcoma, metastatic, uterus			1 (2%)	
Mesentery	(30)	(34)	(32)	(42)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		1 (3%)		1 (2%)
Sarcoma		1 (3%)		
Sarcoma, metastatic, skin	1 (3%)	2 (6%)	2 (6%)	1 (2%)
Sarcoma, metastatic, uterus	1 (3%)		1 (3%)	
Pancreas	(46)	(45)	(46)	(46)
Sarcoma, metastatic, skin			1 (2%)	
Salivary glands	(49)	(49)	(50)	(48)
Stomach, forestomach	(47)	(48)	(49)	(48)
Sarcoma, metastatic, skin			1 (2%)	
Stomach, glandular	(46)	(45)	(44)	(46)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Pericardium, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Pericardium, sarcoma		1 (2%)		

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(48)
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, skin		1 (2%)		1 (2%)
Subcapsular, carcinoma			1 (2%)	
Adrenal medulla	(49)	(49)	(47)	(47)
Pheochromocytoma benign		1 (2%)		
Pituitary gland	(48)	(47)	(45)	(48)
Pars distalis, adenoma	2 (4%)	3 (6%)	4 (9%)	2 (4%)
Pars intermedia, adenoma			1 (2%)	1 (2%)
General Body System				
Peritoneum			(1)	
Sarcoma, metastatic, skin			1 (100%)	
Genital System				
Ovary	(47)	(46)	(47)	(48)
Cystadenoma	1 (2%)	1 (2%)	2 (4%)	
Hemangioma				2 (4%)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma		1 (2%)		1 (2%)
Luteoma		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Uterus	(48)	(49)	(50)	(50)
Histiocytic sarcoma		2 (4%)		
Polyp stromal	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Sarcoma	1 (2%)		1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(48)	(50)	(49)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)	3 (6%)
Lymph node	(6)	(10)	(5)	(10)
Bronchial, histiocytic sarcoma		2 (20%)		
Bronchial, osteosarcoma, metastatic, uncertain primary site			1 (20%)	
Lumbar, histiocytic sarcoma		1 (10%)		
Mediastinal, histiocytic sarcoma		2 (20%)		
Mediastinal, osteosarcoma, metastatic, uncertain primary site			1 (20%)	
Mediastinal, sarcoma, metastatic, skin	1 (17%)			
Pancreatic, sarcoma, metastatic, skin	1 (17%)			
Renal, sarcoma, metastatic, skin		1 (10%)		
Lymph node, mandibular	(33)	(38)	(37)	(39)
Histiocytic sarcoma		1 (3%)		
Lymph node, mesenteric	(47)	(44)	(42)	(45)
Histiocytic sarcoma		1 (2%)		1 (2%)
Sarcoma, metastatic, mesentery		1 (2%)		
Spleen	(47)	(48)	(47)	(46)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)
Thymus	(43)	(38)	(43)	(36)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Sarcoma, metastatic, skin				1 (3%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Sarcoma, metastatic, uterus			1 (2%)	
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		1 (2%)
Subcutaneous tissue, liposarcoma				1 (2%)
Subcutaneous tissue, myxoma				1 (2%)
Subcutaneous tissue, sarcoma	3 (6%)	4 (8%)	2 (4%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland			1 (2%)	
Osteosarcoma	1 (2%)			1 (2%)
Skeletal muscle	(2)		(2)	
Osteosarcoma, metastatic, uncertain primary site			1 (50%)	
Sarcoma, metastatic, uterus	1 (50%)			
Nervous System				
Brain	(50)	(49)	(50)	(50)
Histiocytic sarcoma		2 (4%)		
Meningioma malignant				1 (2%)
Oligodendroglioma benign	1 (2%)			
Sarcoma		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)		
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland			1 (2%)	2 (4%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		2 (4%)	2 (4%)
Histiocytic sarcoma		3 (6%)	1 (2%)	2 (4%)
Liposarcoma, metastatic, skin				1 (2%)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Sarcoma		1 (2%)		
Sarcoma, metastatic, skin		3 (6%)	2 (4%)	1 (2%)
Mediastinum, osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Pleura		(1)		
Sarcoma, metastatic, lung		1 (100%)		
Special Senses System				
Harderian gland	(48)	(41)	(50)	(46)
Adenoma	3 (6%)	3 (7%)	4 (8%)	3 (7%)
Carcinoma		2 (5%)	2 (4%)	2 (4%)
Bilateral, adenoma	1 (2%)			

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Urinary System				
Kidney	(48)	(49)	(48)	(46)
Histiocytic sarcoma		4 (8%)	1 (2%)	1 (2%)
Sarcoma, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skin		1 (2%)		
Transitional epithelium, carcinoma		1 (2%)		
Urinary bladder	(43)	(46)	(47)	(46)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		4 (8%)	1 (2%)	3 (6%)
Lymphoma malignant	7 (14%)	8 (16%)	6 (12%)	16 (32%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	29	34	29	40
Total primary neoplasms	39	50	41	64
Total animals with benign neoplasms	17	16	14	26
Total benign neoplasms	21	20	19	30
Total animals with malignant neoplasms	17	22	19	28
Total malignant neoplasms	18	30	22	34
Total animals with metastatic neoplasms	4	5	7	6
Total metastatic neoplasms	7	13	24	9
Total animals with malignant neoplasms of uncertain primary site			1	

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

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

Number of Days on Study	183	411	456	536	583	636	647	661	667	685	703	717	723	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	238	237	206	212	240	250	229	226	213	202	230	235	242	201	204	207	208	209	210	216	218	220	223	227	228
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	A	A	A	+	+	A	A	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	A	A	A	+	A	A	I	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	A	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	A	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	A	+	+	A	A	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma										X														X	
Hepatocellular adenoma				X											X										
Hepatocellular adenoma, multiple																									
Sarcoma, metastatic, skin												X													
Mesentery		+	+	+		+	+	+			+	+	+			+	+			+			+		
Sarcoma, metastatic, skin												X													
Sarcoma, metastatic, uterus							X																		
Pancreas	A	+	+	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel						+				+															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	+	+	+	M	+	M	I	+	M	+	+	+	M	+	+	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	A	+	+	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 Elmiron®: Vehicle Control

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	2 3 1	2 3 2	2 3 3	2 4 3	2 4 5	2 4 9	2 0 3	2 0 5	2 1 1	2 1 4	2 1 5	2 1 7	2 1 9	2 2 1	2 2 2	2 2 4	2 2 5	2 3 4	2 3 6	2 3 9	2 4 1	2 4 4	2 4 6	2 4 7	2 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Carcinoma			X																							1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Hepatocellular carcinoma			X																							3
Hepatocellular adenoma							X	X		X		X														6
Hepatocellular adenoma, multiple																			X							1
Sarcoma, metastatic, skin																										1
Mesentery	+		+	+				+	+		+	+	+	+	+			+	+		+	+	+	+	+	30
Sarcoma, metastatic, skin																										1
Sarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Pars distalis, adenoma						X		X																		2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
General Body System																										
None																										

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: Vehicle Control

Number of Days on Study	1	4	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	8	1	5	3	8	3	4	6	6	8	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2
	3	1	6	6	3	6	7	1	7	5	3	7	3	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	3	3	0	1	4	5	2	2	1	0	3	3	4	0	0	0	0	0	1	1	1	2	2	2	2
	8	7	6	2	0	0	9	6	3	2	0	5	2	1	4	7	8	9	0	6	8	0	3	7	8
Genital System																									
Clitoral gland	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Sarcoma							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+				+	+									+			
Mediastinal, sarcoma, metastatic, skin								X																	
Pancreatic, sarcoma, metastatic, skin												X													
Lymph node, mandibular	M	+	+	+	M	M	+	+	+	M	M	+	+	+	M	+	M	M	+	+	+	M	+	M	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	M	+	A	M	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma														X											
Subcutaneous tissue, sarcoma								X				X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																				X					
Skeletal muscle			+				+																		
Sarcoma, metastatic, uterus							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign						X																			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Bilateral, adenoma																									

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

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	
Carcass ID Number	231	232	233	243	245	249	203	205	211	214	215	217	219	221	222	224	225	234	236	239	241	244	246	247	248	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	M	+	M	+	M	+	+	+	+	M	+	M	+	+	+	+	I	+	+	+	+	+	39
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	47
Cystadenoma			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp stromal			X									X				X										3
Sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+			+																6
Mediastinal, sarcoma, metastatic, skin																										1
Pancreatic, sarcoma, metastatic, skin																										1
Lymph node, mandibular	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	33
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Subcutaneous tissue, sarcoma																							X			3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Sarcoma, metastatic, uterus																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma benign																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X				X																					2
Alveolar/bronchiolar carcinoma																				X						1
Hepatocellular carcinoma, metastatic, liver			X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Adenoma									X									X								3
Bilateral, adenoma												X														1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: Vehicle Control

Number of Days on Study	183	411	456	536	583	636	647	661	667	685	703	717	723	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	238	237	206	212	240	250	229	226	213	202	230	235	242	201	204	207	208	209	210	216	218	220	223	227	228
Urinary System																									
Kidney	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	A	+	M	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant													X									X	X		

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: Vehicle Control

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
Carcass ID Number	3	3	3	4	4	4	0	0	1	1	1	1	1	2	2	2	2	3	3	3	4	4	4	4	4	Tissues/
	1	2	3	3	5	9	3	5	1	4	5	7	9	1	2	4	5	4	6	9	1	4	6	7	8	Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant							X			X				X	X											7

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	018	281	485	541	555	642	681	681	703	703	711	722	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	283	290	281	289	280	297	267	270	255	299	296	272	252	253	254	259	261	263	264	266	268	269	271	279	285
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	A	+	A	+	+	+	M	A	A	+	+	+	+	+	+	+	+	M	M	+	+	+
Intestine large, colon	+	A	A	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	A	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																	X								
Intestine small, jejunum	+	A	A	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma												X										X			
Hepatocellular adenoma															X										
Hepatocellular adenoma, multiple																									X
Histiocytic sarcoma				X			X																		
Mesentery				+			+	+	+	+	+	+		+		+		+		+	+		+	+	+
Histiocytic sarcoma				X																					
Sarcoma											X														
Sarcoma, metastatic, skin								X																	
Pancreas	+	A	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Pericardium, alveolar/bronchiolar carcinoma, metastatic, lung												X													
Pericardium, sarcoma												X													
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Sarcoma, metastatic, skin																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	A	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	+	+	+	M	+	A	M	+	M	+	+	+	+	M	+	M	+	M	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X												X			
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
General Body System																									
Tissue NOS																		+							

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

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	286	288	291	294	295	298	300	251	256	257	258	260	262	265	273	274	275	276	277	278	282	284	287	292	293	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	44
Polyp adenomatous									X																	2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma		X																								1
Hepatocellular carcinoma							X																			3
Hepatocellular adenoma	X																								X	3
Hepatocellular adenoma, multiple																			X							2
Histiocytic sarcoma																					X					3
Mesentery	+	+	+	+	+	+	+	+	+	+		+		+		+	+		+	+	+			+	+	34
Histiocytic sarcoma																										1
Sarcoma																										1
Sarcoma, metastatic, skin			X																							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	45
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	45
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Pericardium, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Pericardium, sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin			X																							1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	45
Parathyroid gland	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma						X																				3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
General Body System																										
Tissue NOS																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	0	2	4	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	1	8	8	4	5	4	8	8	0	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	8	1	5	1	5	2	1	1	3	3	1	2	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	8	9	8	8	8	9	6	7	5	9	9	7	5	5	5	5	6	6	6	6	6	6	7	7	8
	3	0	1	9	0	7	7	0	5	9	6	2	2	3	4	9	1	3	4	6	8	9	1	9	5
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Cystadenoma															X										
Histiocytic sarcoma				X																					
Luteoma																								X	
Sarcoma, metastatic, mesentery											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X			X																		
Polyp stromal														X											
Hematopoietic System																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma							X																		
Lymph node		+	+	+							+	+						+							
Bronchial, histiocytic sarcoma				X								X													
Lumbar, histiocytic sarcoma				X																					
Mediastinal, histiocytic sarcoma												X													
Renal, sarcoma, metastatic, skin																									
Lymph node, mandibular	+	A	+	+	+	+	+	+	M	+	+	M	M	+	+	M	M	+	+	+	+	+	+	+	M
Histiocytic sarcoma				X																					
Lymph node, mesenteric	+	A	A	M	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Sarcoma, metastatic, mesentery											X														
Spleen	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	M	+	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma				X																					
Subcutaneous tissue, sarcoma					X			X	X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X			X																		
Sarcoma																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

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	286	288	291	294	295	298	300	251	256	257	258	260	262	265	273	274	275	276	277	278	282	284	287	292	293	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Ovary	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	46
Cystadenoma																										1
Histiocytic sarcoma																										1
Luteoma																										1
Sarcoma, metastatic, mesentery																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma		X																								1
Histiocytic sarcoma																										1
Lymph node			+														+	+			+					10
Bronchial, histiocytic sarcoma																										2
Lumbar, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																					X					2
Renal, sarcoma, metastatic, skin			X																							1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	M	M	+	+	38
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	44
Histiocytic sarcoma																										1
Sarcoma, metastatic, mesentery																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma		X																								1
Histiocytic sarcoma																					X					1
Thymus	+	+	M	+	M	+	M	M	+	+	+	M	M	+	+	+	+	+	+	+	A	+	+	+	+	38
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma			X																							4
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Sarcoma															X											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

Number of Days on Study	018	281	485	541	555	642	681	681	703	703	711	722	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	283	290	281	289	280	297	267	270	255	299	296	272	252	253	254	259	261	263	264	266	268	269	271	279	285
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar adenoma, multiple				X																					
Alveolar/bronchiolar carcinoma												X													
Histiocytic sarcoma				X			X																		
Sarcoma												X													
Sarcoma, metastatic, skin								X	X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Pleura												+													
Sarcoma, metastatic, lung												X													
Trachea	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X		X									
Carcinoma																									
Urinary System																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X			X					X													
Sarcoma, metastatic, mesentery											X														
Sarcoma, metastatic, skin									X																
Transitional epithelium, carcinoma															X										
Ureter		A																							
Urethra		+																							
Urinary bladder	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X			X					X													
Lymphoma malignant		X	X								X				X										

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 56 mg/kg

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	286	288	291	294	295	298	300	251	256	257	258	260	262	265	273	274	275	276	277	278	282	284	287	292	293	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																2
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										1
Histiocytic sarcoma																					X					3
Sarcoma																										1
Sarcoma, metastatic, skin			X																							3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Pleura																										1
Sarcoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Harderian gland	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	41
Adenoma												X														3
Carcinoma					X																	X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																					X					4
Sarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, skin																										1
Transitional epithelium, carcinoma																										1
Ureter																										
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																					X					4
Lymphoma malignant						X											X	X		X						8

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

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

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	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	341	345	347	349	350	306	309	310	311	312	314	316	320	321	323	324	325	326	328	332	336	340	342	343	346	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Sarcoma, metastatic, uterus																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Hepatocellular carcinoma	X	X														X		X								5
Hepatocellular adenoma																					X					2
Hepatocellular adenoma, multiple				X									X													2
Histiocytic sarcoma												X														1
Osteosarcoma, metastatic, uncertain primary site																										1
Sarcoma, metastatic, skin													X													2
Sarcoma, metastatic, uterus																										1
Mesentery	+	+		+	+	+		+			+		+	+	+	+	+	+	+		+	+	+	+		32
Sarcoma, metastatic, skin													X													2
Sarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, skin																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcapsular, carcinoma					X																					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	M	M	+	+	M	+	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Pars distalis, adenoma		X				X																				4
Pars intermedia, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
Peritoneum																										1
Sarcoma, metastatic, skin																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

	3	4	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	1	8	0	8	0	2	3	3	4	5	6	7	1	2	2	2	2	2	2	2	2	2	2	2	2
	3	1	9	9	3	1	8	8	7	3	7	7	7	9	9	9	9	9	9	9	9	9	9	9	9
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	0	1	2	3	2	4	0	1	2	4	3	3	1	0	0	0	0	0	1	1	3	3	3	3	3
	3	3	7	5	2	8	7	7	9	4	8	9	9	1	2	4	5	8	5	8	0	1	3	4	7
Genital System																									
Clitoral gland	I	I	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma										X				X											
Hemangiosarcoma																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																		X							
Sarcoma							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node			+	+		+					+				+										
Bronchial, osteosarcoma, metastatic, uncertain primary site				X																					
Mediastinal, osteosarcoma, metastatic, uncertain primary site				X																					
Lymph node, mandibular	M	+	+	+	+	M	+	M	+	+	+	M	M	M	+	M	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	M	+	+	A	+	A	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	A	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	A	+	M	+	+	+	+	M	A	+	+	+	+	+	M	M	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uterus							X																		
Subcutaneous tissue, hemangiosarcoma			X																						
Subcutaneous tissue, sarcoma													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland												X													
Skeletal muscle				+						+															
Osteosarcoma, metastatic, uncertain primary site				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	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	341	345	347	349	350	306	309	310	311	312	314	316	320	321	323	324	325	326	328	332	336	340	342	343	346	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	I	+	+	+	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	47
Cystadenoma																										2
Hemangiosarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																					X					2
Sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X														1
Lymph node																										5
Bronchial, osteosarcoma, metastatic, uncertain primary site																										1
Mediastinal, osteosarcoma, metastatic, uncertain primary site																										1
Lymph node, mandibular	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	37
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma												X														1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	43
Osteosarcoma, metastatic, uncertain primary site																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uterus																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma													X													2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Skeletal muscle																										2
Osteosarcoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	313	481	509	589	603	621	638	638	647	653	667	677	717	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	303	313	327	335	322	348	307	317	329	344	338	339	319	301	302	304	305	308	315	318	330	331	333	334	337
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma		X																							
Carcinoma, metastatic, harderian gland												X													
Hepatocellular carcinoma, metastatic, liver																							X		
Histiocytic sarcoma																									
Osteosarcoma, metastatic, uncertain primary site				X																					
Sarcoma, metastatic, skin													X												
Mediastinum, osteosarcoma, metastatic, uncertain primary site				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X	X									X	
Carcinoma												X													
Urinary System																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant			X			X					X														

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 168 mg/kg

Number of Days on Study	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	341	345	347	349	350	306	309	310	311	312	314	316	320	321	323	324	325	326	328	332	336	340	342	343	346	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X	X																						2
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																X										2
Histiocytic sarcoma												X														1
Osteosarcoma, metastatic, uncertain primary site																										1
Sarcoma, metastatic, skin													X													2
Mediastinum, osteosarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Special Senses System																										
Eye																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			4
Carcinoma																						X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X														1
Lymphoma malignant	X												X								X					6

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	401	509	517	579	621	645	652	660	661	683	698	701	703	708	717	723	729	729	729	729	729	729	729	729	729
Carcass ID Number	371	372	351	382	374	395	376	354	365	380	389	379	353	361	363	370	352	355	357	359	362	368	377	378	384
Alimentary System																									
Esophagus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	A	A	A	+	A	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	I	+	+	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	A	A	A	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, duodenum	M	+	A	+	+	A	A	A	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Polyp adenomatous												X													
Intestine small, jejunum	+	+	+	+	+	A	A	A	+	A	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	A	A	A	+	A	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X					X														
Hepatocellular carcinoma								X			X					X									
Hepatocellular adenoma			X		X				X			X						X						X	
Hepatocellular adenoma, multiple																			X		X				
Histiocytic sarcoma													X												
Mesentery				+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+
Hemangiosarcoma																									
Histiocytic sarcoma														X											
Sarcoma, metastatic, skin												X													
Pancreas	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin												X													
Adrenal medulla	+	+	+	+	+	A	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	A	+	+	+	+	M	M	+	+	+	A	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X															
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	388	390	391	394	396	398	399	400	356	358	360	364	366	367	369	373	375	381	383	385	386	387	392	393	397	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leiomyoma										X																1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma												X										X				4
Hepatocellular carcinoma																										3
Hepatocellular adenoma							X		X								X									9
Hepatocellular adenoma, multiple		X						X							X									X		6
Histiocytic sarcoma															X											2
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	42
Hemangiosarcoma																						X				1
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, skin																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	+	+	M	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma																					X					2
Pars intermedia, adenoma																							X			1
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
General Body System																										
None																										

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	4	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	1	7	2	4	5	6	6	8	9	0	0	0	1	2	2	2	2	2	2	2	2	2	2
	1	9	7	9	1	5	2	0	1	3	8	1	3	8	7	3	9	9	9	9	9	9	9	9	9
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	7	7	5	8	7	9	7	5	6	8	8	7	5	6	6	7	5	5	5	5	6	6	7	7	8
	1	2	1	2	4	5	6	4	5	0	9	9	3	1	3	0	2	5	7	9	2	8	7	8	4
Genital System																									
Clitoral gland	I	M	+	+	+	M	M	I	+	M	M	+	M	+	M	M	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Histiocytic sarcoma														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X	X											
Lymph node					+			+		+				A											
Lymph node, mandibular	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	A	+	A	M	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Thymus	M	+	+	+	+	A	+	A	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+
Sarcoma, metastatic, skin												X													
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma								X																	
Subcutaneous tissue, histiocytic sarcoma														X											
Subcutaneous tissue, liposarcoma																									
Subcutaneous tissue, myxoma																					X				
Subcutaneous tissue, sarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma															X										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma malignant				X																					
Peripheral nerve	+																								
Spinal cord	+																								

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	388	390	391	394	396	398	399	400	356	358	360	364	366	367	369	373	375	381	383	385	386	387	392	393	397	Total Tissues/ Tumors
Genital System																										
Clitoral gland	M	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	I	35
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma												X														2
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal													X													2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma															X											3
Lymph node		+							+	+					+			+	+						+	10
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	M	M	+	+	39
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma															X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Thymus	+	+	M	+	M	+	+	+	M	M	M	+	+	+	+	+	+	I	+	+	+	+	M	+	+	36
Sarcoma, metastatic, skin																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, liposarcoma											X															1
Subcutaneous tissue, myxoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma malignant																										1
Peripheral nerve																										1
Spinal cord																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	401	509	517	579	621	645	652	660	661	683	698	701	703	708	717	723	729	729	729	729	729	729	729	729	729
Carcass ID Number	371	372	351	382	374	395	376	354	365	380	389	379	353	361	363	370	352	355	357	359	362	368	377	378	384
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, harderian gland																									
Hepatocellular carcinoma, metastatic, liver								X								X									
Histiocytic sarcoma													X	X											
Liposarcoma, metastatic, skin																									
Sarcoma, metastatic, skin												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+			+
Adenoma	X																X								
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	A	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X	X											
Lymphoma malignant					X			X										X						X	

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Elmiron®: 504 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	388	390	391	394	396	398	399	400	356	358	360	364	366	367	369	373	375	381	383	385	386	387	392	393	397	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			1
Alveolar/bronchiolar carcinoma							X																			1
Carcinoma, metastatic, harderian gland			X																		X					2
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma																										2
Liposarcoma, metastatic, skin											X															1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye			+																		+					2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																X										3
Carcinoma			X																		X					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma															X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											3
Lymphoma malignant		X		X				X	X	X	X	X			X			X	X					X	X	16

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

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rate[b]	8.9%	6.6%	9.0%	6.5%
Terminal rate[c]	4/37 (11%)	3/38 (8%)	4/37 (11%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)	401
Poly-3 test[d]	P=0.470N	P=0.496N	P=0.641	P=0.486N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	5/50 (10%)	6/50 (12%)	5/50 (10%)
Adjusted rate	8.9%	11.1%	13.4%	10.9%
Terminal rate	4/37 (11%)	5/38 (13%)	5/37 (14%)	4/34 (12%)
First incidence (days)	729 (T)	729 (T)	677	401
Poly-3 test	P=0.520	P=0.505	P=0.369	P=0.516
Liver: Hemangiosarcoma				
Overall rate	1/50 (2%)	1/49 (2%)	1/50 (2%)	4/49 (8%)
Adjusted rate	2.2%	2.2%	2.2%	8.9%
Terminal rate	1/37 (3%)	1/38 (3%)	1/37 (3%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)	645
Poly-3 test	P=0.056	P=0.760N	P=0.760	P=0.177
Liver: Hepatocellular Adenoma				
Overall rate	7/50 (14%)	5/49 (10%)	4/50 (8%)	15/49 (31%)
Adjusted rate	15.4%	11.1%	8.9%	32.8%
Terminal rate	6/37 (16%)	5/38 (13%)	3/37 (8%)	11/34 (32%)
First incidence (days)	536	729 (T)	647	517
Poly-3 test	P=0.003	P=0.388N	P=0.267N	P=0.042
Liver: Hepatocellular Carcinoma				
Overall rate	3/50 (6%)	3/49 (6%)	5/50 (10%)	3/49 (6%)
Adjusted rate	6.7%	6.7%	11.2%	6.7%
Terminal rate	2/37 (5%)	2/38 (5%)	5/37 (14%)	0/34 (0%)
First incidence (days)	685	722	729 (T)	660
Poly-3 test	P=0.583N	P=0.661	P=0.352	P=0.659
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	10/50 (20%)	8/49 (16%)	9/50 (18%)	18/49 (37%)
Adjusted rate	21.9%	17.8%	20.0%	39.1%
Terminal rate	8/37 (22%)	7/38 (18%)	8/37 (22%)	11/34 (32%)
First incidence (days)	536	722	647	517
Poly-3 test	P=0.010	P=0.411N	P=0.514N	P=0.057
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	4.5%	6.6%	4.5%	2.2%
Terminal rate	2/37 (5%)	2/38 (5%)	2/37 (5%)	1/34 (3%)
First incidence (days)	729 (T)	541	729 (T)	729 (T)
Poly-3 test	P=0.303N	P=0.509	P=0.692	P=0.497N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate	6.7%	8.7%	6.6%	4.4%
Terminal rate	3/37 (8%)	2/38 (5%)	2/37 (5%)	2/34 (6%)
First incidence (days)	729 (T)	541	481	729 (T)
Poly-3 test	P=0.335N	P=0.511	P=0.657N	P=0.497N

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	2/48 (4%)	3/47 (6%)	4/45 (9%)	2/48 (4%)
Adjusted rate	4.6%	7.1%	9.8%	4.6%
Terminal rate	2/36 (6%)	2/37 (5%)	4/36 (11%)	1/34 (3%)
First incidence (days)	729 (T)	703	729 (T)	683
Poly-3 test	P=0.497N	P=0.493	P=0.313	P=0.690N
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	3/50 (6%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.6%	8.7%	4.5%	2.2%
Terminal rate	1/37 (3%)	1/38 (3%)	1/37 (3%)	0/34 (0%)
First incidence (days)	661	555	717	701
Poly-3 test	P=0.165N	P=0.510	P=0.504N	P=0.304N
Skin (Subcutaneous Tissue): Myxoma or Sarcoma				
Overall rate	3/50 (6%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.6%	8.7%	4.5%	4.4%
Terminal rate	1/37 (3%)	1/38 (3%)	1/37 (3%)	1/34 (3%)
First incidence (days)	661	555	717	701
Poly-3 test	P=0.338N	P=0.510	P=0.504N	P=0.499N
Uterus: Stromal Polyp				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.7%	2.2%	4.5%	4.4%
Terminal rate	3/37 (8%)	1/38 (3%)	2/37 (5%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.580N	P=0.303N	P=0.502N	P=0.497N
All Organs: Hemangioma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	6.6%
Terminal rate	0/37 (0%)	0/38 (0%)	0/37 (0%)	2/34 (6%)
First incidence (days)	—[e]	—	—	660
Poly-3 test	P=0.008	—[f]	—	P=0.121
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted rate	2.2%	2.2%	6.6%	8.8%
Terminal rate	1/37 (3%)	1/38 (3%)	2/37 (5%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	509	645
Poly-3 test	P=0.093	P=0.759N	P=0.309	P=0.184
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	6/50 (12%)
Adjusted rate	2.2%	2.2%	6.6%	13.1%
Terminal rate	1/37 (3%)	1/38 (3%)	2/37 (5%)	3/34 (9%)
First incidence (days)	729 (T)	729 (T)	509	645
Poly-3 test	P=0.013	P=0.759N	P=0.309	P=0.059
All Organs: Histiocytic Sarcoma				
Overall rate	0/50 (0%)	4/50 (8%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	8.7%	2.2%	6.6%
Terminal rate	0/37 (0%)	1/38 (3%)	1/37 (3%)	1/34 (3%)
First incidence (days)	—	541	729 (T)	703
Poly-3 test	P=0.307	P=0.064	P=0.499	P=0.121

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
All Organs: Malignant Lymphoma				
Overall rate	7/50 (14%)	8/50 (16%)	6/50 (12%)	16/50 (32%)
Adjusted rate	15.6%	17.1%	13.1%	34.9%
Terminal rate	6/37 (16%)	5/38 (13%)	3/37 (8%)	14/34 (41%)
First incidence (days)	723	281	509	621
Poly-3 test	P=0.006	P=0.537	P=0.482N	P=0.028
All Organs: Benign Neoplasms				
Overall rate	17/50 (34%)	16/50 (32%)	14/50 (28%)	26/50 (52%)
Adjusted rate	37.1%	34.9%	30.9%	54.3%
Terminal rate	15/37 (41%)	14/38 (37%)	12/37 (32%)	19/34 (56%)
First incidence (days)	536	541	647	401
Poly-3 test	P=0.019	P=0.497N	P=0.344N	P=0.068
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	22/50 (44%)	20/50 (40%)	28/50 (56%)
Adjusted rate	37.2%	45.3%	41.9%	59.4%
Terminal rate	12/37 (32%)	13/38 (34%)	12/37 (32%)	18/34 (53%)
First incidence (days)	647	281	481	579
Poly-3 test	P=0.023	P=0.279	P=0.401	P=0.024
All Organs: Benign or Malignant Neoplasms				
Overall rate	29/50 (58%)	34/50 (68%)	30/50 (60%)	40/50 (80%)
Adjusted rate	62.2%	69.8%	62.1%	81.5%
Terminal rate	22/37 (60%)	24/38 (63%)	20/37 (54%)	26/34 (77%)
First incidence (days)	536	281	481	401
Poly-3 test	P=0.027	P=0.284	P=0.579N	P=0.026

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pituitary gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparison between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

Table D4a
Historical Incidence of Hemangioma or Hemangiosarcoma (All Organs) in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
Acrylonitrile (gavage)	0/50	4/50	4/50
trans-Cinnamaldehyde (feed)	4/100	1/100	5/100
Citral (feed)	1/99	0/99	1/99
Decalin (inhalation)	1/50	1/50	2/50
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	0/50	0/50
Dipropylene glycol (drinking water)	2/50	3/50	5/50
Elmiron® (gavage)	0/50	1/50	1/50
2,4-Hexadienal (gavage)	0/50	1/50	1/50
Indium phosphide (inhalation)	1/50	3/50	4/50
60-Hz Magnetic fields (whole body exposure)	0/100	2/100	2/100
Methacrylonitrile (gavage)	2/50	2/50	4/50
o-Nitrotoluene (feed)	3/60	0/60	3/60
p-Nitrotoluene (feed)	1/50	1/50	2/50
Riddelliine (gavage)	0/50	0/50	0/50
Sodium nitrite (drinking water)	0/50	1/50	1/50
Vanadium pentoxide (inhalation)	0/50	2/50	2/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	15/959 (1.6%)	22/959 (2.3%)	37/959 (3.9%)
Mean ± standard deviation	1.5% ± 1.8%	2.6% ± 2.4%	4.1% ± 3.1%
Range	0%-5%	0%-8%	0%-10%

[a] Data as of January 30, 2002

Table D4b
Historical Incidence of Liver Neoplasms in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls			
	Hemangiosarcoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]				
Acrylonitrile (gavage)	2/50	14/50	7/50	20/50
trans-Cinnamaldehyde (feed)	0/99	7/99	3/99	9/99
Citral (feed)	0/99	8/99	4/99	12/99
Decalin (inhalation)	0/50	7/50	4/50	11/50
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	4/50	3/50	6/50
Dipropylene glycol (drinking water)	2/50	11/50	7/50	17/50
Elmiron® (gavage)	1/50	7/50	3/50	10/50
2,4-Hexadienal (gavage)	0/50	11/50	3/50	13/50
Indium phosphide (inhalation)	0/50	12/50	6/50	18/50
60-Hz Magnetic fields (whole body exposure)	1/98	17/98	6/98	22/98
Methacrylonitrile (gavage)	0/50	9/50	2/50	10/50
o-Nitrotoluene (feed)	0/60	7/60	2/60	9/60
p-Nitrotoluene (feed)	0/49	6/49	3/49	8/49
Riddelliine (gavage)	0/49	9/49	8/49	16/49
Sodium nitrite (drinking water)	0/50	9/50	2/50	10/50
Vanadium pentoxide (inhalation)	0/50	6/50	6/50	12/50
Overall Historical Incidence in Controls Given NTP-2000 Diet				
Total (%)	6/954 (0.6%)	144/954 (15.1%)	69/954 (7.2%)	203/954 (21.3%)
Mean ± standard deviation	0.7% ± 1.4%	15.9% ± 6.1%	7.8% ± 4.4%	22.6% ± 9.1%
Range	0%-4%	7%-28%	3%-16%	9%-40%

[a] Data as of January 30, 2002

TABLE D4c
Historical Incidence of Malignant Lymphoma in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
Acrylonitrile (gavage)	4/50
trans-Cinnamaldehyde (feed)	23/100
Citral (feed)	7/99
Decalin (inhalation)	11/50
p,p′-Dichlorodiphenyl sulfone (feed)	6/50
Dipropylene glycol (drinking water)	5/50
Elmiron® (gavage)	7/50
2,4-Hexadienal (gavage)	4/50
Indium phosphide (inhalation)	8/50
60-Hz Magnetic fields (whole body exposure)	32/100
Methacrylonitrile (gavage)	9/50
o-Nitrotoluene (feed)	8/60
p-Nitrotoluene (feed)	3/50
Riddelliine (gavage)	7/50
Sodium nitrite (drinking water)	7/50
Vanadium pentoxide (inhalation)	7/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	148/959 (15.4%)
Mean ± standard deviation	14.5% ± 6.8%
Range	6%-32%

[a] Data as of January 30, 2002; includes data for histiocytic, lymphocytic, mixed, unspecified, or undifferentiated cell type lymphomas

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Elmiron®[a]

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1		
Moribund	4	5	3	7
Natural deaths	8	6	10	9
Survivors				
Died last week of study		1		
Terminal sacrifice	37	37	37	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Inflammation, chronic active				1 (2%)
Necrosis		1 (2%)		
Gallbladder	(39)	(40)	(38)	(38)
Cyst		2 (5%)	1 (3%)	1 (3%)
Degeneration, hyaline	1 (3%)	1 (3%)	3 (8%)	2 (5%)
Intestine large, colon	(45)	(44)	(44)	(46)
Necrosis				1 (2%)
Intestine large, rectum	(45)	(45)	(44)	(46)
Infiltration cellular, histiocyte			2 (5%)	10 (22%)
Inflammation, acute	1 (2%)			
Inflammation, chronic active			2 (5%)	32 (70%)
Metaplasia, squamous			1 (2%)	26 (57%)
Myxomatous change		3 (7%)	21 (48%)	31 (67%)
Necrosis			1 (2%)	24 (52%)
Intestine large, cecum	(41)	(43)	(44)	(43)
Inflammation, granulomatous			1 (2%)	
Necrosis			1 (2%)	
Ulcer				1 (2%)
Intestine small, jejunum	(43)	(44)	(42)	(42)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Inflammation, acute	1 (2%)			1 (2%)
Intestine small, ileum	(42)	(44)	(42)	(42)
Infiltration cellular, mixed cell				1 (2%)
Liver	(50)	(49)	(50)	(49)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Basophilic focus	5 (10%)	6 (12%)	8 (16%)	12 (24%)
Clear cell focus		4 (8%)	1 (2%)	21 (43%)
Cyst	1 (2%)	1 (2%)		
Eosinophilic focus	10 (20%)	6 (12%)	7 (14%)	15 (31%)
Fatty change	4 (8%)	2 (4%)	1 (2%)	12 (24%)
Hematopoietic cell proliferation	3 (6%)	7 (14%)	5 (10%)	7 (14%)
Infarct	1 (2%)			
Inflammation, chronic	40 (80%)	37 (76%)	40 (80%)	38 (78%)
Mineralization	1 (2%)		1 (2%)	
Tension lipidosis		2 (4%)	1 (2%)	
Bile duct, hyperplasia		1 (2%)		
Centrilobular, degeneration			1 (2%)	1 (2%)
Centrilobular, necrosis				1 (2%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Alimentary System (continued)				
Mesentery	(30)	(34)	(32)	(42)
Inflammation, chronic active				1 (2%)
Inflammation, suppurative	1 (3%)			
Thrombosis				1 (2%)
Artery, inflammation, chronic active	1 (3%)			
Fat, necrosis	29 (97%)	33 (97%)	31 (97%)	41 (98%)
Pancreas	(46)	(45)	(46)	(46)
Atrophy	1 (2%)			1 (2%)
Basophilic focus		2 (4%)		1 (2%)
Inflammation, acute	1 (2%)			
Lipomatosis		1 (2%)		
Artery, inflammation	1 (2%)			
Salivary glands	(49)	(49)	(50)	(48)
Atrophy			1 (2%)	
Basophilic focus	1 (2%)	1 (2%)		
Infiltration cellular, lymphocyte			2 (4%)	
Stomach, forestomach	(47)	(48)	(49)	(48)
Hyperplasia, squamous	2 (4%)	2 (4%)	2 (4%)	
Inflammation, acute		1 (2%)		
Ulcer	3 (6%)			
Artery, inflammation, chronic active	1 (2%)			
Stomach, glandular	(46)	(45)	(44)	(46)
Hyperplasia		1 (2%)		
Mineralization	1 (2%)			
Necrosis		1 (2%)		
Artery, inflammation, chronic active	1 (2%)			
Cardiovascular System				
Blood vessel	(2)			
Aorta, mineralization	1 (50%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)	2 (4%)	1 (2%)	
Inflammation, suppurative		1 (2%)		
Mineralization	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(48)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	5 (10%)	3 (6%)	2 (4%)	2 (4%)
Hypertrophy	1 (2%)	3 (6%)	3 (6%)	12 (25%)
Necrosis				1 (2%)
Pituitary gland	(48)	(47)	(45)	(48)
Hyperplasia	1 (2%)			
Pars distalis, hyperplasia	11 (23%)	8 (17%)	10 (22%)	11 (23%)
Pars intermedia, hypertrophy	1 (2%)			
Thyroid gland	(46)	(47)	(49)	(46)
Necrosis		1 (2%)		
Follicular cell, hyperplasia		1 (2%)		
General Body System				
None				

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Genital System				
Clitoral gland	(39)	(44)	(42)	(35)
Cyst		1 (2%)		
Inflammation, chronic active	1 (3%)	1 (2%)		
Ovary	(47)	(46)	(47)	(48)
Angiectasis	1 (2%)			2 (4%)
Cyst	10 (21%)	12 (26%)	8 (17%)	7 (15%)
Thrombosis		1 (2%)		
Uterus	(48)	(49)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hydrometra	27 (56%)	21 (43%)	25 (50%)	20 (40%)
Hyperplasia, cystic	8 (17%)	9 (18%)	8 (16%)	10 (20%)
Inflammation, suppurative	2 (4%)			
Hematopoietic System				
Bone marrow	(50)	(48)	(50)	(49)
Atrophy				1 (2%)
Necrosis			1 (2%)	
Lymph node	(6)	(10)	(5)	(10)
Bronchial, hyperplasia, lymphoid		1 (10%)		
Mediastinal, hyperplasia, lymphoid		1 (10%)	1 (20%)	
Pancreatic, hyperplasia, lymphoid				1 (10%)
Renal, hyperplasia, lymphoid		1 (10%)		
Lymph node, mandibular	(33)	(38)	(37)	(39)
Hyperplasia, lymphoid	1 (3%)	1 (3%)	3 (8%)	
Infiltration cellular, plasma cell		1 (3%)	1 (3%)	2 (5%)
Infiltration cellular, histiocyte				3 (8%)
Lymph node, mesenteric	(47)	(44)	(42)	(45)
Hemorrhage			1 (2%)	3 (7%)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	3 (7%)	
Infiltration cellular, plasma cell	1 (2%)		1 (2%)	2 (4%)
Infiltration cellular, histiocyte		23 (52%)	35 (83%)	25 (56%)
Spleen	(47)	(48)	(47)	(46)
Congestion		1 (2%)		1 (2%)
Hematopoietic cell proliferation	10 (21%)	19 (40%)	15 (32%)	18 (39%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)		
Infiltration cellular, histiocyte		3 (6%)	12 (26%)	28 (61%)
Metaplasia, osseous				2 (4%)
Thymus	(43)	(38)	(43)	(36)
Hyperplasia, lymphoid	1 (2%)			
Necrosis		1 (3%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Edema		1 (2%)		
Inflammation, chronic active		1 (2%)		
Artery, inflammation, chronic active	1 (2%)			
Subcutaneous tissue, necrosis, fatty		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	4 (8%)	1 (2%)	5 (10%)	5 (10%)

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Elmiron®

	Vehicle Control	56 mg/kg	168 mg/kg	504 mg/kg
Musculoskeletal System (continued)				
Skeletal muscle	(2)		(2)	
Degeneration			1 (50%)	
Mineralization			1 (50%)	
Artery, inflammation, chronic active	1 (50%)			
Nervous System				
Brain	(50)	(49)	(50)	(50)
Artery, inflammation, chronic active	1 (2%)			
Meninges, infiltration cellular, mononuclear cell			1 (2%)	
Meninges, inflammation, chronic				1 (2%)
Peripheral nerve				(1)
Infiltration cellular, mast cell				1 (100%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation, chronic active		1 (2%)		1 (2%)
Thrombosis		1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	5 (10%)	3 (6%)	1 (2%)	1 (2%)
Alveolus, infiltration cellular, histiocyte			2 (4%)	2 (4%)
Mediastinum, inflammation, acute		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)		2 (4%)	2 (4%)
Olfactory epithelium, atrophy		1 (2%)	1 (2%)	1 (2%)
Olfactory epithelium, metaplasia		2 (4%)		1 (2%)
Trachea	(46)	(48)	(46)	(48)
Metaplasia, squamous		1 (2%)		
Special Senses System				
Eye			(1)	(2)
Degeneration			1 (100%)	
Cornea, inflammation, acute				1 (50%)
Cornea, inflammation, chronic				1 (50%)
Harderian gland	(48)	(41)	(50)	(46)
Atrophy	1 (2%)	1 (2%)		
Hyperplasia	3 (6%)	3 (7%)	2 (4%)	4 (9%)
Inflammation, chronic				1 (2%)
Urinary System				
Kidney	(48)	(49)	(48)	(46)
Cyst		1 (2%)		
Hydronephrosis	1 (2%)			
Infarct		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocyte			1 (2%)	
Metaplasia, osseous				3 (7%)
Mineralization	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Nephropathy	19 (40%)	17 (35%)	22 (46%)	27 (59%)
Artery, inflammation, chronic active	1 (2%)			
Renal tubule, accumulation, hyaline droplet		1 (2%)		
Renal tubule, vacuolization cytoplasmic				1 (2%)
Urinary bladder	(43)	(46)	(47)	(46)
Artery, inflammation, chronic active	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1987). Elmiron® was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 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 five doses of Elmiron®. In the absence of toxicity, 10,000 µg/plate was selected as the high dose. Trials with S9 were repeated at a higher S9 factor.

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

RAT AND MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by Elmiron® exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male F344/N rats and B6C3F$_1$ mice were administered Elmiron® dissolved in phosphate-buffered saline (PBS) by gavage three times at 24-hour intervals. Vehicle control animals were administered PBS only. The positive control animals received cyclophosphamide. The animals were killed 24 hours after the third treatment, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of five animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dosed group is less than or equal to 0.025 divided by the number of dosed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 3-month gavage study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of five animals per dose group. In addition, the percentage of PCEs among 1,000 total erythrocytes was scored for each dose group as a measure of toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed as described for PCEs in the bone marrow micronucleus test.

Evaluation Protocol

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

Results

Elmiron®, tested over a concentration range of 100 to 10,000 µg/plate, was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535 with or without induced rat or hamster liver S9 (Table E1). No consistent increase in the frequency of micronucleated PCEs was seen in bone marrow cells of rats (Table E2) or mice (Table E3) administered 156.25 to 2,500 mg Elmiron®/kg body weight by gavage three times at 24-hour intervals. In the rat study, an initial trial yielded a weakly positive result (trend P value=0.019), but a second trial gave clearly negative results, and Elmiron® was judged to be negative overall in the rat and mouse bone marrow micronucleus tests. No increase in the frequency of micronucleated NCEs was seen in male or female B6C3F$_1$ mice administered a daily dose of 63, 125, 250, 500, or 1,000 mg/kg Elmiron® by gavage for 3 months (Table E4). There were slight decreases in the percentages of PCEs in the circulating blood of 500 and 1,000 mg/kg mice, but the decreases were not significant.

Table E1
Mutagenicity of Elmiron® in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] –S9 Trial 1	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA100	0	91 ± 8.7	131 ± 5.9	142 ± 6.7	136 ± 11.9	134 ± 10.4
	100	95 ± 3.1	124 ± 12.5	137 ± 5.5	114 ± 5.4	151 ± 14.7
	333	104 ± 4.8	134 ± 6.4	132 ± 10.8	125 ± 8.6	148 ± 3.8
	1,000	92 ± 2.1	118 ± 2.0	123 ± 0.7	117 ± 9.8	156 ± 6.8
	3,333	91 ± 3.5	117 ± 12.5	139 ± 5.2	113 ± 6.7	145 ± 10.8
	10,000	105 ± 4.6	131 ± 9.2	111 ± 15.1	125 ± 0.9	143 ± 22.7
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control[c]		1,024 ± 6.2	750 ± 14.5	734 ± 13.6	629 ± 34.4	776 ± 20.5

Strain	Dose (µg/plate)	–S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA1535	0	10 ± 0.9	9 ± 1.7	11 ± 2.3	11 ± 0.9	11 ± 2.2	8 ± 1.0
	100	12 ± 0.3	9 ± 2.0	10 ± 1.5	10 ± 1.5	12 ± 2.0	9 ± 1.5
	333	11 ± 2.1	12 ± 2.3	8 ± 1.9	14 ± 1.5	8 ± 0.6	10 ± 0.3
	1,000	10 ± 1.9	9 ± 1.5	10 ± 1.5	8 ± 0.7	11 ± 1.5	8 ± 1.5
	3,333	10 ± 1.2	7 ± 0.6	8 ± 1.5	8 ± 0.9	11 ± 1.7	9 ± 0.6
	10,000	9 ± 0.6	9 ± 1.7	8 ± 0.9	12 ± 1.2	8 ± 2.3	10 ± 1.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		961 ± 28.7	895 ± 38.9	100 ± 5.0	149 ± 10.4	104 ± 4.1	141 ± 6.4

Strain	Dose (µg/plate)	–S9 Trial 1	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA97	0	123 ± 4.5	155 ± 3.6	166 ± 6.9	149 ± 1.5	159 ± 5.8
	100	129 ± 1.9	157 ± 11.8	175 ± 8.7	162 ± 3.4	158 ± 6.1
	333	136 ± 3.8	158 ± 10.2	148 ± 15.4	163 ± 6.5	162 ± 6.7
	1,000	134 ± 5.5	155 ± 10.8	179 ± 4.9	172 ± 6.8	177 ± 0.9
	3,333	144 ± 3.7	159 ± 5.6	171 ± 6.7	183 ± 9.2	172 ± 8.2
	10,000	134 ± 5.2	135 ± 5.2	194 ± 3.2	154 ± 3.3	175 ± 6.4
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		467 ± 32.3	750 ± 20.2	672 ± 3.4	676 ± 58.9	663 ± 33.8

Table E1
Mutagenicity of Elmiron® in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate –S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA98	0	14 ± 3.4	15 ± 2.3	15 ± 1.5	17 ± 2.3	24 ± 2.8	20 ± 4.6
	100	15 ± 3.0	14 ± 1.2	24 ± 4.0	21 ± 0.3	25 ± 2.8	21 ± 2.5
	333	18 ± 0.7	18 ± 2.0	21 ± 2.1	21 ± 1.5	28 ± 1.2	16 ± 4.3
	1,000	15 ± 1.5	13 ± 2.4	17 ± 1.2	20 ± 0.6	27 ± 0.9	17 ± 1.9
	3,333	15 ± 2.3	17 ± 1.2	17 ± 2.0	22 ± 2.6	22 ± 1.9	15 ± 2.0
	10,000	11 ± 2.3	17 ± 1.7	22 ± 2.9	16 ± 1.3	21 ± 3.9	17 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		389 ± 16.7	262 ± 13.3	512 ± 10.7	231 ± 24.6	407 ± 11.1	262 ± 22.0

[a] Study performed at SRI International. The detailed protocol is presented by Zeiger *et al*. (1987). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

Table E2
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Rats Treated Three Times with Elmiron® by Gavage[a]

	Dose (mg/kg)	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]	PCEs (%)
Trial 1				
Phosphate-buffered saline[d]	0	1.00 ± 0.32		31.50
Elmiron®	156.25	1.30 ± 0.25	0.2657	33.80
	312.5	1.70 ± 0.20	0.0888	37.10
	625	2.30 ± 0.25	0.0118	49.10
	1,250	1.90 ± 0.33	0.0472	37.60
	2,500	2.30 ± 0.34	0.0118	43.90
		P=0.019[e]		
Cyclophosphamide[f]	10	26.20 ± 2.03	0.0000	34.40
Trial 2				
Phosphate-buffered saline	0	1.70 ± 0.37		44.70
Elmiron®	156.25	1.50 ± 0.32	0.6383	48.30
	312.5	1.50 ± 0.50	0.6383	39.40
	625	1.20 ± 0.25	0.8236	37.30
	1,250	1.10 ± 0.29	0.8717	48.30
	2,500	1.40 ± 0.33	0.7051	34.70
		P=0.718		
Cyclophosphamide	10	18.50 ± 0.72	0.0000	36.50

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al*. (1993).
[b] PCE=polychromatic erythrocyte. 2,000 PCEs were scored for frequency of micronuclei in each of five animals per dose group.
[c] Mean ± standard error
Pairwise comparison with the vehicle control. Dosed group values are significant at P≤0.005; positive control values are significant at P≤0.05 (ILS, 1990).
[d] Vehicle control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990).
[f] Positive control

Table E3
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated Three Times with Elmiron® by Gavage[a]

	Dose (mg/kg)	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]	PCEs (%)
Phosphate-buffered saline[d]	0	1.20 ± 0.34		40.42
Elmiron®	156.25	1.20 ± 0.12	0.5380	44.88
	312.5	1.50 ± 0.39	0.3272	48.20
	625	1.10 ± 0.33	0.6152	49.02
	1,250	0.90 ± 0.40	0.7638	49.32
	2,500	1.50 ± 0.35	0.3272	48.18
		P=0.389[e]		
Cyclophosphamide[f]	50	29.00 ± 0.77	0.0000	26.96

a Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al*. (1993). PCE=polychromatic erythrocyte. 2,000 PCEs were scored for frequency of micronuclei in each of five animals per dose group.
b Mean ± standard error
c Pairwise comparison with the vehicle control. Dosed group values are significant at P≤0.005; positive control value is significant at P≤0.05 (ILS, 1990)
d Vehicle control
e Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990).
f Positive control

Table E4
Frequency of Micronuclei in Peripheral Blood Normochromatic Erythrocytes of Mice Following Treatment with Elmiron® by Gavage for 3 Months[a]

	Dose (mg/kg)	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male				
Deionized water[d]	0	0.40 ± 0.10		1.9
Elmiron®	63	0.50 ± 0.32	0.3694	2.3
	125	0.50 ± 0.32	0.3694	2.1
	250	0.40 ± 0.19	0.5000	1.9
	500	0.10 ± 0.10	0.9102	1.6
	1,000	0.40 ± 0.19	0.5000	1.6
		P=0.726[e]		
Female				
Deionized water	0	0.10 ± 0.10		2.3
Elmiron®	63	0.50 ± 0.16	0.0512	2.0
	125	0.40 ± 0.19	0.0898	2.1
	250	0.20 ± 0.20	0.2818	2.2
	500	0.70 ± 0.25	0.0169	1.8
	1,000	0.20 ± 0.12	0.2818	1.8
		P=0.492		

[a] Study was performed at SITEK Research Laboratories, Inc. The detailed protocol is presented by MacGregor *et al*. (1990).
[b] NCE=normochromatic erythrocyte. 2,000 NCEs were scored for frequency of micronuclei in each of five animals per dose group.
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control. Dosed group values are significant at $P \leq 0.005$ (ILS, 1990).
[e] Vehicle control
Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test; significant at $P \leq 0.025$ (ILS, 1990).

APPENDIX F
CLINICAL PATHOLOGY RESULTS

Table F1
Activated Partial Thromboplastin Time (Seconds) for Rats in the 2-Week Gavage Study of Elmiron®[a]

	Vehicle Control	33 mg/kg	111 mg/kg	333 mg/kg	1,000 mg/kg	3,000 mg/kg
Male						
n	5	4	3	3	1	5
	16.3 ± 0.2	16.6 ± 0.2	16.9 ± 0.0*	16.6 ± 0.3	16.5[b]	17.7 ± 0.2**
Female						
n	5	4	5	4	4	4
	15.0 ± 0.2	15.6 ± 0.1*	15.5 ± 0.2	15.4 ± 0.5	15.4 ± 0.3	17.3 ± 0.3**

* Significantly different ($P \leq 0.05$) from the vehicle control group by Shirley's test.
** $P \leq 0.01$
[a] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[b] No standard error was calculated because less than two measurements were available.

Table F2
Hematology and Clinical Chemistry Data for Rats in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
Hematology						
n						
Day 4	10	10	9	10	10	10
Day 23	10	9	10	10	8	10
Week 14	10	8	10	10	9	8
Hematocrit (%)						
Day 4	38.5 ± 0.7	37.9 ± 0.5	38.2 ± 0.6	38.3 ± 0.5	38.2 ± 0.5	37.4 ± 0.5
Day 23	45.2 ± 0.5	45.0 ± 0.6	44.4 ± 0.6	44.1 ± 0.6	42.7 ± 0.5*	45.4 ± 0.7
Week 14	46.7 ± 0.3	46.0 ± 0.7	46.6 ± 0.5	45.7 ± 0.3	45.0 ± 0.5*	44.3 ± 0.7**
Hemoglobin (g/dL)						
Day 4	12.4 ± 0.2	12.2 ± 0.2	12.3 ± 0.2	12.3 ± 0.2	12.3 ± 0.1	12.0 ± 0.1
Day 23	15.0 ± 0.2	15.0 ± 0.2	14.6 ± 0.2	14.7 ± 0.2	14.2 ± 0.2*	15.1 ± 0.2
Week 14	15.4 ± 0.1	15.3 ± 0.2	15.4 ± 0.2	15.1 ± 0.1	14.7 ± 0.1**	14.3 ± 0.2**
Erythrocytes (10^6/µL)						
Day 4	6.45 ± 0.16	6.34 ± 0.09	6.37 ± 0.16	6.46 ± 0.11	6.43 ± 0.11	6.30 ± 0.08
Day 23	7.64 ± 0.09	7.67 ± 0.12	7.44 ± 0.13	7.45 ± 0.11	7.22 ± 0.07	7.67 ± 0.12
Week 14	8.71 ± 0.07	8.60 ± 0.13	8.67 ± 0.10	8.51 ± 0.06	8.42 ± 0.09*	8.28 ± 0.13**
Reticulocytes (10^6/µL)						
Day 4	0.36 ± 0.03	0.55 ± 0.04**	0.46 ± 0.05	0.51 ± 0.03*	0.51 ± 0.04*	0.45 ± 0.04
Day 23	0.32 ± 0.03	0.34 ± 0.03	0.34 ± 0.04	0.33 ± 0.03	0.34 ± 0.03	0.40 ± 0.03
Week 14	0.14 ± 0.01	0.13 ± 0.02	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.01
Nucleated erythrocytes (10^3/µL)						
Day 4	0.05 ± 0.02	0.04 ± 0.02	0.05 ± 0.03	0.03 ± 0.03	0.05 ± 0.02	0.02 ± 0.01
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.02 ± 0.02	0.00 ± 0.00
Week 14	0.02 ± 0.01	0.06 ± 0.02	0.06 ± 0.03	0.03 ± 0.02	0.00 ± 0.00	0.05 ± 0.03
Mean cell volume (fL)						
Day 4	59.8 ± 0.5	59.8 ± 0.3	60.2 ± 0.9	59.3 ± 0.4	59.4 ± 0.2	59.3 ± 0.4
Day 23	59.1 ± 0.2	58.7 ± 0.2	59.7 ± 0.4	59.2 ± 0.2	59.1 ± 0.2	59.1 ± 0.2
Week 14	53.7 ± 0.2	53.4 ± 0.1	53.8 ± 0.2	53.7 ± 0.1	53.5 ± 0.3	53.5 ± 0.3
Mean cell hemoglobin (pg)						
Day 4	19.2 ± 0.2	19.3 ± 0.1	19.4 ± 0.3	19.1 ± 0.2	19.1 ± 0.1	19.1 ± 0.1
Day 23	19.7 ± 0.1	19.5 ± 0.1	19.7 ± 0.2	19.7 ± 0.2	19.7 ± 0.1	19.7 ± 0.1
Week 14	17.8 ± 0.1	17.8 ± 0.0	17.7 ± 0.1	17.7 ± 0.1	17.4 ± 0.1	17.3 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 4	32.2 ± 0.1	32.3 ± 0.2	32.2 ± 0.2	32.2 ± 0.2	32.2 ± 0.1	32.3 ± 0.2
Day 23	33.3 ± 0.2	33.3 ± 0.1	33.0 ± 0.1	33.2 ± 0.2	33.3 ± 0.1	33.3 ± 0.2
Week 14	33.1 ± 0.2	33.3 ± 0.1	33.0 ± 0.1	33.1 ± 0.1	32.6 ± 0.2	32.3 ± 0.1**
Platelets (10^3/µL)						
Day 4	831.1 ± 38.5	887.2 ± 25.5	915.7 ± 30.6	881.4 ± 17.1	903.4 ± 25.8	886.5 ± 21.2
Day 23	797.6 ± 49.9	867.6 ± 49.8	920.0 ± 18.9	941.3 ± 9.9**	928.6 ± 90.1**	970.8 ± 39.8**
Week 14	644.1 ± 12.1	671.8 ± 11.8	729.8 ± 9.4**	775.7 ± 26.8**	799.1 ± 18.4**	778.5 ± 31.9**
Leukocytes (10^3/µL)						
Day 4	6.77 ± 0.31	7.16 ± 0.18	7.78 ± 0.63	7.51 ± 0.47	8.10 ± 0.29**	9.59 ± 0.43**
Day 23	10.27 ± 0.81	9.09 ± 0.80	9.81 ± 0.53	10.27 ± 0.65	11.78 ± 0.63	13.21 ± 1.11*
Week 14	11.31 ± 0.59	11.38 ± 1.02	11.73 ± 0.67	10.86 ± 0.73	12.19 ± 1.46	15.38 ± 0.84*
Segmented neutrophils (10^3/µL)						
Day 4	0.80 ± 0.06	1.17 ± 0.06*	1.06 ± 0.12	0.93 ± 0.07	1.33 ± 0.15**	1.21 ± 0.18
Day 23	1.24 ± 0.08	1.09 ± 0.11	1.47 ± 0.11	1.26 ± 0.18	1.25 ± 0.09	1.39 ± 0.15
Week 14	1.83 ± 0.20	1.97 ± 0.29	2.56 ± 0.19	2.14 ± 0.19	2.12 ± 0.50	2.67 ± 0.30

Table F2
Hematology and Clinical Chemistry Data for Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male (continued)						
Hematology (continued)						
n						
Day 4	10	10	9	10	10	10
Day 23	10	9	10	10	8	10
Week 14	10	8	10	10	9	8
Bands ($10^3/\mu L$)						
Day 4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes ($10^3/\mu L$)						
Day 4	5.66 ± 0.29	5.67 ± 0.15	6.20 ± 0.59	6.18 ± 0.45	6.41 ± 0.17*	7.83 ± 0.38**
Day 23	8.59 ± 0.76	7.53 ± 0.75	7.87 ± 0.47	8.53 ± 0.57	10.07 ± 0.70	11.26 ± 0.99
Week 14	9.27 ± 0.64	9.10 ± 0.85	8.84 ± 0.53	8.42 ± 0.58	9.70 ± 1.18	12.30 ± 0.75
Monocytes ($10^3/\mu L$)						
Day 4	0.28 ± 0.05	0.29 ± 0.03	0.46 ± 0.09	0.37 ± 0.07	0.33 ± 0.05	0.50 ± 0.03**
Day 23	0.38 ± 0.06	0.37 ± 0.07	0.45 ± 0.07	0.45 ± 0.05	0.37 ± 0.06	0.46 ± 0.10
Week 14	0.17 ± 0.04	0.15 ± 0.06	0.27 ± 0.11	0.21 ± 0.06	0.30 ± 0.06	0.35 ± 0.10
Basophils ($10^3/\mu L$)						
Day 4	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)						
Day 4	0.03 ± 0.01	0.04 ± 0.01	0.06 ± 0.02	0.02 ± 0.01	0.03 ± 0.01	0.05 ± 0.02
Day 23	0.06 ± 0.02	0.11 ± 0.03	0.03 ± 0.02	0.03 ± 0.01	0.09 ± 0.02	0.10 ± 0.03
Week 14	0.04 ± 0.02	0.16 ± 0.05	0.06 ± 0.02	0.08 ± 0.03	0.08 ± 0.03	0.05 ± 0.03
Activated partial thromboplastin time (seconds)						
Day 4	17.0 ± 1.0[b]	17.4 ± 1.0[c]	15.5 ± 0.9[d]	18.1 ± 0.2[c]	18.1 ± 0.5[e]	20.2 ± 1.9[e]
Day 23	20.9 ± 0.9[e]	20.4 ± 2.4[e]	23.2 ± 1.0[e]	18.2 ± 4.5[f]	24.0 ± 1.7[e]	21.5 ± 1.9[b]
Week 14	17.9 ± 1.0	17.3 ± 0.8[b]	18.0 ± 0.7[b]	16.6 ± 0.8[b]	19.5 ± 1.0	24.1 ± 1.7**
Clinical Chemistry						
n						
Day 4	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	9	10	10	9	8
Urea nitrogen (mg/dL)						
Day 4	10.2 ± 0.3	10.7 ± 0.4	11.3 ± 0.8	10.4 ± 0.5	9.8 ± 0.6	9.8 ± 0.4
Day 23	10.7 ± 0.5	12.9 ± 0.8	9.9 ± 0.4	10.4 ± 0.6	10.6 ± 0.4	12.5 ± 0.5
Week 14	12.6 ± 0.4	12.0 ± 0.3	12.5 ± 0.6	13.6 ± 0.5	12.1 ± 0.4	10.5 ± 0.4*
Creatinine (mg/dL)						
Day 4	0.54 ± 0.02	0.52 ± 0.01	0.55 ± 0.02	0.55 ± 0.02	0.52 ± 0.02[b]	0.50 ± 0.00
Day 23	0.68 ± 0.02	0.73 ± 0.02	0.66 ± 0.02	0.68 ± 0.02	0.63 ± 0.02	0.68 ± 0.02
Week 14	0.74 ± 0.02	0.70 ± 0.02	0.70 ± 0.02	0.75 ± 0.02	0.73 ± 0.02	0.71 ± 0.01
Total protein (g/dL)						
Day 4	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.2 ± 0.1
Day 23	6.6 ± 0.1	6.8 ± 0.1	6.4 ± 0.1	6.5 ± 0.1	6.3 ± 0.1	6.6 ± 0.1
Week 14	7.0 ± 0.1	7.0 ± 0.1	7.2 ± 0.1	7.2 ± 0.0	7.1 ± 0.1	7.1 ± 0.1

Table F2
Hematology and Clinical Chemistry Data for Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male (continued)						
Clinical Chemistry (continued)						
n						
Day 4	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	9	10	10	9	8
Albumin (g/dL)						
Day 4	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.0	4.0 ± 0.0	3.9 ± 0.0	3.8 ± 0.0
Day 23	4.7 ± 0.1	4.8 ± 0.1	4.5 ± 0.0	4.6 ± 0.1	4.5 ± 0.0	4.7 ± 0.0
Week 14	4.9 ± 0.1	4.8 ± 0.1	4.9 ± 0.0	5.0 ± 0.0	4.8 ± 0.0	4.7 ± 0.1
Alanine aminotransferase (IU/L)						
Day 4	101 ± 2	105 ± 2	105 ± 3	103 ± 1	110 ± 2**	103 ± 2
Day 23	81 ± 3	76 ± 3	77 ± 3	72 ± 2*	72 ± 3*	65 ± 3**
Week 14	89 ± 4	79 ± 7	83 ± 4	75 ± 4	81 ± 4	71 ± 3*
Alkaline phosphatase (IU/L)						
Day 4	1,944 ± 53	1,872 ± 38	1,841 ± 28	1,889 ± 44	1,895 ± 38	1,804 ± 43*
Day 23	1,541 ± 46	1,467 ± 31	1,486 ± 32	1,451 ± 29	1,362 ± 24**	1,387 ± 28**
Week 14	613 ± 12	596 ± 16	557 ± 17*	544 ± 8**	591 ± 13	565 ± 13
Creatine kinase (IU/L)						
Day 4	209 ± 16	199 ± 13	256 ± 32	179 ± 4	206 ± 11[b]	211 ± 15
Day 23	496 ± 97	504 ± 42	392 ± 59	393 ± 45	384 ± 59	432 ± 57
Week 14	213 ± 28	179 ± 16	175 ± 17	162 ± 21	384 ± 76	150 ± 13
Sorbitol dehydrogenase (IU/L)						
Day 4	17 ± 1	16 ± 1	19 ± 1	17 ± 1	21 ± 2	16 ± 1
Day 23	35 ± 4	33 ± 2	35 ± 3	32 ± 3	31 ± 2	34 ± 4
Week 14	36 ± 3	29 ± 4	29 ± 3	33 ± 4	39 ± 3	36 ± 2
Bile acids (µmol/L)						
Day 4	57.2 ± 5.2[b]	60.7 ± 4.7	54.6 ± 4.3	70.2 ± 4.4	55.7 ± 6.2[b]	63.3 ± 4.5
Day 23	37.5 ± 2.9	32.1 ± 3.2	43.5 ± 3.2	38.4 ± 3.0	32.7 ± 2.8	30.6 ± 3.1
Week 14	34.2 ± 2.4	31.6 ± 2.1	31.2 ± 2.0	33.8 ± 1.9	37.7 ± 3.0	40.8 ± 2.1

Table F2
Hematology and Clinical Chemistry Data for Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Female						
Hematology						
n						
Day 4	10	10	9	9	10	10
Day 23	9	10	9	8	10	10
Week 14	8	9	8	9	10	10
Hematocrit (%)						
Day 4	39.2 ± 0.4	41.4 ± 0.2**	40.9 ± 0.3*	40.0 ± 0.3	40.6 ± 0.5	41.2 ± 0.3**
Day 23	46.5 ± 0.7	46.0 ± 0.5	45.6 ± 0.5	44.7 ± 0.6	45.0 ± 0.6	44.6 ± 0.4
Week 14	45.7 ± 0.5	44.5 ± 0.6*	45.8 ± 0.6	44.4 ± 0.4	45.3 ± 0.6	42.2 ± 0.5**
Hemoglobin (g/dL)						
Day 4	12.8 ± 0.1	13.4 ± 0.1**	13.3 ± 0.1	13.0 ± 0.1	13.3 ± 0.2	13.3 ± 0.2**
Day 23	15.3 ± 0.2	15.2 ± 0.1	15.1 ± 0.2	14.8 ± 0.2	14.9 ± 0.2	14.8 ± 0.2
Week 14	15.2 ± 0.1	14.9 ± 0.1	15.3 ± 0.2	14.8 ± 0.1	15.0 ± 0.2	14.0 ± 0.2**
Erythrocytes ($10^6/\mu L$)						
Day 4	6.66 ± 0.10	6.99 ± 0.03	6.90 ± 0.08	6.82 ± 0.08	6.94 ± 0.09	7.04 ± 0.06**
Day 23	7.86 ± 0.13	7.77 ± 0.10	7.65 ± 0.10	7.47 ± 0.11*	7.54 ± 0.11	7.48 ± 0.10*
Week 14	8.17 ± 0.08	7.93 ± 0.09*	8.21 ± 0.09	7.90 ± 0.06	8.05 ± 0.10	7.48 ± 0.08**
Reticulocytes ($10^6/\mu L$)						
Day 4	0.34 ± 0.04	0.39 ± 0.05	0.37 ± 0.04	0.31 ± 0.03	0.36 ± 0.03	0.32 ± 0.03
Day 23	0.18 ± 0.02	0.20 ± 0.02	0.22 ± 0.04	0.21 ± 0.01	0.23 ± 0.02	0.21 ± 0.02
Week 14	0.16 ± 0.02	0.13 ± 0.01	0.16 ± 0.02	0.14 ± 0.02	0.14 ± 0.01	0.13 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)						
Day 4	0.04 ± 0.02	0.08 ± 0.03	0.05 ± 0.02	0.02 ± 0.01	0.06 ± 0.03	0.04 ± 0.02
Day 23	0.02 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.03
Week 14	0.04 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.02
Mean cell volume (fL)						
Day 4	58.9 ± 0.5	59.3 ± 0.2	59.2 ± 0.4	58.6 ± 0.4	58.5 ± 0.3	58.5 ± 0.2
Day 23	59.1 ± 0.3	59.3 ± 0.2	59.7 ± 0.3	59.9 ± 0.3	59.8 ± 0.3	59.7 ± 0.3
Week 14	55.9 ± 0.2	56.2 ± 0.2	55.8 ± 0.3	56.1 ± 0.1	56.2 ± 0.2	56.4 ± 0.1
Mean cell hemoglobin (pg)						
Day 4	19.2 ± 0.1	19.2 ± 0.1	19.2 ± 0.2	19.1 ± 0.2	19.1 ± 0.1	18.9 ± 0.2
Day 23	19.5 ± 0.1	19.6 ± 0.1	19.8 ± 0.1	19.8 ± 0.2	19.8 ± 0.1	19.8 ± 0.1
Week 14	18.6 ± 0.0	18.8 ± 0.1	18.7 ± 0.1	18.8 ± 0.1	18.6 ± 0.1	18.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 4	32.5 ± 0.2	32.4 ± 0.1	32.5 ± 0.2	32.6 ± 0.2	32.7 ± 0.1	32.4 ± 0.3
Day 23	33.0 ± 0.2	33.0 ± 0.1	33.1 ± 0.1	33.0 ± 0.2	33.1 ± 0.2	33.1 ± 0.2
Week 14	33.2 ± 0.1	33.5 ± 0.2	33.5 ± 0.1	33.5 ± 0.1	33.1 ± 0.1	33.3 ± 0.2
Platelets ($10^3/\mu L$)						
Day 4	771.3 ± 33.7	830.1 ± 14.0	790.9 ± 45.2	824.6 ± 11.8[d]	814.5 ± 43.8	752.7 ± 25.2
Day 23	834.4 ± 21.0	834.8 ± 19.5	834.7 ± 20.6	846.4 ± 31.3	841.3 ± 19.6	958.2 ± 23.1**
Week 14	698.8 ± 25.2	681.2 ± 22.7	688.0 ± 21.2	718.4 ± 23.0	775.4 ± 26.1*	869.1 ± 14.3**
Leukocytes ($10^3/\mu L$)						
Day 4	7.83 ± 0.32	8.30 ± 0.46	8.96 ± 0.28*	9.21 ± 0.29*	10.49 ± 0.36**	12.08 ± 0.70**
Day 23	9.00 ± 0.90	9.60 ± 0.50	10.90 ± 0.66	10.05 ± 0.30	11.17 ± 0.65*	13.55 ± 1.00**
Week 14	10.23 ± 0.49	10.27 ± 0.62	11.71 ± 0.82	10.96 ± 1.07	12.88 ± 1.28*	17.27 ± 1.09**[b]
Segmented neutrophils ($10^3/\mu L$)						
Day 4	1.06 ± 0.07	0.96 ± 0.06	0.95 ± 0.07	0.95 ± 0.07	1.29 ± 0.16	1.21 ± 0.07
Day 23	1.35 ± 0.27	1.16 ± 0.10	1.32 ± 0.10	1.30 ± 0.20	1.58 ± 0.29	1.79 ± 0.20
Week 14	1.74 ± 0.12	2.07 ± 0.18	2.05 ± 0.18	1.96 ± 0.23	2.46 ± 0.29*	4.08 ± 0.41**[b]

Table F2
Hematology and Clinical Chemistry Data for Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Female (continued)						
Hematology (continued)						
n						
Day 4	10	10	9	9	10	10
Day 23	9	10	9	8	10	10
Week 14	8	9	8	9	10	10
Bands ($10^3/\mu L$)						
Day 4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[b]
Lymphocytes ($10^3/\mu L$)						
Day 4	6.28 ± 0.25	6.98 ± 0.42	7.55 ± 0.29*	7.87 ± 0.33**	8.78 ± 0.39**	10.23 ± 0.70**
Day 23	7.08 ± 0.68	8.03 ± 0.44	8.96 ± 0.56	8.33 ± 0.24	9.15 ± 0.38*	11.30 ± 0.87**
Week 14	8.03 ± 0.42	7.66 ± 0.51	9.19 ± 0.61	8.63 ± 0.88	9.89 ± 0.98*	12.39 ± 1.02**[b]
Monocytes ($10^3/\mu L$)						
Day 4	0.40 ± 0.06	0.29 ± 0.05	0.36 ± 0.06	0.33 ± 0.07	0.36 ± 0.06	0.53 ± 0.06
Day 23	0.41 ± 0.06	0.30 ± 0.07	0.50 ± 0.09	0.32 ± 0.05	0.34 ± 0.07	0.39 ± 0.04
Week 14	0.34 ± 0.07	0.47 ± 0.07	0.37 ± 0.09	0.26 ± 0.07	0.44 ± 0.09	0.70 ± 0.11[b]
Basophils ($10^3/\mu L$)						
Day 4	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000[b]
Eosinophils ($10^3/\mu L$)						
Day 4	0.09 ± 0.02	0.07 ± 0.01	0.09 ± 0.02	0.06 ± 0.02	0.07 ± 0.02	0.11 ± 0.03
Day 23	0.15 ± 0.04	0.10 ± 0.03	0.12 ± 0.02	0.10 ± 0.02	0.10 ± 0.02	0.07 ± 0.03
Week 14	0.13 ± 0.04	0.08 ± 0.03	0.10 ± 0.03	0.10 ± 0.04	0.10 ± 0.05	0.11 ± 0.05[b]
Activated partial thromboplastin time (seconds)						
Day 4	19.2 ± 1.1[e]	18.1 ± 1.1[d]	16.8 ± 0.7[d]	19.0 ± 0.9[g]	19.7 ± 1.4[e]	18.1 ± 1.6[c]
Day 23	17.6 ± 1.8[e]	15.3 ± 1.4[b]	16.1 ± 1.7	14.2 ± 2.3[e]	17.0 ± 1.0	17.8 ± 1.7[b]
Week 14	20.4 ± 1.0[h]	19.0 ± 1.7[h]	20.9 ± 1.7[b]	19.0 ± 1.3	21.1 ± 1.6[b]	22.9 ± 2.0[b]
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 4	11.0 ± 0.5	11.8 ± 0.8	9.7 ± 0.7	10.0 ± 0.7	9.7 ± 0.3	10.5 ± 0.3
Day 23	13.9 ± 0.6	12.9 ± 0.4	13.1 ± 0.6	12.3 ± 0.5	12.5 ± 0.4	13.1 ± 0.7
Week 14	14.8 ± 0.3	14.8 ± 0.5	17.4 ± 0.6*	14.6 ± 0.5	14.7 ± 0.5	14.0 ± 0.4
Creatinine (mg/dL)						
Day 4	0.51 ± 0.01	0.50 ± 0.00	0.50 ± 0.00	0.51 ± 0.01	0.50 ± 0.00	0.52 ± 0.01
Day 23	0.71 ± 0.01	0.67 ± 0.02	0.66 ± 0.02	0.67 ± 0.03	0.65 ± 0.02	0.65 ± 0.02
Week 14	0.77 ± 0.02	0.76 ± 0.02	0.77 ± 0.03	0.74 ± 0.02	0.79 ± 0.01	0.71 ± 0.01
Total protein (g/dL)						
Day 4	5.5 ± 0.1	5.6 ± 0.1	5.4 ± 0.1	5.4 ± 0.1	5.5 ± 0.1	5.5 ± 0.1
Day 23	6.6 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.2 ± 0.1*	6.2 ± 0.1**	6.3 ± 0.1
Week 14	7.0 ± 0.2	7.0 ± 0.2	7.3 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	6.9 ± 0.1

Table F2
Hematology and Clinical Chemistry Data for Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Female (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	10
Albumin (g/dL)						
Day 4	4.2 ± 0.1	4.3 ± 0.0	4.2 ± 0.0	4.3 ± 0.1	4.3 ± 0.1	4.2 ± 0.0
Day 23	4.9 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.6 ± 0.1*	4.6 ± 0.0*	4.7 ± 0.1
Week 14	5.1 ± 0.1	5.1 ± 0.1	5.3 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	4.9 ± 0.1
Alanine aminotransferase (IU/L)						
Day 4	90 ± 3	91 ± 3	88 ± 3	94 ± 3	95 ± 4	85 ± 3
Day 23	68 ± 2	62 ± 3	62 ± 2	62 ± 2*	62 ± 2*	59 ± 1**
Week 14	106 ± 7	101 ± 10	132 ± 13	81 ± 6*	75 ± 5**	59 ± 2**
Alkaline phosphatase (IU/L)						
Day 4	1,593 ± 34	1,526 ± 36	1,522 ± 50	1,547 ± 52	1,573 ± 51	1,446 ± 56
Day 23	1,137 ± 28	1,076 ± 18*	1,064 ± 25*	1,048 ± 37*	1,018 ± 15**	950 ± 21**
Week 14	518 ± 15	451 ± 13**	485 ± 11*	420 ± 7**	422 ± 15**	435 ± 9**
Creatine kinase (IU/L)						
Day 4	191 ± 24	189 ± 13	224 ± 19	225 ± 27	227 ± 32	243 ± 24
Day 23	361 ± 38	316 ± 33	241 ± 32	360 ± 42	255 ± 33	310 ± 50
Week 14	215 ± 61	158 ± 20	213 ± 29	224 ± 75	181 ± 20	197 ± 61
Sorbitol dehydrogenase (IU/L)						
Day 4	14 ± 0	14 ± 1	15 ± 1	15 ± 1	17 ± 2	14 ± 1
Day 23	32 ± 3	28 ± 2	30 ± 2	26 ± 3	32 ± 4	28 ± 1
Week 14	33 ± 3	39 ± 3	49 ± 4*	39 ± 4	40 ± 3	31 ± 2
Bile acids (µmol/L)						
Day 4	46.4 ± 5.5	40.1 ± 2.9	46.2 ± 4.6	44.3 ± 3.6	55.8 ± 7.8	48.2 ± 5.6
Day 23	39.7 ± 4.2	34.1 ± 2.4	36.6 ± 3.5	30.1 ± 4.6	36.4 ± 3.3	30.3 ± 1.5
Week 14	38.6 ± 4.8	43.5 ± 3.3	55.4 ± 5.5*	45.9 ± 4.2	41.1 ± 3.5	38.3 ± 1.8

* Significantly different (P≤0.05) from the vehicle control group by Dunn's or Shirley's test
** P≤0.01
[a] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=6
[d] n=8
[e] n=7
[f] n=4
[g] n=5
[h] n=10

Table F3
Hematology Data for Mice in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
n	10	10	10	10	10	10
Hematocrit (%)	49.8 ± 0.8	49.6 ± 1.2	49.2 ± 0.3	48.2 ± 0.5	47.3 ± 0.6*	47.1 ± 0.5**
Hemoglobin (g/dL)	16.5 ± 0.3	16.5 ± 0.4	16.3 ± 0.2	16.0 ± 0.2	15.7 ± 0.2*	15.9 ± 0.1*
Erythrocytes (10^6/µL)	10.63 ± 0.19	10.68 ± 0.30	10.62 ± 0.08	10.44 ± 0.12	10.30 ± 0.13	10.62 ± 0.13
Reticulocytes (10^6/µL)	0.15 ± 0.03	0.18 ± 0.01	0.15 ± 0.02	0.16 ± 0.02	0.14 ± 0.01	0.14 ± 0.02
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	46.9 ± 0.2	46.6 ± 0.2	46.2 ± 0.1**	46.2 ± 0.1**	45.9 ± 0.1**	44.4 ± 0.2**
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.5 ± 0.1	15.3 ± 0.1	15.4 ± 0.1	15.3 ± 0.0*	14.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.1 ± 0.1	33.3 ± 0.1	33.2 ± 0.2	33.3 ± 0.1	33.3 ± 0.1	33.7 ± 0.1*
Platelets (10^3/µL)	721.4 ± 54.0	757.0 ± 54.0	756.6 ± 25.4	794.7 ± 21.0	876.7 ± 38.8*	970.3 ± 39.8**
Leukocytes (10^3/µL)	4.82 ± 0.29	6.29 ± 0.51*	6.02 ± 0.21*	6.23 ± 0.34*	5.80 ± 0.53*	8.36 ± 0.50**
Segmented neutrophils (10^3/µL)	0.62 ± 0.05	0.69 ± 0.10	0.78 ± 0.12	0.79 ± 0.12	0.63 ± 0.11	0.76 ± 0.12
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/µL)	4.07 ± 0.24	5.34 ± 0.41*	5.05 ± 0.20*	5.32 ± 0.30**	5.01 ± 0.42*	7.44 ± 0.40**
Monocytes (10^3/µL)	0.09 ± 0.02	0.17 ± 0.02	0.11 ± 0.03	0.07 ± 0.02	0.11 ± 0.02	0.13 ± 0.02
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)	0.05 ± 0.01	0.10 ± 0.02	0.08 ± 0.03	0.05 ± 0.01	0.05 ± 0.01	0.03 ± 0.01
Female						
n	10	10	9	9	10	10
Hematocrit (%)	48.0 ± 0.7	46.5 ± 0.5*	45.4 ± 0.6**	45.7 ± 0.6**	44.1 ± 0.4**	43.6 ± 0.4**
Hemoglobin (g/dL)	16.1 ± 0.3	15.7 ± 0.2	15.3 ± 0.2*	15.3 ± 0.2**	15.0 ± 0.1**	14.8 ± 0.2**
Erythrocytes (10^6/µL)	10.18 ± 0.16	9.92 ± 0.10*	9.64 ± 0.12**	9.83 ± 0.12*	9.58 ± 0.09**	9.77 ± 0.11**
Reticulocytes (10^6/µL)	0.14 ± 0.02	0.14 ± 0.02	0.15 ± 0.02	0.17 ± 0.03	0.14 ± 0.02	0.13 ± 0.01
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.2 ± 0.2	46.9 ± 0.1*	47.0 ± 0.1	46.5 ± 0.2**	46.1 ± 0.2**	44.6 ± 0.2**
Mean cell hemoglobin (pg)	15.8 ± 0.1	15.9 ± 0.1	15.8 ± 0.1	15.6 ± 0.1*	15.6 ± 0.1	15.1 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.1	33.8 ± 0.1	33.6 ± 0.1	33.5 ± 0.2	33.9 ± 0.1	33.9 ± 0.1
Platelets (10^3/µL)	608.9 ± 35.7	666.3 ± 38.4	743.4 ± 27.7*	724.7 ± 23.1*	771.3 ± 30.7**	871.1 ± 33.3**
Leukocytes (10^3/µL)	4.77 ± 0.28	5.62 ± 0.36	5.31 ± 0.27	6.08 ± 0.54	6.11 ± 0.27**	8.33 ± 0.57**
Segmented neutrophils (10^3/µL)	0.69 ± 0.08	0.99 ± 0.16	0.93 ± 0.14	0.91 ± 0.15	0.74 ± 0.07	0.88 ± 0.10
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/µL)	3.93 ± 0.24	4.50 ± 0.28	4.22 ± 0.15	4.97 ± 0.54	5.15 ± 0.26**	7.28 ± 0.54**
Monocytes (10^3/µL)	0.11 ± 0.04	0.10 ± 0.03	0.10 ± 0.03	0.15 ± 0.04	0.13 ± 0.03	0.15 ± 0.05
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)	0.05 ± 0.01	0.04 ± 0.01	0.06 ± 0.02	0.04 ± 0.01	0.09 ± 0.02	0.02 ± 0.01

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.

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 2-Week Gavage Study of Elmiron®[a]

	Vehicle Control	33 mg/kg	111 mg/kg	333 mg/kg	1,000 mg/kg	3,000 mg/kg
Male						
n	5	5	5	5	5	5
Necropsy body wt	204 ± 8	200 ± 7	204 ± 8	204 ± 13	207 ± 7	204 ± 9
Heart						
Absolute	0.661 ± 0.015	0.644 ± 0.018	0.670 ± 0.019	0.658 ± 0.023	0.671 ± 0.024	0.653 ± 0.033
Relative	3.252 ± 0.086	3.226 ± 0.086	3.288 ± 0.065	3.250 ± 0.113	3.248 ± 0.077	3.208 ± 0.059
R. Kidney						
Absolute	0.702 ± 0.025	0.717 ± 0.029	0.712 ± 0.028	0.688 ± 0.036	0.745 ± 0.031	0.742 ± 0.032
Relative	3.442 ± 0.051	3.582 ± 0.067	3.487 ± 0.070	3.384 ± 0.083	3.605 ± 0.074	3.648 ± 0.065
Liver						
Absolute	8.487 ± 0.333	8.119 ± 0.253	8.721 ± 0.351	8.670 ± 0.589	9.553 ± 0.315	9.949 ± 0.519*
Relative	41.62 ± 0.732	40.63 ± 0.469	42.70 ± 0.477	42.39 ± 0.511	46.27 ± 0.849**	48.82 ± 0.795**
Lung						
Absolute	1.029 ± 0.028	0.972 ± 0.040	0.984 ± 0.043	1.015 ± 0.053	1.004 ± 0.024	1.037 ± 0.048
Relative	5.054 ± 0.098	4.865 ± 0.160	4.817 ± 0.093	5.022 ± 0.330	4.867 ± 0.083	5.094 ± 0.060
Spleen						
Absolute	0.529 ± 0.022	0.500 ± 0.010	0.519 ± 0.016	0.518 ± 0.025	0.553 ± 0.010	0.551 ± 0.020
Relative	2.595 ± 0.071	2.508 ± 0.082	2.546 ± 0.081	2.550 ± 0.086	2.681 ± 0.055	2.711 ± 0.049
R. Testis						
Absolute	1.204 ± 0.021	1.182 ± 0.032	1.230 ± 0.036	1.194 ± 0.053	1.190 ± 0.025	1.253 ± 0.030
Relative	5.927 ± 0.196	5.920 ± 0.101	6.033 ± 0.106	5.890 ± 0.243	5.783 ± 0.192	6.196 ± 0.273
Thymus						
Absolute	0.456 ± 0.041	0.371 ± 0.011	0.447 ± 0.015	0.430 ± 0.030	0.446 ± 0.016	0.412 ± 0.023
Relative	2.237 ± 0.195	1.862 ± 0.063	2.199 ± 0.110	2.130 ± 0.193	2.168 ± 0.109	2.028 ± 0.087

Table G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Week Gavage Study of Elmiron®

	Vehicle Control	33 mg/kg	111 mg/kg	333 mg/kg	1,000 mg/kg	3,000 mg/kg
Female						
n	5	5	5	5	5	5
Necropsy body wt	144 ± 2	135 ± 2	143 ± 4	134 ± 1	137 ± 3	135 ± 6
Heart						
Absolute	0.517 ± 0.020	0.485 ± 0.013	0.508 ± 0.023	0.473 ± 0.010	0.503 ± 0.012	0.490 ± 0.018
Relative	3.598 ± 0.141	3.608 ± 0.123	3.564 ± 0.141	3.529 ± 0.073	3.677 ± 0.057	3.627 ± 0.065
R. Kidney						
Absolute	0.544 ± 0.014	0.496 ± 0.005	0.527 ± 0.019	0.525 ± 0.005	0.524 ± 0.010	0.533 ± 0.023
Relative	3.789 ± 0.084	3.692 ± 0.059	3.697 ± 0.104	3.918 ± 0.055	3.830 ± 0.067	3.933 ± 0.038
Liver						
Absolute	5.710 ± 0.110	5.288 ± 0.077	5.737 ± 0.230	5.506 ± 0.099	5.975 ± 0.209	6.469 ± 0.241**
Relative	39.76 ± 0.571	39.34 ± 0.668	40.17 ± 0.728	41.10 ± 0.817	43.66 ± 1.337**	47.82 ± 0.390**
Lung						
Absolute	0.842 ± 0.017	0.749 ± 0.010*	0.805 ± 0.024	0.778 ± 0.014	0.790 ± 0.030	0.762 ± 0.029
Relative	5.863 ± 0.118	5.573 ± 0.127	5.644 ± 0.108	5.807 ± 0.128	5.765 ± 0.140	5.638 ± 0.121
Spleen						
Absolute	0.392 ± 0.010	0.364 ± 0.008	0.398 ± 0.014	0.374 ± 0.009	0.366 ± 0.013	0.416 ± 0.022
Relative	2.732 ± 0.066	2.705 ± 0.063	2.790 ± 0.047	2.793 ± 0.054	2.673 ± 0.071	3.084 ± 0.173*
Thymus						
Absolute	0.367 ± 0.009	0.363 ± 0.017	0.368 ± 0.033	0.359 ± 0.010	0.361 ± 0.022	0.369 ± 0.026
Relative	2.557 ± 0.057	2.699 ± 0.120	2.573 ± 0.197	2.677 ± 0.071	2.635 ± 0.139	2.730 ± 0.175

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

Table G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
n	10	9	10	10	9	8
Necropsy body wt	351 ± 5	363 ± 6	347 ± 6	356 ± 7	333 ± 5	351 ± 8
Heart						
Absolute	1.042 ± 0.028	1.053 ± 0.022	1.028 ± 0.022	1.093 ± 0.018	1.003 ± 0.020	1.040 ± 0.020
Relative	2.966 ± 0.070	2.900 ± 0.050	2.965 ± 0.075	3.074 ± 0.033	3.010 ± 0.039	2.964 ± 0.021
R. Kidney						
Absolute	0.975 ± 0.024	1.016 ± 0.027	0.989 ± 0.031	1.034 ± 0.027	0.973 ± 0.017	1.035 ± 0.043
Relative	2.774 ± 0.056	2.795 ± 0.037	2.845 ± 0.066	2.908 ± 0.053	2.924 ± 0.054	2.942 ± 0.069
Liver						
Absolute	12.48 ± 0.331	12.92 ± 0.363	12.34 ± 0.327	13.91 ± 0.285*	13.51 ± 0.310*	15.91 ± 0.730**
Relative	35.50 ± 0.795	35.53 ± 0.538	35.53 ± 0.783	39.11 ± 0.490**	40.53 ± 0.546**	45.18 ± 1.240**
Lung						
Absolute	1.931 ± 0.124	2.149 ± 0.128	1.982 ± 0.091	1.870 ± 0.101	1.965 ± 0.148	2.120 ± 0.173
Relative	5.477 ± 0.299	5.910 ± 0.327	5.711 ± 0.256	5.264 ± 0.288	5.919 ± 0.465	5.985 ± 0.369
Spleen						
Absolute	0.665 ± 0.012	0.723 ± 0.011	0.717 ± 0.015	0.750 ± 0.015**	0.752 ± 0.024**	0.893 ± 0.049**
Relative	1.892 ± 0.029	1.994 ± 0.034	2.064 ± 0.023*	2.109 ± 0.020**	2.255 ± 0.052**	2.538 ± 0.105**
R. Testis						
Absolute	1.486 ± 0.021	1.515 ± 0.020	1.478 ± 0.027	1.515 ± 0.028	1.477 ± 0.019	1.534 ± 0.028
Relative	4.229 ± 0.042	4.172 ± 0.041	4.259 ± 0.062	4.260 ± 0.037	4.441 ± 0.085*	4.375 ± 0.058*
Thymus						
Absolute	0.320 ± 0.009	0.348 ± 0.010	0.339 ± 0.008	0.346 ± 0.013	0.293 ± 0.013	0.326 ± 0.009
Relative	0.910 ± 0.025	0.961 ± 0.034	0.977 ± 0.026	0.973 ± 0.034	0.880 ± 0.037	0.930 ± 0.025

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Female						
n	10	10	10	10	10	10
Necropsy body wt	191 ± 4	197 ± 3	204 ± 5*	198 ± 4	191 ± 3	195 ± 4
Heart						
Absolute	0.645 ± 0.016	0.662 ± 0.015	0.678 ± 0.010	0.685 ± 0.014	0.655 ± 0.015	0.697 ± 0.017
Relative	3.382 ± 0.056	3.362 ± 0.067	3.339 ± 0.067	3.460 ± 0.059	3.424 ± 0.071	3.581 ± 0.072
R. Kidney						
Absolute	0.596 ± 0.017	0.599 ± 0.013	0.617 ± 0.014	0.601 ± 0.012	0.602 ± 0.011	0.653 ± 0.018*
Relative	3.123 ± 0.050	3.038 ± 0.040	3.032 ± 0.051	3.035 ± 0.033	3.150 ± 0.065	3.349 ± 0.054*
Liver						
Absolute	5.929 ± 0.117	6.677 ± 0.137**	7.021 ± 0.175**	6.928 ± 0.114**	7.009 ± 0.096**	8.901 ± 0.182**
Relative	31.12 ± 0.487	33.89 ± 0.487**	34.48 ± 0.573**	35.01 ± 0.598**	36.73 ± 0.798**	45.73 ± 0.643**
Lung						
Absolute	1.058 ± 0.033	1.114 ± 0.039	1.220 ± 0.025*	1.149 ± 0.042*	1.157 ± 0.027*	1.235 ± 0.048**
Relative	5.558 ± 0.161	5.659 ± 0.186	6.000 ± 0.128	5.793 ± 0.163	6.065 ± 0.192	6.336 ± 0.194**
Spleen						
Absolute	0.511 ± 0.013	0.514 ± 0.018	0.529 ± 0.012	0.545 ± 0.013	0.553 ± 0.016	0.615 ± 0.015**
Relative	2.680 ± 0.055	2.609 ± 0.092	2.601 ± 0.057	2.753 ± 0.052	2.898 ± 0.100	3.169 ± 0.094**
Thymus						
Absolute	0.252 ± 0.012	0.255 ± 0.008	0.257 ± 0.007	0.261 ± 0.009	0.247 ± 0.009	0.256 ± 0.010
Relative	1.324 ± 0.059	1.294 ± 0.035	1.261 ± 0.034	1.317 ± 0.041	1.291 ± 0.039	1.314 ± 0.050

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

Table G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Gavage Study of Elmiron®[a]

	Vehicle Control	33 mg/kg	111 mg/kg	333 mg/kg	1,000 mg/kg	3,000 mg/kg
Male						
n	5	5	5	5	5	5
Necropsy body wt	25.4 ± 0.4	25.9 ± 0.3	26.1 ± 0.8	26.3 ± 0.6	26.2 ± 0.6	25.9 ± 0.2
Heart						
Absolute	0.177 ± 0.003[b]	0.120 ± 0.003	0.122 ± 0.005	0.121 ± 0.003	0.115 ± 0.003	0.113 ± 0.003
Relative	4.590 ± 0.075[b]	4.623 ± 0.065	4.682 ± 0.090	4.605 ± 0.072	4.395 ± 0.087	4.383 ± 0.110
R. Kidney						
Absolute	0.200 ± 0.004	0.219 ± 0.004	0.218 ± 0.011	0.227 ± 0.010	0.219 ± 0.003	0.227 ± 0.008
Relative	7.854 ± 0.124	8.479 ± 0.151	8.342 ± 0.228	8.651 ± 0.299	8.351 ± 0.239	8.775 ± 0.267*
Liver						
Absolute	1.289 ± 0.021	1.330 ± 0.014	1.396 ± 0.048	1.373 ± 0.032	1.415 ± 0.042*	1.448 ± 0.048**
Relative	50.71 ± 0.128	51.43 ± 0.383	53.54 ± 1.196	52.25 ± 0.865	53.93 ± 0.884*	55.94 ± 1.690**
Lung						
Absolute	0.165 ± 0.006	0.142 ± 0.008*	0.153 ± 0.007	0.157 ± 0.003	0.164 ± 0.006	0.161 ± 0.002
Relative	6.505 ± 0.175	5.484 ± 0.324**	5.878 ± 0.212	5.978 ± 0.165	6.248 ± 0.142	6.214 ± 0.089
Spleen						
Absolute	0.067 ± 0.002	0.067 ± 0.002	0.072 ± 0.003	0.070 ± 0.001	0.073 ± 0.003	0.076 ± 0.002*
Relative	2.643 ± 0.078	2.590 ± 0.067	2.761 ± 0.065	2.674 ± 0.037	2.795 ± 0.134	2.944 ± 0.077
R. Testis						
Absolute	0.104 ± 0.005	0.107 ± 0.002	0.102 ± 0.003	0.105 ± 0.005	0.105 ± 0.004	0.097 ± 0.007
Relative	4.095 ± 0.155	4.155 ± 0.066	3.895 ± 0.045	4.015 ± 0.180	4.004 ± 0.182	3.748 ± 0.267
Thymus						
Absolute	0.049 ± 0.003	0.044 ± 0.002	0.046 ± 0.003	0.051 ± 0.003	0.051 ± 0.002	0.052 ± 0.003
Relative	1.938 ± 0.106	1.721 ± 0.101	1.777 ± 0.113	1.961 ± 0.126	1.936 ± 0.038	1.992 ± 0.104

Table G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Gavage Study of Elmiron®

	Vehicle Control	33 mg/kg	111 mg/kg	333 mg/kg	1,000 mg/kg	3,000 mg/kg
Female						
n	5	5	5	5	5	5
Necropsy body wt	22.6 ± 0.6	21.6 ± 0.5	21.5 ± 0.6	21.8 ± 0.6	22.5 ± 0.8	22.6 ± 0.4
Heart						
Absolute	0.105 ± 0.003	0.105 ± 0.003	0.105 ± 0.002	0.105 ± 0.002	0.102 ± 0.003	0.100 ± 0.003
Relative	4.667 ± 0.049	4.854 ± 0.114	4.872 ± 0.061	4.817 ± 0.128	4.521 ± 0.068	4.447 ± 0.109
R. Kidney						
Absolute	0.152 ± 0.003	0.150 ± 0.005	0.142 ± 0.006	0.152 ± 0.002	0.145 ± 0.005	0.151 ± 0.006
Relative	6.741 ± 0.154	6.945 ± 0.183	6.633 ± 0.239	6.969 ± 0.096	6.441 ± 0.029	6.677 ± 0.200
Liver						
Absolute	1.108 ± 0.057	0.980 ± 0.044	0.988 ± 0.036	1.086 ± 0.037	1.158 ± 0.067	1.166 ± 0.027
Relative	48.97 ± 1.304	45.21 ± 1.089	45.97 ± 0.759	49.73 ± 0.844	51.25 ± 1.310	51.64 ± 0.710
Lung						
Absolute	0.163 ± 0.002	0.156 ± 0.005	0.160 ± 0.005	0.161 ± 0.009	0.160 ± 0.010	0.165 ± 0.005
Relative	7.236 ± 0.186	7.253 ± 0.418	7.453 ± 0.201	7.361 ± 0.335	7.086 ± 0.291	7.310 ± 0.110
Spleen						
Absolute	0.087 ± 0.004	0.082 ± 0.005	0.084 ± 0.003	0.091 ± 0.005	0.084 ± 0.003	0.091 ± 0.004
Relative	3.830 ± 0.113	3.792 ± 0.189	3.904 ± 0.137	4.149 ± 0.213	3.734 ± 0.092	4.056 ± 0.208
Thymus						
Absolute	0.068 ± 0.006	0.067 ± 0.004	0.065 ± 0.003	0.064 ± 0.004	0.069 ± 0.005	0.066 ± 0.003
Relative	3.017 ± 0.220	3.119 ± 0.197	3.031 ± 0.094	2.946 ± 0.214	3.067 ± 0.125	2.899 ± 0.098

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

Table G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Male						
n	10	10	10	10	10	10
Necropsy body wt	35.6 ± 1.1	35.7 ± 0.8	36.1 ± 1.0	35.5 ± 0.7	37.6 ± 1.0	35.3 ± 0.8
Heart						
Absolute	0.177 ± 0.011	0.170 ± 0.010	0.173 ± 0.006	0.174 ± 0.008	0.168 ± 0.007	0.161 ± 0.003
Relative	4.943 ± 0.212	4.739 ± 0.211	4.821 ± 0.193	4.890 ± 0.196	4.486 ± 0.198	4.586 ± 0.158
R. Kidney						
Absolute	0.261 ± 0.008	0.259 ± 0.008	0.259 ± 0.005	0.265 ± 0.006	0.265 ± 0.004	0.268 ± 0.006
Relative	7.349 ± 0.143	7.240 ± 0.139	7.207 ± 0.145	7.454 ± 0.164	7.090 ± 0.188	7.616 ± 0.178
Liver						
Absolute	1.493 ± 0.065	1.495 ± 0.036	1.573 ± 0.051	1.545 ± 0.034	1.714 ± 0.047**	1.831 ± 0.046**
Relative	41.86 ± 0.879	41.84 ± 0.545	43.56 ± 0.501	43.53 ± 0.795	45.63 ± 0.532**	51.89 ± 0.896**
Lung						
Absolute	0.304 ± 0.014	0.291 ± 0.020	0.301 ± 0.013	0.299 ± 0.009	0.290 ± 0.009	0.304 ± 0.017
Relative	8.563 ± 0.363	8.119 ± 0.507	8.406 ± 0.433	8.442 ± 0.277	7.769 ± 0.346	8.618 ± 0.451
Spleen						
Absolute	0.071 ± 0.002	0.073 ± 0.002	0.079 ± 0.003	0.073 ± 0.001	0.074 ± 0.002	0.083 ± 0.002**
Relative	2.003 ± 0.047	2.047 ± 0.051	2.194 ± 0.061	2.061 ± 0.035	1.986 ± 0.040	2.370 ± 0.081**
R. Testis						
Absolute	0.118 ± 0.004	0.116 ± 0.003	0.119 ± 0.003	0.117 ± 0.002	0.119 ± 0.001	0.120 ± 0.002
Relative	3.323 ± 0.064	3.262 ± 0.079	3.308 ± 0.129	3.289 ± 0.072	3.191 ± 0.083	3.419 ± 0.101
Thymus						
Absolute	0.044 ± 0.003	0.052 ± 0.003	0.049 ± 0.004	0.050 ± 0.002	0.054 ± 0.005	0.039 ± 0.002
Relative	1.228 ± 0.061	1.445 ± 0.088	1.369 ± 0.096	1.418 ± 0.056	1.436 ± 0.124	1.113 ± 0.053

Table G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Gavage Study of Elmiron®

	Vehicle Control	63 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
Female						
n	10	10	10	9	10	10
Necropsy body wt	27.9 ± 0.8	27.9 ± 1.0	29.9 ± 0.9	28.0 ± 0.5	27.4 ± 0.8	29.3 ± 0.8
Heart						
Absolute	0.134 ± 0.005	0.128 ± 0.006	0.138 ± 0.004	0.135 ± 0.005	0.136 ± 0.008	0.134 ± 0.007
Relative	4.795 ± 0.163	4.582 ± 0.164	4.634 ± 0.164	4.844 ± 0.209	4.977 ± 0.234	4.601 ± 0.258
R. Kidney						
Absolute	0.156 ± 0.003	0.154 ± 0.004	0.161 ± 0.004	0.161 ± 0.005	0.155 ± 0.004	0.165 ± 0.004
Relative	5.605 ± 0.067	5.544 ± 0.148	5.396 ± 0.088	5.769 ± 0.168	5.679 ± 0.127	5.669 ± 0.147
Liver						
Absolute	1.218 ± 0.030	1.226 ± 0.030	1.298 ± 0.037	1.325 ± 0.033	1.297 ± 0.038	1.591 ± 0.076**
Relative	43.69 ± 0.795	44.16 ± 0.760	43.51 ± 0.460	47.39 ± 1.122*	47.50 ± 0.695*	54.32 ± 1.888**
Lung						
Absolute	0.281 ± 0.009	0.281 ± 0.015	0.262 ± 0.011	0.273 ± 0.008	0.249 ± 0.012	0.258 ± 0.016
Relative	10.05 ± 0.193	10.08 ± 0.387	8.808 ± 0.365	9.769 ± 0.211	9.116 ± 0.336	8.791 ± 0.436*
Spleen						
Absolute	0.091 ± 0.003	0.090 ± 0.002	0.103 ± 0.006	0.103 ± 0.007	0.095 ± 0.003	0.106 ± 0.005
Relative	3.268 ± 0.111	3.232 ± 0.087	3.433 ± 0.127	3.679 ± 0.275	3.469 ± 0.093	3.640 ± 0.180
Thymus						
Absolute	0.046 ± 0.003	0.049 ± 0.002	0.049 ± 0.003	0.049 ± 0.002	0.049 ± 0.002	0.050 ± 0.002
Relative	1.656 ± 0.062	1.746 ± 0.038	1.636 ± 0.087	1.735 ± 0.068	1.772 ± 0.055	1.721 ± 0.075

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

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

Table H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	250 mg/kg	500 mg/kg	1,000 mg/kg
n	10	10	9	8
Weights (g)				
Necropsy body wt	351 ± 5	356 ± 7	333 ± 5	351 ± 8
L. Cauda epididymis	0.146 ± 0.00	0.140 ± 0.00	0.143 ± 0.00	0.148 ± 0.00
L. Epididymis	0.432 ± 0.00	0.424 ± 0.01	0.431 ± 0.01	0.438 ± 0.01
L. Testis	1.554 ± 0.02	1.570 ± 0.03	1.532 ± 0.02	1.597 ± 0.04
Spermatid measurements				
Spermatid heads (10^7/g testis)	6.704 ± 0.28	7.196 ± 0.35	6.700 ± 0.43	6.503 ± 0.20
Spermatid heads (10^7/testis)	10.410 ± 0.44	11.280 ± 0.53	10.222 ± 0.56	10.363 ± 0.33
Spermatid count (mean/10^{-4} mL suspension)	52.050 ± 2.18	56.400 ± 2.67	51.111 ± 2.79	51.813 ± 1.66
Epididymal spermatozoal measurements				
Motility (%)	71.95 ± 0.71	69.97 ± 0.99	70.34 ± 1.50	71.08 ± 1.62
Concentration (10^6/g cauda epididymal tissue)	636 ± 33	689 ± 40	628 ± 39	575 ± 30

[a] Data are given as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).

Table H2
Estrous Cycle Characterization for Female Rats in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	250 mg/kg	500 mg/kg	1,000 mg/kg
n	10	10	10	10
Necropsy body wt (g)	191 ± 3	198 ± 3	191 ± 3	195 ± 4
Estrous cycle length (days)	5.0 ± 0.5	4.7 ± 0.2	4.6 ± 0.2	4.7 ± 0.1
Estrous stages (% of cycle)				
Diestrus	23.3	20.8	29.2	21.7
Proestrus	25.8	29.2	23.3	24.2
Estrus	33.3	25.8	25.8	27.5
Metestrus	17.5	24.2	21.7	26.7

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	250 mg/kg	500 mg/kg	1,000 mg/kg
n	10	10	10	10
Weights (g)				
Necropsy body wt	35.6 ± 1.1	35.5 ± 0.7	37.6 ± 1.0	35.3 ± 0.8
L. Cauda epididymis	0.0139 ± 0.0004	0.0139 ± 0.0005	0.0135 ± 0.0005	0.0131 ± 0.0004
L. Epididymis	0.0416 ± 0.0011	0.0420 ± 0.0007	0.0418 ± 0.0009	0.0414 ± 0.0008
L. Testis	0.1145 ± 0.0039	0.1106 ± 0.0019	0.1143 ± 0.0016	0.1143 ± 0.0019
Spermatid measurements				
Spermatid heads (10^7/g testis)	14.9 ± 0.8	15.1 ± 1.2	14.6 ± 0.8	13.8 ± 0.4
Spermatid heads (10^7/testis)	1.719 ± 0.128	1.659 ± 0.119	1.667 ± 0.090	1.581 ± 0.063
Spermatid count (mean/10^{-4} mL suspension)	53.750 ± 4.018	51.800 ± 3.720	52.100 ± 2.817	49.400 ± 1.976
Epididymal spermatozoal measurements				
Motility (%)	72.52 ± 0.90[b]	71.29 ± 1.70	71.73 ± 1.05	71.41 ± 0.84
Concentration (10^6/g cauda epididymal tissue)	832 ± 109	954 ± 110	1,111 ± 70	1,061 ± 86

[a] Data are given as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).
[b] n=9

TABLE H4
Estrous Cycle Characterization for Female Mice in the 3-Month Gavage Study of Elmiron®[a]

	Vehicle Control	250 mg/kg	500 mg/kg	1,000 mg/kg
n	10	10	10	10
Necropsy body wt (g)	27.9 ± 0.8	28.2 ± 0.5	27.4 ± 0.8	29.3 ± 0.8
Estrous cycle length (days)	4.7 ± 0.4[b]	4.2 ± 0.1[b]	4.3 ± 0.2[b]	4.7 ± 0.4
Estrous stages (% of cycle)				
Diestrus	15.0	21.7	10.0	17.5
Proestrus	24.2	25.8	32.5	20.8
Estrus	24.2	24.2	30.8	28.3
Metestrus	36.7	28.3	26.7	33.3

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF ELMIRON®

Elmiron® was obtained from Baker Norton Pharmaceuticals (Miami, FL) in three lots. Lot 30018-01 was used in the 2-week studies, lot R50996-08 was used in the 3-month studies, and lot R60819-10 was used in the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory (Research Triangle Institute, Research Triangle Park, NC) and by the 3-month and 2-year study laboratory. Reports on analyses performed in support of the Elmiron® studies are on file at the National Institute of Environmental Health Sciences.

All lots of the chemical, a white powder, were identified as Elmiron® by the analytical chemistry laboratory using molecular weight, refractive index, pH, optical rotation, and sulfur content (determined by Galbraith Laboratories, Knoxville, TN). Lots R50996-08 and R60819-10 were identified by the study laboratory with infrared spectroscopy. Molecular weight was determined using gel permeation high-performance liquid chromatography (HPLC) by systems A (lot 30018-01), B (lot R50996-08), or C and D (lot R60819-10) (Table I1). Sulfur content was determined by elemental analysis. The observed molecular weights of 3,428 (lot 30018-01), 2,766 (lot R50996-08), and 4,556 or 5,020 (HPLC systems C and D, respectively; lot R60819-10) were consistent with the literature range (*Merck Index*, 1996). The refractive indices of 1.3444 ± 0.002 (lot 30018-01), 1.3453 ± 0.0001 (lot R50996-08), and 1.3444 ± 0.0002 (lot R60819-10) were in agreement with the literature value of 1.344 (*Merck Index*, 1996). The pH values of 5.79 (lot 30018-01), 5.22 (lot R50996-08), and 6.44 (lot R60819-10) were consistent with the literature value of approximately 6.0 (*Merck Index*, 1996). The optical rotations of –56.5° ± 1.0° (lot 30018-01), –58.0° ± 0.9° (lot R50996-08), and –56.6° ± 0.18° (lot R60819-10) were consistent with the literature value of –57° (*Merck Index*, 1996). The sulfur contents of all lots were greater than 15%, consistent with manufacturer specifications. Because all measured parameters were in general agreement with manufacturer specifications, the three lots of chemical were presumed to consist largely, if not wholly, of sulfated xylan. The infrared spectra were consistent with the structure of Elmiron®. The infrared spectrum of lot R60819-10 is presented in Figure I1.

Purity analysis of this test article was not typical because the characteristics of the material were defined by manufacturing specifications. Therefore, chromatographic analyses were conducted to characterize the molecular weight profile over the course of the studies. Characterization of all three Elmiron® lots was conducted by the analytical chemistry laboratory using Karl Fischer titration and HPLC. HPLC analyses were performed with the systems described for molecular weight determinations.

For lot 30018-01, Karl Fischer titration indicated 6.88% ± 0.94% water. HPLC by system A indicated a major peak, one lesser peak with an area of 13% of the total area, and three minor impurities with areas of 0.2% or less. For lot R50996-08, Karl Fischer titration indicated 4.06% ± 0.83% water. HPLC by system B indicated a major peak only. For lot R60819-10, Karl Fischer titration indicated 3.37% ± 0.17% water. HPLC by system C indicated a major peak and one impurity peak accounting for 10.4% of the total peak area. HPLC by system D indicated a major peak and two impurity peaks with areas of 11.3% and 0.7% of the total peak area.

Stability data provided by the manufacturer showed no degradation of the bulk chemical when stored at 80° C for 48 hours. All lots of the bulk chemical were stored in amber glass containers with Teflon®-lined lids at room temperature, protected from light. Stability of the bulk chemical was monitored by the study laboratory during the 3-month and 2-year studies using HPLC by systems A and B. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

Dose formulations were prepared once (2-week studies) or every 4 weeks (3-month and 2-year studies) by mixing Elmiron® with deionized water (Table I2). Formulations were stored refrigerated in glass bottles for up to 4 weeks (2-week studies) or 35 days.

Stability studies of a 2.53 mg/mL dose formulation were conducted by the analytical chemistry laboratory using HPLC by system A. Stability was confirmed for 35 days for dose formulations stored in polypropylene vials at temperatures up to 28°C or for 3 hours under simulated animal room conditions.

During the 2-week studies, the dose formulations were analyzed once by the analytical chemistry laboratory using HPLC by system E; animal room samples (samples taken after dosing from the dosing vials) of these dose formulations were also analyzed with HPLC by system A (Table I3). All 10 dose formulations were within 10% of the target concentrations, with no value greater than 108% of the target concentrations; all animal room samples were also within 10% of the target concentrations. During the 3-month studies, the dose formulations were analyzed by the study laboratory using HPLC by system A at the beginning, midpoint, and end of the studies; animal room samples of these dose formulations were also analyzed (Table I4). All 18 dose formulations analyzed were within 10% of the target concentrations, with no value greater than 106% of the target concentration; all animal room samples analyzed were also within 10% of the target concentrations. During the 2-year studies, the dose formulations were analyzed by the study laboratory using HPLC by system B approximately every 8 or 12 weeks; animal room samples were analyzed periodically (Table I5). Of the dose formulations analyzed, all 66 were within 10% of the target concentrations, with no value greater than 109% of the target concentration; all animal room samples analyzed were also within 10% of the target concentrations.

Table I1
High-Performance Liquid Chromatography Systems Used in the Gavage Studies of Elmiron®[a]

Detection System	Column	Solvent System
System A		
Refractive index	Diol GPC (25 cm × 7.8 mm) with 300-Å pore size and Diol GPC (25 cm × 7.8 mm) with 60-Å pore size, in series (ES Industries, West Berlin, NJ)	25 mM potassium phosphate, monobasic: 25 mM potassium phosphate, dibasic: 50 mM potassium chloride; flow rate 0.7 mL/minute
System B		
Refractive index	Diol GPC (30 cm × 8.0 mm) with 300-Å pore size and Diol GPC (30 cm × 8.0 mm) with 60-Å pore size, in series (YMC, Komatsu City, Japan)	25 mM potassium phosphate, monobasic: 25 mM potassium phosphate, dibasic: 50 mM potassium chloride; flow rate 0.7 mL/minute
System C		
Refractive index	YMC-Pack Diol-AP (30 cm × 8.0 mm) with 300-Å pore size and YMC-Pack Diol-ASP (30 cm × 8.0 mm) with 60-Å pore size, in series (YMC)	25 mM potassium phosphate, monobasic: 25 mM potassium phosphate, dibasic: 50 mM potassium chloride in water; flow rate 0.7 mL/minute
System D		
Refractive index	BioSep SEC-S2000 (30 cm × 7.8 mm) (Phenomenex, Torrance, CA)	0.9% sodium chloride in water; flow rate 0.5 mL/minute
System E		
Refractive index	YMC-Pack Diol GPC (30 cm × 8.0 mm) with 300-Å pore size and YMC-Pack Diol GPC (30 cm × 8.0 mm) with 60 Å pore size, in series (YMC)	Acetonitrile in water (5:95): 25 mM potassium phosphate, monobasic: 25 mM potassium phosphate, dibasic: 50 mM potassium chloride; flow rate 0.7 mL/minute

[a] High-performance liquid chromatographs were manufactured by Waters Corp. (Milford, MA).

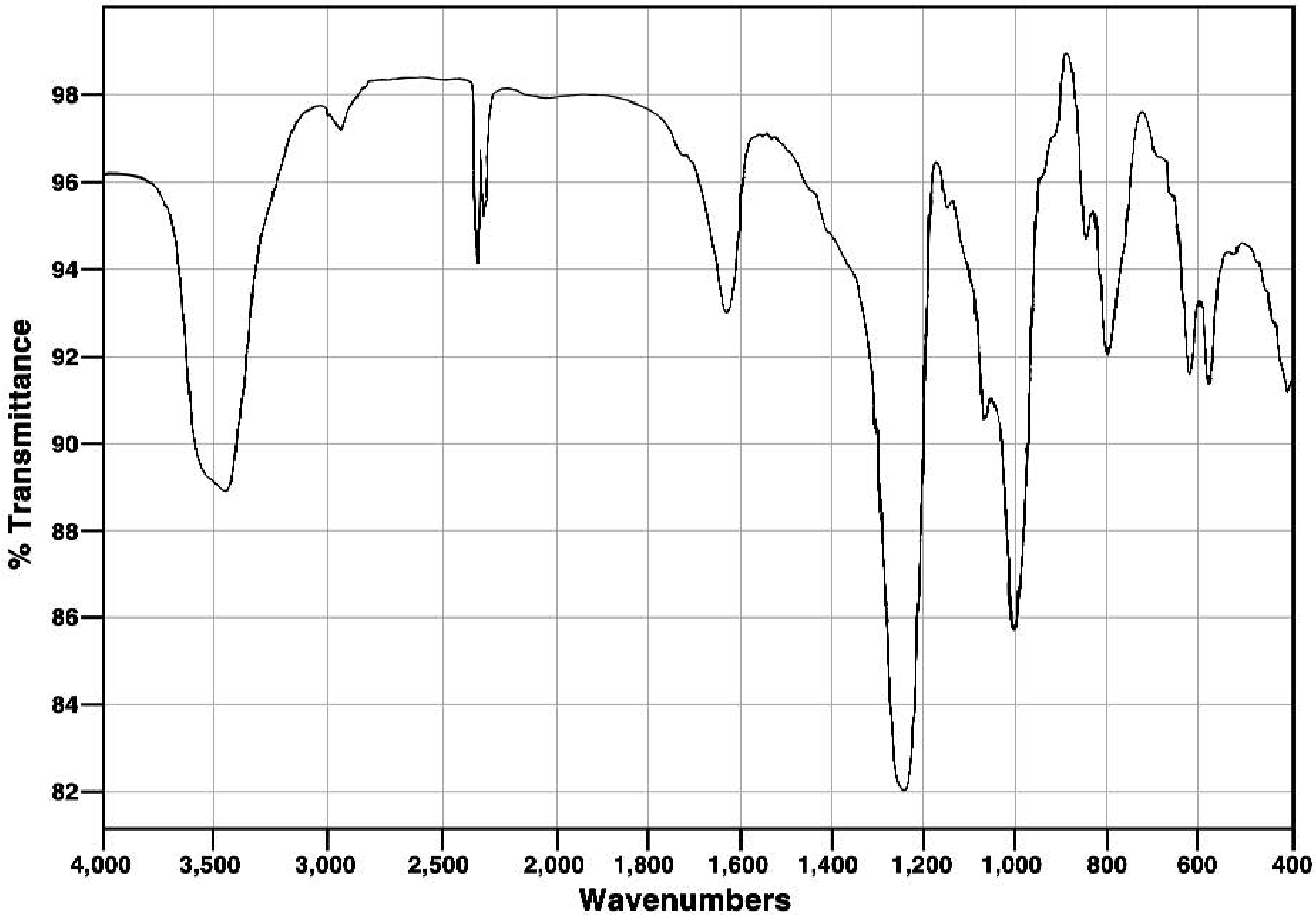

FIGURE I1
Infrared Absorption Spectrum of Elmiron®

Table I2
Preparation and Storage of Dose Formulations in the Gavage Studies of Elmiron®

2-Week Studies	3-Month Studies	2-Year Studies
Preparation		
Elmiron® was mixed with Milli-Q deionized water. The dose formulations were prepared once.	Elmiron® was added to deionized water and stirred with a magnetic stir bar until a solution was formed. The dose formulations were prepared every 4 weeks.	Same as 3-month studies.
Chemical Lot Number		
30018-01	R50996-08	R60819-10
Maximum Storage Time		
4 weeks	35 days	35 days
Storage Conditions		
Stored refrigerated in glass bottles	amber glass containers with Teflon®-lined lids	amber glass containers with Teflon®-lined lids
Study Laboratory		
Microbiological Associates, Inc. (Bethesda, MD)	Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)

Table I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Week Gavage Studies of Elmiron®

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
March 23, 1995	May 4-5, 1995	7	7.50	+7
		22	23.6	+7
		67	69.1	+3
		200	211	+6
		600	585	–2
	May 5, 1995[b]	7	7.11	+2
		22	22.5	+2
		67	68.9	+3
		200	215	+8
		600	588	–2
Mice				
March 23, 1995	May 4-5, 1995	3.3	3.44	+4
		11	11.9	+8
		33	34.7	+5
		100	104	+4
		300	314	+5
	May 5, 1995[b]	3.3	3.21	–3
		11	11.9	+8
		33	33.8	+2
		100	105	+5
		300	325	+8

[a] Results of duplicate analyses due to analytical problems. For rats, dosing volume=5 mL/kg; 7 mg/mL=33 mg/kg, 22 mg/mL=111 mg/kg, 67 mg/mL=333 mg/kg, 200 mg/mL=1,000 mg/kg, 600 mg/mL=3,000 mg/kg; for mice, dosing volume=10 mL/kg; 3.3 mg/mL=33 mg/kg, 11 mg/mL=111 mg/kg, 33 mg/mL=333 mg/kg, 100 mg/mL=1,000 mg/kg, 300 mg/mL=3,000 mg/kg

[b] Animal room samples

Table I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Gavage Studies of Elmiron®

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
March 18, 1996	March 19-21, 1996	12.5	12.39	–1
		25	24.40	–2
		50	50.95	+2
		100	97.98	–2
		200	200.4	0
	April 22-23, 1996[b]	12.5	12.87	+3
		25	26.22	+5
		50	51.50	+3
		100	102.8	+3
		200	200.3	0
May 13, 1996	May 14-15, 1996	12.5	12.85	+3
		25	25.75	+3
		50	51.25	+3
		100	105.5	+6
		200	205.9	+3
	June 18-19, 1996[b]	12.5	12.59	+1
		25	25.27	+1
		50	49.96	0
		100	97.82	–2
		200	203.8	+2
June 10, 1996	June 11-12, 1996	12.5	12.64	+1
		25	24.60	–2
		50	51.40	+3
		100	103.9	+4
		200	206.7	+3
	July 1-2, 1996[b]	12.5	12.39	–1
		25	24.92	0
		50	50.79	+2
		100	102.9	+3
		200	209.4	+5

Table I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Gavage Studies of Elmiron®

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Mice				
March 18, 1996	March 19-21, 1996	6.3	6.090	–3
		12.5	12.39	–1
		25	24.40	–2
		50	50.95	+2
		100	97.98	–2
	April 22-23, 1996[b]	6.3	6.228	–1
		12.5	12.82	+3
		25	26.00	+4
		50	50.35	+1
		100	103.9	+4
May 13, 1996	May 14-15, 1996	6.3	6.037	–4
		12.5	12.85	+3
		25	25.75	+3
		50	51.25	+3
		100	105.5	+6
	June 18-19, 1996[b]	6.3	6.223	–1
		12.5	12.59	+1
		25	25.05	0
		50	50.64	+1
		100	98.87	–1
June 10, 1996	June 11-12, 1996	6.3	6.439	+2
		12.5	12.64	+1
		25	24.60	–2
		50	51.40	+3
		100	103.9	+4
	July 1-2, 1996[b]	6.3	6.333	+1
		12.5	12.67	+1
		25	25.47	+2
		50	50.95	+2
		100	102.3	+2

[a] Results of duplicate analyses. For rats, dosing volume=5 mL/kg; 12.5 mg/mL=63 mg/kg, 25 mg/mL=125 mg/kg, 50 mg/mL=250 mg/kg, 100 mg/mL=500 mg/kg, 200 mg/mL=1,000 mg/kg; for mice, dosing volume=10 mL/kg; 6.3 mg/mL=63 mg/kg, 12.5 mg/mL=125 mg/kg, 25 mg/mL=250 mg/kg, 50 mg/mL=500 mg/kg, 100 mg/mL=1,000 mg/kg

[b] Animal room samples

Table I5
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Elmiron®

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
June 18, 1997	June 19-21, 1997	2.8	2.803	0
		5.6	5.585	0
		8.4	8.178	–3
		16.8	16.44	–2
		25.2	24.77	–2
		50.4	50.07	–1
	July 23-25, 1997[b]	2.8	2.830	+1
		5.6	5.536	–1
		8.4	8.174	–3
		16.8	16.40	–2
		25.2	24.33	–3
		50.4	49.89	–1
August 13, 1997	August 22-24, 1997	2.8	2.703	–3
		5.6	5.475	–2
		8.4	8.290	–1
		16.8	16.77	0
		25.2	24.69	–2
		50.4	51.02	+1
November 5, 1997	November 6-8, 1997	2.8	2.820	+1
		5.6	5.688	+2
		8.4	8.335	–1
		16.8	17.17	+2
		25.2	25.35	+1
		50.4	51.86	+3
December 31, 1997	January 5-7, 1998	2.8	2.962	+6
		5.6	5.798	+4
		8.4	8.648	+3
		16.8	17.70	+5
		25.2	25.98	+3
		50.4	52.96	+5
	February 6-8, 1998[b]	2.8	2.974	+6
		5.6	5.884	+5
		8.4	8.448	+1
		16.8	17.18	+2
		25.2	25.35	+1
		50.4	52.59	+4
March 25, 1998	March 25-27, 1998	2.8	2.866	+2
		5.6	5.744	+3
		8.4	8.770	+4
		16.8	17.44	+4
		25.2	26.36	+5
		50.4	52.61	+4

Table I5
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Elmiron®

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)				
May 20, 1998	May 21-22, 1998	2.8	2.828	+1
		5.6	5.747	+3
		8.4	8.397	0
		16.8	16.96	+1
		25.2	25.78	+2
		50.4	51.32	+2
August 12, 1998	August 13-14, 1998	2.8	2.919	+4
		5.6	5.805	+4
		8.4	8.887	+6
		16.8	17.80	+6
		25.2	25.84	+3
		50.4	52.36	+4
	September 18-20, 1998[b]	2.8	3.024	+8
		5.6	5.948	+6
		8.4	9.077	+8
		16.8	17.84	+6
		25.2	26.37	+5
		50.4	54.24	+8
October 7, 1998	October 8-10, 1998	2.8	3.024	+8
		5.6	5.751	+3
		8.4	8.781	+5
		16.8	17.45	+4
		25.2	26.34	+5
		50.4	53.38	+6
December 30, 1998	December 31, 1998-January 1, 1999	2.8	2.921	+4
		5.6	5.941	+6
		8.4	8.816	+5
		16.8	17.68	+5
		25.2	26.40	+5
		50.4	53.40	+6
February 24, 1999	February 24-25, 1999	2.8	2.839	+1
		5.6	5.697	+2
		8.4	8.588	+2
		16.8	17.32	+3
		25.2	25.55	+1
		50.4	51.26	+2
	April 6-8, 1999[b]	2.8	3.058	+9
		5.6	5.867	+5
		8.4	8.706	+4
		16.8	17.66	+5
		25.2	26.52	+5
		50.4	52.32	+4

Table I5
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Elmiron®

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)				
May 19, 1999	May 20-21, 1999	2.8	3.045	+9
		5.6	5.770	+3
		8.4	8.784	+5
		16.8	17.59	+5
		25.2	26.54	+5
		50.4	53.25	+6
Mice				
June 18, 1997	June 19-21, 1997	5.6	5.585	0
		16.8	16.44	-2
		50.4	50.07	-1
	July 23-25, 1997[b]	5.6	5.625	0
		16.8	16.38	-2
		50.4	50.56	0
August 13, 1997	August 22-24, 1997	5.6	5.475	-2
		16.8	16.77	0
		50.4	51.02	+1
November 5, 1997	November 6-8, 1997	5.6	5.688	+2
		16.8	17.17	+2
		50.4	51.86	+3
December 31, 1997	January 5-7, 1998	5.6	5.798	+4
		16.8	17.70	+5
		50.4	52.96	+5
	February 6-8, 1998[b]	5.6	5.923	+6
		16.8	17.49	+4
		50.4	53.37	+6
March 25, 1998	March 25-27, 1998	5.6	5.744	+3
		16.8	17.44	+4
		50.4	52.61	+4
May 20, 1998	May 21-22, 1998	5.6	5.747	+3
		16.8	16.96	+1
		50.4	51.32	+2
August 12, 1998	August 13-14, 1998	5.6	5.805	+4
		16.8	17.80	+6
		50.4	52.36	+4
	September 18-20, 1998[b]	5.6	6.119	+9
		16.8	18.08	+8
		50.4	54.18	+8

Table I5
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Elmiron®

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
October 7, 1998	October 8-10, 1998	5.6	5.751	+3
		16.8	17.45	+4
		50.4	53.38	+6
December 30, 1998	December 31, 1998-January 1, 1999	5.6	5.941	+6
		16.8	17.68	+5
		50.4	53.40	+6
February 24, 1999	February 24-25, 1999	5.6	5.697	+2
		16.8	17.32	+3
		50.4	51.26	+2
	April 6-8, 1999[b]	5.6	5.833	+5
		16.8	17.54	+4
		50.4	53.58	+6
May 19, 1999	May 20-21, 1999	5.6	5.770	+3
		16.8	17.59	+5
		50.4	53.25	+6

[a] Results of duplicate analyses. For rats, dosing volume=5 mL/kg; 2.8 mg/mL=14 mg/kg, 5.6 mg/mL=28 mg/kg, 8.4 mg/mL=42 mg/kg, 16.8 mg/mL=84 mg/kg, 25.2 mg/mL=126 mg/kg, 50.4 mg/mL=252 mg/kg; for mice, dosing volume=10 mL/kg; 5.6 mg/mL=56 mg/kg, 16.8 mg/mL=168 mg/kg, 50.4 mg/mL=504 mg/kg

[b] Animal room samples

APPENDIX J
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

Table J1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

Table J2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

Table J3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.1 ± 0.36	12.5 – 13.8	24
Crude fat (% by weight)	8.1 ± 0.26	7.6 – 8.6	24
Crude fiber (% by weight)	9.3 ± 0.71	7.9 – 10.3	24
Ash (% by weight)	5.0 ± 0.16	4.7 – 5.3	24
Amino Acids (% of total diet)			
Arginine	0.731 ± 0.050	0.670 – 0.800	8
Cystine	0.224 ± 0.012	0.210 – 0.240	8
Glycine	0.684 ± 0.041	0.620 – 0.740	8
Histidine	0.333 ± 0.018	0.310 – 0.350	8
Isoleucine	0.524 ± 0.046	0.430 – 0.590	8
Leucine	1.061 ± 0.061	0.960 – 1.130	8
Lysine	0.708 ± 0.056	0.620 – 0.790	8
Methionine	0.401 ± 0.035	0.350 – 0.460	8
Phenylalanine	0.598 ± 0.036	0.540 – 0.640	8
Threonine	0.501 ± 0.051	0.430 – 0.590	8
Tryptophan	0.126 ± 0.014	0.110 – 0.150	8
Tyrosine	0.390 ± 0.056	0.280 – 0.460	8
Valine	0.640 ± 0.049	0.550 – 0.690	8
Essential Fatty Acids (% of total diet)			
Linoleic	3.97 ± 0.284	3.59 – 4.54	8
Linolenic	0.30 ± 0.042	0.21 – 0.35	8
Vitamins			
Vitamin A (IU/kg)	5,390 ± 1,203	3,280 – 7,790	24
Vitamin D (IU/kg)	1,000[a]		
α -Tocopherol (ppm)	82.2 ± 14.08	62.2 – 107.0	8
Thiamine (ppm)[b]	7.6 ± 0.91	6.1 – 9.3	24
Riboflavin (ppm)	5.6 ± 1.12	4.20 – 7.70	8
Niacin (ppm)	74.3 ± 5.94	66.4 – 85.8	8
Pantothenic acid (ppm)	22.5 ± 3.96	17.4 – 29.1	8
Pyridoxine (ppm)[b]	9.04 ± 2.37	6.4 – 12.4	8
Folic acid (ppm)	1.64 ± 0.38	1.26 – 2.32	8
Biotin (ppm)	0.333 ± 0.15	0.225 – 0.704	8
Vitamin B_{12} (ppb)	68.7 ± 63.0	18.3 – 174.0	8
Choline (ppm)	3,155 ± 325	2,700 – 3,790	8
Minerals			
Calcium (%)	0.970 ± 0.040	0.905 – 1.050	24
Phosphorus (%)	0.544 ± 0.024	0.496 – 0.582	24
Potassium (%)	0.659 ± 0.022	0.627 – 0.691	8
Chloride (%)	0.357 ± 0.027	0.300 – 0.392	8
Sodium (%)	0.189 ± 0.019	0.160 – 0.212	8
Magnesium (%)	0.199 ± 0.009	0.185 – 0.213	8
Sulfur (%)	0.178 ± 0.021	0.153 – 0.209	8
Iron (ppm)	160 ± 14.7	135 – 177	8
Manganese (ppm)	50.3 ± 4.82	42.1 – 56.0	8
Zinc (ppm)	50.7 ± 6.59	43.3 – 61.1	8
Copper (ppm)	6.29 ± 0.828	5.08 – 7.59	8
Iodine (ppm)	0.461 ± 0.187	0.233 – 0.843	8
Chromium (ppm)	0.542 ± 0.128	0.330 – 0.707	7
Cobalt (ppm)	0.23 ± 0.049	0.20 – 0.30	7

[a] From formulation
[b] As hydrochloride

TABLE J4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.20 ± 0.133	0.10 – 0.50	24
Cadmium (ppm)	0.04 ± 0.012	0.04 – 0.10	24
Lead (ppm)	0.09 ± 0.039	0.06 – 0.25	24
Mercury (ppm)	<0.02		24
Selenium (ppm)	0.17 ± 0.033	0.13 – 0.28	24
Aflatoxins (ppb)	<5.00		24
Nitrate nitrogen (ppm)[c]	16.1 ± 8.17	9.04 – 39.6	24
Nitrite nitrogen (ppm)[c]	<0.61		24
BHA (ppm)[d]	1.1 ± 0.37	1.0 – 2.5	24
BHT (ppm)[d]	1.0 ± 0.14	1.0 – 1.7	24
Aerobic plate count (CFU/g)	<10		24
Coliform (MPN/g)	1.3 ± 0.61	0 – 3	24
Escherichia coli (MPN/g)	<10		24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[e]	5.0 ± 1.83	2.1 – 8.8	24
N-Nitrosodimethylamine (ppb)[e]	2.0 ± 0.92	1.0 – 5.1	24
N-Nitrosopyrrolidine (ppb)[e]	3.0 ± 1.37	1.0 – 5.6	24
Pesticides (ppm)			
α-BHC	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.10		24
Estimated PCBs	<0.20		24

Table J4
Contaminant Levels in NTP-2000 Rat and Mouse Ration

	Mean ± Standard Deviation	Range	Number of Samples
Pesticides (ppm) (continued)			
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl chlorpyrifos	0.101 ± 0.086	0.020 – 0.368	24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.330 ± 0.568	0.020 – 2.810	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

[a] All samples were irradiated. CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX K
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 3-month and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to MA Bioservices/BioReliance (Rockville, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
3-Month Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	1 month, study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	1 month, study termination
Sendai	1 month, study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	1 month, study termination
KRV (Kilham rat virus)	1 month, study termination
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
RCV/SDA	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
M. arthritidis	Study termination
Parvovirus	6, 12, and 18 months, study termination
RCV/SDA	18 months
Sendai	12 months
Hemagglutination Inhibition	
H-1	1 month
KRV	1 month

Method and Test	Time of Analysis
MICE	
3-Month Study	
ELISA	
Ectromelia virus	1 month, study termination
EDIM (epizootic diarrhea of infant mice)	1 month, study termination
GDVII (mouse encephalomyelitis virus)	1 month, study termination
LCM (lymphocytic choriomeningitis virus)	1 month, study termination
Mouse adenoma virus-FL	1 month, study termination
MHV (mouse hepatitis virus)	1 month, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1 month, study termination
Reovirus 3	1 month, study termination
Sendai	1 month, study termination
Immunofluorescence Assay	
EDIM	1 month
GDVII	1 month
LCM	1 month
Mouse adenoma virus-FL	1 month
MCMV (mouse cytomegalovirus)	Study termination
MHV	1 month
Reovirus 3	1 month
Hemagglutination Inhibition	
K (papovavirus)	1 month, study termination
MVM (minute virus of mice)	1 month, study termination
Polyoma virus	1 month, study termination

Method and Test	Time of Analysis
MICE	
2-Year Study	
ELISA	
Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM	1, 6, 12, and 18 months, study termination
GDVII	1, 6, 12, and 18 months, study termination
LCM	1, 6, 12, and 18 months, study termination
Mouse adenoma virus-FL	1, 6, 12, and 18 months, study termination
MHV	1, 6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Mouse adenoma virus-FL	18 months, study termination
MCMV	Study termination
M. arthritidis	Study termination
Parvovirus	6, 12, and 18 months, study termination
PVM	18 months, study termination
Hemagglutination Inhibition	
K	1 month
MVM	1 month
Polyoma virus	1 month

RESULTS

All test results were negative.

APPENDIX L
ELMIRON® TOXICITY
TO RAT ALVEOLAR MACROPHAGES

ELMIRON® TOXICITY TO RAT ALVEOLAR MACROPHAGES

Methods

Experiment 1: Dose-Response

1. Lavage alveolar macrophages (AMs) from male Sprague-Dawley rats, and plate 2×10^5 cells/well in 24-well plates in Earle's minimal essential medium (EMEM) containing 5% fetal bovine serum (FBS).
2. Incubate cells for 2 hours, then gently rinse twice with EMEM + 5% FBS to remove unattached cells.
3. Add fresh EMEM + 5% FBS and incubate overnight.
4. Remove media and add fresh EMEM + 5% FBS containing Elmiron® (0, 0.01, 0.1, 1, 10, or 100 mg/mL).
5. Incubate cells for 24 hours, then collect media for lactate dehydrogenase assay (store at –80° C).
6. Measure viability of AMs by the MTT assay [MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide].

   (one control and five Elmiron® concentrations)(three wells/concentration) = 18 wells

   (18 wells)(2×10^5 AMs/well) = 3.6×10^6 AMs

Experiment 2: Staining of Fixed Cells

1. Lavage AMs from Sprague-Dawley rats, and plate 2×10^5 AMs/well in 24-well glass TekLad plates in EMEM + 5% FBS.
2. Incubate cells for 2 hours, then gently rinse twice with EMEM + 5% FBS to remove unattached cells.
3. Add fresh EMEM + 5% FBS and incubate overnight.
4. Remove media and add fresh EMEM + 5% FBS containing Elmiron® (0, 0.01, 0.1, 1, 10, or 100 mg/mL).
5. Incubate cells for 24 hours, then gently rinse once with phosphate-buffered saline, fix, and stain.
   a. PAS (periodic acid-Schiff)
   b. Oil red-O
   c. AB (Alcian Blue)

Results

In an *in vitro* study, cytoplasm of lavaged alveolar macrophages from Sprague-Dawley rats exposed for 24 hours to 1, 10, or 100 mg/mL of Elmiron® stained positively in a dose-related fashion with AB. Lavaged macrophages incubated similarly without Elmiron® were AB negative. Positive staining with AB is indicative of the presence of acidic sulfated mucopolysaccharides, hyaluronic acid, and sialomucin. The accumulation of this material was associated with cellular enlargement.

Table L1
Elmiron® Dose-Response *In Vitro* Viability Assay in Rat Alveolar Macrophages[a]

Dose (mg/mL)	Absorbance	Absorbance (Mean ± Standard Deviation)	Viability (% of Control)
0	0.279	0.344 ± 0.038	
	0.318		
	0.398		
	0.317		
.01	0.244	0.244 ± 0.009	71
	0.230		
	0.244		
	0.258		
0.1	0.229	0.305 ± 0.013	89
	0.296		
	0.323		
	0.296		
1.0	0.265	0.288 ± 0.022	84
	0.304		
	0.316		
	0.267		
10	0.253	0.277 ± 0.023	81
	0.257		
	0.306		
	0.293		
100	0.232	0.241 ± 0.013	70
	0.226		
	0.251		
	0.256		

[a] Viability was measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

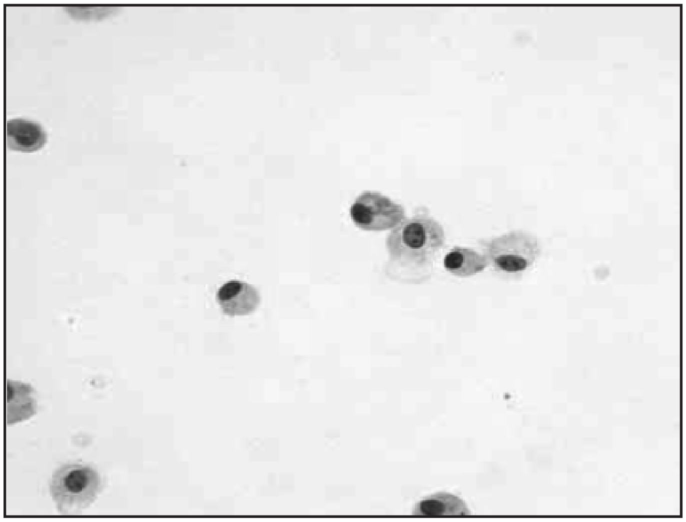

FIGURE L1. 0 mg Elmiron®/mL

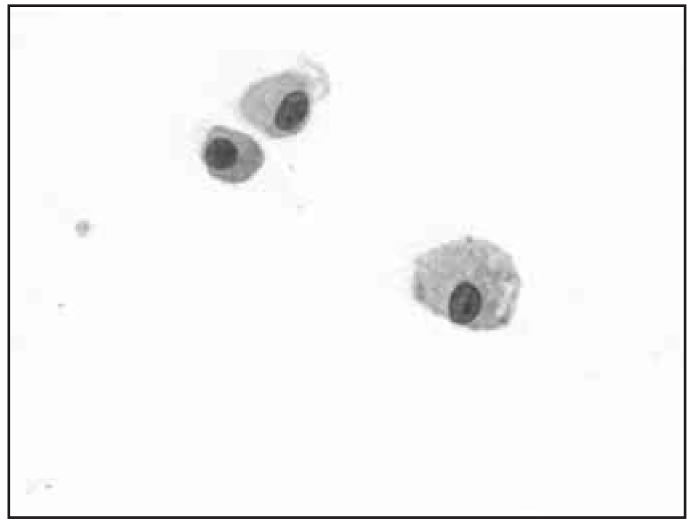

FIGURE L2. 1 mg Elmiron®/mL

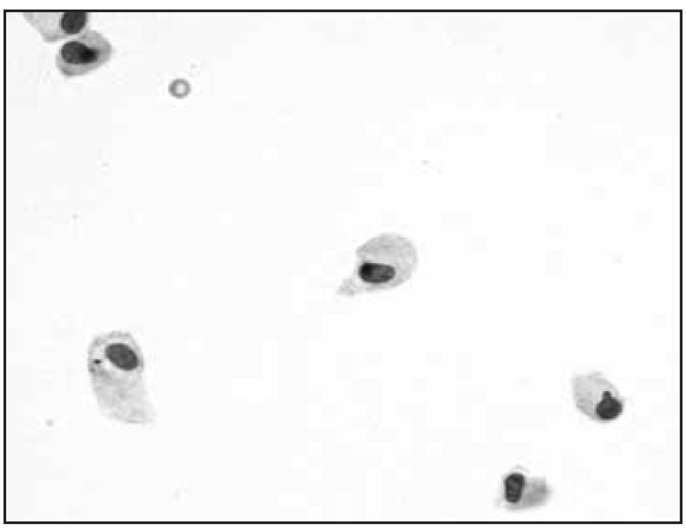

FIGURE L3. 10 mg Elmiron®/mL

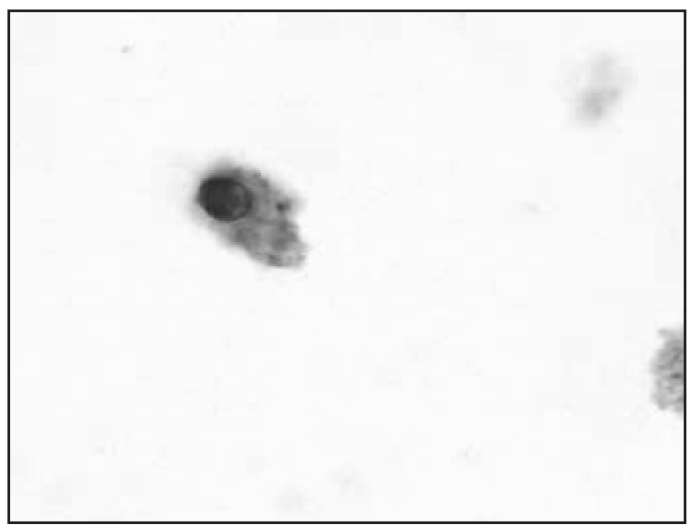

FIGURE L4. 100 mg Elmiron®/mL

The cytoplasm of alveolar macrophages exposed to Elmiron® *in vitro* shows the presence of Alcian Blue-positive material, which increases with increasing Elmiron® concentration. This is indicative of acidic sulfated mucopolysaccharides, hyaluronate, and mucin contents. The accumulation of the material is associated with cellular enlargement.

National Toxicology Program Technical Reports

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Chemical	TR No.
Acetaminophen	394
Acetonitrile	447
Acrylonitrile	506
Agar	230
Allyl Glycidyl Ether	376
Allyl Isothiocyanate	234
Allyl Isovalerate	253
1-Amino-2,4-Dibromoanthraquinone	383
2-Amino-4-Nitrophenol	339
2-Amino-5-Nitrophenol	334
11-Aminoundecanoic Acid	216
dl-Amphetamine Sulfate	387
Ampicillin Trihydrate	318
Asbestos, Amosite (Hamsters)	249
Asbestos, Amosite (Rats)	279
Asbestos, Chrysotile (Hamsters)	246
Asbestos, Chrysotile (Rats)	295
Asbestos, Crocidolite	280
Asbestos, Tremolite	277
L-Ascorbic Acid	247
AZT and AZT/α-Interferon A/D	469
Barium Chloride Dihydrate	432
Benzaldehyde	378
Benzene	289
Benzethonium Chloride	438
Benzofuran	370
Benzyl Acetate (Gavage)	250
Benzyl Acetate (Feed)	431
Benzyl Alcohol	343
o-Benzyl-*p*-Chlorophenol (Gavage)	424
o-Benzyl-*p*-Chlorophenol (Mouse Skin)	444
2-Biphenylamine Hydrochloride	233
2,2-Bis(Bromomethyl)-1,3-Propanediol	452
Bis(2-Chloro-1-Methylethyl) Ether	239
Bisphenol A	215
Boric Acid	324
Bromodichloromethane	321
Bromoethane	363
1,3-Butadiene	288
1,3-Butadiene	434
t-Butyl Alcohol	436
Butyl Benzyl Phthalate	213
Butyl Benzyl Phthalate	458
n-Butyl Chloride	312
t-Butylhydroquinone	459
γ-Butyrolactone	406
Caprolactam	214
d-Carvone	381
Chloral Hydrate	502
Chloral Hydrate	503
Chlorinated and Chloraminated Water	392
Chlorendic Acid	304
Chlorinated Paraffins: C_{23}, 43% Chlorine	305
Chlorinated Paraffins: C_{12}, 60% Chlorine	308
Chlorinated Trisodium Phosphate	294
2-Chloroacetophenone	379
p-Chloroaniline Hydrochloride	351
Chlorobenzene	261
Chlorodibromomethane	282
Chloroethane	346
2-Chloroethanol	275
3-Chloro-2-Methylpropene	300
Chloroprene	467
1-Chloro-2-Propanol	477
Chlorpheniramine Maleate	317
C.I. Acid Orange 3	335
C.I. Acid Orange 10	211
C.I. Acid Red 14	220
C.I. Acid Red 114	405
C.I. Basic Red 9 Monohydrochloride	285
C.I. Direct Blue 15	397
C.I. Direct Blue 218	430
C.I. Disperse Blue 1	299
C.I. Disperse Yellow 3	222
C.I. Pigment Red 3	407
C.I. Pigment Red 23	411
C.I. Solvent Yellow 14	226
trans-Cinnamaldehyde	514
Citral	505
Cobalt Sulfate Heptahydrate	471
Coconut Oil Acid Diethanolamine Condensate	479
Codeine	455
Comparative Initiation/Promotion Studies (Mouse Skin)	441
Corn Oil, Safflower Oil, and Tricaprylin	426
Coumarin	422
CS2	377
Cytembena	207
D&C Red No. 9	225
D&C Yellow No. 11	463
Decabromodiphenyl Oxide	309
Diallyl Phthalate (Mice)	242
Diallyl Phthalate (Rats)	284
4,4′-Diamino-2,2′-Stilbenedisulfonic Acid, Disodium Salt	412
2,4-Diaminophenol Dihydrochloride	401
1,2-Dibromo-3-Chloropropane	206
1,2-Dibromoethane	210
2,3-Dibromo-1-Propanol	400
1,2-Dichlorobenzene (*o*-Dichlorobenzene)	255
1,4-Dichlorobenzene (*p*-Dichlorobenzene)	319
p,p′-Dichlorodiphenyl sulfone	501
2,4-Dichlorophenol	353
2,6-Dichloro-*p*-Phenylenediamine	219
1,2-Dichloropropane	263
1,3-Dichloropropene (Telone II)	269
Dichlorvos	342
Dietary Restriction	460
Diethanolamine	478
Di(2-Ethylhexyl) Adipate	212
Di(2-Ethylhexyl) Phthalate	217
Diethyl Phthalate	429
Diglycidyl Resorcinol Ether	257
3,4-Dihydrocoumarin	423
1,2-Dihydro-2,2,4-Trimethylquinoline (Monomer)	456
Dimethoxane	354
3,3′-Dimethoxybenzidine Dihydrochloride	372
N,N-Dimethylaniline	360
3,3′-Dimethylbenzidine Dihydrochloride	390
Dimethyl Hydrogen Phosphite	287
Dimethyl Methylphosphonate	323
Dimethyl Morpholinophosphoramidate	298
Dimethylvinyl Chloride	316
Diphenhydramine Hydrochloride	355
5,5-Diphenylhydantoin	404
Elmiron®	512
Emodin	493
Ephedrine Sulfate	307
Epinephrine Hydrochloride	380
1,2-Epoxybutane	329

Chemical	TR No.
Erythromycin Stearate	338
Ethyl Acrylate	259
Ethylbenzene	466
Ethylene Glycol	413
Ethylene Glycol Monobutyl Ether	484
Ethylene Oxide	326
Ethylene Thiourea	388
Eugenol	223
FD&C Yellow No. 6	208
Fumonisin B_1	496
Furan	402
Furfural	382
Furfuryl Alcohol	482
Furosemide	356
Gallium Arsenide	492
Geranyl Acetate	252
Glutaraldehyde	490
Glycidol	374
Guar Gum	229
Gum Arabic	227
HC Blue 1	271
HC Blue 2	293
HC Red 3	281
HC Yellow 4	419
Hexachlorocyclopentadiene	437
Hexachloroethane	361
2,4-Hexadienal	509
4-Hexylresorcinol	330
Hydrochlorothiazide	357
Hydroquinone	366
8-Hydroxyquinoline	276
Indium Phosphide	499
Iodinated Glycerol	340
Isobutene	487
Isobutyl Nitrite	448
Isobutyraldehyde	472
Isophorone	291
Isoprene	486
Lauric Acid Diethanolamine Condensate	480
d-Limonene	347
Locust Bean Gum	221
60-Hz Magnetic Fields	488
Magnetic Field Promotion	489
Malonaldehyde, Sodium Salt	331
Manganese Sulfate Monohydrate	428
D-Mannitol	236
Marine Diesel Fuel and JP-5 Navy Fuel	310
Melamine	245
2-Mercaptobenzothiazole	332
Mercuric Chloride	408
Methacrylonitrile	497
8-Methoxypsoralen	359
α-Methylbenzyl Alcohol	369
Methyl Bromide	385
Methyl Carbamate	328
Methyldopa Sesquihydrate	348
Methylene Chloride	306
4,4´-Methylenedianiline Dihydrochloride	248
Methyleugenol	491
Methyl Methacrylate	314
N-Methylolacrylamide	352
Methylphenidate Hydrochloride	439
Mirex	313
Molybdenum Trioxide	462
Monochloroacetic Acid	396
Monuron	266
Nalidixic Acid	368
Naphthalene (Mice)	410
Naphthalene (Rats)	500
Nickel (II) Oxide	451
Nickel Sulfate Hexahydrate	454

Chemical	TR No.
Nickel Subsulfide	453
p-Nitroaniline	418
o-Nitroanisole	416
p-Nitrobenzoic Acid	442
Nitrofurantoin	341
Nitrofurazone	337
Nitromethane	461
p-Nitrophenol	417
o-Nitrotoluene	504
p-Nitrotoluene	498
Ochratoxin A	358
Oleic Acid Diethanolamine Condensate	481
Oxazepam (Mice)	443
Oxazepam (Rats)	468
Oxymetholone	485
Oxytetracycline Hydrochloride	315
Ozone and Ozone/NNK	440
Penicillin VK	336
Pentachloroanisole	414
Pentachloroethane	232
Pentachloronitrobenzene	325
Pentachlorophenol, Purified	483
Pentachlorophenol, Technical Grade	349
Pentaerythritol Tetranitrate	365
Phenolphthalein	465
Phenylbutazone	367
Phenylephrine Hydrochloride	322
N-Phenyl-2-Naphthylamine	333
o-Phenylphenol	301
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Gavage)	244
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Feed)	398
Polysorbate 80 (Glycol)	415
Polyvinyl Alcohol	474
Primidone	476
Probenecid	395
Promethazine Hydrochloride	425
Propylene	272
Propylene Glycol Mono-t-butyl Ether	515
1,2-Propylene Oxide	267
Propyl Gallate	240
Pyridine	470
Quercetin	409
Riddelliine	508
Resorcinol	403
Rhodamine 6G	364
Rotenone	320
Roxarsone	345
Salicylazosulfapyridine	457
Scopolamine Hydrobromide Trihydrate	445
Sodium Azide	389
Sodium Fluoride	393
Sodium Nitrite	495
Sodium Xylenesulfonate	464
Stannous Chloride	231
Succinic Anhydride	373
Talc	421
Tara Gum	224
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Dermal)	201
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Gavage)	209
1,1,1,2-Tetrachloroethane	237
Tetrachloroethylene	311
Tetracycline Hydrochloride	344
Tetrafluoroethylene	450
1-Trans-Delta^9-Tetrahydrocannabinol	446
Tetrahydrofuran	475
Tetrakis(Hydroxymethyl)Phosphonium Sulfate	296
Tetrakis(Hydroxymethyl)Phosphonium Chloride	296
Tetranitromethane	386
Theophylline	473
4,4-Thiobis(6-*t*-Butyl-*m*-Cresol)	435
Titanocene Dichloride	399

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
P.O. Box 12233, MD K2-05
Durham, NC 27709
Tel: 984-287-3211
ntpwebrequest@niehs.nih.gov

https://ntp.niehs.nih.gov

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