NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDY OF GENISTEIN

(CAS NO. 446-72-0)

IN SPRAGUE-DAWLEY RATS

(FEED STUDY)

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

December 2007

NTP TR 545

NIH Publication No. 08-4430

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

FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

The NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use are in accordance with the Public Health Service Policy on Humane Care and Use of Animals. Studies are subjected to retrospective quality assurance audits before being presented for public review.

NTP Technical Reports are indexed in the NIH/NLM PubMed database and are available free of charge electronically on the NTP website (*http://ntp.niehs.nih.gov*) or in hardcopy upon request from the NTP Central Data Management group at *cdm@niehs.nih.gov* or (919) 541-3419.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDY OF GENISTEIN

(CAS NO. 446-72-0)

IN SPRAGUE-DAWLEY RATS

(FEED STUDY)

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

January 2008

NTP TR 545

NIH Publication No. 08-4430

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

CONTRIBUTORS

The study on genistein was conducted at the FDA's National Center for Toxicological Research under an interagency agreement between the FDA and the NIEHS. The study was designed and monitored by a Toxicology Study Selection and Review Committee composed of representatives from the NCTR and other FDA product centers, NIEHS, and other *ad hoc* members from other government agencies and academia. The interagency agreement was designed to use the staff and facilities of the NCTR in the testing of FDA priority chemicals and to provide FDA scientists and regulatory policymakers information for hazard identification and risk assessment.

Toxicology Study Selection and Review Committee

D.A. Casciano, Ph.D., Chairperson
National Center for Toxicological Research
W.T. Allaben, Ph.D.
National Center for Toxicological Research
F.A. Beland, Ph.D.
National Center for Toxicological Research
J.R. Bucher, Ph.D.
National Institute of Environmental Health Sciences
K.J. Greenlees, Ph.D.
Center for Veterinary Medicine,
Food and Drug Administration
R.J. Lorentzen, Ph.D.
Center for Food Safety and Applied Nutrition,
Food and Drug Administration
M. Miller, Ph.D.
Office of Women's Health,
Food and Drug Administration
R.R. Newbold, M.S.
National Institute of Environmental Health Sciences
F.D. Sistare, Ph.D.
Center for Drug Evaluation and Research,
Food and Drug Administration
E. Yetley, Ph.D.
Center for Food Safety and Applied Nutrition,
Food and Drug Administration

Bionetics

Prepared animal feed and cared for rats

J. Carson, B.S.
A. Matson, B.S.
M. Moore
S. Moore

National Center for Toxicological Research, Food and Drug Administration

Conducted study, evaluated and interpreted results and pathology findings, and reported findings

K.B. Delclos, Ph.D., Study Scientist
R.R. Newbold, M.S., Co-Study Scientist
National Institute of Environmental Health Sciences
S.A. Ferguson, Ph.D., Co-Study Scientist
A.C. Scallet, Ph.D., Co-Study Scientist
C.C. Weis, B.S., Study Coordinator
W.T. Allaben, Ph.D.
J.R. Appleget, B.S.
F.A. Beland, Ph.D.
W. Campbell, B.S.
M.I. Churchwell, B.S.
D.R. Doerge, Ph.D.
K.M. Flynn, Ph.D.
C.E. Hotchkiss, D.V.M., Ph.D.
J.M. Meredith, Ph.D.
J.M. Reed, M.S.
W.M. Witt, D.V.M., Ph.D.

Conducted chemical analysis of the feed and purity of the test chemical

W.M. Cooper, B.S.
F.E. Evans, Ph.D.
R.L. Evans, M.S.
J.P. Freeman, Ph.D.
T.M. Heinze, M.S.
C. Holder, B.S.
P.H. Siitonen, B.S.

Conducted quality assurance audits

S.J. Culp, Ph.D.
R.D. Smith, B.S.
Y.E. Whiteside, B.S.

Pathology Associates, A Charles River Company

Evaluated pathology findings

T.J. Bucci, V.M.D., Ph.D.
G.R. Olson, D.V.M., Ph.D.

NTP Pathology Working Group

Evaluated slides and prepared pathology report on rats (October 10, 2003)

C.C. Shackelford, D.V.M., M.S., Ph.D., Chairperson
Experimental Pathology Laboratories, Inc.
C.H. Frith, D.V.M., Ph.D.
Tox-Path Associates
R.A. Herbert, D.V.M., Ph.D.
National Institute of Environmental Health Sciences
J.R. Latendresse, D.V.M., Ph.D.
National Center for Toxicological Research
R.A. Miller, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
G.R. Olson, D.V.M., Ph.D.
National Center for Toxicological Research
R.W. Trotter, D.V.M.
National Center for Toxicological Research
M.J. van Zwieten, D.V.M., Ph.D.
Merck (retired)

R.O.W. Sciences

Provided statistical analyses and software systems development

S. Appana, M.S.
X. Ding, M.S.
D. Hussen, M.S.
C.C. McCarty, B.S.
W.A. McCracken, M.S.
B.T. Thorn, M.S.

Biotechnical Services, Inc.

Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
B.F. Hall, M.S.
L.M. Harper, B.S.
E.S. Rathman, M.S.
D.C. Serbus, Ph.D.
R.E. Shaver, B.A.

CONTENTS

ABSTRACT 7

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 11

TECHNICAL REPORTS REVIEW SUBCOMMITTEE 12

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS 13

OVERVIEW 15

INTRODUCTION 19

MATERIALS AND METHODS 25

RESULTS 35

DISCUSSION AND CONCLUSIONS 55

REFERENCES 61

APPENDIX A Summary of Lesions in Male Rats in the 2-Year Feed Study of Genistein 71

APPENDIX B Summary of Lesions in Female Rats in the 2-Year Feed Study of Genistein 131

APPENDIX C Chemical Characterization and Dose Formulation Studies 171

APPENDIX D Body Weights 181

APPENDIX E Feed Consumption in the 2-Year Feed Study of Genistein 195

APPENDIX F Onset of Aberrant Estrous Cycles 209

APPENDIX G Organ Weights and Organ-Weight-to-Body-Weight Ratios 217

APPENDIX H Ingredients, Nutrient Composition, and Contaminant Levels in Purina 5K96 Rat Ration 233

APPENDIX I Sentinel Animal Program 237

APPENDIX J Associated Publications 239

SUMMARY

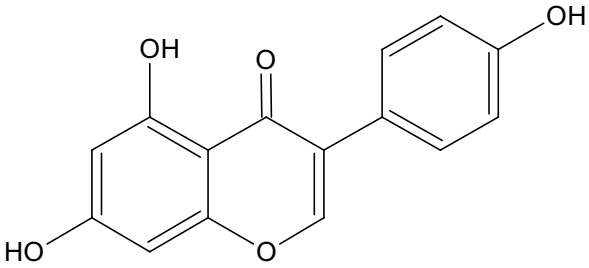
Background
Genistein is an isoflavone that occurs in soy products including soy-based infant formulas. Genistein is one of a class of chemicals known as "environmental estrogens" which can affect the hormone activities and possibly reproductive function of wildlife and humans through exposure. The NTP conducted a series of studies on three such chemicals to detect if exposure to such chemicals over the course of multiple generations could have any cumulative effect on animals' reproductive systems or development of cancers. This report describes the results of a set of studies in which rats were exposed to genistein for part or all of the study period and examined at the end of two years.

Methods
The study consisted of three separate study components; in each, animals were exposed to genistein from the time of conception and through weaning through their mothers, who were given genistein in their feed. In one study, we gave feed containing 5, 100, or 500 parts per million (ppm) of genistein to groups of 50 male and female rats from conception through two years. In the second study, groups of 50 male and female rats were given the same feed concentrations up to 20 weeks following birth, followed by untreated feed for the remainder of the two years. In the third study, groups of 50 male and female rats were exposed from conception through weaning, and then given untreated feed for the duration of the study. Control animals received the same feed with no chemical added. At the end of the study, tissues from more than 40 sites were examined for every animal.

Results
In none of the three studies were there any increased rates of cancer in male rats. In female rats exposed to genistein from conception and throughout two years, the rates of adenoma or adenocarcinoma of the mammary gland and pituitary gland adenoma or carcinoma were increased. In female rats exposed to genistein for 20 weeks following birth, the rates of pituitary gland adenoma or carcinoma were slightly increased, and in female rats exposed to genistein just from conception through weaning, the rates of mammary gland adenoma or adenocarcinoma were slightly increased.

Conclusions
We conclude that exposure to genistein for two years caused tumors of the mammary gland and pituitary gland in female rats. Exposure to genistein for shorter durations following birth was also possibly associated with increased rates of pituitary gland and mammary gland tumors.

ABSTRACT



GENISTEIN

CAS No. 446-72-0

Chemical Formula: $C_{15}H_{10}O_5$ Molecular Weight: 270.23

Synonym: 4′,5,7-Trihydroxyisoflavone

Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products, including soy-based infant formula and dietary supplements. Consumption of soy and genistein has been associated with a variety of beneficial effects in animals and humans, but concerns have also been raised regarding potential adverse effects of genistein, particularly with regard to reproductive toxicity and the induction or potentiation of carcinogenesis, due primarily to its weak estrogenic activity. Because of these concerns, genistein was selected as one of the compounds to be examined using a protocol designed to evaluate the effects of multigenerational and long-term exposures to doses of estrogenic agents that produce subtle reproductive tract lesions in developmentally exposed Sprague-Dawley rat pups. Results from the 2-year study are reported here, and results from the multigenerational reproductive toxicology feed study are reported separately (NTP, 2008a). Data from a preliminary reproductive dose range-finding feed study (NTP, 2007) that utilized exposure concentrations up to 1,250 ppm genistein were used to select dietary exposure concentrations of 0, 5, 100, and 500 ppm for the current study.

The multigenerational reproductive toxicology study examined F_0 through F_4 generations with F_5 litters terminated at weaning and focused on reproductive endpoints (NTP, 2008a). Animals were exposed from the time that the F_0 generation was 6 weeks old through weaning of the F_3 generation, and animals of the F_0 through F_4 generations were necropsied at 20 weeks of age.

The current study was a 2-year dietary study utilizing three exposure arms: continuous exposure from conception through 2 years (designated F_1 continuous, or F_1C), exposure from conception through 20 weeks followed by control diet to 2 years [designated F_1 truncated at postnatal day (PND) 140, or F_1T140], and exposure from conception through weaning followed by control diet to 2 years (designated F_3 truncated at PND 21, or F_3T21). The "F_3" designation for the F_3T21 arm indicates that these animals were siblings of the F_3 animals from the multigenerational reproductive toxicology study (NTP, 2008a). The F_1C and F_1T140 animals were also siblings but were derived from a separate breeding that was identical to the procedure used to produce the F_1 generation of the multigenerational reproductive toxicology study. The animals in this study were exposed to genistein during various phases of their lives from

conception until termination at 2 years, and the ingested doses varied over the course of the study. During pregnancy, the ingested doses of the dams were approximately 0, 0.5, 9, or 45 mg/kg body weight per day. During lactation, the dams' ingested doses were 0, 0.7, 15, or 75 mg/kg per day. Supplementary studies, which are described in the multigenerational reproductive toxicology study, indicated minimal transfer of genistein to pups via the dams' milk. The mean directly ingested genistein doses during the period prior to PND 140 were approximately 0.4, 8, or 44 mg/kg per day for females and 0.4, 7, or 37 mg/kg per day for males. For the period between PND 140 and the end of the study, mean ingested doses were approximately 0.3, 5, or 29 mg/kg per day for females and 0.2, 4, or 20 mg/kg per day for males.

For the current study, 50 animals per sex were initially assigned to each exposure group in each arm of the study. In control groups, histopathology data from one to four additional animals that had been assigned as sentinels but that became moribund or died early were also included in the analysis and presentation. Survival was similar in all control and exposed groups and ranged from 62% to 86% for males and 43% to 64% for females. Mean body weights of 500 ppm F_1C females were less than those of the controls throughout the study. Mean body weights of 500 ppm F_1T140 rats were less than those of the controls throughout the study. In females of all study arms (F_1C, F_1T140, and F_3T21) an early onset of aberrant estrous cycles, suggesting early reproductive senescence, was observed in the 500 ppm groups. In the F_3T21 arm, there were also significant effects on the onset of aberrant estrous cycles in the 5 and 100 ppm groups. Pituitary gland weights were significantly increased in females in the 500 ppm groups of the F_1C and F_1T140 study arms and in the 100 ppm group of the F_3T21 arm.

In F_1C females, there was a significant positive trend in the incidences of mammary gland adenoma or adenocarcinoma (combined) regardless of whether an unmodified or natural log-transformed dose scale was used in the analysis, and the incidence in the 500 ppm group was significantly greater than that in the control group. A significant negative trend occurred in the incidences of benign mammary gland fibroadenoma in F_1C females, and the incidence in the 500 ppm group was significantly less than that in the control group. In 5 and 100 ppm F_1T140 females, the combined incidences of adenoma and adenocarcinoma were less than those in the control or 500 ppm groups, although these were not statistically significant differences. When the natural log-transformed dose scale was used, a marginally significant positive trend occurred in the incidences of adenoma or adenocarcinoma (combined) in F_3T21 females. There were positive trends in the incidences of adenoma or carcinoma (combined) in the pars distalis of the pituitary gland of females in the F_1C and F_1T140 arms, and the incidence in the 500 ppm group was significantly greater than that in the controls in the F_1C study arm.

In F_1C males, a significant positive trend (unmodified dose scale only) occurred in the incidences of combined adenoma or carcinoma of the pancreatic islets. While the incidence in the 500 ppm group was elevated relative to that in the control group (6/49 versus 1/49), this was not statistically significant. The fact that transitional lesions (i.e., hyperplasia) were not observed combined with variable control rates in males of this substrain of rats led to the conclusion that this lesion was not likely to be related to genistein treatment.

CONCLUSIONS

Under the conditions of this 2-year feed study with continuous exposure to the test compound from conception through termination (F_1C), there was *no evidence of carcinogenic activity** of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was *some evidence of carcinogenic activity* of genistein in female Sprague-Dawley rats based on increased incidences of mammary gland adenoma or adenocarcinoma (combined) and pituitary gland neoplasms. The incidence of benign mammary gland fibroadenoma in female rats was significantly decreased in the 500 ppm group.

Under the conditions of this 2-year feed study with exposure to the test compound from conception through 20 weeks followed by control feed until termination (F_1T140), there was *no evidence of carcinogenic activity* of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was *equivocal evidence of carcinogenic activity* of genistein in female Sprague-Dawley rats based on marginally increased incidences of pituitary gland neoplasms.

Under the conditions of this 2-year feed study where offspring of three prior generations of animals exposed to the test compound were exposed from conception through weaning (PND 21) followed by control feed until termination (F_3T21), there was *no evidence of carcinogenic activity* of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was *equivocal evidence of carcinogenic activity* of genistein in female Sprague-Dawley rats based on increased incidences of mammary gland adenoma or adenocarcinoma (combined).

Exposure to genistein was also shown to accelerate the onset of aberrant estrous cycles in female Sprague-Dawley rats whether exposures were continuous or truncated at PND 140 or at weaning. The effects of genistein on estrous cycling and the incidences of common hormonally related spontaneous neoplasms of female Sprague-Dawley rats are consistent with an estrogenic mechanism of toxicity.

---

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

Summary of the 2-Year Carcinogenesis Study of Genistein in Sprague-Dawley Rats

	F_1C		F_1T140		F_3T21	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
Concentrations in feed	0, 5, 100, or 500 ppm	0, 5, 100, or 500 ppm	0, 5, 100, or 500 ppm	0, 5, 100, or 500 ppm	0, 5, 100, or 500 ppm	0, 5, 100, or 500 ppm
Body weights	Exposed groups generally similar to control group	500 ppm group less than the control group	500 ppm group less than the control group	500 ppm group less than the control group	Exposed groups generally similar to the control group	Exposed groups generally similar to the control group
Survival rates	36/54, 41/50, 43/50, 31/50	26/54, 28/50, 22/50, 21/49	36/54, 34/50, 32/50, 38/50	26/54, 31/50, 32/50, 23/50	33/52, 42/50, 33/50, 36/50	33/53, 30/50, 29/50, 25/50
Early onset of aberrant estrous cycles	N/A	500 ppm	N/A	500 ppm	N/A	500 ppm (also some evidence for effects at 5 and 100 ppm)
Nonneoplastic effects	None	None	None	None	None	None
Neoplastic effects	None	Mammary gland: adenoma or adenocarcinoma (9/54, 4/50, 8/50, 16/49) Pituitary gland: adenoma or carcinoma (38/54, 40/50, 34/50, 46/49)	None	None	None	None
Equivocal findings	None	None	None	Pituitary gland: adenoma or carcinoma (38/54, 32/49, 40/50, 44/50)	None	Mammary gland: adenoma or adenocarcinoma (7/53, 8/49, 11/50, 13/50)
Decreased incidences	None	Mammary gland: fibroadenoma (32/54, 27/50, 28/50, 12/49)	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	Some evidence	No evidence	Equivocal evidence	No evidence	Equivocal evidence

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 genistein on June 12, 2006, 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.

Charlene A. McQueen, Ph.D., Chairperson
College of Pharmacy
Department of Pharmacology and Toxicology
University of Arizona
Tucson, AZ

Diane F. Birt, Ph.D.
Department of Food Science and Human Nutrition
Iowa State University
Ames, IA

Christopher Bradfield, Ph.D., Principal Reviewer
McArdle Laboratory for Cancer Research
University of Wisconsin
Madison, WI

Kenny S. Crump, Ph.D.
Environ International
Ruston, LA

George P. Daston, Ph.D.
Miami Valley Laboratories
The Procter and Gamble Company
Cincinnati, OH

Prescott L. Deininger, Ph.D.
Tulane University Medical Center
New Orleans, LA

John P. Giesy, Jr., Ph.D.*
Department of Zoology
Michigan State University
East Lansing, MI

Nancy Kerkvliet, Ph.D.
Department of Environmental and Molecular Toxicology
Oregon State University
Corvallis, OR

Jon Mirsalis, Ph.D., Principal Reviewer
SRI International
Menlo Park, CA

Harish C. Sikka, Ph.D.
Environmental Toxicology and Chemistry Laboratory
State University of New York College at Buffalo
Buffalo, NY

Keith A. Soper, Ph.D., Principal Reviewer
Merck Research Laboratories
West Point, PA

Vernon E. Walker, D.V.M., Ph.D.
Lovelace Respiratory Research Institute
University of New Mexico
Albuquerque, NM

Special Ad Hoc Reviewers

Paul Cooke, Ph.D.
Department of Veterinary Biosciences
University of Illinois
Urbana, IL

Leena Hilakivi-Clarke, Ph.D.
Lombardi Comprehensive Cancer Center
Georgetown University
Washington, DC

---

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 12, 2006, the draft Technical Report on the toxicology and carcinogenicity study of genistein 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.B. Delclos, National Center for Toxicological Research (NCTR), introduced the toxicology and carcinogenicity study of genistein by discussing the uses of the chemical and the rationale for study; describing the experimental design; and reporting on survival, body and organ weight effects, aberrant estrous cyclicity, and compound-related neoplasms in rats. The proposed conclusions for the 2-year study were:

Under the conditions of this 2-year feed study with continuous exposure to genistein from conception through termination (F_1C), there was *no evidence of carcinogenic activity* in male Sprague-Dawley rats and *some evidence of carcinogenic activity* in female Sprague-Dawley rats.

Under the conditions of this 2-year feed study with exposure to genistein from conception through 20 weeks followed by control feed until termination (F_1T140), there was *no evidence of carcinogenic activity* of genistein in male Sprague-Dawley rats and *equivocal evidence of carcinogenic activity* in female Sprague-Dawley rats.

Under the conditions of this 2-year feed study with continuous exposure to genistein from conception through weaning (PND 21) followed by control feed until termination (F_3T21), there was *no evidence of carcinogenic activity* in male Sprague-Dawley rats and *equivocal evidence of carcinogenic activity* in female Sprague-Dawley rats.

Exposure to genistein was also shown to accelerate the onset of aberrant estrous cycles in female Sprague-Dawley rats whether exposures were continuous or truncated at PND 140 or at weaning. The effects of genistein on estrous cycling and the incidences of common spontaneous neoplasms of female Sprague-Dawley rats are more consistent with an estrogenic mechanism of toxicity than with genotoxic effects.

Dr. Delclos also stated that genistein was shown to accelerate the onset of aberrant estrous cycles in female Sprague-Dawley rats whether exposures were continuous or truncated at PND 140 or at weaning, and he noted that the effects of genistein on estrous cycling and the incidences of common spontaneous neoplasms of female Sprague-Dawley rats are more consistent with an estrogenic mechanism of toxicity than with genotoxic effects.

Dr. Mirsalis, the first principal reviewer, noted that genistein is being studied by the National Cancer Institute as a cancer preventative agent and that some of those studies might be mentioned in the background information. He thought the increased incidence of pancreatic islet adenoma was worth noting. He thought a comparison of the administered doses with human exposure should be mentioned in the discussion. He also questioned whether the report reflected Good Laboratory Practice compliance, largely in administrative detail.

Dr. Bradfield, the second principal reviewer, thought the study was well designed. He suggested that the study was more a test of the aglycone rather than the glucoside form, and that the latter may be of greater significance. He also noted that exposure during the neonatal time was not mimicked in this model.

Dr. Soper, the third principal reviewer, felt the studies were well designed and agreed with the proposed conclusions.

Dr. Kerkvliet suggested that more of the rationale for dose selection be carried from the reproductive dose range-finding study report into the text or discussion of this report. She questioned the use of terms such as 'slightly' or 'marginally' increased or 'generally similar' in descriptions of lesion incidences. She also questioned the use of the term "carcinogenic" to describe the action of a chemical that elevated the incidence of tumors that occur spontaneously with high frequency, and inquired if reduced incidences of tumors would be attributed to "anticarcinogenic" properties of the chemical.

Dr. Hilakivi-Clarke suggested that not all the effects observed should be described entirely as estrogenic, but that some may have a genotoxic component as well. She inquired why hormone levels were not measured and also why the rats were singly housed.

Dr. Delclos responded that the discussion of pancreatic islet tumors would be expanded. He explained that the full laboratory report, with all the administrative and procedural details, was prepared and audited for GLP compliance at the NCTR prior to the preparation of the Technical Report, which focuses more on the study findings and scientific interpretations. He agreed to expand the references to the beneficial effects of genistein in the introduction and to enhance the distinction between the aglycone and glucoside forms. He explained that limitations of study size precluded including extra animals for hormone measures.

Dr. Kerkvliet inquired about the immunotoxicity data for this study, and Dr. Delclos explained that those were presented together with the reproductive dose range-finding study.

Dr. Sikka also thought that statements about genistein acting through an estrogenic mechanism should be modified to include the possibility of genotoxicity as well, and that more emphasis should be made on the chemopreventative as well as carcinogenic effects of the compound. Dr. Daston noted the high rate of false positives in *in vitro* genotoxicity tests and thought the overall study results outweighed such individual tests. He also inquired if more use of the epidemiology literature could help interpret the present rodent study results. He noted also that not all estrogen-receptor tissues might be expected to respond similarly; for example, the uterus contains predominantly estrogen receptor alpha, while the chemical in the study interacts predominantly with estrogen receptor beta.

Dr. J.R. Bucher, NIEHS, said that caution must be exercised in applying human data to interpretation of the animal studies. The primary purpose of the current review is to evaluate the animal data by themselves, and extrapolation of findings to (or from) human health effects belongs to a different part of the program, the Center for the Evaluation of Risks to Human Reproduction.

Dr. Walker also noted that all the tissues affected were hormonally related and favored retaining a statement suggested by Dr. Hilakivi-Clarke that they were consistent with an estrogenic effect without making conclusions about genotoxicity.

For considering the conclusions, Dr. McQueen suggested they be taken paragraph by paragraph. Dr. Daston inquired if exposure concentrations at which a particular effect was seen could be included. Dr. Bucher replied that was not the normal practice, as not all possible exposure concentrations were used. Dr. Walker asked if it were possible to mention in the conclusion that the incidence of pancreatic tumors was increased in the 500 ppm F_1C male rat group without saying it was considered related to genistein exposure. Dr. Bucher suggested it might be sufficient to mention this in the body of the abstract and Dr. Walker agreed.

For the first conclusion paragraph, Dr. Daston moved and Dr. Mirsalis seconded inclusion of the exposure concentrations at which increased incidences of mammary gland and pituitary gland adenomas occurred. Dr. C.J. Portier, NIEHS, argued that including those numbers might be interpreted as implying a threshold for response. Drs. Walker and Birt spoke against including specific exposure concentrations in the conclusions as this might oversimplify more complex patterns available in the full results text. Dr. Bucher noted that in some cases there were statistically significant trends that included increased incidences in lower exposure concentration groups that were not significant by pairwise comparisons. Drs. Kerkvliet, Soper, and Crump cited examples of complications that might arise from stating specific exposure concentrations for a carcinogenic effect. The motion was defeated with one yes vote (Dr. Daston) and nine no votes. Dr. Birt then moved, and Dr. Soper seconded, to approve the first three paragraphs of the conclusions as written. The motion was approved unanimously with 10 votes.

For the remaining conclusions, Dr. Daston moved that the final sentence of the last paragraph end with "are consistent with an estrogenic mechanism of toxicity" and to refer to the tumors as "hormonally related spontaneous neoplasms." Dr. Walker seconded the motion, which was approved unanimously with 10 votes.

OVERVIEW

Study Rationale and General Design

Following a 1994 meeting sponsored by the National Institute for Environmental Health Sciences (NIEHS) entitled "Estrogens in the Environment III," the NIEHS (1995) proposed to expand and develop mammalian animal models to determine if environmentally relevant doses of endocrine-disrupting chemicals and mixtures of these chemicals during exposure windows that included development could cause reproductive problems or influence the incidence of reproductive tract cancers. Investigation of the potential for magnification of subtle reproductive effects over multiple generations, the importance of exposure windows, and whether effects are reversible or are imprinted to carry over across generations were also deemed to be important. The utility of such a program was agreed to by the National Toxicology Program (NTP) Board of Scientific Counselors at their meeting on October 18, 1994. The series of studies related to this initiative were conducted under an Interagency Agreement between the NIEHS/NTP and the Food and Drug Administration/National Center for Toxicological Research (FDA/NCTR). Study protocols were generated and reproductive dose range-finding studies were initiated at NCTR in 1997.

The overall goal of this series of studies was to evaluate the long-term consequences of exposure to endocrine-active agents that produce subtle short-term effects in exposed animals. The idea behind the studies was to evaluate aspects of the "endocrine disruptor hypothesis," which is the hypothesis that environmental exposure to endocrine-active chemicals is contributing to a variety of adverse effects in wildlife and humans (NRC, 1999). As originally conceived, the plan was to evaluate neurobiological, behavioral, immunological, reproductive, and chronic toxicities in the main studies. This plan was modified to assess all of these endpoints in short-term studies conducted prior to the main studies that focused on reproductive and chronic toxicity. The compounds selected for multigenerational reproductive toxicology studies were three agents that vary in estrogenic potency: the soy isoflavone, genistein; the industrial intermediate, *p*-nonylphenol; and the potent and widely used synthetic estrogen, ethinyl estradiol.

A short-term reproductive dose range-finding study was conducted for each compound to assess general and reproductive toxicity, behavioral toxicity, neurotoxicity, and immunotoxicity. The test compounds were administered in a soy- and alfalfa-free rodent diet (see below). Pregnant females were given dosed feed from gestation day 7 (GD 7) until the pups were weaned, and the pups were continued on the same diet as their dams until termination. Separate sets of animals were bred for the reproductive, behavioral, and immunological studies. One pup per sex per litter from the reproductive toxicity study was used for the neurotoxicity study. Data from the reproductive dose range-finding study were the primary data used for selection of exposure concentrations for the subsequent multigenerational reproductive toxicology and chronic studies (see below), although data from the other studies were considered in choosing the range of exposure concentrations to be tested. All of these studies utilized outbred CD (Sprague-Dawley) rats from the NCTR breeding colony. The Sprague-Dawley rat was selected because of its widespread use in reproductive toxicology studies, including those conducted by the NTP, its robust breeding performance, and its relatively low background incidences of testicular Leydig cell tumors and large granular lymphocyte leukemia relative to the F344/N rat commonly used in NTP carcinogenesis studies. The relatively high background incidences of pituitary gland and female mammary gland tumors in Sprague-Dawley rats were recognized as a possible concern. The relatively poor breeding performance of the F344/N rat would have presented a considerable challenge to the conduct of the studies described here, as it would for any evaluation of reproductive toxicity. Reproductive toxicity testing guidelines, for example, those of the EPA, FDA, and The Organization for Economic Cooperation and Development, generally indicate that animals with low fecundity not be used. The NCTR breeding colony was established in 1972 using Sprague-Dawley rats from the Charles River

Laboratories. The NCTR colony at present is a distinct substrain of the Sprague-Dawley rat and has been previously shown to differ substantially from the Charles River and other strains of Sprague-Dawley rat in terms of body weight, which is lower than that reported for other substrains, and survival, which is longer than that reported for other substrains (Duffy *et al.,* 2001). The sensitivity of the NCTR CD rat to the potent estrogen ethinyl estradiol was evaluated as part of this series of studies and will be reported separately.

It was intended that exposure concentrations that were within the range of human exposures and/or below previously reported No-observed-adverse-effect-levels be incorporated in the main studies. The experimental design was intended to determine if subtle effects would be magnified in subsequent generations and if observed effects were reversible. In standard reproductive toxicity studies conducted for regulatory purposes, high doses are chosen to produce some maternal toxicity while the low dose is selected with the goal of not producing parental effects (OECD, 2004; CFSAN, 2006). The high dose for chronic studies is set as the maximum tolerated dose. In the present series of studies, the goal was to select a high dose, based on the results of the reproductive dose range-finding study, that did not produce significant maternal toxicity but did produce reproductive tract lesions in the offspring of a degree that would not severely affect reproductive capacity in the first generation. The questions addressed in the chronic studies were whether exposures producing subtle modifications of the reproductive tract could produce chronic toxicity and whether any observed chronic toxicity was induced by early developmental exposure or rather required continuous long-term exposure.

The need to maintain consistent dietary composition was taken into account in the design of this series of studies. A soy- and alfalfa-free diet (Purina 5K96; Appendix H) with consistently low concentrations of the phytoestrogens genistein and daidzein was used in all studies. A preliminary study indicated that rats fed this diet had reproductive capacity equivalent to rats fed NIH-31 diet, the standard soy- and alfalfa-containing diet used at the test facility (NCTR), although feed consumption in both sexes and the body weights of males fed PMI 5K96 were significantly lower than in rats fed NIH-31.

Design of the Multigenerational Reproductive Toxicology and Chronic Studies Conducted Subsequent to the Reproductive Dose Range-Finding Studies

As in the short-term studies, the multigenerational reproductive toxicology and chronic studies were conducted with the NCTR CD (Sprague-Dawley) rat and test compounds were administered in the soy- and alfalfa-free 5K96 diet. The design of the multigenerational reproductive toxicology and chronic studies is outlined in Figure 1. For the multigenerational reproductive toxicology studies, males and females of the original parental generation (F_0) were placed on the 5K96 diet at weaning, and dosed feed was administered starting on postnatal day (PND) 42, 4 to 6 weeks before breeding. The F_0 generation was maintained on dosed feed until termination at PND 140. For breeding, one male was cohabited with one female for 14 days or until a vaginal plug (*in situ* or in pan below cage) was detected. Subsequent generations (F_1 through F_4) were bred similarly. The F_1 and F_2 generations were exposed to the test compound administered in the diet continuously from conception through termination at PND 140; the F_3 generation was removed from exposure at weaning (PND 21) and continued on control feed until PND 140, while the F_4 generation received no dietary exposure to the test compound. The F_4 generation was bred to produce an unexposed F_5 generation. The F_5 litters were terminated at weaning following collection of basic litter information. Thus, this design incorporated an evaluation of the magnification (or reduction) of effects across exposed generations, an evaluation of the reversibility of effects, and an evaluation of the carryover of effects into subsequent unexposed generations. Standard toxicological data and reproductive development and performance data were collected for all generations, and organ weights and histopathology data were collected for 25 randomly selected animals per sex per exposure concentration for each generation at necropsy.

Chronic toxicity was examined for two test compounds (genistein and ethinyl estradiol). Three exposure windows were examined in the chronic studies (Figure 1): 1) Continuous exposure from conception through 2 years (designated F_1 continuous, or F_1C) to evaluate the effects of lifelong exposure, 2) Exposure

from conception through PND 140 followed by control diet to 2 years (designated F_1 truncated at PND 140, or F_1T140) to determine if effects observed in the multigenerational study led to long-term adverse effects, and 3) Exposure from conception through weaning followed by control diet to 2 years (designated F_3 truncated at PND 21, or F_3T21) to evaluate the long-term effects of developmental exposure. The F_3 designation for the F_3T21 exposure indicates that these animals were siblings of the F_3 animals from the current study. Because of the number of animals required for the chronic study of each test chemical, separate sets of animals were used for the multigenerational reproductive toxicology study and the F_1 generation chronic study. The assessment of chronic toxicity resulting from dietary exposure from conception through weaning was conducted with animals from the F_3 generation of the multigenerational reproductive toxicology study.

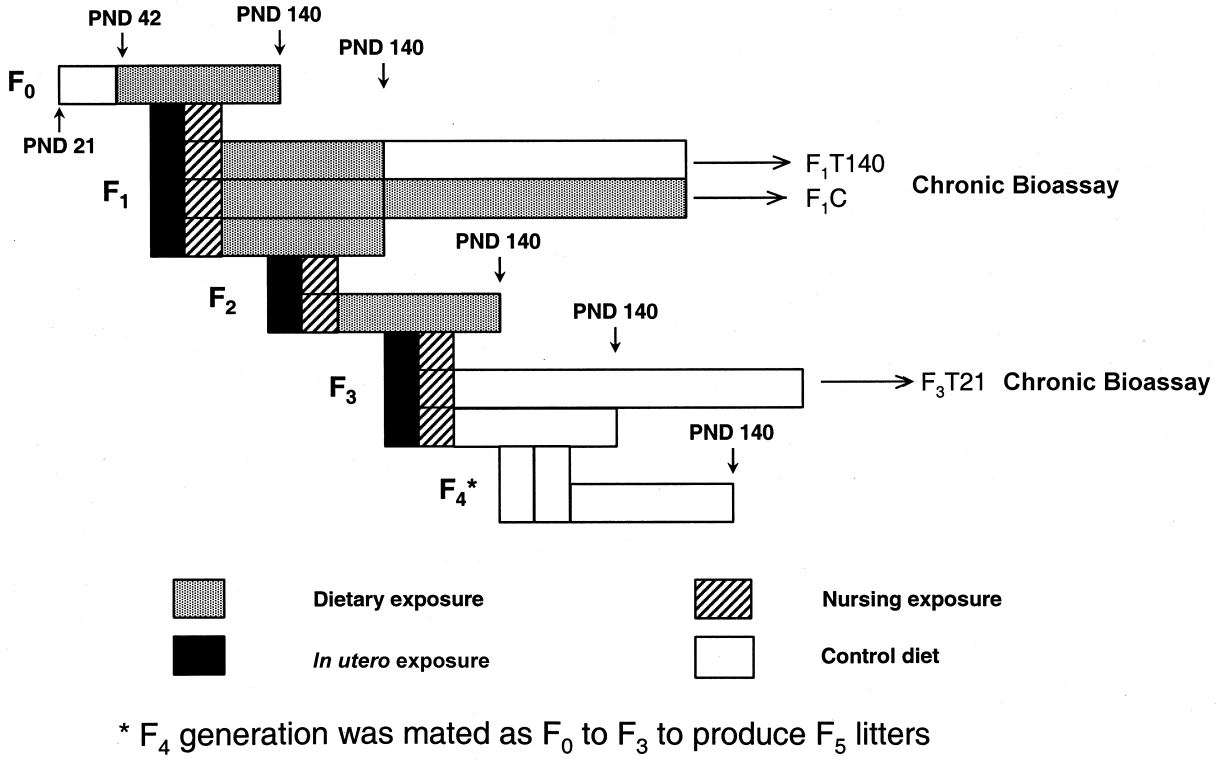
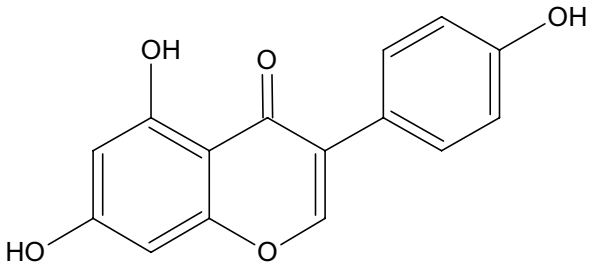


FIGURE 1
Dosing Schedule for the Multigenerational Reproductive Toxicology and Chronic Studies

INTRODUCTION



GENISTEIN

CAS No. 446-72-0

Chemical Formula: $C_{15}H_{10}O_5$ Molecular Weight: 270.23

Synonym: 4′,5,7-Trihydroxyisoflavone

Physical Properties, Production, Use, and Exposure

Genistein belongs to the class of chemicals designated isoflavones. It has a molecular weight of 270.23 and in pure form is a pale-yellow crystalline solid that is practically insoluble in water but freely soluble in methanol and ethanol (*Merck,* 1996). In nature, genistein is primarily found in legumes where it is produced by a branch of the phenylpropanoid pathway of secondary metabolism through the action of the enzyme isoflavone synthase on the flavanone intermediate naringenin (Dixon and Ferreira, 2002; Jackson and Rupasinghe, 2002). Products derived from soybeans are the primary source of human exposure to genistein. Genistein content of soybeans varies according to the cultivar and season, and processing of the soybean and soy foods further affects both the genistein content and the form of genistein present (Gugger, 2002; Jackson and Rupasinghe, 2002). The aglycone genistein (shown above) is present primarily in fermented products such as miso and tempeh, while genistein exists predominantly as the glucoside conjugate (genistin) or acetyl or malonyl derivatives of genistin in whole soybean and nonfermented products such as tofu or soy drinks. Glucosides and glucoside derivatives are hydrolyzed to the aglycone genistein in the gut by gut bacteria or gut wall enzymes. This metabolism of the glucoside has been shown to be a critical factor in the absorption of orally ingested isoflavones (Setchell *et al.,* 2002). In rats, the oral administration of the aglycone has been shown to result in faster uptake relative to the glucoside, although the exposures measured by the area under the curve (AUC) are similar (King *et al.,* 1996). Similar results have been reported in humans, although the administration of the glucoside appears to result in a higher AUC than does administration of the aglycone (Setchell *et al.,* 2001). Regardless of whether the glucoside or the aglycone is administered, the predominant circulating forms of genistein in rats and humans are glucuronide conjugates (Chang *et al.,* 2000; Setchell *et al.,* 2001) and similar effects of the aglycone and glucosides at doses resulting in equivalent serum concentrations would be expected (Allred *et al.,* 2001a; Satoh *et al.,* 2006).

Intake patterns and isoflavone content of ingested products vary widely, but the Committee on Toxicity of Chemicals in Food Consumer Products and the Environment of the United Kingdom (COT, 2003) has recently estimated an approximate rank order of daily

isoflavone exposure as follows: infant on soy formula (40 mg genistein/day), average Japanese consumer (25 to 100 mg/day), vegetarian consumer (3 mg/day), and the average British consumer (1 mg/day). The typical ingestion by the average consumer in the United States is likely to be similar to that by a consumer in the United Kingdom. Data on isoflavone intake from dietary supplements are sparse, but the COT estimated that manufacturers' recommended daily dosages would result in exposures of 29 to 88 mg isoflavones per day, or about 0.4 to 1.3 mg/kg per day for a 70 kg person. On a body weight basis, infants consuming soy formula are exposed to the highest doses, with mean doses estimated to be 6 to 9 mg/kg per day (Setchell *et al.*, 1997).

The consumption of diets with high levels of soy has been proposed to have multiple beneficial effects, including chemopreventive activities against various cancers and alleviation of some of the adverse consequences of menopause, although the epidemiological evidence for many of these beneficial effects is controversial (Adlercreutz, 2002; Messina *et al.,* 2006; Sacks *et al.,* 2006; Trock *et al.,* 2006; Williamson-Hughes *et al.,* 2006). Diets high in soy contain multiple agents that may contribute to these effects, and consumption of these diets is also associated with lower calorie and fat intake. Nonetheless, much research attention has focused on the isoflavones, and particularly genistein, as the active components contributing to (or responsible for) the beneficial effects of soy. This is due to the demonstrated interaction of soy isoflavones, particularly genistein, with estrogen receptors, effects on hormone synthesis and metabolism and sex hormone binding proteins, and genistein's ability to inhibit multiple enzymes involved in growth regulation, including tyrosine kinases and topoisomerases. These activities have been extensively reviewed (see above references). Genistein has been demonstrated in numerous studies to act as an estrogen by stimulating uterine growth in immature or ovariectomized rodents and has been shown to induce a similar, though not identical, pattern of gene expression as ethinyl estradiol in the developing rat uterus (Naciff *et al.*, 2002) and in developing rat testes and epididymides (Naciff *et al.*, 2005). Recent studies, published after the current study was completed, have also indicated that genistein, at concentrations above 1 µM, can modulate the expression of androgen-regulated genes and peroxisome proliferator activated receptor-α- and -γ-regulated genes (Dang *et al.*, 2003; Mezei *et al.*, 2003; Takahashi *et al.*, 2004; Kim *et al.*, 2005), thus adding to the potential complexity of genistein-mediated effects. The association of diets containing soy with lower rates of many common Western health problems has led to the development of concentrated isoflavone-containing plant extracts for use as dietary supplements (Hodgson *et al.*, 1998; Nestel *et al.*, 1999; Kurzer, 2003). In addition, soy-based infant formulas have been available for decades, and infants consuming soy formula have been shown to have concentrations of circulating isoflavones as high as 5 to 10 µM (Setchell *et al.*, 1997).

Research assessing the potential adverse effects associated with isoflavone consumption is directed toward defining any potential risk from exposure to a range of doses of isoflavones during different life stages. Developmental stages are of particular concern because of the demonstrated adverse consequences of exposure to hormonally active agents such as diethylstilbestrol during development (Bern, 1992; Newbold, 1995; NIH, 1999), although potential adverse stimulatory effects of genistein on reproductive and breast tissues of postmenopausal women also require particular attention (Petrakis *et al.*, 1996; Hargreaves *et al.,* 1999). With regard to potentially estrogenic effects of genistein in estrogen-responsive tissues in humans, several studies in female nonhuman primates have failed to demonstrate estrogenic effects of soy protein isolate or soy isoflavone mixtures that included approximately 10 mg genistein/kg per day and resulted in serum concentrations of genistein equivalent to those achieved from high dose soy ingestion in women (Wood *et al.,* 2004, 2006a,b,c).

Adverse effects of soy-containing foods and soy components on reproductive processes of animals had been reported prior to the initiation of this study (East, 1955; Stob, 1983; Price and Fenwick, 1985), and some human studies had suggested that the consumption of soy products could have hormonal effects in women (Wilcox *et al.*, 1990; Cassidy *et al.*, 1994, 1995; Baird *et al.*, 1995; Nagata *et al.*, 1997, 1998; Xu *et al.*, 1998; Duncan *et al.*, 1999). It has further been suggested, based on studies in ovariectomized rodents and nonhuman primates, that beneficial effects of soy and its component isoflavones on the cardiovascular system and bone occur at doses that do not adversely affect the reproductive tract (Anthony *et al.*, 1996; Ishimi *et al.*, 1999). In addition, inhibition of chemically induced mammary gland cancer in rats has been reported at doses that did not produce adverse effects on reproductive tissues (Murrill *et al.,* 1996; Fritz *et al.*, 1998; Lamartiniere *et al.,* 1998). Given the potential range of effects of soy and its

components and the magnitude of human exposure, comprehensive toxicological evaluations of these agents were conducted to better understand potential adverse effects that could result from their use in products such as dietary supplements and soy infant formula.

Results of the multigenerational reproductive toxicology study that evaluated the potential reproductive toxicity of genistein are reported in Technical Report 539 (NTP, 2008a).

CARCINOGENICITY

The association of low incidences of cancers such as breast and prostate cancer in populations with relatively high soy consumption has been a major driving force for investigations into the chemopreventive activity of genistein and soy. Epidemiological studies of the association between the consumption of soy diets and breast cancer risk have been mixed, and there are unresolved questions concerning the role of ethnicity, the nature of the ingested soy products, age, ovarian function (premenopausal versus postmenopausal), and the importance of the daidzein metabolite equol or soy components other than isoflavones in the potential protective effects of soy (Wu *et al.,* 2002; Peeters *et al.,* 2003; Yamamoto *et al.,* 2003; Keinan-Boker *et al.,* 2004; Atkinson *et al.,* 2005; Hirose *et al.,* 2005). Grace *et al.* (2004) conducted a study with subjects from the United Kingdom and reported an association between soy intake and an increased risk of breast cancer. Similarly, human studies on the relationship of soy consumption to prostate cancer are not conclusive (Chan *et al.,* 2005; Ganry 2005), although there have not been reports of soy or genistein potentially stimulating prostate cancer growth. Sun *et al.* (2002, 2004) found an association between soy consumption and an increased risk of urinary bladder cancer. No studies linking exposure to enriched or purified genistein or isoflavone preparations to increased cancer incidence in humans have been reported.

In animal models, genistein has been clearly shown to inhibit chemically induced mammary gland carcinogenesis when exposure occurs peripubertally, apparently by affecting differentiation of the terminal end buds (Murrill *et al.,* 1996; Fritz *et al.,* 1998; Hilakivi-Clarke *et al.,* 1998, 1999a). In human studies, early (prepubertal) exposure to soy has also been associated with lower breast cancer incidence (Wu *et al.,* 2002). However, animal studies have indicated that genistein can enhance carcinogenesis under certain circumstances. Hilakivi-Clarke *et al.* (1999b) found that *in utero* exposure to genistein increased tumor incidence when 20, 100, or 300 µg was administered by subcutaneous injection to dams on gestational days (GDs) 15 to 20, although 20 µg of the more potent estrogen zearalenone was not effective. In mice, *in utero* exposure to genistein (subcutaneous injection, 20 µg on GDs 15 to 20) increased the density of terminal end buds at postnatal day (PND) 35 and PND 46. Similar treatment with 2 µg of zearalenone showed this effect at PND 35, but not at PND 46 when the gland showed an increase in differentiated structures (terminal ducts and alveolar buds) (Hilakivi-Clarke *et al.,* 1998). The authors proposed that the differences between genistein and zearalenone may be because zearalenone produced a significant increase in persistent estrus, consistent with its higher estrogenic potency, and because it does not bind preferentially to estrogen receptor-β as does genistein. Yang *et al.* (2000) found that *in utero* exposure to genistein, combined with exposure to a carcinogen at an earlier time when an increase in differentiation was not evident in genistein-treated rats, did not inhibit and in fact slightly enhanced tumor multiplicity. How well these developmental rodent models translate to the human situation, where the nature and timing of carcinogen exposure are not clear, remains to be determined.

Genistein, genistin, and soy protein isolate have also been shown to promote the growth of MCF-7 mammary gland cancer cells transplanted into ovariectomized immune compromised mice (Hsieh *et al.,* 1998; Allred *et al.,* 2001a,b; Ju *et al.,* 2001). Genistein at 750 ppm also stimulated the growth of carcinogen-induced mammary gland tumors in ovariectomized rats administered genistein in feed after the tumors had developed (Allred *et al.,* 2004a). Daily subcutaneous injections of 1 mg/kg genistein after treatment with a carcinogen were also reported to enhance mammary tumor growth and multiplicity in rats (Kijkuokool *et al.*, 2006). The degree of processing of soy has been shown to be an important modifier of the enhancing effect in the transplanted MCF-7 mouse model; soy products with more processing showed greater effects (Allred *et al.,* 2004b). The diet in which genistein is administered has also been shown to modify the inhibitory effect of genistein on cancer development (Kim *et al.,* 2004). Day *et al.* (2001) reported that 1,000 ppm dietary genistein enhanced the development of adenocarcinoma in DMBA-treated wild-type, but not estrogen receptor-α knockout, mice. Rao *et al.* (1997) also reported an increased multiplicity of chemically induced colon tumors in rats dosed orally with genistein.

No standard 2-year bioassays of genistein have been reported. Neonatal treatment of mice with subcutaneous injections of 50 mg/kg from PNDs 1 to 5 induced uterine adenocarcinomas in mice (Newbold *et al.,* 2001). Thigpen *et al.* (2001) reported an increase in the incidence of spontaneous vulvar carcinomas in strain 129/J mice associated with the presence of genistein and daidzein in the diet. Misra *et al.* (2002) reported that an isoflavone mixture containing 40% to 50% genistein, 18% to 25% daidzein, and 1% to 4% glycitein did not enhance tumor formation in p53 knockout mice at a dietary concentration that delivered 50 to 60 mg genistein/kg body weight per day. A subsequent gavage study indicated that this isoflavone mixture did not induce tumors in any organ at doses up to 2,500 mg/kg per day for up to 6 months (Johnson *et al.,* 2006).

Genetic Toxicity

While much of the focus on the potential induction or modulation of cancer development by genistein has been on its activity as a phytoestrogen, the potential for genotoxicity has also been evaluated. Genistein has been tested for mutagenicity in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA1535, and TA1538 with and without a rat liver S9 metabolic activation system, and the results were negative (Bartholomew and Ryan, 1980; Nagao *et al.,* 1981; McClain *et al.,* 2006a). Misra *et al.* (2002) also reported a statistically significant but modest (less than twofold) positive mutagenic response in TA100 with S9 activation using an isoflavone mixture containing 40% to 50% genistein, 18% to 25% daidzein, and 1% to 4% glycitein.

Genistein has been shown to bind to DNA topoisomerase II to produce DNA strand breaks (Markovits *et al.,* 1989; Snyder and Gillies, 2002). DNA strand breaks, micronucleus formation, and mutations at the hypoxanthine phosphoribosyltransferase and thymidine kinase genes in mammalian cells *in vitro* have been reported with and without coincubation with a rat liver S9 metabolic activation system at concentrations as low as 3 to 5 µM genistein (Yamashita *et al.,* 1990; Record *et al.,* 1995; Kulling and Metzler, 1997; Morris *et al.,* 1998; Kulling *et al.,* 1999; Boos and Stopper, 2000; Snyder and Gillies, 2003; Di Virgilio *et al.,* 2004; McClain *et al.,* 2006a). Of particular concern was the demonstration of genistein-induced translocations and deletions in the mixed-lineage leukemia (MLL) gene in hematopoietic mononuclear cells isolated from umbilical cord blood, because this gene is associated with acute myelogenous leukemia (AML) (Strick *et al.,* 2000). Epidemiological studies have been interpreted to suggest a possible association between consumption of diets high in DNA topoisomerase II inhibitors, although not necessarily genistein, with the development of MLL-positive AML (Ross *et al.,* 1996; Spector *et al.,* 2005). *In vivo* studies with genistein in mice and rats, however, have not demonstrated an increase in micronucleus frequency (Record *et al.,* 1995; Misra *et al.,* 2002; McClain *et al.,* 2006a) nor an increase in mutations in the lac I or cII genes of several organs of transgenic Big Blue rats (Chen *et al.,* 2005; Manjanatha *et al.,* 2005). Morris *et al.* (2003) did report an increasing proportion of small intestine cells in S-phase and a decreasing proportion in G_0 over a dose range of 100 to 2,000 ppm dietary genistein (approximately 17 to 460 mg/kg per day) in C57BL6 mice, which they interpreted as consistent with *in vivo* inhibition of DNA topoisomerase II. A clinical study in 20 prostate cancer patients who received 300 mg genistein (approximately 4 mg/kg per day) for 28 days followed by 600 mg genistein per day for 56 days was reported by Miltyk *et al.* (2003). These doses resulted in plasma concentrations of total genistein ranging from 4 to 27 µM and aglycone concentrations ranging from 0.02 to 0.32 µM. There was no evidence of increases in DNA strand breaks, micronucleus formation, or translocations in the MLL gene in peripheral lymphocytes. Thus, while the ability of genistein to induce chromosomal damage has been clearly demonstrated in *in vitro* systems, conditions under which such damage may be induced *in vivo* have not been demonstrated. In addition, genistein was reported to be negative in the *in vitro* Syrian hamster embryo cell transformation assay (Harvey *et al.,* 2005).

Dose Selection for the 2-Year Feed Study of Genistein

Results from the reproductive dose range-finding feed study of genistein and the rationale for exposure concentration selection for the multigenerational reproductive toxicology and 2-year studies are presented in Toxicity Study Report 79 (NTP, 2007). Dietary exposures of 5, 25, 100, 250, 625, or 1,250 ppm were evaluated in the dose range-finding study. Pups in the 1,250 ppm groups had significantly decreased body weights relative to controls at the time of sacrifice (males, 9% decrease; females, 12% decrease). The most pronounced organ weight effects in the pups were decreased ventral

prostate gland weight in 1,250 ppm males (absolute weight, 28% decrease; relative weight, 20% decrease) and a trend toward higher relative pituitary gland weights in both sexes. Histopathologic examination of female pups revealed increased incidences of mammary gland ductal/alveolar hyperplasia at 250 ppm or greater. Increased incidences of mammary gland ductal/alveolar hyperplasia and hypertrophy occurred in exposed males, with significant increases seen at exposure concentrations of 25 ppm or greater for hypertrophy and 250 ppm or greater for hyperplasia. In 625 and 1,250 ppm females, the incidences of abnormal cellular maturation (mucocyte metaplasia) in the vagina were significantly increased; in addition, the incidence of abnormal ovarian antral follicles was significantly increased in 1,250 ppm females. In 1,250 ppm males, the incidence of aberrant or delayed spermatogenesis in the seminiferous tubules was significantly increased. Histological evaluation indicated a deficit of sperm in the epididymis of 625 and 1,250 ppm males relative to controls, although testicular spermatid head counts and epididymal spermatozoa counts did not show significant differences from controls at these exposure concentrations. Control females had a high incidence of renal tubule mineralization, and the severities of this lesion were significantly increased in groups exposed to 250 ppm or greater. Males showed no renal tubule mineralization below 250 ppm, but incidences and severities increased with exposures of 250 ppm or greater. A 1,250 ppm exposure concentration was clearly ruled out for further testing based on the effects on body weights, histopathological observations in males and females, and a reduction in the proportion of mated dams producing litters. While the effects observed at 625 ppm would not be predicted to significantly impair reproduction, the observation of significant effects at 250 ppm (hyperplasia in the mammary gland of both sexes) and the suggestion of subtle effects at this and lower exposure concentrations in the parallel immunotoxicity and neuroanatomical studies indicated that a high exposure concentration between 250 ppm and 625 ppm would be appropriate for the 2-year study. Accordingly, the highest exposure concentration chosen for the multigenerational reproductive toxicology study (NTP, 2008a) and the 2-year study was 500 ppm. A low exposure concentration of 5 ppm, where no significant effects were observed in the reproductive dose range-finding study (NTP, 2007), and an intermediate exposure concentration of 100 ppm were also selected. The calculated ingested doses of genistein by animals consuming these dietary concentrations are given in Table 1.

TABLE 1
Approximate Ingested Doses of Genistein in Rats Exposed to 5, 100, or 500 ppm Genistein in the 2-Year Feed Study of Genistein[a]

	5 ppm	100 ppm	500 ppm
F_0 Dams, nonlactating period	0.5 ± 0.0 (9)	8.9 ± 0.5 (9)	44.7 ± 2.6 (9)
F_0 Dams, lactating period	0.7 ± 0.1 (3)	14.9 ± 1.3 (3)	74.7 ± 5.2 (3)
F_1 Female pups, continuous dosing, before PND 140	0.4 ± 0.0 (17)	8.4 ± 0.6 (17)	43.7 ± 2.8 (17)
F_1 Female pups, truncated dosing, before PND 140	0.4 ± 0.0 (17)	8.4 ± 0.5 (17)	44.3 ± 2.8 (17)
F_1 Female pups, continuous dosing, after PND 140	0.3 ± 0.0 (21)	5.1 ± 0.1 (21)	28.9 ± 0.7 (21)
F_1 Male pups, continuous dosing, before PND 140	0.4 ± 0.0 (17)	7.2 ± 0.7 (17)	36.8 ± 3.6 (17)
F_1 Male pups, truncated dosing, before PND 140	0.4 ± 0.0 (17)	7.2 ± 0.6 (17)	36.9 ± 3.3 (17)
F_1 Male pups, continuous dosing after PND 140	0.2 ± 0.0 (21)	4.0 ± 0.1 (21)	20.2 ± 0.4 (21)

[a] Data are presented as mg genistein/kg body weight per day [mean ± standard error (number of weeks measured)]. PND=postnatal day. The mean ingested dose was calculated for each available week by multiplying the dietary concentration of genistein (ppm) by the mean measured amount of feed ingested weekly and dividing the result by the mean body weight for the week. These values were divided by 7 to give the mean daily dose given in the table. Weekly body weight and feed consumption data were used for the F_0 calculations and for the F_1 animals prior to PND 140; monthly data (one week per month) were used for the F_1 animals after PND 140. For the F_0 dams, data are reported separately for the nonlactating period and the lactating period. The values presented for the lactating females include the period, primarily during the last week of nursing, during which the pups were beginning to directly consume feed. For F_1 animals, data are reported separately for the time before PND 140 and from PND 140 to termination at 2 years for the subset of animals that were continuously dosed over this time period. F_3T21 animals are not included in this table; they were exposed only through gestation and lactation, and the relevant information on the exposure of the F_2 dams during pregnancy and lactation is presented in Technical Report 539 (NTP, 2008a). Ingested doses were similar to those presented here for the F_0 dams.

MATERIALS AND METHODS

Procurement and Characterization of Genistein

Genistein was obtained from Toronto Research Chemicals, Inc. (North York, Ontario, Canada), in two lots (2-BP-136-6 and 1-SOP-59-3). Identity and purity analyses were conducted by the study laboratory at the National Center for Toxicological Research (NCTR; Jefferson, AR) (Appendix C). Reports on analyses performed in support of the genistein study are on file at the NCTR.

Lots 2-BP-136-6 and 1-SOP-59-3 of the chemical, a pale yellow crystalline solid, were identified as genistein by proton nuclear magnetic resonance (NMR) spectroscopy. NMR spectra were in agreement with the structure of genistein and spectra obtained from other lots of genistein.

The purities of lots 2-BP-136-6 and 1-SOP-59-3 were determined by high-performance liquid chromatography (HPLC) with ultraviolet (UV) and mass spectrophotometric (MS) detection, by gas chromatography (GC) with MS detection, and by probe/MS methods.

HPLC/UV and HPLC/MS spectra agreed with the structure of genistein and matched the spectra obtained from a purchased standard of genistein, indicating a purity of essentially 100% for each lot. GC/MS spectra indicated one major peak and minor impurities with a purity greater than 99%. Probe/MS testing indicated one major component with two minor components, suggesting little to no impurities. The overall purity of each lot was determined to be greater than 99%.

To ensure stability, the bulk chemical was stored at –70° C, protected from light in the original shipping containers. Purity was periodically measured during the study; no degradation of the bulk chemical was detected.

Background Isoflavone Content of Base Diet

The base diet used for the current study was an irradiated soy- and alfalfa-free rodent feed, designated 5K96, obtained from Purina Mills, Inc. (Richmond, IN), in an attempt to maintain consistently low background exposure to phytoestrogens. In some associated publications resulting from this study (Appendix J), this feed is referred to as NIH-31C because it maintains the nutritional specifications of the NIH-31 feed and contains casein. The composition of this diet and the results of the routine monitoring of the diet conducted throughout the study are presented in Appendix H. The control feed was routinely assayed for total isoflavone content after acid hydrolysis by the study laboratory using HPLC/MS methods.

Analyses of 10 consecutive lots of 5K96 feed by these methods indicated 0.417 ± 0.213 ppm genistein and 0.271 ± 0.161 ppm daidzein. These results were consistent with an earlier study of four lots of 5K96 feed assayed at the study laboratory using a liquid chromatography-tandem mass spectrometry method that yielded concentrations of 0.54 ± 0.31 ppm genistein and 0.48 ± 0.21 ppm daidzein (Doerge *et al.,* 2000). Animals consuming control feed were ingesting a concentration of genistein approximately 10-fold lower than that of the groups exposed to the lowest experimental exposure concentration, a concentration consistent with the isoflavone intake of individuals consuming typical Western diets.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared every 5 weeks or as needed by mixing genistein with feed (Table C1). Homogeneity (analysis of three samples each from the top, middle, and bottom of a blend) and stability studies of a 5 ppm dose formulation using lot 1-BP-118-3 were

conducted by the study laboratory as part of the reproductive dose range-finding study (NTP, 2007) using HPLC/UV. Homogeneity was confirmed, and stability in stainless steel cans was confirmed for up to 17 days at ambient temperature and for up to 32 weeks at 2° to 8° C.

Periodic analyses of the dose formulations of genistein (analysis of one sample each from the top, middle, and bottom of a blend) were conducted by the study laboratory using HPLC/UV. The dose formulations were analyzed at intervals of 1 to 4 weeks; 124 of the 125 dose formulations analyzed and used in the study were within 10% of the target concentrations (Table C2). Animal room samples of these dose formulations were also periodically analyzed to confirm that the correct exposure concentrations were being fed (Table C3).

2-YEAR STUDY

Study Design

Three exposure windows were examined in the 2-year study: continuous exposure from conception through 2 years (F_1C); exposure from conception through postnatal day 140 (PND 140), followed by control diet until termination (F_1T140); and exposure from conception through weaning at PND 21, followed by control diet until termination (F_3T21).

Groups of 35 (F_0) or 50 (F_1 and F_3) male and female rats (control groups had 52 to 54 animals which included those originally designated as sentinels) were exposed to diets containing 0, 5, 100, or 500 ppm genistein for 77 (F_0 generation), 756 (F_1C), 161 (F_1T140), or 42 (F_3T21) days. The same sets of dams produced F_1 offspring for both the F_1C and F_1T140 exposure groups. The F_0 ancestral generation of the F_3T21 animals was that used in the separate multigenerational reproductive toxicology study (NTP, 2008a). Exposure schedules for the three treatment arms of the study are shown in Figure 1.

Source and Specification of Animals

The Multigeneration Support System, which was developed by R.O.W. Sciences at the NCTR, was used to track the genealogy of all animals in the current study and to collect animal data. For the parental (F_0) generation, 140 male and 140 female weanling NCTR CD rats (Strain Code 23) were obtained from the NCTR breeding colony and placed on irradiated control 5K96 feed. Until weaning, these rats and their dams had been maintained on NIH-31 pellets. NIH-31 has been reported to contain approximately 30 ppm each of the soy-derived isoflavones genistein and daidzein, which are present predominantly as the glucosides genistin and daidzin (Thigpen *et al.,* 1999). The NCTR CD rat strain was founded in 1972 from Sprague-Dawley rats from Charles River Laboratories and has been maintained in the NCTR breeding facility since that time. Rats of the F_0 generation were acclimated to the Purina 5K96 diet for 3 weeks from PND 21 to PND 42 and were 6 weeks old at the beginning of the study. Animals in the F_1 and F_3 generations were on-study from conception. The health of the animals in all generations was monitored during the study according to the protocols of the Study Laboratory's Sentinel Animal Program (Appendix I).

Animal Breeding and Maintenance

Animals were identified by tail tattoos and housed in pairs until assignment to exposure groups. On PND 42, animals in the F_0 generation were weighed and allocated to one of four exposure groups by a stratified randomization procedure based on body weight to give 35 males and 35 females in each exposure group. Animals were reidentified with a unique tail tattoo after assignment to exposure groups. Males were housed individually in wire breeding cages between PND 56 to PND 60 for acclimation. Pairings within exposure groups were randomly generated by the Multigeneration Support System, and females were introduced into breeding cages with the males. The F_0 animals were no younger than PND 70 and no older than PND 84 at the time they were paired.

The date of vaginal plug detection (*in situ* or in pan below the cage) was designated as the day of conception or gestation day 0 (GD 0). In order to maximize mating success and thus the number of litters and pups available for the study, breeders used to generate the F_1C and F_1T140 animals were kept together in the breeding cage for an additional 5 days (the length of one estrous cycle) if a vaginal plug was detected within the first 3 days of the mating period. The 2-year study animals that had exposure truncated at weaning (F_3T21) were from the F_3 generation of the previous multigenerational reproductive toxicology study (NTP, 2008a). Briefly, F_0 animals were exposed to 0, 5, 100, or 500 ppm genistein from PND 42, and they and their descendants were exposed continuously to the same dosed feed through the F_2 generation. All groups in the F_3 generation were placed on

control 5K96 feed at weaning. In all generations, on postconception day 23, corresponding to PND 2, litters were randomly standardized to four males and four females per litter. Animals were occasionally fostered within exposure groups to maintain constant litter size. After standardization, excess pups were sacrificed. Pups were marked on the day of standardization by paw tattoos so that a unique animal identification was provided by cage number, sex, and tattoo pattern. Animals were identified with a unique identification number by tail tattoo at weaning.

At weaning of the F_1 generation, 50 control animals of each sex and 100 animals of each sex from the three other exposure groups were selected for continuation on the study and were housed individually until termination. Additional control animals were designated as sentinel animals, housed with the study animals, and removed for microbiological assessment at 6-month intervals over the course of the study. After weaning, animals were maintained on the same feed as their dams. At PND 140, one half of the animals in the three exposed groups (5, 100, and 500 ppm) were placed on control feed until termination of the study. Fifty animals from the 0, 5, 100, and 500 ppm groups in the F_3 generation were placed on control feed at weaning until termination of the study. In all cases, study animals were selected so that the maximum number of litters was represented and no more than two animals of the same sex were taken from a single litter. The number of litters from which the animals were derived in each exposure group were as follows: F_1 0 ppm, 30 litters; F_1 5 ppm, 26 litters; F_1 100 ppm, 30 litters; F_1 500 ppm, 27 litters; F_3 0 ppm, 26 litters; F_3 5 ppm, 31 litters; F_3 100 ppm, 33 litters; F_3 500 ppm, 36 litters.

Animals were maintained on soy- and alfalfa-free Purina 5K96 meal available *ad libitum* until the day before necropsy. Millipore-filtered tap water, which was analyzed routinely by the Divisions of Microbiology and Chemistry, NCTR, was provided *ad libitum.* The 5K96 meal underwent routine analyses as well as periodic analyses for isoflavone levels. Feeders were gently agitated daily with a vibrating tool (Dremel, Racine, WI) to prevent caking and were changed once per week. Cages were changed weekly. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix H.

In-life Examinations and Pathology

The data collected during the in-life phase of the study and at necropsy are detailed in Table 2. Animals were observed twice daily, and clinical findings were recorded weekly. Animals in the F_1 generation were weighed weekly until postnatal week 21, then approximately every 4 weeks for the remainder of the study and at termination of the study. Animals in the F_3 generation were weighed weekly until postnatal week 15, then approximately every 4 weeks for the remainder of the study and at termination of the study. Feed consumption was recorded every 4 weeks after weaning for the F_1 and F_3 generations. Weekly body weight and feed consumption data were also monitored for the parental generation (F_0) for the F_1 animals in order to assess ingested doses during pregnancy and lactation (Table 1). Body weight and feed consumption data for the ancestral generations of the F_3T21 animals were collected as part of the multigenerational reproductive toxicology study and are reported elsewhere (NTP, 2008a).

One half of the females in each exposure group were subjected to vaginal smears for 5 consecutive days once per month. These smears were then evaluated for stage of the estrous cycle. If there was evidence that the animals were not cycling normally (i.e., 3 consecutive days of estrus, 4 consecutive days of diestrus) for 2 consecutive months, the animal was considered to have begun to show aberrant cycles during the first month in which abnormal cycling was observed.

Complete necropsies and microscopic evaluations were performed on all F_1C, F_1T140, and F_3T21 rats. From terminal sacrifice animals, the following organs were weighed prior to fixation: adrenal gland (left and right), brain, epididymis, kidney (left and right), liver, ovary/oviduct (left and right), seminal vesicle with coagulating gland, spleen, testis (left and right), thymus, and uterus. The following organs were weighed after fixation: dorsal, lateral, and ventral prostate gland (lobes were separated after fixation), pituitary gland, and thyroid gland. All organs and tissues were examined for grossly visible lesions, and lesion descriptions were recorded on the Individual Animal Necropsy Record. All major tissues except the testis were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in Tissue Prep II, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. The testis was

similarly treated, except that it was fixed in Bouin's fixative and stained with periodic acid-Schiff stain to better aid in the characterization of sperm maturation. When applicable, nonneoplastic lesions were graded for severity as 1 (minimal), 2 (mild), 3 (moderate), or 4 (marked). All tissues examined microscopically are listed in Table 2.

Microscopic evaluations were completed by two NCTR pathologists, one for males and one for females. Pathology data were entered into NCTR's Micropath Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to NCTR's Block and Slide Laboratory for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, pathology tables, and study pathologists' narrative were evaluated by an independent quality assessment group. The individual animal records were compared for accuracy; the slide and tissue counts were verified; and the histotechnique was evaluated. Quality assessment pathologists evaluated all lesions diagnosed by the study pathologists. 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 slides reviewed by the PWG included the mammary gland of male and female rats and the pancreatic islets, seminal vesicle, and pituitary gland of male rats. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of 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 pathologists, 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 2
Experimental Design and Materials and Methods in the 2-Year Feed Study of Genistein

Study Laboratory
National Center for Toxicological Research (NCTR) (Jefferson, AR)

Strain and Species
Sprague-Dawley/CD23/NCTR BR rats

Animal Source
NCTR Breeding colony (Jefferson, AR)

Acclimation Time
3 weeks: F_0 animals were allocated to the study at weaning and placed on a soy- and alfalfa-free meal diet (Purina 5K96).

Average Age When Study Began
F_0: 6 weeks (PND 42)
F_1 and F_3: 0 weeks (on study from conception)

Date of First Exposure (Conception Date for F_1 and F_3)
F_0: January 29, 1999
F_1: March 5, 1999
F_3: April 18, 1999

Duration of Exposure
F_0: From PND 42 until F_1 weaning (77 days)
F_1 (F_1C): From conception to 2 years (756 days)
F_1 (F_1T140): From conception to PND 140 (161 days), then fed control diet to 2 years
F_3 (F_3T21): From conception to PND 21 (42 days), then fed control diet to 2 years

Date of Final Necropsy
F_1: March 30, 2001
F_3: May 21, 2001

Average Age at Necropsy
108 weeks

Size of Study Groups
35 males and 35 females (F_0 generation) or 50 males and 49 females (F_1 and F_3 generations); control groups had 52 to 54 animals which included those originally designated as sentinels which were necropsied if they became moribund or died prior to their scheduled necropsy date (four F_1 control males, four F_1 control females, two F_3 control males, and three F_3 control females)

Method of Distribution
F_0 animals were allocated to exposure groups by a stratified randomization procedure to give groups of approximately the same initial mean body weight; litters of subsequent generations were randomly culled to eight pups on PND 2. At weaning, 50 male and 50 female F_1 pups were allocated to the control groups to serve as controls for both the F_1C and F_1T140 study arms and 100 male and 100 female F_1 pups were allocated to each exposed group. All available litters were represented as equally as possible, with no more than two animals of the same sex from a single litter.

For the F_3 animals, which were exposed to dosed feed only through weaning, 50 male and 50 female pups per exposure group were allocated from the litters produced in the previous multigenerational reproductive toxicology study (NTP, 2008a). All available litters were represented as equally as possible, and no more than two animals of the same sex from a single litter were used.

Animals per Cage
F_0 animals were held two per cage from weaning until allocation to exposure groups, then single housed. F_1 and F_3 animals were single housed from the time of weaning.

Method of Animal Identification
Tail tattoo; newborns were identified by paw tattoo until tail tattoo identification at weaning.

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Feed Study of Genistein

Diet
Purina 5K96 Rodent Chow, irradiated (Test Diets, Purina Mills, Inc., Richmond, IN), available *ad libitum* until the day before sacrifice

Water
Millipore-filtered tap water (Jefferson, AR, municipal supply) via water bottles, available *ad libitum*

Cages
Solid-bottom polycarbonate (Allentown Caging Equipment Co., Allentown, NJ), changed weekly

Bedding
Heat-treated hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed weekly

Cage Bonnets
Microisolator tops (Lab Products, Inc., Maywood, NJ)

Racks
Metal animal cage racks (Allentown Caging Equipment Co., Allentown, NJ), changed every 28 days

Animal Room Environment
Temperature: 23° ± 3° C
Relative humidity: 50% ± 20%
Room fluorescent light: 12 hours/day
Room air changes: at least 10/hour

Exposure Concentrations
0, 5, 100, or 500 ppm in feed, available *ad libitum*

Type and Frequency of Observation
Observed twice daily and clinical findings were recorded weekly. Animals in the F_1 generation were weighed weekly until postnatal week 21, then approximately every 4 weeks for the remainder of the study and at termination of the study. Animals in the F_3 generation were weighed weekly until postnatal week 15, then approximately every 4 weeks for the remainder of the study and at termination of the study. Feed consumption was recorded every 4 weeks after weaning for the F_1 and F_3 generations.

Weekly body weight and feed consumption data were also monitored for the parental generation (F_0) for the F_1 animals in order to assess ingested doses during pregnancy and lactation. Body weight and feed consumption data for the ancestral generations of the F_3T21 animals were collected as part of the previous multigenerational reproductive toxicology study (NTP, 2008a).

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
Necropsies were performed on all F_1C, F_1T140, and F_3T21 animals. From terminal sacrifice animals, the following organs were weighed prior to fixation: adrenal gland (left and right), brain, epididymis, kidney (left and right), liver, ovary/oviduct (left and right), seminal vesicle with coagulating gland, spleen, testis (left and right), thymus, and uterus. The following organs were weighed after fixation: pituitary gland; dorsal, lateral, and ventral prostate gland (lobes were separated after fixation); and thyroid gland.

Histopathology
Complete histopathology was performed on all rats. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone marrow (femur and sternum), brain (cerebellum, cerebrum, stem), clitoral gland, coagulating gland, epididymis, esophagus, eye, harderian gland, heart with aorta, 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 (dorsal and ventral lobes), salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, uterus, vagina, and Zymbal's gland.

Onset of Aberrant Estrous Cycles
Starting at 5 months of age, vaginal smears were obtained from 25 females in each exposure group to evaluate the stage of the estrous cycle for 5 consecutive days every 4 weeks until they were determined not to be cycling for 2 consecutive months.

STATISTICAL METHODS

Survival Analyses and Time of Onset of Aberrant Estrous Cycles

Probabilities of survival were estimated by the product-limited procedure of Kaplan and Meier (1958) and are presented graphically. The data were analyzed within each of the three arms of the study using a log-rank test for homogeneity and Tarone's test (Tarone, 1975) for overall trend. For pairwise comparisons, Tarone's and the log-rank test are equivalent, but Tarone's was preferred because the trend direction may be noted. P values reported are right sided unless the trend was negative. In this case, the trend was left sided and an "N" was appended to the P value.

Vaginal cytology data collected to evaluate whether exposure to genistein affected the time that female rats began to show aberrant cycles prior to reproductive senescence were analyzed by an accelerated failure time model. The data for this endpoint contained all three classical types of censoring, that is left, right, and interval censoring. Left censoring occurred because some animals had begun to show aberrant cycles prior to the time that observations were begun at 5 months of age. Right censoring occurred because some animals died or reached the end of the study without showing evidence of aberrant cycles. Finally, the intermittent nature of the data collection (one 5-day period every month) made it impossible to determine the exact time when aberrant cycles began, so the data exhibited interval censoring. The accelerated failure time Kaplan-Meier model utilized accommodated all three types of censoring. Several different distributional models [Weibull (1951), exponential, generalized gamma, normal, logistic, lognormal, and log-logistic] were applied, and the probability plots of the residuals and the fitted models were examined to determine goodness-of-fit. The Weibull, lognormal, log-logistic, and generalized gamma models all fit reasonably well and gave similar, but not identical, results.

Analysis of Continuous Variables

A mixed models approach to repeated measures ANOVA was used to analyze body weights and feed consumption. Testing for linear and quadratic exposure concentration trends was conducted at each time interval. In the course of analyzing the data from these studies, it was recognized that, because of the spacing of the exposure concentrations, a standard linear trend analysis would cause the 0, 5, and 100 ppm groups to basically be averaged, or treated as a single point, and compared to the 500 ppm group. For this reason, trend analyses for many endpoints were also conducted using a natural log-transformed dose scale [ln(dose + 1)] that resulted in a more evenly weighted scale (0, 1.8, 4.6, and 6.2). Organ weights, terminal body weights, and the ratios of organ weight to terminal body weight for terminally sacrificed animals were analyzed using ANOVA procedures. Terminal body weights were also used as a covariate in an ANCOVA procedure for organ weight analyses. For each endpoint analyzed, Dunnett's two-sided test (Dunnett, 1955) was used to compare the control group mean to each exposed group mean, either overall or at each point of time, whichever was appropriate. Results of one-way tests of exposure concentration effects within each of the three arms of the study are reported.

The separate F_0 generations used to generate the F_1 and F_3 animals used in this 2-year study were derived from breeders in the NCTR colony. The breeders used to produce the F_0 generations did cross breed, that is, sires were mated with multiple dams to produce litters from which the F_0 animals were derived. If a litter or family line effect was causing differences between exposure groups, then isolating and measuring the family line variation and removing it would increase confidence in significant exposure effects. To dispense with possible nuisance variation, an F_0 mother (that is, the mothers giving rise to the F_0 animals) random effect, an F_0 father (that is, the fathers giving rise to the F_0 animals) random effect, and an interaction of F_0 mother and F_0 father random effect were incorporated as random effects into the covariance structure of the model when any of these effects were significant via a log-likelihood ratio test at an α of 0.50 and their inclusion was computationally feasible. The high α value of 0.50 was selected to guard against Type II error. In this case, Type II error occurs when one falsely assumes no random effect. It was deemed to be a more serious error to incorrectly assume no random "litter" effect was present than to incorrectly assume a random "litter" effect was present. Therefore, α was chosen to be high in order to err on the side of inclusion of the effect rather than exclusion. Nesting of original sires and dams that produced the F_0 generation within exposure groups could not be done because there were instances of progeny in more than one exposure group arising from the same original sire or dam.

Statistical Analysis of Histopathology Data

Analyses of the incidences of neoplastic lesions were conducted separately for each of the three arms of the study (F_1C, F_1T140, and F_3T21). As discussed previously, because of the wide spacing between exposure concentrations, analyses were conducted using both an unmodified dose scale and a natural log-transformed dose scale [ln(dose + 1)]. The modified dose scale gave a more evenly weighted scale.

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1a,b,c, A3a,b,c, B1a,b,c, and B3a,b,c 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 A2a,b,c and B2a,b,c) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. Tables A2a,b,c and B2a,b,c 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, only to site-specific, lesion-free animals that do not reach terminal sacrifice.

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm 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). 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 exposed group with controls and tests for overall exposure concentration-related trends. As described previously, trend analyses were conducted using both a standard linear dose trend analysis and a transformed dose scale [ln(dose + 1)] that resulted in a more evenly weighted scale (0, 1.8, 4.6, and 6.2). 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).

With the exception of the incidences of hyperplasia in the male mammary gland (identified as an affected endpoint in the previous reproductive dose range-finding and multigenerational reproductive toxicology studies), nonneoplastic lesions were not statistically evaluated. These data were analyzed by a Jonckheere-Terpstra (Jonckheere, 1954) test for increasing trend, which presumes a monotonic dose-response relationship and allows both incidence and severity information to be used.

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. Note that there are two control groups in the present study: a single control group for both the F_1C and F_1T140 arms of the study and a separate control group for the F_3T21 arm. 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. There are sparse directly relevant historical data from 2-year studies on the NCTR CD rat [males only, receiving NIH-31 diet *ad libitum* or with three levels of dietary restriction, or

AIN-93M diet *ad libitum* or with one level of dietary restriction evaluated at approximately 1 and 2 years of age (Duffy *et al.,* 2001, 2002, 2004)]. Control data are available from a companion NTP study of ethinyl estradiol (NTP 2008b); this study was of identical design to the current study, and the relevant control data from the two control groups in that study are discussed as appropriate. Historical data on spontaneous neoplastic lesions in Sprague-Dawley rats of various origins have been published (Chandra *et al.,* 1992; McMartin *et al.,* 1992; Pettersen *et al.,* 1996; Kaspareit and Rittinghausen, 1999; Giknis and Clifford, 2004; Tennekes *et al.,* 2004; Baldrick, 2005; Brix *et al.,* 2005), although these data are of limited utility given the differences in genetic background, diet, and other study conditions. A particularly important limitation in using these studies for comparison is the fact that these historical data were obtained in most cases with diets of unknown and variable isoflavone content with levels of genistein that could be as high or higher than the 100 ppm concentration used in the current study (Thigpen *et al.,* 2004).

Quality Assurance Methods

This study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). The Quality Assurance Unit of the NCTR performed audits and inspections of protocols, procedures, data, and reports throughout the course of the study. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at the NCTR. The audit findings were reviewed and assessed by NCTR staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

RESULTS

RATS

Survival

Survival data for males and females are shown in Tables 3 and 4. Kaplan-Meier survival plots for males and females under the three exposure regimens are presented in Figures 2 and 3. The mean percentage of animals that survived to terminal sacrifice was 72% for males (range 62% to 86%) and 54% for females (range 43% to 64%). There were no consistent effects of genistein exposure on survival, although there were sporadic cases of enhanced survival in the 5 and 100 ppm groups relative to controls (males: F_1C, 100 ppm; F_3T21, 5 ppm; females: F_1T140, 100 ppm).

TABLE 3
Survival of Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_1C[a]				
Animals initially in study	54	50	50	50
Moribund	8	5	7	12
Natural deaths	10	4	0	7
Animals surviving to study termination	36	41	43	31
Percent survival at end of study	67	82	86	62
Survival analysis[b]	P=0.046/0.456	P=0.056N	P=0.016N	P=0.348
F_1T140[a]				
Animals initially in study	54	50	50	50
Moribund	8	9	11	5
Natural deaths	10	7	7	7
Animals surviving to study termination	36	34	32	38
Percent survival at end of study	67	68	64	76
Survival analysis	P=0.120N/0.231N	P=0.480N	P=0.408	P=0.146N
F_3T21				
Animals initially in study	52	50	50	50
Moribund	8	1	11	4
Natural deaths	11	7	6	10
Animals surviving to study termination	33	42	33	36
Percent survival at end of study	63	84	67	73
Survival analysis	P=0.442/0.488	P=0.016N	P=0.424N	P=0.225N

[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] The results of life table trend tests (Tarone, 1975) are in the control column [dose trend/ln(dose + 1) trend] and the results of the pairwise comparisons (Tarone, 1975) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposed group is indicated by **N**.

TABLE 4
Survival of Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_1C[a]				
Animals initially in study	54	50	50	49
Moribund	25	14	21	21
Natural deaths	3	8	7	7
Animals surviving to study termination	26	28	22	21
Percent survival at end of study	48	56	44	43
Survival analysis[b]	P=0.160/0.174	P=0.253N	P=0.397	P=0.248
F_1T140[a]				
Animals initially in study	54	50	50	50
Moribund	25	12	14	18
Natural deaths	3	7	4	9
Animals surviving to study termination	26	31	32	23
Percent survival at end of study	48	62	64	46
Survival analysis	P=0.081/0.471	P=0.091N	P=0.038N	P=0.365
F_3T21				
Animals initially in study	53	50	50	50
Moribund	15	14	16	17
Natural deaths	5	6	5	8
Animals surviving to study termination	33	30	29	25
Percent survival at end of study	62	60	58	50
Survival analysis	P=0.084/0.112	P=0.386	P=0.350	P=0.096

[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] The results of life table trend tests (Tarone, 1975) are in the control column [dose trend/ln(dose + 1) trend] and the results of the pairwise comparisons (Tarone, 1975) with the controls are in the exposed group columns. Lower mortality in an exposed group is indicated by **N**.

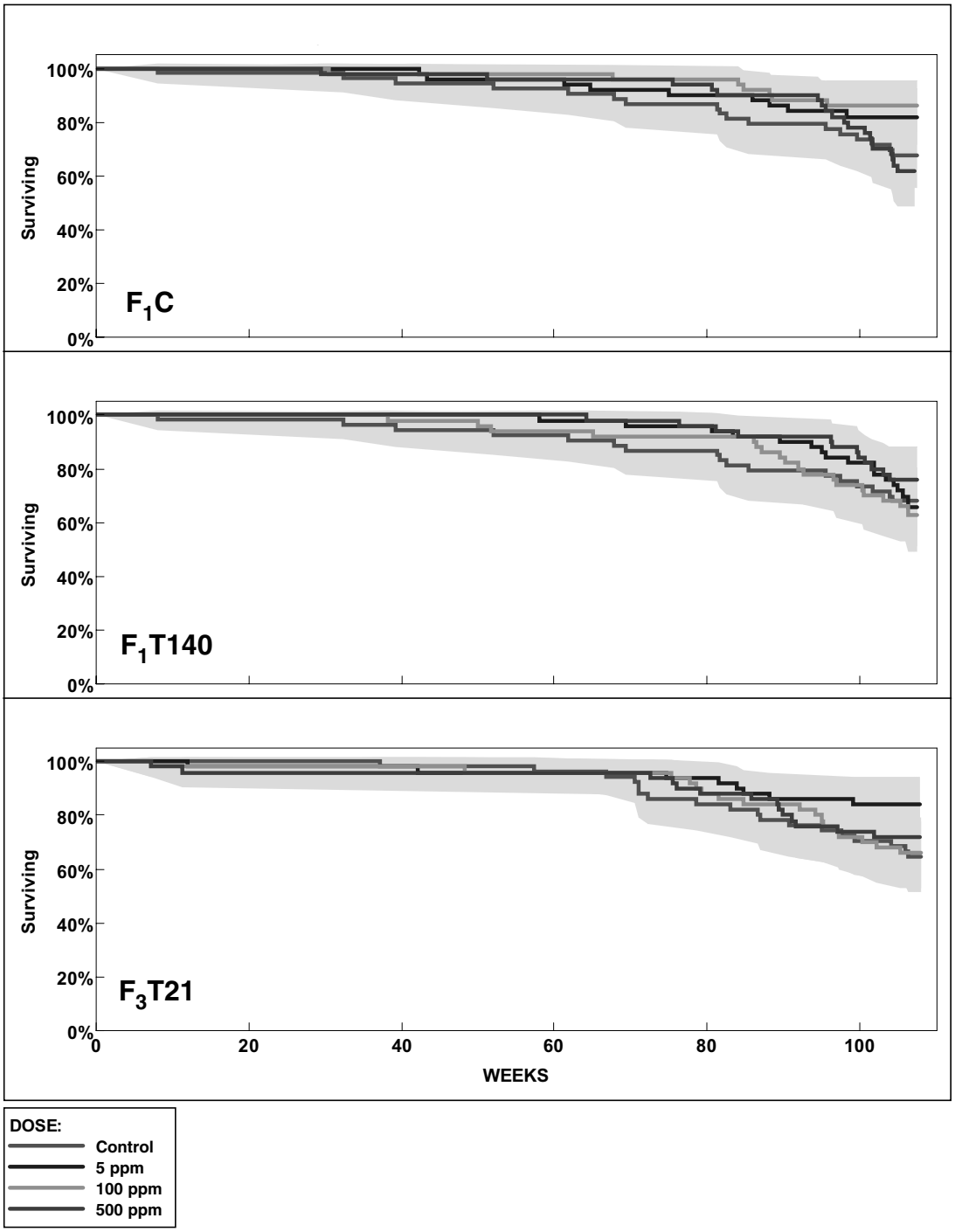


FIGURE 2
Kaplan-Meier Survival Curves for Male Rats in the 2-Year Feed Study of Genistein

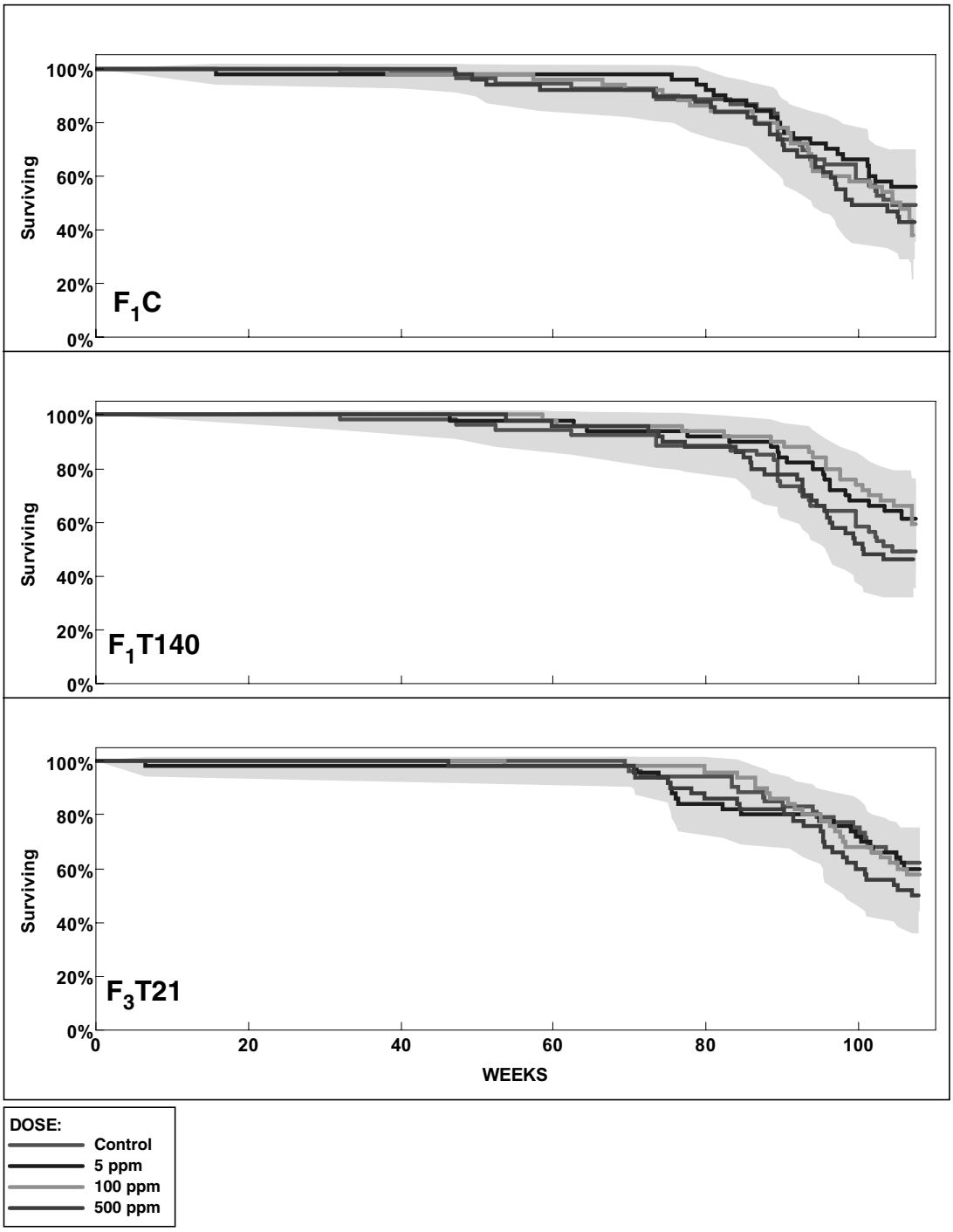


FIGURE 3
Kaplan-Meier Survival Curves for Female Rats in the 2-Year Feed Study of Genistein

Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of male and female rats in the F_1C, F_1T140, and F_3T21 treatment arms of the study are shown in Figures 4, 5, and 6, and Tables D1 through D6. Mean body weights of 500 ppm F_1C females were less than those of the controls throughout the study. Mean body weights of 500 ppm F_1T140 rats were less than those of the controls throughout the study. Mean body weights of the exposed groups of F_3T21 rats were generally similar to those of the controls throughout the study.

Other than a minimal (<10%) depression of feed consumption during several early weeks in F_1C and F_1T140 females, genistein did not show any consistent effects on feed consumption in this study (Appendix E). While there were cases of inflammation of the foot in both sexes (Tables A3a,b,c, and B3a,b,c) that sometimes became severe enough to require early removal from the study, these were not related to exposure. There were no exposure-related clinical findings.

Onset of Aberrant Estrous Cycles

Starting at 5 months of age, vaginal smears from 25 females per exposure group were taken for 5 consecutive days on a monthly basis and the stage of the estrous cycle was determined. Statistical analyses of these data are found in Appendix F. Animals showing aberrant cycles (3 or more consecutive days of estrus or 4 or more consecutive days of diestrus) for 2 consecutive months were considered to be showing persistent aberrant cycles and were no longer sampled. Survival curves (time to onset of aberrant cycles) are shown in Figures F1, F2, and F3, along with the results of fitted models based on the generalized gamma distribution function. As is evident from the starting point of the curves in Figures F1, F2, and F3, some animals, including some control animals, were determined to be having aberrant cycles at the start of monitoring at 5 months of age.

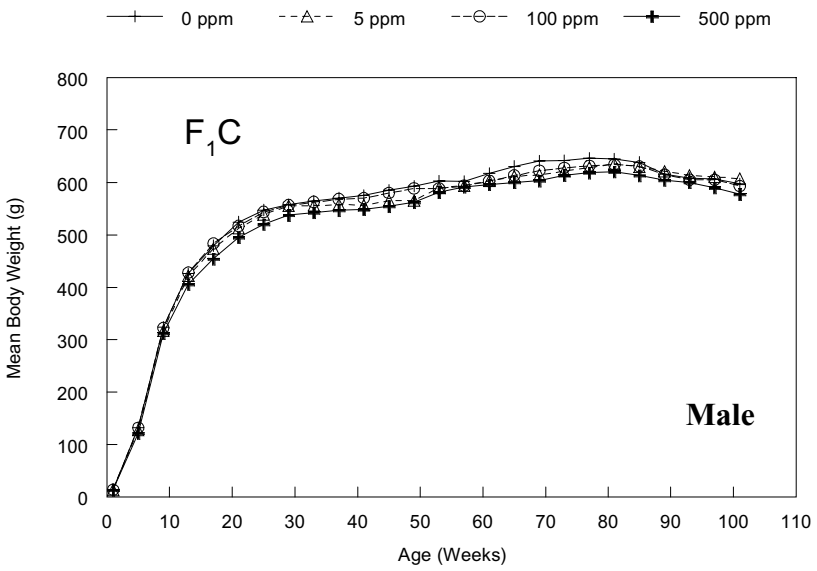
Several distributional models for the cycle-cessation curves were tested, and the results obtained with all of the models are discussed in Appendix F. It is clear that for all treatment regimens, regardless of the distributional model applied, exposure to 500 ppm genistein resulted in an acceleration of the onset of aberrant cycles that was highly significant. In addition, for the F_3T21 animals, all models showed a significant effect of exposure to 100 ppm genistein, and two models showed a significant effect of exposure to 5 ppm (only results from the generalized gamma model are shown in Appendix F). It should be noted that the P values provided were not adjusted for multiple comparisons, and the effects at 5 and 100 ppm should thus be considered marginal. In all cases, the prevalent stage that caused the judgment of aberrant cycling was estrus, which appeared consistent with an acceleration of the senescence pattern typical of the Sprague-Dawley rat (Table F1).

Organ Weights

Significant effects of genistein exposure on organ weights in males were limited to the prostate gland and the liver. The absolute and relative weights of the lateral prostate gland, the relative weight of the dorsal prostate gland, and the relative weight of the liver were significantly increased in 500 ppm F_1C males (Table G1). Absolute and relative liver weights of 500 ppm F_3T21 males and relative liver weight of 100 ppm F_3T21 males were significantly decreased (Table G5).

In female rats, the absolute and relative weights of the pituitary gland were significantly increased in the 500 ppm F_1C (Table G2), 500 ppm F_1T140 (Table G4), and 100 ppm F_3T21 (Table G6) groups. Sporadic differences were seen between exposed and control groups of females in the weights of the adrenal gland, brain, spleen, and uterus, but the differences were of little apparent biological relevance.

With the exception of the increased weights of the pituitary gland in females, observed organ weight changes in genistein-exposed rats were not clearly associated with adverse histopathologic effects (see below).



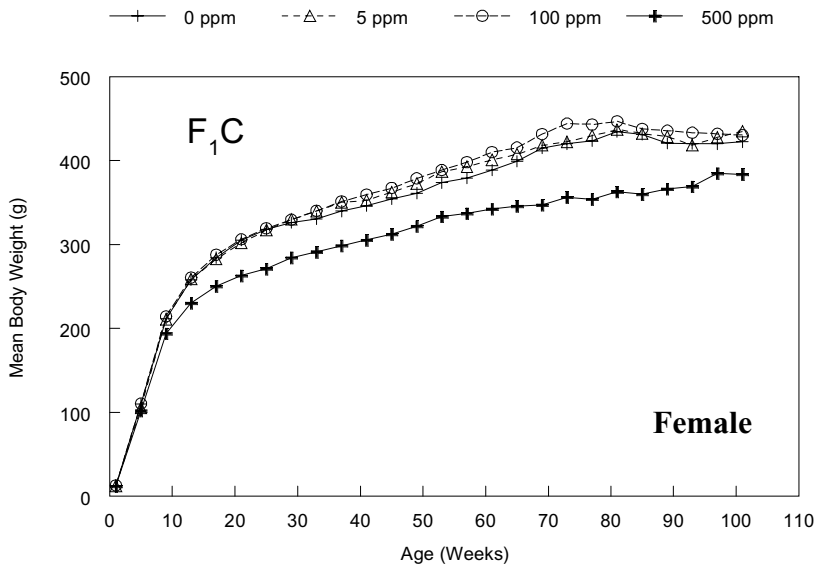


FIGURE 4
Growth Curves for F_1C Rats in the 2-Year Feed Study of Genistein

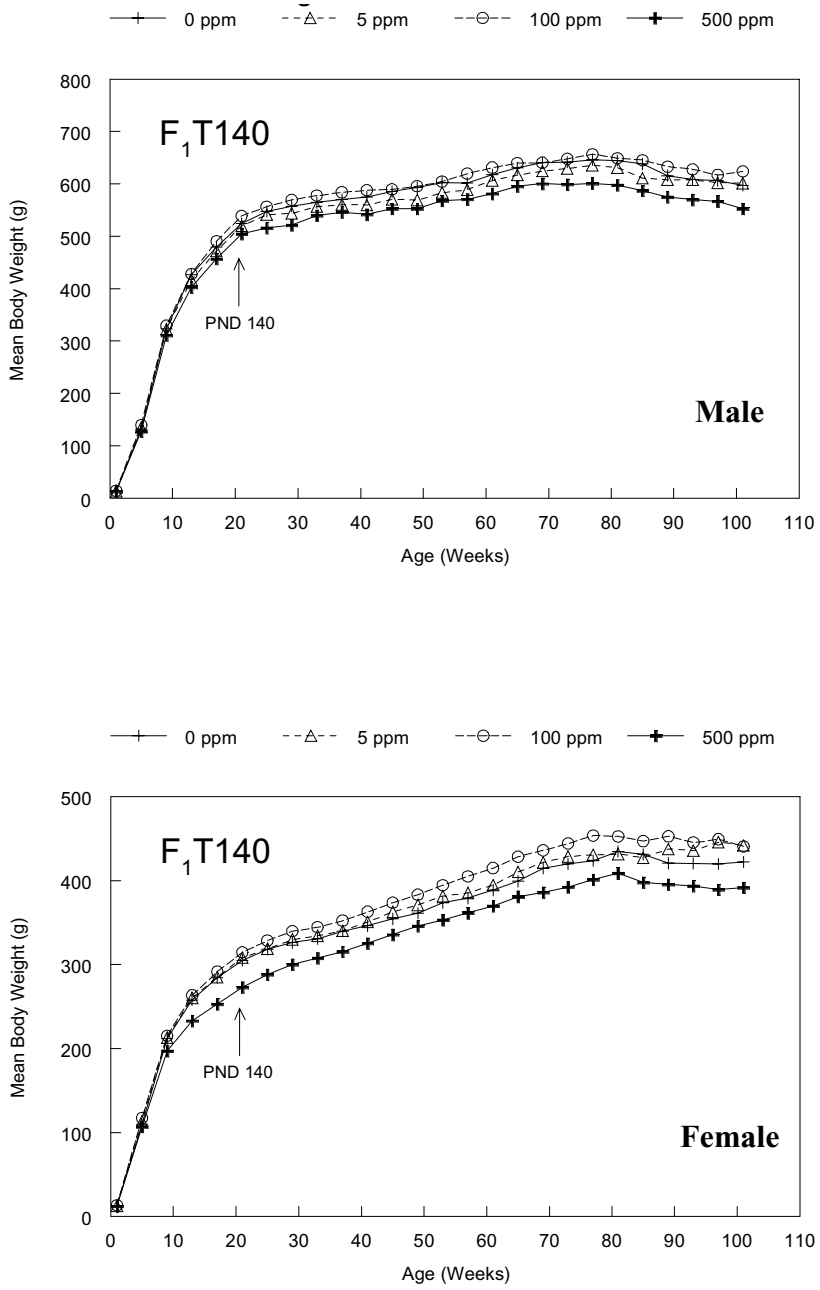


FIGURE 5
Growth Curves for F_1T140 Rats in the 2-Year Feed Study of Genistein

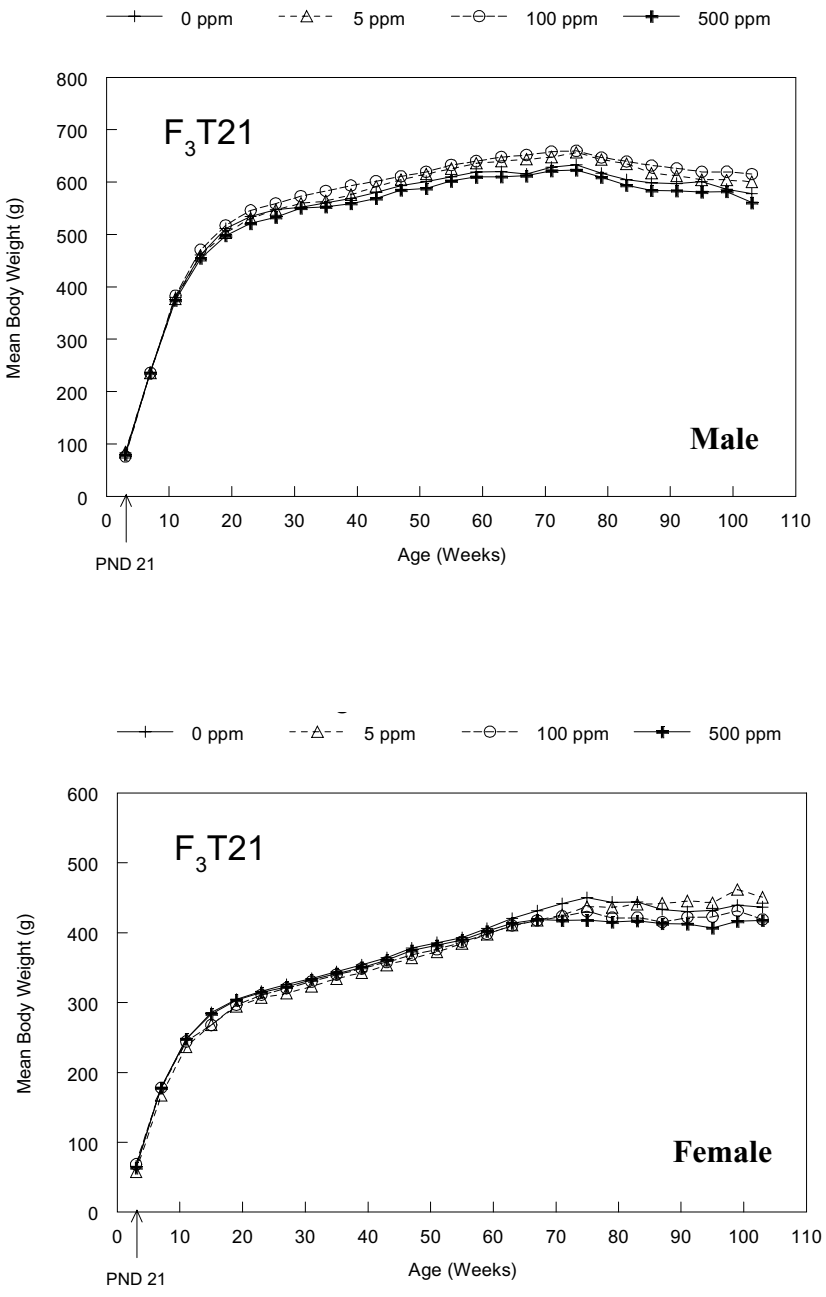


FIGURE 6
Growth Curves for F_3T21 Rats in the 2-Year Feed Study of Genistein

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the mammary gland, pituitary gland (pars distalis), pancreatic islets, preputial gland, adrenal medulla, and nose. Summaries of the incidences of neoplasms and nonneoplastic lesions 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. For the most part, the nonneoplastic lesions observed in the current study were consistent with lesions typically observed in aging Sprague-Dawley rats, and there were no biologically significant adverse exposure-related effects.

Mammary Gland: In F_1C females, there was a significant positive trend in the incidences of mammary gland adenoma or adenocarcinoma (combined) regardless of whether an unmodified or natural log-transformed dose scale was used in the analysis (Tables 5 and B2a), and the incidence in the 500 ppm group was significantly greater than that in the control group. In 5 and 100 ppm F_1T140 females, the combined incidences of adenoma and adenocarcinoma were less than those in the control or 500 ppm groups; however, these were not statistically significant differences (Tables 5 and B2b). When the natural log-transformed dose scale was used, a marginally significant positive trend occurred in the incidences of adenoma or adenocarcinoma (combined) in F_3T21 females (Table 5).

Adenoma and adenocarcinoma are common neoplasms in the mammary gland of female Sprague-Dawley rats. The control incidences of adenocarcinoma in the current study are similar to the control incidences [8/51 (16%) and 6/52 (12%), respectively, in the two control groups] observed in an NTP feed study of ethinyl estradiol conducted under identical conditions as the current study (NTP, 2008b). The NTP ethinyl estradiol 2-year study is the only other study that provides spontaneous neoplasm data for the NCTR female CD rat with the 5K96 diet. The stability and consistency of the control data in the current and previous NTP studies (two control groups in each study) supports the conclusion that continuous exposure of female rats to 500 ppm genistein enhances the development of mammary gland adenoma or adenocarcinoma. The lack of a significant exposure effect in the F_1T140 females mitigates the biological significance of the marginally significant trend in the F_3T21 females; thus, exposures restricted to early life did not convincingly enhance the incidences of adenoma or adenocarcinoma.

Incidences of mammary gland fibroadenoma in F_1C females occurred with negative trends (with both dose scales), and the incidence in the 500 ppm group was significantly less than that in the controls (Tables 5 and B2a). Fibroadenomas ranged in size from microscopic to very large, and in some cases, adenocarcinomas arose from within fibroadenomas. The incidence of fibroadenoma was marginally less in 5 ppm F_3T21 females than in the controls (Tables 5 and B2c). Fibroadenoma is a common lesion in female Sprague-Dawley rats. In the two control groups in the NTP ethinyl estradiol 2-year feed study, spontaneous incidences of 32/51 (63%) and 36/52 (69%) occurred (NTP, 2008b). Comparisons to these relevant control data support the conclusion that continuous exposure to 500 ppm genistein decreases the occurrence of mammary gland fibroadenoma in females.

TABLE 5
Incidences of Neoplasms of the Mammary Gland in Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_1C[a]				
Number Examined Microscopically	54	50	50	49
Fibroadenoma (includes multiple)				
Overall rate[b]	32/54 (59.3%)	27/50 (54.0%)	28/50 (56.0%)	12/49 (24.5%)
Adjusted rate[c]	32/47.8 (66.9%)	27/46.1 (58.6%)	28/43.8 (63.9%)	12/39.3 (30.6%)
Terminal rate[d]	17/26 (65.4%)	14/28 (50.0%)	14/22 (63.6%)	7/21 (33.3%)
First incidence (days)	330	527	464	549
Poly-3 test[e]	P=0.001N/0.003N	P=0.261N	P=0.466N	P=0.001N
Adenoma[f]	2	1	0	5
Adenocarcinoma (includes multiple)	8	3	8	13
Adenoma or Adenocarcinoma				
Overall rate	9/54 (16.7%)	4/50 (8.0%)	8/50 (16.0%)	16/49 (32.7%)
Adjusted rate	9/44.8 (20.1%)	4/42.4 (9.4%)	8/40.9 (19.6%)	16/40.4 (39.6%)
Terminal rate	2/26 (7.7%)	1/28 (3.6%)	4/22 (18.2%)	7/21 (33.3%)
First incidence (days)	366	604	519	549
Poly-3 test	P=0.001/0.011	P=0.135N	P=0.584N	P=0.037
F_1T140[a]				
Number Examined Microscopically	54	50	50	50
Fibroadenoma (includes multiple)				
Overall rate	32/54 (59.3%)	30/50 (60.0%)	31/50 (62.0%)	25/50 (50.0%)
Adjusted rate	32/47.8 (66.9%)	30/45.8 (65.5%)	31/48.3 (64.2%)	25/44.1 (56.7%)
Terminal rate	17/26 (65.4%)	20/31 (64.5%)	19/32 (59.4%)	13/23 (56.5%)
First incidence (days)	330	542	422	375
Poly-3 test	P=0.173N/0.195N	P=0.530N	P=0.474N	P=0.206N
Adenoma	2	0	2	1
Adenocarcinoma (includes multiple)	8	3	3	9
Adenoma or Adenocarcinoma				
Overall rate	9/54 (16.7%)	3/50 (6.0%)	5/50 (10.0%)	10/50 (20.0%)
Adjusted rate	9/44.8 (20.1%)	3/43.7 (6.9%)	5/44.4 (11.3%)	10/41.0 (24.4%)
Terminal rate	2/26 (7.7%)	0/31 (0.0%)	3/32 (9.4%)	3/23 (13.0%)
First incidence (days)	366	580	682	594
Poly-3 test	P=0.069/0.316	P=0.063N	P=0.196N	P=0.413

TABLE 5
Incidences of Neoplasms of the Mammary Gland in Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_3T21				
Number Examined Microscopically	53	49	50	50
Fibroadenoma (includes multiple)				
Overall rate	32/53 (60.4%)	20/49 (40.8%)	33/50 (66.0%)	28/50 (56.0%)
Adjusted rate	32/49.1 (65.2%)	20/43.5 (46.0%)	33/45.9 (72.0%)	28/44.2 (63.4%)
Terminal rate	23/33 (69.7%)	15/30 (50.0%)	22/29 (75.9%)	15/25 (60.0%)
First incidence (days)	499	524	558	590
Poly-3 test	P=0.335/0.225	P=0.043N	P=0.304	P=0.516N
Adenoma	0	0	1	1
Adenocarcinoma (includes multiple)	7	8	10	12
Adenoma or Adenocarcinoma				
Overall rate	7/53 (13.2%)	8/49 (16.3%)	11/50 (22.0%)	13/50 (26.0%)
Adjusted rate	7/47.2 (14.8%)	8/42.9 (18.6%)	11/44.8 (24.6%)	13/43.2 (30.1%)
Terminal rate	3/33 (9.1%)	4/30 (13.3%)	7/29 (24.1%)	6/25 (24.0%)
First incidence (days)	611	574	558	323
Poly-3 test	P=0.067/0.039	P=0.421	P=0.180	P=0.065

[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] Number of animals with neoplasm per number of animals with mammary gland examined microscopically
[c] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control group incidence are P values associated with the trend tests [dose trend/ln(dose + 1) trend]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[f] Number of animals with neoplasm

In males, atrophy of the mammary gland occurs with age, and glandular tissue was not present in all sections taken for the current evaluation; thus, the numbers of males examined for mammary gland are generally lower than the number examined for other tissues. No incidences of fibroma or fibroadenoma occurred in control males in any of the three arms of the study (Tables 6 and A1a,b,c). Two 500 ppm F_3T21 males were diagnosed with fibroma, and two were diagnosed with fibroadenoma (Tables 6 and A1c). These lesions are of different origins and thus were considered separately. There was no significant treatment effect. Incidences of alveolar/ductal hyperplasia of the mammary gland were significantly increased on PND 140 in genistein-exposed males in the multigenerational reproductive toxicology study, particularly in continuously exposed (F_1 and F_2) generations (NTP, 2008a). In contrast, while positive trends in the incidences of male mammary gland hyperplasia were observed in the F_1C and F_1T140 study arms (Table 6), incidences in the 500 ppm groups (about 20%) were considerably less than the rates of 60% and 72% observed in some of the 500 ppm groups in the multigenerational reproductive toxicology study (NTP, 2008a).

Only limited historical control data are available on the incidences of spontaneous mammary gland neoplasms in male NCTR CD rats, but in an NTP study of ethinyl estradiol conducted under identical conditions to those used in the current study (NTP, 2008b), mammary gland fibroma and/or fibroadenoma occurred in two control groups of males [2/44 (4%) and 1/42 (2%)]. In addition, Duffy *et al.* (2004 and unpublished data) found fibroadenomas in approximately 10% to 12% of control NCTR CD male rats fed NIH-31 or AIN-93M diets *ad libitum*.

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_1C[a]				
Number Examined Microscopically	41	43	40	42
Alveolar Hyperplasia[b,c]	3 (1.7)[d]	2 (1.5)	6 (1.7)	8 (1.4)
Fibroadenoma				
Overall rate[e]	0/41 (0.0%)	1/43 (2.3%)	0/40 (0.0%)	2/42 (4.8%)
Adjusted rate[f]	0/36.7 (0.0%)	1/39.7 (2.5%)	0/38.8 (0.0%)	2/38.8 (5.1%)
Terminal rate[g]	0/33 (0.0%)	1/38 (2.6%)	0/38 (0.0%)	0/30 (0.0%)
First incidence (days)	—[i]	749 (T)	—[j]	527
Poly-3 test[h]	P=0.164/0.226	P=0.515	—	P=0.249
F_1T140[a]				
Number Examined Microscopically	41	42	34	45
Alveolar Hyperplasia[c]	3 (1.7)	1 (1.0)	1 (2.0)	9 (1.4)
Fibroadenoma	0	0	0	0
F_3T21				
Number Examined Microscopically	39	43	41	41
Alveolar Hyperplasia	4 (1.5)	5 (1.2)	6 (1.3)	6 (2.0)
Fibroma				
Overall rate	0/39 (0.0%)	0/43 (0.0%)	0/41 (0.0%)	2/41 (4.9%)
Adjusted rate	0/37.1 (0.0%)	0/42.5 (0.0%)	0/37.4 (0.0%)	2/37.4 (5.3%)
Terminal rate	0/33 (0.0%)	0/42 (0.0%)	0/32 (0.0%)	2/34 (5.9%)
First incidence (days)	—	—	—	754 (T)
Poly-3 test	P=0.038/0.078	—	—	P=0.238
Fibroadenoma				
Overall rate	0/39 (0.0%)	0/43 (0.0%)	0/41 (0.0%)	2/41 (4.9%)
Adjusted rate	0/37.1 (0.0%)	0/42.5 (0.0%)	0/37.4 (0.0%)	2/37.4 (5.3%)
Terminal rate	0/33 (0.0%)	0/42 (0.0%)	0/32 (0.0%)	2/34 (5.9%)
First incidence (days)	—	—	—	753 (T)
Poly-3 test	P=0.038/0.078	—	—	P=0.238

(T)Terminal sacrifice
[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] Number of animals with lesion
[c] Significant trend ($P \leq 0.05$) by the Jonckheere-Terpstra test
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[e] Number of animals with neoplasm per number of animals with mammary gland examined microscopically
[f] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the control group incidence are P values associated with the trend tests [dose trend/ln(dose + 1) trend]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[i] Not applicable; no neoplasms in animal group
[j] Value of statistic cannot be computed.

Pituitary Gland (Pars distalis): As is typical for Sprague-Dawley rats of this age, adenoma occurred in high proportions of both males (Tables 7 and A2a,b,c) and females (Tables 7 and B2a,b,c). In F_1T140 males, a significant negative trend (natural log-transformed dose scale only) occurred in the incidences of adenoma, and the incidence in the 100 ppm group was significantly less than that in the controls (Tables 7 and A2b). The incidence of adenoma was significantly decreased in 5 ppm F_1C males (Tables 7 and A2a).

As expected, the incidences of adenoma or carcinoma (combined) were greater in females than in males. Significant positive trends (using both dose scales) occurred in the incidences of adenoma or carcinoma (combined) in F_1C and F_1T140 females, and the incidence was significantly increased in the 500 ppm F_1C group (Tables 7 and B2a,b). Three carcinomas were observed in the females (one each in F_1C, 100 ppm, F_1T140, 500 ppm, and F_3T21, 5 ppm; Tables 7 and B1a,b,c). In the two female control groups in the NTP ethinyl estradiol 2-year feed study (NTP, 2008b), incidences of pituitary gland adenoma or carcinoma (combined) [38/51 (75%) and 32/52 (62%)] were similar to those reported in the current study. These historical control rates are consistent with what has generally been reported for spontaneous rates in female Sprague-Dawley rats, although spontaneous rates as high as 93% have been reported in the Crl:CD® (SD) rat (Giknis and Clifford, 2004). As previously mentioned, these historical controls are of doubtful value for comparison with the current study due to the unknown isoflavone concentrations in the feed of the earlier studies.

TABLE 7
Incidences of Neoplasms of the Pituitary Gland (Pars Distalis) in Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Male				
F_1C[a]				
Adenoma (includes multiple)				
Overall rate[b]	23/49 (46.9%)	14/46 (30.4%)	22/50 (44.0%)	22/49 (44.9%)
Adjusted rate[c]	23/42.5 (54.1%)	14/42.6 (32.8%)	22/47.8 (46.0%)	22/44.0 (49.9%)
Terminal rate[d]	19/35 (54.3%)	12/39 (30.8%)	19/43 (44.2%)	16/31 (51.6%)
First incidence (days)	571	601	473	664
Poly-3 test[e]	P=0.289/0.465	P=0.036N	P=0.290N	P=0.432N
F_1T140[a]				
Adenoma (includes multiple)				
Overall rate	23/49 (46.9%)	18/49 (36.7%)	13/48 (27.1%)	16/48 (33.3%)
Adjusted rate	23/42.3 (54.1%)	18/45.7 (39.4%)	13/41.7 (31.2%)	16/45.5 (35.2%)
Terminal rate	19/35 (54.3%)	13/34 (38.2%)	8/30 (26.7%)	12/37 (32.4%)
First incidence (days)	571	564	455	698
Poly-3 test	P=0.180N/0.032N	P=0.118N	P=0.025N	P=0.055N
F_3T21				
Adenoma (includes multiple)				
Overall rate	17/49 (34.7%)	18/46 (39.1%)	17/48 (35.4%)	15/48 (31.3%)
Adjusted rate	17/44.8 (38.0%)	18/43.0 (41.8%)	17/42.4 (40.1%)	15/42.7 (35.1%)
Terminal rate	10/33 (30.3%)	17/41 (41.5%)	13/32 (40.6%)	12/36 (33.3%)
First incidence (days)	505	521	549	531
Poly-3 test	P=0.348N/0.420N	P=0.440	P=0.505	P=0.479N

TABLE 7
Incidences of Neoplasms of the Pituitary Gland (Pars Distalis) in Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Female				
F_1C[a]				
Number Examined Microscopically	54	50	50	49
Adenoma[f]	38	40	33	46**
Carcinoma	0	0	1	0
Adenoma or Carcinoma				
Overall rate	38/54 (70.4%)	40/50 (80.0%)	34/50 (68.0%)	46/49 (93.9%)
Adjusted rate	38/47.9 (79.4%)	40/47.3 (84.5%)	34/44.9 (75.8%)	46/47.2 (97.4%)
Terminal rate	21/26 (80.8%)	22/28 (78.6%)	15/22 (68.2%)	20/21 (95.2%)
First incidence (days)	424	559	485	344
Poly-3 test	P=0.004/0.036	P=0.345	P=0.430N	P=0.004
F_1T140[a]				
Number Examined Microscopically	54	49	50	50
Adenoma	38	32	40	43
Carcinoma	0	0	0	1
Adenoma or Carcinoma				
Overall rate	38/54 (70.4%)	32/49 (65.3%)	40/50 (80.0%)	44/50 (88%)
Adjusted rate	38/47.9 (79.4%)	32/46.9 (68.3%)	40/48.4 (82.7%)	44/48.1 (91.4%)
Terminal rate	21/26 (80.8%)	17/31 (54.8%)	26/32 (81.3%)	20/23 (87.0%)
First incidence (days)	424	450	409	417
Poly-3 test	P=0.009/0.019	P=0.151N	P=0.439	P=0.068
F_3T21				
Number Examined Microscopically	53	50	50	50
Adenoma	41	42	42	40
Carcinoma	0	1	0	0
Adenoma or Carcinoma				
Overall rate	41/53 (77.4%)	43/50 (86.0%)	42/50 (84.0%)	40/50 (80.0%)
Adjusted rate	41/50.5 (81.2%)	43/48.1 (89.3%)	42/48.6 (86.5%)	40/47.8 (83.6%)
Terminal rate	25/33 (75.8%)	26/30 (86.7%)	24/29 (82.8%)	20/25 (80.0%)
First incidence (days)	499	495	558	493
Poly-3 test	P=0.467N/0.471	P=0.187	P=0.324	P=0.478

** Significantly different ($P \leq 0.01$) from the control group by the Poly-3 test
[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] Number of animals with neoplasm per number of animals with pituitary gland examined microscopically
[c] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control group incidence are P values associated with the trend tests [dose trend/ln(dose + 1) trend]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[f] Number of animals with neoplasm

Pancreatic Islets: A significant positive trend (unmodified dose scale only) occurred in the incidences of adenoma or carcinoma (combined) in F_1C males, although no exposed group differed significantly from the controls (Tables 8 and A2a). In the two male control groups in the NTP ethinyl estradiol 2-year feed study (NTP, 2008b), incidences of pancreatic islet adenoma or carcinoma (combined) [0/46 (0%) and 2/48 (4%)] were generally similar to those reported in the current study. On the other hand, Duffy *et al.* (2004 and unpublished data) reported spontaneous incidences of these neoplasms as high as 38% in male NCTR CD rats fed NIH-31 or AIN-93M diets. Together with the lack of corresponding transitional lesions (i.e. hyperplasia) in male rats, this lesion was judged unlikely to be related to treatment. There is little evidence that the slight increases in the incidences of these lesions in the current study are biologically meaningful.

TABLE 8
Incidences of Pancreatic Islet Neoplasms in Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_1C[a]				
Number Examined Microscopically	49	49	50	49
Adenoma[b]	1	3	1	5
Carcinoma	0	0	0	1
Adenoma or Carcinoma				
Overall rate[c]	1/49 (2.0%)	3/49 (6.1%)	1/50 (2.0%)	6/49 (12.2%)
Adjusted rate[d]	1/41.2 (2.4%)	3/43.7 (6.9%)	1/46.1 (2.2%)	6/43.4 (13.8%)
Terminal rate[e]	1/36 (2.8%)	3/41 (7.3%)	1/43 (2.3%)	3/31 (9.7%)
First incidence (days)	748 (T)	738 (T)	742 (T)	710
Poly-3 test[f]	P=0.029/0.090	P=0.327	P=0.735N	P=0.064
F_1T140[a]				
Adenoma				
Overall rate	1/49 (2.0%)	0/49 (0.0%)	1/46 (2.2%)	3/48 (6.3%)
Adjusted rate	1/41.2 (2.4%)	0/44.6 (0.0%)	1/39.8 (2.5%)	3/45.2 (6.6%)
Terminal rate	1/36 (2.8%)	0/34 (0.0%)	0/31 (0.0%)	2/38 (5.3%)
First incidence (days)	748 (T)	—[g]	736	710
Poly-3 test	P=0.086/0.122	P=0.484N	P=0.753	P=0.339
F_3T21				
Number Examined Microscopically	45	49	48	48
Adenoma	3	3	2	0
Carcinoma	0	0	1	0
Adenoma or Carcinoma				
Overall rate	3/45 (6.7%)	3/49 (6.1%)	3/48 (6.3%)	0/48 (0.0%)
Adjusted rate	3/39.8 (7.5%)	3/44.4 (6.8%)	3/42.0 (7.1%)	0/41.4 (0.0%)
Terminal rate	3/32 (9.4%)	3/42 (7.1%)	3/33 (9.1%)	0/36 (0.0%)
First incidence (days)	751 (T)	753 (T)	750 (T)	—
Poly-3 test	P=0.083N/0.133N	P=0.612N	P=0.638N	P=0.111N

(T)Terminal sacrifice
[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] Number of animals with neoplasm
[c] Number of animals with neoplasm per number of animals with pancreatic islets examined microscopically
[d] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control group incidence are P values associated with the trend tests [dose trend/ln(dose + 1) trend]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed 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 an exposed group is indicated by **N**.
[g] Not applicable; no neoplasms in animal group

Preputial Gland: A significant positive trend (natural log-transformed dose scale only) occurred in the incidences of squamous cell carcinoma in F_3T21 males, and the incidence in the 100 ppm group was significantly greater than that in the controls (Tables 9 and A2c). In the two male control groups in the NTP ethinyl estradiol 2-year feed study (NTP, 2008b), incidences of preputial gland squamous cell carcinoma [4/51 (8%) and 2/49 (4%)] were slightly greater than those found in the current study. The incidences in the current study were not considered related to genistein exposure.

TABLE 9
Incidences of Preputial Gland Squamous Cell Carcinoma in Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_1C[a]				
Overall rate[b]	1/49 (2.0%)	3/48 (6.3%)	1/49 (2.0%)	2/49 (4.1%)
Adjusted rate[c]	1/41.3 (2.4%)	3/43.9 (6.8%)	1/45.1 (2.2%)	2/43.2 (4.6%)
Terminal rate[d]	1/35 (2.9%)	3/41 (7.3%)	1/42 (2.4%)	1/31 (3.2%)
First incidence (days)	743 (T)	738 (T)	746 (T)	704
Poly-3 test[e]	P=0.616/0.581N	P=0.328	P=0.741N	P=0.515
F_1T140[a]				
Overall rate	1/49 (2.0%)	2/50 (4.0%)	2/48 (4.2%)	1/49 (2.0%)
Adjusted rate	1/41.3 (2.4%)	2/45.7 (4.4%)	2/41.7 (4.8%)	1/46.0 (2.2%)
Terminal rate	1/35 (2.9%)	1/34 (2.9%)	1/32 (3.1%)	0/38 (0.0%)
First incidence (days)	743 (T)	626	626	710
Poly-3 test	P=0.471N /0.568N	P=0.535	P=0.504	P=0.736N
F_3T21				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	5/47 (10.6%)	3/47 (6.4%)
Adjusted rate	0/40.4 (0.0%)	0/43.9 (0.0%)	5/42.7 (11.7%)	3/42.5 (7.1%)
Terminal rate	0/33 (0.0%)	0/42 (0.0%)	1/33 (3.0%)	2/36 (5.6%)
First incidence (days)	—[f]	—	644	600
Poly-3 test	P=0.151/0.012	—[g]	P=0.035	P=0.127

(T)Terminal sacrifice
[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] Number of animals with squamous cell carcinoma per number of animals with preputial gland examined microscopically
[c] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control group incidence are P values associated with the trend tests [dose trend/ln(dose + 1) trend]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed 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 an exposed group is indicated by **N**.
[f] Not applicable; no neoplasms in animal group
[g] Value of statistic cannot be computed.

Adrenal Medulla: Significant positive trends (using both dose scales) occurred in the incidences of benign pheochromocytoma in F_1C males, and significant positive trends (unmodified dose scale only) occurred in the incidences of benign, complex, or malignant pheochromocytoma (combined) in F_1C and F_1T140 males (Tables 10 and A2a,b). Slight, but not statistically significant, increases occurred in the incidences of benign pheochromocytomas in 500 ppm F_1C males and benign, complex, or malignant pheochromocytoma (combined) in 500 ppm F_1C and F_1T140 males. Lower incidences of benign or complex pheochromocytoma occurred in females (Tables B1a,b,c), and no statistically significant exposure effects on the incidences of these lesions were seen in females. Based on the marginal effects observed in males and the spontaneous incidences in control males in the current study and in the NTP ethinyl estradiol 2-year feed study (NTP, 2008b) [benign pheochromocytoma 2/46 (4%), 4/49 (8%); benign, complex, or malignant pheochromocytoma (combined) 4/46 (9%), 5/49 (10%)], there is little evidence that genistein exposure affects the incidences of adrenal medulla pheochromocytomas.

TABLE 10
Incidences of Adrenal Medulla Pheochromocytoma in Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_1C[a]				
Benign Pheochromocytoma (includes bilateral)				
Overall rate[b]	2/47 (4.3%)	1/49 (2.0%)	2/50 (4.0%)	7/49 (14.3%)
Adjusted rate[c]	2/41.3 (4.8%)	1/44.0 (2.3%)	2/46.1 (4.3%)	7/42.9 (16.3%)
Terminal rate[d]	2/36 (5.6%)	1/41 (2.4%)	2/43 (4.7%)	7/31 (22.6%)
First incidence (days)	742 (T)	749 (T)	737 (T)	741 (T)
Poly-3 test[e]	P=0.006/0.034	P=0.478N	P=0.654N	P=0.087
Complex Pheocromocytoma[f]	1	0	0	0
Malignant Pheocromocytoma	0	1	0	0
Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/47 (6.4%)	2/49 (4.1%)	2/50 (4.0%)	7/49 (14.3%)
Adjusted rate	3/41.3 (7.3%)	2/44.0 (4.5%)	2/46.1 (4.3%)	7/42.9 (16.3%)
Terminal rate	3/36 (8.3%)	2/41 (4.9%)	2/43 (4.7%)	7/31 (22.6%)
First incidence (days)	742 (T)	738 (T)	737 (T)	741 (T)
Poly-3 test	P=0.028/0.125	P=0.471N	P=0.450N	P=0.172
F_1T140[a]				
Benign Pheochromocytoma (includes bilateral)				
Overall rate	2/47 (4.3%)	3/47 (6.4%)	0/46 (0.0%)	4/45 (8.9%)
Adjusted rate	2/41.3 (4.8%)	3/43.5 (6.9%)	0/39.4 (0.0%)	4/42.6 (9.4%)
Terminal rate	2/36 (5.6%)	2/34 (5.9%)	0/31 (0.0%)	4/36 (11.1%)
First incidence (days)	742 (T)	712	—[g]	736 (T)
Poly-3 test	P=0.230/0.449	P=0.523	P=0.248N	P=0.351
Complex Pheochromocytoma	1	0	0	1
Malignant Pheochromocytoma	0	1	1	2
Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/47 (6.4%)	3/47 (6.4%)	1/46 (2.2%)	7/45 (15.6%)
Adjusted rate	3/41.3 (7.3%)	3/43.5 (6.9%)	1/39.4 (2.5%)	7/42.6 (16.4%)
Terminal rate	3/36 (8.3%)	2/34 (5.9%)	1/31 (3.2%)	7/36 (19.4%)
First incidence (days)	742 (T)	712	748 (T)	736 (T)
Poly-3 test	P=0.039/0.155	P=0.639N	P=0.322N	P=0.169

TABLE 10
Incidences of Adrenal Medulla Pheochromocytoma in Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
F_3T21				
Benign Pheochromocytoma				
Overall rate	4/48 (8.3%)	3/46 (6.5%)	4/47 (8.5%)	2/45 (4.4%)
Adjusted rate	4/41.7 (9.6%)	3/42.4 (7.1%)	4/41.0 (9.7%)	2/40.5 (4.9%)
Terminal rate	4/33 (12.1%)	3/41 (7.3%)	3/33 (9.1%)	1/36 (2.8%)
First incidence (days)	753 (T)	751 (T)	701	712
Poly-3 test	P=0.332N/0.366N	P=0.492N	P=0.635	P=0.351N
Malignant Pheocromocytoma	1	0	0	0
Benign or Malignant Pheochromocytoma				
Overall rate	5/48 (10.4%)	3/46 (6.5%)	4/47 (8.5%)	2/45 (4.4%)
Adjusted rate	5/41.7 (12.0%)	3/42.4 (7.1%)	4/41.0 (9.7%)	2/40.5 (4.9%)
Terminal rate	5/33 (15.2%)	3/41 (7.3%)	3/33 (9.1%)	1/36 (2.8%)
First incidence (days)	753 (T)	751 (T)	701	712
Poly-3 test	P=0.269N/0.247N	P=0.348N	P=0.511N	P=0.228N

(T)Terminal sacrifice
[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.
[b] Number of animals with neoplasm per number of animals with adrenal medulla examined microscopically
[c] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control group incidence are P values associated with the trend tests [dose trend/ln(dose + 1) trend]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed 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 an exposed group is indicated by **N**.
[f] Number of animals with neoplasm
[g] Not applicable; no neoplasms in animal group

Nose: A significant positive trend (unmodified dose scale only) occurred in the incidences of squamous cell carcinoma in F_1C males (Table 11). Low incidences of this neoplasm, which was found primarily in the oral mucosa of the palate with invasion into the nasal cavity, occurred sporadically in exposed groups of males and in control and exposed groups of females (Tables 11, A1a,b,c, and B1a,b,c). Across all exposure groups, there were six incidences of squamous cell carcinoma in males and nine in females, and this neoplasm was listed as the cause of death for four males and three females. Similar squamous cell carcinomas were found in approximately 5% of the controls in the NTP ethinyl estradiol 2-year feed study (NTP, 2008b), where they were reported as squamous cell carcinomas of the oral mucosa. Thus, available evidence suggests that incidences of squamous cell carcinoma of the nose in the current study were not related to genistein exposure.

TABLE 11
Incidences of Squamous Cell Carcinoma of the Nose in Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Male				
F_1C[a]				
Overall rate[b]	0/48 (0.0%)	0/48 (0.0%)	0/50 (0.0%)	2/48 (4.2%)
Adjusted rate[c]	0/41.2 (0.0%)	0/43.7 (0.0%)	0/46.1 (0.0%)	2/42.5 (4.7%)
Terminal rate[d]	0/35 (0.0%)	0/41 (0.0%)	0/43 (0.0%)	0/31 (0.0%)
First incidence (days)	—[f]	—	—	711
Poly-3 test[e]	P=0.040/0.088	—[g]	—	P=0.244
F_1T140[a]				
Overall rate	0/48 (0.0%)	0/47 (0.0%)	1/45 (2.2%)	0/48 (0.0%)
Adjusted rate	0/41.2 (0.0%)	0/42.9 (0.0%)	1/39.6 (2.5%)	0/44.9 (0.0%)
Terminal rate	0/35 (0.0%)	0/34 (0.0%)	0/32 (0.0%)	0/37 (0.0%)
First incidence (days)	—	—	702	—
Poly-3 test	P=0.753N/0.512	—	P=0.492	—
F_3T21				
Overall rate	0/46 (0.0%)	1/45 (2.2%)	1/49 (2.0%)	1/45 (2.2%)
Adjusted rate	0/40.2 (0.0%)	1/42.6 (2.3%)	1/42.5 (2.4%)	1/40.1 (2.5%)
Terminal rate	0/33 (0.0%)	1/42 (2.4%)	0/33 (0.0%)	0/36 (0.0%)
First incidence (days)	—	753 (T)	592	712
Poly-3 test	P=0.549/0.345	P=0.511	P=0.511	P=0.500
Female				
F_1C[a]				
Overall rate	0/54 (0.0%)	0/50 (0.0%)	1/50 (2.0%)	2/49 (4.1%)
Adjusted rate	0/42.0 (0.0%)	0/41.4 (0.0%)	1/39.5 (2.5%)	2/37.2 (5.4%)
Terminal rate	0/26 (0.0%)	0/28 (0.0%)	0/22 (0.0%)	1/21 (4.8%)
First incidence (days)	—	—	656	725
Poly-3 test	P=0.085/0.061	—	P=0.488	P=0.210
F_1T140[a]				
Overall rate	0/54 (0.0%)	0/50 (0.0%)	0/50 (0.0%)	1/50 (2.0%)
Adjusted rate	0/42.0 (0.0%)	0/42.6 (0.0%)	0/44.0 (0.0%)	1/39.3 (2.5%)
Terminal rate	0/26 (0.0%)	0/31 (0.0%)	0/32 (0.0%)	0/23 (0.0%)
First incidence (days)	—	—	—	672
Poly-3 test	P=0.223/0.269	—	—	P=0.487
F_3T21				
Overall rate	1/53 (1.9%)	1/50 (2.0%)	0/50 (0.0%)	3/49 (6.1%)
Adjusted rate	1/46.6 (2.1%)	1/41.8 (2.4%)	0/43.2 (0.0%)	3/39.8 (7.5%)
Terminal rate	0/33 (0.0%)	1/30 (3.3%)	0/29 (0.0%)	2/25 (8.0%)
First incidence (days)	589	750 (T)	—	735
Poly-3 test	P=0.094/0.252	P=0.737	P=0.515N	P=0.251

(T)Terminal sacrifice

[a] A single group of animals served as the control group for the F_1C and F_1T140 study arms.

[b] Number of animals with neoplasm per number of animals with nose examined microscopically

[c] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality

[d] Observed incidence at terminal kill

[e] Beneath the control group incidence are P values associated with the trend tests [dose trend/ln(dose + 1) trend]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed 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 an exposed group is indicated by **N**.

[f] Not applicable; no neoplasms in animal group

[g] Value of statistic cannot be computed.

DISCUSSION AND CONCLUSIONS

Interest in soy-containing foods and supplements has increased based on the possibility of health benefits associated with the consumption of soy and its components. Genistein is the major soy isoflavone, and while there are many bioactive components of soy, genistein has been a subject of much research due to the variety of biochemical effects that have been demonstrated; however, the weak estrogenic activity of soy, as well as its potential to induce DNA damage, have raised concerns about potential toxicity. The exposure concentrations used in the current study (5, 100, and 500 ppm) were selected based on a reproductive dose range-finding study that produced little or no toxicity in the parental generation but subtle effects in the reproductive tissues of pups (NTP, 2007). The mean daily doses during the 2-year study associated with these dietary concentrations are shown in Table 1 in the Introduction section of this Technical Report.

The compound consumption by animals exposed to 500 ppm genistein was considerably greater than the doses ingested by even the most heavily exposed human consumers of soy. Setchell *et al.* (1997) reported that infants consuming soy formula as their sole source of nutrition ingested 6 to 9 mg/kg per day of total isoflavones, of which approximately half would be genistein. However, it is known that blood concentrations are generally higher in humans than in rodents for an equivalent oral dose (Holder *et al.*, 1999; Chang *et al.*, 2000; Whitten and Patisaul, 2001), and thus measures of internal dose are more appropriate for comparison with human exposures. In conjunction with the experiments reported here, blood and tissue concentrations of genistein were measured in adult animals (Chang *et al.*, 2000), fetal animals (Doerge *et al.*, 2001), and nursing animals (Doerge *et al.*, 2006). In adult rats consuming 500 ppm dietary genistein, total circulating genistein reached concentrations of approximately 6 to 8 µM, with conjugated forms, primarily glucuronides, accounting for 95% to 99% of the total. Tissue/serum partition coefficients ranged from 0.05 to 0.2 for total genistein and from 0.6 to 26 for aglycone genistein, consistent with significant tissue exposures to the aglycone, which is the predominant active estrogenic form of genistein (Morito *et al.*, 2001; Kinjo *et al.*, 2004).

Genistein was detected in fetal plasma and the brain 2 hours after oral dosing of pregnant rats (Doerge *et al.*, 2001). Total genistein concentrations were lower in fetal plasma than in the plasma of the dams, although the percent present as aglycone was higher (approximately 30%) in the fetus, possibly due to the less efficient glucuronidation capacity of the fetus. This higher aglycone exposure and possible differences in blood-brain barrier resulted in brain levels of aglycone genistein that were approximately 5-fold higher than in a correspondingly exposed adult. These findings suggested that significant exposures to the active form of genistein could occur during the fetal period.

Prior to the start of the current study, the data of Fritz *et al.* (1998) were the most relevant to lactational exposure of Sprague-Dawley rats to genistein. Specifically, while lactating dams fed 250 ppm genistein in AIN-76A diet had serum total genistein concentrations of 0.42 µM, their pups were reported to have serum concentrations of 0.73 µM on postnatal day 7 (PND 7). Milk from the dams contained 0.14 µM total genistein, but the pup stomach contents reportedly contained 4.4 µM. Stomach contents and pup serum contained genistein aglycone at percentages greater than 75% and 14%, respectively, and were considerably higher than the aglycone percentages found in the milk (57%) or serum (2%) of dams. Thus, it appeared that genistein aglycone was present in rat milk at high concentrations and was efficiently transferred to the serum of pups. Weber *et al.* (2001) also reported high concentrations of total isoflavones in the plasma of infant rats and concluded that there was efficient transfer of genistein from the mother's plasma to milk, although milk concentrations were not reported. On the other hand, a more recent study by Lewis *et al.* (2003) reported less efficient transfer of genistein to the milk in dams administered a single gavage dose of 50 mg/kg. Peak concentrations of total genistein in milk (0.63 µM) were approximately 9% of those in dam plasma (6.7 µM). Given the conflicting data in the literature, exposure of 10-day-old pups to genistein solely through their dams' milk was evaluated under the conditions of the current study (Doerge *et al.*, 2006). The results indicated that exposure of rat pups to genistein through lactation from dams consuming

dietary genistein produced modest circulating concentrations of both total and aglycone genistein. Serum collected on PND 10 from control pups consistently had serum genistein concentrations below the detection limits of the analytical methods (0.0005 µM). Serum from pups consuming milk from 500 ppm dams contained litter mean values for total genistein concentrations in the range of 0.022 to 0.053 µM, with associated aglycone concentrations that were 1.2% to 4.6% of the total. The ratio of litter mean serum genistein concentrations in the pups to serum genistein concentrations in the dams ranged between 0.01 and 0.28 for total genistein, and between 0.01 and 0.15 for aglycone genistein, with respective means of 0.12 ± 0.12 and 0.07 ± 0.08. Data on serum and urine genistein concentrations from human infants consuming soy infant formula suggest that absorption and excretion of genistein is efficient (Setchell *et al.,* 1997; Irvine *et al.,* 1998). The low internal exposure of nursing pups in the current study apparently results from the minimal amount of genistein secreted into the milk (approximately 0.12 ppm), relative to either the concentration in dam feed (500 ppm) or blood. The higher concentration of aglycone genistein observed in milk relative to dam blood suggests that preferential secretion occurs, but this does not appear to facilitate overall absorption by the pups. Similar to the observations in the current study on genistein concentrations in the dams' milk, concentrations of isoflavones in the breast milk of humans consuming soy are low relative to concentrations found in soy infant formulas (Setchell *et al.,* 1998). Thus, dietary exposure of nursing dams as used in the current study does not mimic developmental exposure to soy infant formula.

Thus, under the conditions of the current study, fetal, weanling, and adult animals were exposed to internal (serum and tissue) concentrations of genistein that are achievable in humans ingesting soy products. The fact that genistein exposure was extremely limited in neonatal pups, and lower than in the fetal animals, is important to the interpretation of the data. On the one hand, effects attributable to early (preweaning) exposure are more likely to result from fetal exposure, because of the higher *in utero* concentrations of the active estrogenic aglycone form of genistein, or from direct exposures after the pups begin directly consuming dosed feed. On the other hand, the low exposure to genistein during the sensitive early postnatal period resulting from dietary exposure of the dams needs to be considered when making safety evaluations based on the results of these studies. The early neonatal period in rodents, which roughly corresponds to the second and third trimester of human gestation (Pryor *et al.*, 2000), is known to be a period of development that is highly sensitive to disruption by exposure to estrogenic agents, including genistein (Faber and Hughes, 1993; Yang *et al.*, 2000; Nagao *et al.*, 2001; Newbold *et al.*, 2001; Jefferson *et al.*, 2002, 2005; Foster *et al.*, 2004). Thus, negative results, particularly with respect to endpoints reported in other studies to be affected by neonatal dosing with genistein, must be interpreted with caution. Concentrations of serum genistein in weanling animals at approximately PND 21 were 20% to 55% of the concentrations found in adults (Chang *et al.,* 2000), indicating that exposure increased considerably after pups began directly ingesting dosed feed.

Three exposure windows were examined in the current study: continuous exposure to genistein from conception through 2 years (designated F_1C), exposure from conception through PND 140 followed by control diet to 2 years (designated F_1T140), and exposure from conception through weaning at PND 21 followed by control diet to 2 years (designated F_3T21). Survival was similar in exposed and control groups of males and females in this study (mean of 72% with a range of 62% to 86% for males and mean of 54% with a range of 43% to 64% for females). In the NTP ethinyl estradiol 2-year feed study conducted under identical conditions to the present genistein study, survivals were 67% and 60% in two male control groups and 51% and 52% in two female control groups (NTP, 2008b). Duffy *et al.* (2001, 2002) had previously reported that the survival of male NCTR CD rats fed NIH-31 or AIN-93M diets *ad libitum* were 63% and 45%, respectively, after 104 weeks on study (age 110 weeks) and indicated that these survival rates were better than those generally reported for other stocks of Sprague-Dawley rats. A recent compilation of approximately 30 studies using the Crl:CD® (SD) rat (Giknis and Clifford, 2004) reported a mean 2-year survival rate of 39% (range 17% to 63%) for males and 37% (range 20% to 62%) for females. Thus, the survival rates for both sexes in the current study are at the upper ends of the ranges that have been previously reported for 2-year studies with *ad libitum*-fed Sprague-Dawley rats.

In the current study, final mean body weights of control males consuming 5K96 diet were 581 g (F_1C/F_1T140 shared controls) and 564 g (F_3T21 controls). The 5K96 diet has not been used previously in 2-year studies, although a similar diet from a different manufacturer

was used in a contemporary 52-week study with Wistar rats (McClain *et al.,* 2006b). There are no data available for female NCTR Sprague Dawley rats for comparison with the 409 g (F_1C/F_1T140 shared controls) and 413 g (F_3T21 controls) final mean body weights of control females in the current study. The final mean body weights of the NCTR Sprague-Dawley rats used in the current study [males: 581 g (F_1C/F_1T140 shared controls) and 564 g (F_3T21 controls); females: 409 g (F_1C/F_1T140 shared controls) and 413 g (F_3T21 controls)] were less than those generally achieved in other stocks of Sprague-Dawley rats fed *ad libitum* for 2 years. This could be due to a combination of the strain of rat and the diet used. For male NCTR CD rats fed either NIH-31 or AIN-93M diets *ad libitum*, Duffy *et al.* (2001, 2002) reported 2-year mean final body weights of 657 g and 747 g, respectively. In the NTP ethinyl estradiol 2-year feed study (NTP, 2008b) that was conducted with the NCTR Sprague-Dawley rat and 5K96 diet, the mean final control body weights (two control groups for each sex) were 676 g for males and 490 g for females.

In the multigenerational reproductive toxicology study (NTP, 2008a) conducted in conjunction with this 2-year study, males continuously exposed from conception to PND 140 to feed containing 100 or 500 ppm genistein showed significant increases in the incidences of mammary gland alveolar/ductal hyperplasia. The effect was confined to the 500 ppm group and was lower in magnitude in animals exposed to genistein from conception to weaning and then fed control diet until termination at PND 140. You *et al.* (2002) have reported sensitivity of the male mammary gland to genistein, and this was also observed in the reproductive dose range-finding feed study of genistein (Delclos *et al.,* 2001; NTP, 2007). In the current study, modest exposure-related increases in the incidences of alveolar hyperplasia in the mammary gland were evident in F_1C and F_1T140 male rats, but there were no significant increases in the incidences of neoplasms in the mammary gland of these rats or in F_3T21 males. Thus, the results of this 2-year study indicate that the increased incidences of mammary gland alveolar/ductal hyperplasia in the PND 140 animals in the multigenerational reproductive toxicology study did not lead to chronic adverse effects. Other neoplasms for which there were positive statistically significant exposure-related trends or incidence differences between exposed and control groups of males in at least one arm of the study included adenoma or carcinoma (combined) of the pancreatic islets, pheochromocytoma of the adrenal medulla, and squamous cell carcinoma of the preputial gland and nose.

Other statistically significant effects of genistein in males included increased relative weights of the dorsal and lateral lobes of the prostate gland (approximately 25%) and liver (approximately 8%) in the 500 ppm F_1C group. Increased relative prostate gland weight was reported by McClain *et al.* (2006b) in Wistar rats treated with 500 mg/kg genistein (well above the exposures used in the present study) for 52 weeks, and this effect was not seen in animals removed from exposure for 8 weeks. A change in relative liver weights in males in the multigenerational reproductive toxicology study of genistein (NTP, 2008a) treated with identical doses and necropsied at PND 140 was observed only in 500 ppm F_1 males, and similar increases in relative liver weight were reported in a 28-day repeated dose study in males gavaged with 400 or 1,000 mg/kg genistein (Okazaki *et al.,* 2002). In F_3T21 males in the current study, relative liver weights were decreased by 8% to 10% in the 100 and 500 ppm groups. Thus, potentially adverse effects indicated by organ weight changes were limited to the continuously exposed males.

Effects of genistein in females, while relatively few, were more pronounced than the effects in males. Consistent with what had been observed in the multigenerational reproductive toxicology study (NTP, 2008a), body weight gain was reduced by 500 ppm genistein in the F_1C and F_1T140 arms but not in the F_3T21 arm where exposure was discontinued at weaning. The reduction in body weight gain in younger F_1C and F_1T140 females, which was accompanied by a transient early decrease in feed consumption (<10%), did not persist to termination of the study, since final mean body weights of females in these 500 ppm groups were not statistically different from those of controls.

In the multigenerational reproductive toxicology study (NTP, 2008a), 500 ppm genistein was found to accelerate vaginal opening and produce aberrant estrous cycles in animals that were monitored shortly after vaginal opening but not in animals that were evaluated just prior to termination at PND 140. In the current study, the estrous cycles of female rats were monitored starting at 5 months of age to provide an estimate of when the animals began to show aberrant cycles, a condition known to precede reproductive senescence. While the differences in the nature of reproductive senescence in women and in rats, and Sprague-Dawley rats in particular, have led to arguments disputing the relevance of events in the rat to those in humans, the discovery of similarities in central nervous system events in women in the perimenopause and rats undergoing senescence have

generated awareness of the possible relevance of aspects of the rat model to the onset of menopause (Wise *et al.,* 1996; Rubin, 2000; Weiss *et al.,* 2004). In all three arms of the current study, the 500 ppm groups were found to have earlier onsets of aberrant estrous cycles than control animals, with some animals, including some animals in the control groups, showing aberrant cycles at the earliest observation time. Sprague-Dawley rats are known to show relatively early declines in the control of estrous cycles, but this has generally been reported to become evident at about 8 to 10 months of age (Wise *et al.,* 1991). Historical control data are not available for the NCTR CD rat on this endpoint, but 5 months is very early for occurrence of disturbed estrous cycles in control rats. Factors such as single housing and virginity, both of which apply in the current study, can accelerate the process of reproductive aging in rats (Matt *et al.,* 1987; LeFevre and McClintock, 1991; Rubin, 2000). Nonetheless, the effect of the genistein-containing diets in accelerating the onset of aberrant cycles was clear. There was no evidence of the induction of aberrant cycles by genistein in rats in the multigenerational reproductive toxicology study (NTP, 2008a) when vaginal cytology was monitored for 10 consecutive days from approximately PND 130 to PND 140, nor were ovarian follicle counts altered by genistein in that study. One major difference between the female rats monitored in the current study and those monitored in the multigenerational reproductive toxicology study was that rats in the latter study had all delivered and nursed litters shortly before they were evaluated, and this may have had an impact on the observed cycle effects. Likewise, the observation in the multigenerational reproductive toxicology study that genistein induced alterations of the estrous cycle in rats immediately after vaginal opening but not in older rats immediately prior to termination of the study may indicate that the older rats were affected by their prior pregnancy and nursing experience. Follicle counts are not necessarily altered in rats showing aberrant estrous cycles, as modulation of the cycle by the hypothalamus and pituitary gland are more likely to be involved in this process in the rat. For example, prepubertal exposures to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin were recently shown to accelerate the onset of reproductive senescence in female Sprague-Dawley rats without affecting the ovarian follicles (Franczak *et al.,* 2006). While 500 ppm genistein accelerated the onset of aberrant estrous cycles in all three arms of the study, there was also some evidence for a similar effect at the 5 and 100 ppm exposure concentrations in the F_3T21 study arm. Although placental transfer of genistein under the conditions of this study has been demonstrated (Doerge *et al.,* 2001), exposure of the pups via the dam's milk under the conditions of this study was low (Doerge *et al.,* 2006; NTP, 2008a), suggesting that any effects observed in the F_3T21 arm of the study would be induced by *in utero* exposure or be a very sensitive response to neonatal exposure. The neonatal period is known to be a sensitive window for the effects of estrogenic agents in rodents, and Jefferson *et al.* (2005) recently demonstrated the induction of early reproductive senescence in female mice treated neonatally with subcutaneous injection of 0.5 to 50 mg/kg genistein. Earlier experiments examining the effects of prenatal and neonatal exposure of rats to genistein had indicated that the effect of genistein on pituitary gland responsiveness to gonadotropin releasing hormone was complex with regard to timing of exposure and exposure concentration (Faber and Hughes, 1993; Levy *et al.,* 1995). Pituitary gland responsiveness was decreased in ovariectomized female rats exposed to genistein as neonates (Faber and Hughes, 1993) but not in rats exposed *in utero* (Levy *et al.,* 1995). It is thus not clear why the effects of 5 and 100 ppm genistein would be evident only when exposure was restricted to the *in utero* and preweaning period.

Pituitary gland adenoma and mammary gland neoplasms are well established as the major spontaneous neoplasms in female Sprague-Dawley rats, with pituitary gland adenoma being a major cause of morbidity and mortality (McComb *et al.,* 1984; Keenan *et al.,* 1995), as was the case with females in the current study. Pituitary gland adenomas produce multiple hormones, including prolactin, which is implicated in development of the mammary gland neoplasms (McComb *et al.,* 1984; Keenan *et al.,* 1995). In F_1C females in the current study, there were significant positive trends for the combined incidences of adenoma or adenocarcinoma in the mammary gland and the combined incidences of adenoma or carcinoma in the pituitary gland, with the incidences in the 500 ppm group significantly increased compared to those in the controls at both sites. In F_1T140 females, there was a significant positive trend in the incidences of the combined pituitary gland neoplasms and a nonsignificantly (P=0.068) increased incidence in the 500 ppm group relative to that in the controls. In F_3T21 females, there was a significant positive trend in the incidences of mammary gland adenoma or adenocarcinoma (combined) (P=0.039) and the incidence of the combined neoplasms was marginally increased (P=0.065) in the 500 ppm group. Thus, the effects of genistein on the incidences of adenoma or adenocarcinoma (combined)

in the mammary gland and the incidences of adenoma or carcinoma (combined) in the pituitary gland are evident in the F_1C arm, but the effects in the other exposure arms are less convincing. Foster *et al.* (2004) reported that subcutaneous injections of 10 mg genistein/kg to Sprague-Dawley rats on PNDs 2 to 8 induced significant alterations in the mammary gland of females consistent with estrogenic stimulation that could enhance tumor development. As noted earlier, the early postnatal exposure of the animals in the current study was limited, and this may have contributed to the limited response of the F_3T21 animals. Body weight decreases have been linked to decreases in both mammary gland and pituitary gland neoplasm incidences in F344/N (Seilkop, 1995; Haseman *et al.,* 1997) and Sprague-Dawley (Keenan *et al.,* 1995; Molon-Noblot *et al.,* 2003) rats. The increases in incidences of neoplasms in the F_1C females, which showed a significant decrease in body weight gain, strengthens the conclusion that genistein enhanced neoplasm incidences under this continuous-exposure regimen.

The acceleration of reproductive aging and the development of persistent estrus in the Sprague-Dawley rat by compounds such as atrazine and related triazine herbicides (Stevens *et al.,* 1994, 1999; Wetzel *et al.,* 1994) and rolipram (Nishiyama *et al.,* 2006) has been implicated in increased rates of development and incidences of mammary gland neoplasms. As reported by these investigators, the incidences of pituitary gland adenoma may or may not be increased in these cases, but development is accelerated, and prolactin concentrations are increased. It has been argued that this mechanism is irrelevant to humans (Stevens *et al.,* 1994, 1999; Meek *et al.,* 2003), although this conclusion has been questioned (Harvey, 2005). In the current study, while hormone concentrations were not evaluated, there was evidence for accelerated reproductive senescence and extended estrus in all groups of females exposed to 500 ppm genistein. When data from all arms of the study combined were analyzed by a Poly-3 weighted logistic regression, there was a significant association between the time of onset of aberrant cycles and incidences of mammary gland adenocarcinoma (P=0.005). When the combined incidences of adenoma and adenocarcinoma were analyzed, the association was also significant (P=0.030). Additionally, increased incidences of pituitary gland adenoma or carcinoma (combined) and mammary gland adenoma or adenocarcinoma (combined) were only evident in the F_1C arm. Unlike triazine herbicides and rolipram, genistein does interact directly with estrogen receptors and induces the expression of estrogen-regulated genes. While the induction of early, persistent estrus may have contributed to the increased incidences of the pituitary gland and mammary gland neoplasms observed in the F_1C animals, it is apparent that the continuous presence of the estrogenic stimulation of genistein also played a role in enhancing the development of these neoplasms. Considering that the only neoplasms whose development was enhanced by genistein are common estrogen-responsive neoplasms, that there is no clear evidence of neoplasm induction at other less common sites, and that there is a lack of clear evidence of *in vivo* genotoxicity of genistein, it is suggested that the enhancement of tumorigenesis occurred through a hormonal mechanism rather than through a genotoxic mechanism. Consistent with this view, genistein has been reported to support the growth of mammary gland neoplasms in ovariectomized rodents (Hsieh *et al.,* 1998; Allred *et al.,* 2001a,b, 2004a,b; Ju *et al.,* 2001) and to enhance chemical-induced mammary gland neoplasms in intact rats (Kijkuokool *et al.,* 2006). Under differing exposure conditions, genistein has been demonstrated to inhibit carcinogenesis in rodent models (Magee and Rowland, 2004). In addition, several studies in female nonhuman primates have failed to demonstrate estrogenic effects of soy protein isolate or soy isoflavone mixtures that included genistein up to doses approximating 10 mg genistein/kg per day and resulted in serum concentrations of genistein equivalent to those achieved from high dose soy ingestion in women (Wood *et al.,* 2004, 2006a,b,c).

The incidence of fibroadenoma, the other common mammary gland neoplasm in female Sprague-Dawley rats, was significantly decreased in 500 ppm F_1C females. Although mammary gland adenocarcinomas are sometimes observed to arise within fibroadenomas, these lesions are generally believed to arise independently (Shellabarger *et al.,* 1979, 1987; Boorman *et al.,* 1990), and the development of these neoplasms has been shown to be affected by body weight gain and dietary restriction (Keenan *et al.,* 1995; Seilkop*,* 1995; Haseman *et al.,* 1997). The decreased body weight gain in the F_1C females of the current study may thus have contributed to the decreased incidence of mammary gland

fibroadenoma in these animals. Mammary gland adenoma, adenocarcinoma, and fibroadenoma have shown inconsistent responses in studies with compounds thought to induce mammary gland adenoma or adenocarcinoma and pituitary gland neoplasms through acceleration of the development of persistent estrus (Stevens *et al.,* 1999; Nishiyama *et al.,* 2006). In the case of atrazine and related compounds, fibroadenoma showed variable, increased incidences (Stevens *et al.,* 1999), while in the case of rolipram, incidences of fibroadenoma appeared to decrease in a manner similar to that observed in the current study, although this reduction was not analyzed or discussed by the authors of the study (Nishiyama *et al.,* 2006).

CONCLUSIONS

Under the conditions of this 2-year feed study with continuous exposure to the test compound from conception through termination (F_1C), there was *no evidence of carcinogenic activity** of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was *some evidence of carcinogenic activity* of genistein in female Sprague-Dawley rats based on increased incidences of mammary gland adenoma or adenocarcinoma (combined) and pituitary gland neoplasms. The incidence of benign mammary gland fibroadenoma in female rats was significantly decreased in the 500 ppm group.

Under the conditions of this 2-year feed study with exposure to the test compound from conception through 20 weeks followed by control feed until termination (F_1T140), there was *no evidence of carcinogenic activity* of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was *equivocal evidence of carcinogenic activity* of genistein in female Sprague-Dawley rats based on marginally increased incidences of pituitary gland neoplasms.

Under the conditions of this 2-year feed study where offspring of three prior generations of animals exposed to the test compound were exposed from conception through weaning (PND 21) followed by control feed until termination (F_3T21), there was *no evidence of carcinogenic activity* of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was *equivocal evidence of carcinogenic activity* of genistein in female Sprague-Dawley rats based on increased incidences of mammary gland adenoma or adenocarcinoma (combined).

Exposure to genistein was also shown to accelerate the onset of aberrant estrous cycles in female Sprague-Dawley rats whether exposures were continuous or truncated at PND 140 or at weaning. The effects of genistein on estrous cycling and the incidences of common hormonally related spontaneous neoplasms of female Sprague-Dawley rats are consistent with an estrogenic mechanism of toxicity.

---

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

REFERENCES

Adlercreutz, H. (2002). Phyto-oestrogens and cancer. *Lancet Oncol.* **3**, 364-373.

Allred, C.D., Ju, Y.H., Allred, K.F., Chang, J., and Helferich, W.G. (2001a). Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. *Carcinogenesis* **22**, 1667-1673.

Allred, C.D., Allred, K.F., Ju, Y.H., Virant, S.M., and Helferich, W.G. (2001b). Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. *Cancer Res.* **61**, 5045-5050.

Allred, C.D., Allred, K.F., Ju, Y.H., Clausen, L.M., Doerge, D.R., Schantz, S.L., Korol, D.L., Wallig, M.A., and Helferich, W.G. (2004a). Dietary genistein results in larger MNU-induced, estrogen-dependent mammary tumors following ovariectomy of Sprague-Dawley rats. *Carcinogenesis* **25**, 211-218.

Allred, C.D., Allred, K.F., Ju, Y.H., Goeppinger, T.S., Doerge, D.R., and Helferich, W.G. (2004b). Soy processing influences growth of estrogen-dependent breast cancer tumors. *Carcinogenesis* **25**, 1649-1657.

Anthony, M.S., Clarkson, T.B., Hughes, C.L., Jr., Morgan, T.M., and Burke, G.L. (1996). Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys. *J. Nutr.* **126**, 43-50.

Atkinson, C., Frankenfeld, C.L., and Lampe, J.W. (2005). Gut bacterial metabolism of the soy isoflavone daidzein: Exploring the relevance to human health. *Exp. Biol. Med. (Maywood)* **230**, 155-170.

Bailer, A.J., and Portier, C.J. (1988). Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* **44**, 417-431.

Baird, D.D., Umbach, D.M., Lansdell, L., Hughes, C.L., Setchell, K.D.R., Weinberg, C.R., Haney, A.F., Wilcox, A.J., and McLachlan, J.A. (1995). Dietary intervention study to assess estrogenicity of dietary soy among postmenopausal women. *J. Clin. Endocrinol. Metab.* **80**, 1685-1690.

Baldrick, P. (2005). Carcinogenicity evaluation: Comparison of tumor data from dual control groups in the Sprague-Dawley rat. *Toxicol. Pathol.* **33**, 283-291.

Bartholomew, R.M., and Ryan, D.S. (1980). Lack of mutagenicity of some phytoestrogens in the salmonella/mammalian microsome assay. *Mutat. Res.* **78**, 317-321.

Bern, H.A. (1992). The fragile fetus. In *Advances in Modern Environmental Toxicology, Vol. XXI. Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection* (T. Colborn and C. Clement, Eds.), pp. 9-15. Princeton Scientific Publishing Co., Inc., Princeton, NJ.

Bieler, G.S., and Williams, R.L. (1993). Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics* **49**, 793-801.

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

Boorman, G.A., Wilson, J.T., van Zwieten, M.J., and Eustis, S.L. (1990). Mammary gland. In *Pathology of the Fischer Rat. Reference and Atlas* (G.A. Boorman, S.L. Eustis, M.R. Elwell, C.A. Montgomery Jr., and W.F. MacKenzie, Eds.), pp. 295-313. Academic Press, Inc., San Diego.

Boos, G., and Stopper, H. (2000). Genotoxicity of several clinically used topoisomerase II inhibitors. *Toxicol. Lett.* **116**, 7-16.

Brix, A.E., Nyska, A., Haseman, J.K., Sells, D.M., Jokinen, M.P., and Walker, N.J. (2005). Incidences of selected lesions in control female Harlan Sprague-Dawley rats from two-year studies performed by the National Toxicology Program. *Toxicol. Pathol.* **33**, 477-483.

Cassidy, A., Bingham, S., and Setchell, K.D.R. (1994). Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. *Am. J. Clin. Nutr.* **60**, 333-340.

Cassidy, A., Bingham, S., and Setchell, K.D.R. (1995). Biological effects of isoflavones in young women: Importance of the chemical composition of soyabean products. *Br. J. Nutr.* **74**, 587-601.

Center for Food Safety and Applied Nutrition (CFSAN) (2006). *Redbook 2000 - Toxicological Principles for the Safety Assessment of Food Ingredients.* U.S. Food and Drug Administration, Rockville, MD.

Chan, J.M., Gann, P.H., and Giovannucci, E.L. (2005). Role of diet in prostate cancer development and progression. *J. Clin. Oncol.* **23**, 8152-8160.

Chandra, M., Riley, M.G., and Johnson, D.E. (1992). Spontaneous neoplasms in aged Sprague-Dawley rats. *Arch. Toxicol.* **66**, 496-502.

Chang, H.C., Churchwell, M.I., Delclos, K.B., Newbold, R.R., and Doerge, D.R. (2000). Mass spectrometric determination of genistein tissue distribution in diet-exposed Sprague-Dawley rats. *J. Nutr.* **130**, 1963-1970.

Chen, T., Hutts, R.C., Mei, N., Liu, X., Bishop, M.E., Shelton, S., Manjanatha, M.G., and Aidoo, A. (2005). Endogenous estrogen status, but not genistein supplementation, modulates 7,12-dimethylbenz[a]anthracene-induced mutation in the liver cII gene of transgenic Big Blue rats. *Environ. Mol. Mutagen.* **45**, 409-418.

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

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (2003). *Phytoestrogens and Health* (I. Hughes, Ed.), pp. 1-444. Food Standards Agency, London.

Dang, Z.C., Audinot, V., Papapoulos, S.E., Boutin, J.A., and Lowik, C.W. (2003). Peroxisome proliferator-activated receptor gamma (PPARgamma) as a molecular target for the soy phytoestrogen genistein. *J. Biol. Chem.* **278**, 962-967.

Day, J.K., Besch-Williford, C., McMann, T.R., Hufford, M.G., Lubahn, D.B., and MacDonald, R.S. (2001). Dietary genistein increased DMBA-induced mammary adenocarcinoma in wild-type, but not ER alpha KO, mice. *Nutr. Cancer* **39**, 226-232.

Delclos, K.B., Bucci, T.J., Lomax, L.G., Latendresse, J.R., Warbritton, A., Weis, C.C., and Newbold, R.R. (2001). Effects of dietary genistein exposure during development on male and female CD (Sprague-Dawley) rats. *Reprod. Toxicol.* **15**, 647-663.

Di Virgilio, A.L., Iwami, K., Watjen, W., Kahl, R., and Degen, G.H. (2004). Genotoxicity of the isoflavones genistein, daidzein and equol in V79 cells. *Toxicol. Lett.* **151**, 151-162.

Dixon, R.A., and Ferreira, D. (2002). Genistein. *Phytochemistry* **60**, 205-211.

Doerge, D.R., Chang, H.C., Churchwell, M.I., and Holder, C.L. (2000). Analysis of soy isoflavone conjugation in vitro and in human blood using liquid chromatography-mass spectrometry. *Drug. Metab. Dispos.* **28**, 298-307.

Doerge, D.R., Churchwell, M.I., Chang, H.C., Newbold, R.R., and Delclos, K.B. (2001). Placental transfer of the soy isoflavone genistein following dietary and gavage administration to Sprague Dawley rats. *Reprod. Toxicol.* **15**, 105-110.

Doerge, D.R., Twaddle, N.C., Churchwell, M.I., Newbold, R.R., and Delclos, K.B. (2006). Lactational transfer of the soy isoflavone, genistein, in Sprague-Dawley rats consuming dietary genistein. *Reprod. Toxicol.* **21**, 307-312.

Duffy, P.H., Seng, J.E., Lewis, S.M., Mayhugh, M.A., Aidoo, A., Hattan, D.G., Casciano, D.A., and Feuers, R.J. (2001). The effects of different levels of dietary restriction on aging and survival in the Sprague-Dawley rat: Implications for chronic studies. *Aging (Milano)* **13**, 263-272.

Duffy, P.H., Lewis, S.M., Mayhugh, M.A., McCracken, A., Thorn, B.T., Reeves, P.G., Blakely, S.A., Casciano, D.A., and Feuers, R.J. (2002). Effect of the AIN-93M purified diet and dietary restriction on survival in Sprague-Dawley rats: Implications for chronic studies. *J. Nutr.* **132**, 101-107.

Duffy, P.H., Lewis, S.M., Mayhugh, M.A., Trotter, R.W., Latendresse, J.R., Thorn, B.T., and Feuers, R.J. (2004). The effects of different levels of dietary restriction on neoplastic pathology in the male Sprague-Dawley rat. *Aging Clin. Exp. Res.* **16**, 448-456.

Duncan, A.M., Merz, B.E., Xu, X., Nagel, T.C., Phipps, W.R., and Kurzer, M.S. (1999). Soy isoflavones exert modest hormonal effects in premenopausal women. *J. Clin. Endocrinol. Metab.* **84**, 192-197.

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

East, J. (1955). The effect of genistein on the fertility of mice. *J. Endocrinol.* **13**, 94-100.

Faber, K.A., and Hughes, C.L., Jr. (1993). Dose-response characteristics of neonatal exposure to genistein on pituitary responsiveness to gonadotropin releasing hormone and volume of the sexually dimorphic nucleus of the preoptic area (SDN-POA) in postpubertal castrated female rats. *Reprod. Toxicol.* **7**, 35-39.

Foster, W.G., Younglai, E.V., Boutross-Tadross, O., Hughes, C.L., and Wade, M.G. (2004). Mammary gland morphology in Sprague-Dawley rats following treatment with an organochlorine mixture in utero and neonatal genistein. *Toxicol. Sci.* **77**, 91-100.

Franczak, A., Nynca, A., Valdez, K.E., Mizinga, K.M., and Petroff, B.K. (2006). Effects of acute and chronic exposure to the aryl hydrocarbon receptor agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin on the transition to reproductive senescence in female Sprague-Dawley rats. *Biol. Reprod.* **74**, 125-130.

Fritz, W.A., Coward, L., Wang, J., and Lamartiniere, C.A. (1998). Dietary genistein: Perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. *Carcinogenesis* **19**, 2151-2158.

Ganry, O. (2005). Phytoestrogens and prostate cancer risk. *Prev. Med.* **41**, 1-6.

Giknis, M.L.A., and Clifford, C.B. (2004). Compilation of spontaneous neoplastic lesions and survival in Crl:CD® (SD) rats from control groups. Charles River Laboratories.

Grace, P.B., Taylor, J.I., Low, Y.L., Luben, R.N., Mulligan, A.A., Botting, N.P., Dowsett, M., Welch, A.A., Khaw, K.T., Wareham, N.J., Day, N.E., and Bingham, S.A. (2004). Phytoestrogen concentrations in serum and spot urine as biomarkers for dietary phytoestrogen intake and their relation to breast cancer risk in European prospective investigation of cancer and nutrition-Norfolk. *Cancer Epidemiol. Biomarkers Prev.* **13**, 698-708.

Gugger, E.T. (2002). Industrial processing and preparation of isoflavones. In *Phytoestrogens and Health* (G.S. Gilani and J.J.B. Anderson, Eds.), pp. 83-93. AOCS Press, Champaign, IL.

Hargreaves, D.F., Potten, C.S., Harding, C., Shaw, L.E., Morton, M.S., Roberts, S.A., Howell, A., and Bundred, N.J. (1999). Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. *J. Clin. Endocrinol. Metab.* **84**, 4017-4024.

Harvey, J.S., Howe, J.R., Lynch, A.M., and Rees, R.W. (2005). The results of five coded compounds: Genistein, metaproterenol, rotenone, p-anisidine and resorcinol tested in the pH 6.7 Syrian hamster embryo cell morphological transformation assay. *Mutagenesis* **20**, 51-56.

Harvey, P.W. (2005). Human relevance of rodent prolactin-induced non-genotoxic mammary carcinogenesis: Prolactin involvement in human breast cancer and significance for toxicology risk assessments. *J. Appl. Toxicol.* **25**, 179-183.

Haseman, J.K., Young, E., Eustis, S.L., and Hailey, J.R. (1997). Body weight-tumor incidence correlations in long-term rodent carcinogenicity studies. *Toxicol. Pathol.* **25**, 256-263.

Hilakivi-Clarke, L., Cho, E., and Clarke, R. (1998). Maternal genistein exposure mimics the effects of estrogen on mammary gland development in female mouse offspring. *Oncol. Rep.* **5**, 609-616.

Hilakivi-Clarke, L., Onojafe, I., Raygada, M., Cho, E., Skaar, T., Russo, I., and Clarke, R. (1999a). Prepubertal exposure to zearalenone or genistein reduces mammary tumorigenesis. *Br. J. Cancer* **80**, 1682-1688.

Hilakivi-Clarke, L., Cho, E., Onojafe, I., Raygada, M., and Clarke, R. (1999b). Maternal exposure to genistein during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. *Oncol. Rep.* **6**, 1089-1095.

Hirose, K., Imaeda, N., Tokudome, Y., Goto, C., Wakai, K., Matsuo, K., Ito, H., Toyama, T., Iwata, H., Tokudome, S., and Tajima, K. (2005). Soybean products and reduction of breast cancer risk: A case-control study in Japan. *Br. J. Cancer* **93**, 15-22.

Hodgson, J.M., Puddey, I.B., Beilin, L.J., Mori, T.A., and Croft, K.D. (1998). Supplementation with isoflavonoid phytoestrogens does not alter serum lipid concentration: A randomized control trial in humans. *J. Nutr.* **128**, 728-732.

Holder, C.L., Churchwell, M.I., and Doerge, D.R. (1999). Quantification of soy isoflavones, genistein and daidzein, and conjugates in rat blood using LC/ES-MS. *J. Agric. Food Chem.* **47**, 3764-3770.

Hsieh, C.-Y., Santell, R.C., Haslam, S.Z., and Helferich, W.G. (1998). Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells *in vitro* and *in vivo*. *Cancer Res.* **58**, 3833-3838.

Irvine, C.H., Shand, N., Fitzpatrick, M.G., and Alexander, S.L. (1998). Daily intake and urinary excretion of genistein and daidzein by infants fed soy- or dairy-based infant formulas. *Am. J. Clin. Nutr.* **68**, 1462S-1465S.

Ishimi, Y., Miyaura, C., Ohmura, M., Onoe, Y., Sato, T., Uchiyama, Y., Ito, M., Wang, X., Suda, T., and Ikegami, S. (1999). Selective effects of genistein, a soybean isoflavone, on B-lymphopoiesis and bone loss caused by estrogen deficiency. *Endocrinology* **140**, 1893-1900.

Jackson, C.C., and Rupasinghe, H.P.V. (2002). Human dietary sources of phytoestrogens and methods of determination. In *Phytoestrogens and Health* (G.S. Gilani and J.J.B. Anderson, Eds.), pp. 95-123. AOCS Press, Champaign, IL.

Jefferson, W.N., Couse, J.F., Padilla-Banks, E., Korach, K.S., and Newbold, R.R. (2002). Neonatal exposure to genistein induces estrogen receptor (ER) alpha expression and multioocyte follicles in the maturing mouse ovary: Evidence for ERbeta-mediated and nonestrogenic actions. *Biol. Reprod.* **67**, 1285-1296.

Jefferson, W.N., Padilla-Banks, E., and Newbold, R.R. (2005). Adverse effects on female development and reproduction in CD-1 mice following neonatal exposure to the phytoestrogen genistein at environmentally relevant doses. *Biol. Reprod.* **73**, 798-806.

Johnson, W.D., Dooley, L., Morrissey, R.L., Arp, L., Kapetanovic, I., Crowell, J.A., and McCormick, D.L. (2006). Oncogenicity evaluations of chemopreventive soy components in p53(+/-) (p53 knockout) mice. *Int. J. Toxicol.* **25**, 219-228.

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

Ju, Y.H., Allred, C.D., Allred, K.F., Karko, K.L., Doerge, D.R., and Helferich, W.G. (2001). Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *J. Nutr.* **131**, 2957-2962.

Kalbfleisch, J.D., and Prentice, R.L. (2002). *The Statistical Analysis of Failure Time Data*, 2nd ed. John Wiley & Sons, Inc., New York.

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

Kaspareit, J., and Rittinghausen, S. (1999). Spontaneous neoplastic lesions in Harlan Sprague-Dawley rats. *Exp. Toxicol. Pathol.* **51**, 105-107.

Keenan, K.P., Soper, K.A., Smith, P.F., Ballam, G.C., and Clark, R.L. (1995). Diet, overfeeding, and moderate dietary restriction in control Sprague-Dawley rats: I. Effects on spontaneous neoplasms. *Toxicol. Pathol.* **23**, 269-286.

Keinan-Boker, L., van Der Schouw, Y.T., Grobbee, D.E., and Peeters, P.H. (2004). Dietary phytoestrogens and breast cancer risk. *Am. J. Clin. Nutr.* **79**, 282-288.

Kijkuokool, P., Parhar, I.S., and Malaivijitnond, S. (2006). Genistein enhances N-nitrosomethylurea-induced rat mammary tumorigenesis. *Cancer Lett.* **242**, 5359.

Kim, H., Hall, P., Smith, M., Kirk, M., Prasain, J.K., Barnes, S., and Grubbs, C. (2004). Chemoprevention by grape seed extract and genistein in carcinogen-induced mammary cancer in rats is diet dependent. *J. Nutr.* **134**, 3445S-3452S.

Kim, S., Sohn, I., and Lee, Y.S. (2005). Hepatic gene expression profiles are altered by genistein supplementation in mice with diet-induced obesity. *J. Nutr.* **135**, 33-41.

King, R.A., Broadbent, J.L., and Head, R.J. (1996). Absorption and excretion of the soy isoflavone genistein in rats. *J. Nutr.* **126**, 176-182.

Kinjo, J., Tsuchihashi, R., Morito, K., Hirose, T., Aomori, T., Nagao, T., Okabe, H., Nohara, T., and Masamune, Y. (2004). Interactions of phytoestrogens with estrogen receptors alpha and beta (III). Estrogenic activities of soy isoflavone aglycones and their metabolites isolated from human urine. *Biol. Pharm. Bull.* **27**, 185-188.

Kulling, S.E., and Metzler, M. (1997). Induction of micronuclei, DNA strand breaks and HPRT mutations in cultured Chinese hamster V79 cells by the phytoestrogen coumoestrol. *Food Chem. Toxicol.* **35**, 605-613.

Kulling, S.E., Rosenberg, B., Jacobs, E., and Metzler, M. (1999). The phytoestrogens coumoestrol and genistein induce structural chromosomal aberrations in cultured human peripheral blood lymphocytes. *Arch. Toxicol.* **73**, 50-54.

Kurzer, M.S. (2003). Phytoestrogen supplement use by women. *J. Nutr.* **133**, 1983S-1986S.

Lamartiniere, C.A., Zhang, J.-X., and Cotroneo, M.S. (1998). Genistein studies in rats: Potential for breast cancer prevention and reproductive and developmental toxicity. *Am. J. Clin. Nutr.* **68**, 1400S-1405S.

LeFevre, J., and McClintock, M.K. (1991). Isolation accelerates reproductive senescence and alters its predictors in female rats. *Horm. Behav*. **25**, 258-272.

Levy, J.R., Faber, K.A., Ayyash, L., and Hughes, C.L., Jr. (1995). The effect of prenatal exposure to the phytoestrogen genistein on sexual differentiation in rats. *Proc. Soc. Exp. Biol. Med.* **208**, 60-66.

Lewis, R.W., Brooks, N., Milburn, G.M., Soames, A., Stone, S., Hall, M., and Ashby, J. (2003). The effects of the phytoestrogen genistein on the postnatal development of the rat. *Toxicol. Sci.* **71**, 74-83.

McClain, R.M., Wolz, E., Davidovich, A., and Bausch, J. (2006a). Genetic toxicity studies with genistein. *Food Chem. Toxicol.* **44**, 42-55.

McClain, R.M., Wolz, E., Davidovich, A., Pfannkuch, F., Edwards, J.A., and Bausch, J. (2006b). Acute, subchronic and chronic safety studies with genistein in rats. *Food Chem. Toxicol.* **44**, 56-80.

McComb, D.J., Kovacs, K., Beri, J., and Zak, F. (1984). Pituitary adenomas in old Sprague-Dawley rats: A histologic, ultrastructural, and immunocytochemical study. *JNCI* **73**, 1143-1166.

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

McMartin, D.N., Sahota, P.S., Gunson, D.E., Hsu, H.H., and Spaet, R.H. (1992). Neoplasms and related proliferative lesions in control Sprague-Dawley rats from carcinogenicity studies. Historical data and diagnostic considerations. *Toxicol. Pathol.* **20**, 212-225.

Magee, P.J., and Rowland, I.R. (2004). Phyto-oestrogens, their mechanism of action: Current evidence for a role in breast and prostate cancer. *Br. J. Nutr.* **91**, 513-531.

Manjanatha, M.G., Shelton, S.D., Rhodes, B.S., Bishop, M.E., Lyn-Cook, L.E., and Aidoo, A. (2005). 17 Beta-estradiol and not genistein modulates lacI mutant frequency and types of mutation induced in the heart of ovariectomized Big Blue rats treated with 7,12-dimethylbenz[a]anthracene. *Environ. Mol. Mutagen.* **45**, 70-79.

Markovits, J., Linassier, C., Fosse, P., Couprie, J., Pierre, J., Jacquemin-Sablon, A., Saucier, J.M., Le Pecq, J.B., and Larsen, A.K. (1989). Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II. *Cancer Res.* **49**, 5111-5117.

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

Matt, D.W., Sarver, P.L., and Lu, J.K.H. (1987). Relation of parity and estrous cyclicity to the biology of pregnancy in aging female rats. *Biol. Reprod.* **37**, 421-430.

Meek, M.E., Bucher, J.R., Cohen, S.M.,Dellarco, V., Hill, R.N., Lehman-McKeeman, L.D., Longfellow, D.G., Pastoor, T., Seed, J., and Patton, D.E. (2003). A framework for human relevance analysis of information on carcinogenic modes of action. *Crit. Rev. Toxicol.* **33**, 591-653.

The Merck Index (1996). 12th ed. (S. Budavari, Ed.), p. 744. Merck and Company, Inc., Whitehouse Station, NJ.

Messina, M., Kucuk, O., and Lampe, J.W. (2006). An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels. *J. AOAC Int.* **89**, 1121-1134.

Mezei, O., Banz, W.J., Steger, R.W., Peluso, M.R., Winters, T.A., and Shay, N. (2003). Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells. *J. Nutr.* **133**, 1238-1243.

Miltyk, W., Craciunescu, C.N., Fischer, L., Jeffcoat, R.A., Koch, M.A., Lopaczynski, W., Mahoney, C., Jeffcoat, R.A., Crowell, J., Paglieri, J., and Zeisel, S.H. (2003). Lack of significant genotoxicity of purified soy isoflavones (genistein, daidzein, and glycitein) in 20 patients with prostate cancer. *Am. J. Clin. Nutr.* **77**, 875-882.

Misra, R.R., Hursting, S.D., Perkins, S.N., Sathyamoorthy, N., Mirsalis, J.C., Riccio, E.S., and Crowell, J.A. (2002). Genotoxicity and carcinogenicity studies of soy isoflavones. *Int. J. Toxicol.* **21**, 277-285.

Molon-Noblot, S., Laroque, P., Coleman, J.B., Hoe, C.M., and Keenan, K.P. (2003). The effects of ad libitum overfeeding and moderate and marked dietary restriction on age-related spontaneous pituitary gland pathology in Sprague-Dawley rats. *Toxicol. Pathol.* **31**, 310-320.

Morito, K., Hirose, T., Kinjo, J., Hirakawa, T., Okawa, M., Nohara, T., Ogawa, S., Inoue, S., Muramatsu, M., and Masamune, Y. (2001). Interaction of phytoestrogens with estrogen receptors alpha and beta. *Biol. Pharm. Bull.* **24**, 351-356.

Morris, S.M., Chen, J.J., Domon, O.E., McGarrity, L.J., Bishop, M.E., Manjanatha, M.G., and Casciano, D.A. (1998). *p53*, mutations, and apoptosis in genistein-exposed human lymphoblastoid cells. *Mutat. Res.* **405**, 41-56.

Morris, S.M., Akerman, G.S., Warbritton, A.R., Patton, R.E., Doerge, D.R., Ding, X., and Chen, J.J. (2003). Effect of dietary genistein on cell replication indices in C57BL6 mice. *Cancer Lett.* **195**, 139-145.

Murrill, W.B., Brown, N.M., Zhang, J.-X., Manzolillo, P.A., Barnes, S., and Lamartiniere, C.A. (1996). Prepubertal genistein exposure suppresses mammary cancer and enhances gland differentiation in rats. *Carcinogenesis* **17**, 1451-1457.

Naciff, J.M., Jump, M.L., Torontali, S.M., Carr, G.J., Tiesman, J.P., Overmann, G.J., and Daston, G.P. (2002). Gene expression profile induced by 17alpha-ethynyl estradiol, bisphenol A, and genistein in the developing female reproductive system of the rat. *Toxicol. Sci.* **68**, 184-199.

Naciff, J.M., Hess, K.A., Overmann, G.J., Torontali, S.M., Carr, G.J., Tiesman, J.P., Foertsch, L.M., Richardson, B.D., Martinez, J.E., and Daston, G.P. (2005). Gene expression changes induced in the testis by transplacental exposure to high and low doses of 17{alpha}-ethynyl estradiol, genistein, or bisphenol A. *Toxicol. Sci.* **86**, 396-416.

Nagao, M., Morita, N., Yahagi, T., Shimizu, M., Kuroyanagi, M., Fukuoka, M., Yoshihira, K., Natori, S., Fujino, T., and Sugimura, T. (1981). Mutagenicities of 61 flavonoids and 11 related compounds. *Environ. Mutagen.* **3**, 401-419.

Nagao, T., Yoshimura, S., Saito, Y., Nakagomi, M., Usumi, K., and Ono, H. (2001). Reproductive effects in male and female rats of neonatal exposure to genistein. *Reprod. Toxicol.* **15**, 399-411.

Nagata, C., Kabuto, M., Kurisu, Y., and Shimizu, H. (1997). Decreased serum estradiol concentration associated with high dietary intake of soy products in premenopausal Japanese women. *Nutr. Cancer* **29**, 228-233.

Nagata, C., Takatsuka, N., Inaba, S., Kawakami, N., and Shimizu, H. (1998). Effect of soymilk consumption on serum estrogen concentrations in premenopausal Japanese women. *J. Natl. Cancer Inst.* **90**, 1830-1835.

National Institute for Environmental Health Sciences (NIEHS) (1995). Estrogens in the Environment III. Global Health Implications. *Environ. Health Perspect.* **103** (Suppl. 7), 1-178.

National Institutes of Health (NIH) (1999). DES Research Update 1999: Current Knowledge, Future Directions. Meeting Summary, NIH Publication No. 00-4722. National Institutes of Health, Bethesda, MD.

National Research Council (NRC) (1999). *Hormonally Active Agents in the Environment.* National Academy Press, Washington, DC.

National Toxicology Program (NTP) (2007). Reproductive Dose Range-Finding Study of Genistein (CAS No. 446-72-0) Administered in Feed to Sprague-Dawley Rats. Toxicity Report Series No. 79. NIH Publication No. 08-5960. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC.

National Toxicology Program (NTP) (2008a). Multigenerational Reproductive Toxicology Study of Genistein (CAS No. 446-72-0) in Sprague-Dawley Rats (Feed Study). Technical Report Series No. 539. NIH Publication No. 08-4477. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC.

National Toxicology Program (NTP) (2008b). Toxicology and Carcinogenesis Study of Ethinyl Estradiol (CAS No. 57-63-6) in Sprague-Dawley Rats (Feed Study). Technical Report Series No. 548. NIH Publication No. 08-5889. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC.

Nestel, P.J., Pomeroy, S., Kay, S., Komersaroff, P., Behrsing, J., Cameron, J.D., and West, L. (1999). Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J. Clin. Endocrinol. Metab.* **84**, 895-898.

Newbold, R.R. (1995). Cellular and molecular effects of developmental exposure to diethylstilbestrol: Implications for other environmental estrogens. *Environ. Health Perspect.* **103** (Suppl. 7), 83-87.

Newbold, R.R., Banks, E.P., Bullock, B., and Jefferson, W.N. (2001). Uterine adenocarcinoma in mice treated neonatally with genistein. *Cancer Res.* **61**, 4325-4328.

Nishiyama, S., Okudaira, M., and Saito, N. (2006). Mechanisms of rolipram-induced increase in the incidence of mammary adenocarcinoma: Histopathological study of a 104-week oral carcinogenicity study in female Sprague-Dawley rats. *Arch. Toxicol.* **80**, 88-97.

Okazaki, K., Okazaki, S., Nakamura, H., Kitamura, Y., Hatayama, K., Wakabayashi, S., Tsuda, T., Katsumata, T., Nishikawa, A., and Hirose, M. (2002). A repeated 28-day oral dose toxicity study of genistein in rats, based on the 'Enhanced OECD Test Guideline 407' for screening endocrine-disrupting chemicals. *Arch. Toxicol.* **76**, 553-559.

Organisation for Economic Co-operation and Development (OECD) (2004). Draft Guidance Document on Reproductive Toxicity Testing and Assessment. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 43, Paris.

Peeters, P.H., Keinan-Boker, L., van der Schouw, Y.T., and Grobbee, D.E. (2003). Phytoestrogens and breast cancer risk. Review of the epidemiological evidence. *Breast Cancer Res. Treat.* **77**, 171-183.

Petrakis, N.L., Barnes, S., King, E.B., Lowenstein, J., Wiencke, J., Lee, M.M., Miike, R., Kirk, M., and Coward, L. (1996). Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. *Cancer Epidemiol. Biomarkers Prev.* **5**, 785-794.

Pettersen, J.C., Morrissey, R.L., Saunders, D.R., Pavkov, K.L., Luempert, L.G., III, Turnier, J.C., Matheson, D.W., and Schwartz, D.R. (1996). A 2-year comparison study of Crl:CD BR and Hsd:Sprague-Dawley SD rats. *Fundam. Appl. Toxicol.* **33**, 196-211.

Piegorsch, W.W., and Bailer, A.J. (1997). *Statistics for Environmental Biology and Toxicology,* Section 6.3.2. Chapman and Hall, London.

Portier, C.J., and Bailer, A.J. (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam. Appl. Toxicol.* **12**, 731-737.

Portier, C.J., Hedges, J.C., and Hoel, D.G. (1986). Age specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. *Cancer Res.* **46**, 4372-4378.

Price, K.R., and Fenwick, G.R. (1985). Naturally occurring oestrogens in foods – A review. *Food Addit. Contam.* **2**, 73-106.

Pryor, J.L., Hughes, C., Foster, W., Hales, B.F., and Robaire, B. (2000). Critical windows of exposure for children's health: The reproductive system in animals and humans. *Environ. Health Perspect.* **108** (Suppl. 3), 491-503.

Rao, C.V., Wang, C.X., Simi, B., Lubet, R., Kelloff, G., Steele, V., and Reddy, B.S. (1997). Enhancement of experimental colon cancer by genistein. *Cancer Res.* **57**, 3717-3722.

Record, I.R., Jannes, M., Dreosti, I.E., and King, R.A. (1995). Induction of micronucleus formation in mouse splenocytes by the soy isoflavone genistein in vitro but not in vivo. *Food Chem. Toxicol.* **33**, 919-922.

Ross, J.A., Potter, J.D., Reaman, G.H., Pendergrass, T.W., and Robison, L.L. (1996). Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): A report from the Children's Cancer Group. *Cancer Causes Control* **7**, 581-590.

Rubin, B.S. (2000). Hypothalamic alterations and reproductive aging in female rats: Evidence of altered leuteinizing hormone-releasing hormone neuronal function. *Biol. Reprod.* **63**, 968-976.

Sacks, F.M., Lichtenstein, A., Van Horn, L., Harris, W., Kris-Etherton, P., and Winston, M. (2006). Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation* **113**, 1034-1044.

Satoh, T., Yamakoshi, J., Saito, M., Izumi, T., Matsuyama, A., Kikuchi, M., and Yamaguchi, T. (2006). Nephrocalcinosis formation by soy isoflavones in male rats. *J. Agric. Food Chem.* **54**, 5659-5663.

Seilkop, S.K. (1995). The effect of body weight on tumor incidence and carcinogenicity testing in B6C3F_1 mice and F344 rats. *Fundam. Appl. Toxicol.* **24**, 247-259.

Setchell, K.D.R., Zimmer-Nechemias, L., Cai, J., and Heubi, J.E. (1997). Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* **350**, 23-27.

Setchell, K.D.R., Zimmer-Nechemias, L., Cai, J., and Heubi, J.E. (1998). Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. *Am. J. Clin. Nutr.* **68**, 1453S-1461S.

Setchell, K.D.R., Brown, N.M., Desai, P., Zimmer-Nechemias, L., Wolfe, B.E., Brashear, W.T., Kirschner, A.S., Cassidy, A., and Heubi, J.E. (2001). Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy supplements. *J. Nutr.* **131**, 1362S-1375S.

Setchell, K.D.R., Brown, N.M., Zimmer-Nechemias, L., Brashear, W.T., Wolfe, B.E., Kirschner, A.S., and Heubi, J.E. (2002). Evidence for lack of absorption of soy isoflavone glycosides in humans, supporting the crucial role of intestinal metabolism for bioavailability. *Am. J. Clin. Nutr.* **76**, 447-453.

Shellabarger, C.J., Holtzman, S., and Stone, J.P. (1979). Apparent rat strain-related sensitivity to phorbol promotion of mammary carcinogenesis. *Cancer Res.* **39**, 3345-3348.

Shellabarger, C.J., Machado, S.G., Holtzman, S., and Stone, J.P. (1987). Assessment of interaction among three carcinogens on rat mammary carcinogenesis in a factorially designed experiment. *JNCI* **79**, 549-554.

Snyder, R.D., and Gillies, P.J. (2002). Evaluation of the clastogenic, DNA intercalative, and topoisomerase II-interactive properties of bioflavonoids in Chinese hamster V79 cells. *Environ. Mol. Mutagen.* **40**, 266-276.

Snyder, R.D., and Gillies, P.J. (2003). Reduction of genistein clastogenicity in Chinese hamster V79 cells by daidzein and other flavonoids. *Food Chem. Toxicol.* **41**, 1291-1298.

Spector, L.G., Xie, Y., Robison, L.L., Heerema, N.A., Hilden, J.M., Lange, B., Felix, C.A., Davies, S.M., Slavin, J., Potter, J.D., Blair, C.K., Reaman, G.H., and Ross, J.A. (2005). Maternal diet and infant leukemia: The DNA topoisomerase II inhibitor hypothesis: A report from the children's oncology group. *Cancer Epidemiol. Biomarkers Prev.* **14**, 651-655.

Stevens, J.T., Breckenridge, C.B., Wetzel, L.T., Gillis, J.H., Luempert, L.G., III, and Eldridge, J.C. (1994). Hypothesis for mammary tumorigenesis in Sprague-Dawley rats exposed to certain triazine herbicides. *J. Toxicol. Environ. Health* **43**, 139-153.

Stevens, J.T., Breckenridge, C.B., and Wetzel, L. (1999). A risk characterization for atrazine: Oncogenicity profile. *J. Toxicol. Environ. Health A* **56**, 69-109.

Stob, M. (1983). Naturally occurring food toxicants: Estrogens. In *Handbook of Naturally Occurring Food Toxicants* (M. Rechcigl, Jr., Ed.), pp. 81-100. CRC Press, Boca Raton, FL.

Strick, R., Strissel, P.L., Borgers, S., Smith, S.L., and Rowley, J.D. (2000). Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. *Proc. Natl. Acad. Sci. U.S.A.* **97**, 4790-4795.

Sun, C.L., Yuan, J.M., Arakawa, K., Low, S.H., Lee, H.P., and Yu, M.C. (2002). Dietary soy and increased risk of bladder cancer: The Singapore Chinese Health Study. *Cancer Epidemiol. Biomarkers Prev.* **11**, 1674-1677.

Sun, C.L., Yuan, J.M., Wang, X.L., Gao, Y.T., Ross, R.K., and Yu, M.C. (2004). Dietary soy and increased risk of bladder cancer: A prospective cohort study of men in Shanghai, China. *Int. J. Cancer* **112**, 319-323.

Takahashi, Y., Lavigne, J.A., Hursting, S.D., Chandramouli, G.V., Perkins, S.N., Barrett, J.C., and Wang, T.T. (2004). Using DNA microarray analyses to elucidate the effects of genistein in androgen-responsive prostate cancer cells: Identification of novel targets. *Mol. Carcinog.* **41**, 108-119.

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

Tennekes, H., Gembardt, C., Dammann, M., and van Ravenzwaay, B. (2004). The stability of historical control data for common neoplasms in laboratory rats: Adrenal gland (medulla), mammary gland, liver, endocrine pancreas, and pituitary gland. *Regul. Toxicol. Pharmacol.* **40**, 18-27.

Thigpen, J.E., Setchell, K.D., Ahlmark, K.B., Locklear, J., Spahr, T., Caviness, G.F., Goelz, M.F., Haseman, J.K., Newbold, R.R., and Forsythe, D.B. (1999). Phytoestrogen content of purified, open- and closed-formula laboratory animal diets. *Lab. Anim. Sci.* **49**, 530-536.

Thigpen, J.E., Locklear, J., Haseman, J.K., Saunders, H., Grant, M.F., and Forsythe, D.B. (2001). Effects of the dietary phytoestrogens daidzein and genistein on the incidence of vulvar carcinomas in 129/J mice. *Cancer Detect. Prev.* **25**, 527-532.

Thigpen, J.E., Setchell, K.D.R., Saunders, H.E., Haseman, J.K., Grant, M.G., and Forsythe, D.B. (2004). Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. *ILAR J.* **45**, 401-416.

Trock, B.J., Hilakivi-Clarke, L., and Clarke, R. (2006). Meta-analysis of soy intake and breast cancer risk. *J. Natl. Cancer Inst.* **98**, 459-471.

Weber, K.S., Setchell, K.D.R., and Lephart, E.D. (2001). Maternal and perinatal brain aromatase: Effects of dietary soy phytoestrogens. *Brain Res. Dev. Brain Res.* **126**, 217-221.

Weibull, W. (1951). A statistical distribution function of wide applicability. *J. Appl. Mechanics* **18**, 292-297.

Weiss, G., Skurnick, J.H., Goldsmith, L.T., Santoro, N.F., and Park, S.J. (2004). Menopause and hypothalamic-pituitary sensitivity to estrogen. *JAMA* **292**, 2991-2996 (Erratum **293**, 163).

Wetzel, L.T., Luempert, L.G., III, Breckenridge, C.B., Tisdel, M.O., Stevens, J.T., Thakur, A.K., Extrom, P.J., and Eldridge, J.C. (1994). Chronic effects of atrazine on estrus and mammary tumor formation in female Sprague-Dawley and Fischer 344 rats. *J. Toxicol. Environ. Health* **43**, 169-182.

Whitten, P.L., and Patisaul, H.B. (2001). Cross-species and interassay comparisons of phytoestrogen action. *Environ. Health Perspect.* **109**, 5-20.

Wilcox, G., Wahlqvist, M.L., Burger, H.G., and Medley, G. (1990). Oestrogenic effects of plant foods in postmenopausal women. *Br. J. Med.* **301**, 905-906.

Williamson-Hughes, P.S., Flickinger, B.D., Messina, M.J., and Empie, M.W. (2006). Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: A critical review of published studies. *Menopause* **13**, 831-839.

Wise, P.M., Scarbrough, K., Larson, G.H., Lloyd, J.M., Weiland, N.G., and Chiu, S. (1991). Neuroendocrine influences on aging of the female reproductive system. *Front. Neuroendocrinol.* **12**, 323-356.

Wise, P.M., Krajnak, K.M., and Kashon, M.L. (1996). Menopause: The aging of multiple pacemakers. *Science* **273**, 67-70.

Wood, C.E., Register, T.C., Anthony, M.S., Kock, N.D., and Cline, J.M. (2004). Breast and uterine effects of soy isoflavones and conjugated equine estrogens in post-menopausal female monkeys. *J. Clin. Endocrinol. Metab.* **89**, 3462-3468.

Wood, C.E., Kaplan, J.R., Stute, P., and Cline, J.M. (2006a). Effects of soy on the mammary glands of pre-menopausal female monkeys. *Fertil. Steril.* **85**, 1179-1186.

Wood, C.E., Register, T.C., Franke, A.A., Anthony, M.S., and Cline, J.M. (2006b). Dietary soy isoflavones inhibit estrogen effects in the post-menopausal breast. *Cancer Res.* **66**, 1241-1249.

Wood, C.E., Appt, S.E., Clarkson, T.B., Franke, A.A., Lees, C.J., Doerge, D.R., and Cline, J.M. (2006c). Effects of high-dose soy isoflavones and equol on reproductive tissues in female cynomolgus monkeys. *Biol. Reprod.* **75**, 477-486.

Wu, A.H., Wan, P., Hankin, J., Tseng, C.C., Yu, M.C., and Pike, M.C. (2002). Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. *Carcinogenesis* **23**, 1491-1496.

Xu, X., Duncan, A.M., Merz, B.E., and Kurzer, M.S. (1998). Effects of soy isoflavones on estrogen and phytoestrogen metabolism in premenopausal women. *Cancer Epidemiol. Biomarkers Prev.* **7**, 1101-1111.

Yamamoto, S., Sobue, T., Kobayashi, M., Sasaki, S., and Tsugane, S. (2003). Soy, isoflavones, and breast cancer risk in Japan. *J. Natl. Cancer. Inst.* **95**, 906-913.

Yamashita, Y., Kawada, S., and Nakano, H. (1990). Induction of mammalian topoisomerase II dependent DNA cleavage by nonintercalative flavonoids, genistein and orobol. *Biochem. Pharmacol.* **39**, 737-744.

Yang, J., Nakagawa, H., Tsuta, K., and Tsubura, A. (2000). Influence of perinatal genistein exposure on the development of MNU-induced mammary carcinoma in female Sprague-Dawley rats. *Cancer Lett.* **149**, 171-179.

You, L., Sar, M., Bartolucci, E.J., McIntyre, B.S., and Sriperumbudur, R. (2002). Modulation of mammary gland development in prepubertal male rats exposed to genistein and methoxychlor. *Toxicol. Sci.* **66**, 216-225.

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

TABLE A1a Summary of the Incidence of Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein 72
TABLE A1b Summary of the Incidence of Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein 77
TABLE A1c Summary of the Incidence of Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein 81
TABLE A2a Statistical Analysis of Primary Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein 86
TABLE A2b Statistical Analysis of Primary Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein 88
TABLE A2c Statistical Analysis of Primary Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein 90
TABLE A3a Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein 92
TABLE A3b Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein 105
TABLE A3c Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein 118

TABLE A1a
Summary of the Incidence of Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	78	72	80
Early deaths				
Dead	10	4		7
Dead no CID		1	1	1
Discard		1		
Issue other	4	4	4	4
Missing	1	2	1	
Moribund	8	5	7	12
Surplus	38	20	16	25
Survey/sentinel	31			
Survivors				
Terminal sacrifice	36	41	43	31
Animals examined microscopically	54	50	50	50
Alimentary System				
Intestine large, cecum	(44)	(46)	(50)	(46)
Carcinoma, metastatic, serosa, prostate				1 (2%)
Lymphoma malignant		1 (2%)	2 (4%)	
Intestine large, colon	(46)	(46)	(50)	(46)
Adenoma		1 (2%)		
Carcinoma, metastatic, serosa, prostate				1 (2%)
Lymphoma malignant		2 (4%)		
Intestine small, duodenum	(46)	(45)	(50)	(46)
Carcinoma, metastatic, serosa, prostate				1 (2%)
Intestine small, ileum	(43)	(47)	(50)	(44)
Adenocarcinoma		1 (2%)		
Lymphoma malignant		1 (2%)		
Intestine small, jejunum	(44)	(45)	(50)	(43)
Adenocarcinoma	1 (2%)	1 (2%)		
Lymphoma malignant			1 (2%)	
Liver	(51)	(48)	(50)	(48)
Carcinoma, metastatic, prostate				1 (2%)
Hepatocellular adenoma	1 (2%)	2 (4%)	2 (4%)	
Hepatocellular carcinoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (4%)	3 (6%)	3 (6%)	2 (4%)
Mesentery	(1)	(1)		(1)
Lymphoma malignant				1 (100%)
Oral mucosa				(1)
Osteosarcoma				1 (100%)
Pancreas	(50)	(49)	(50)	(49)
Carcinoma, metastatic, prostate				1 (2%)
Lymphoma malignant	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Salivary glands	(49)	(49)	(50)	(47)
Lymphoma malignant	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Neurofibrosarcoma	1 (2%)			
Stomach, glandular	(45)	(47)	(50)	(44)
Lymphoma malignant			1 (2%)	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Animals initially in study refers to animals born into the study. Pups were randomly selected for continuation on the study and were necropsied in pathology if they survived to terminal sacrifice or died or became moribund prior to scheduled necropsy. All other pups were allocated to addenda studies or euthanized (Discard, Issue other, Surplus). In some cases, young pups that died were likely cannibalized by the dam and were thus indicated as Missing. Survey/sentinel animals were microbiological sentinels. Animals designated Dead no CID (carcass identification number) were animals that were not selected for continuation on study but died prior to weaning. Only animals processed by pathology received CIDs.

TABLE A1a
Summary of the Incidence of Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Cardiovascular System				
Heart	(52)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (4%)	1 (2%)	1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(47)	(50)	(48)
Adenoma	1 (2%)	1 (2%)		1 (2%)
Lymphoma malignant	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Adrenal medulla	(47)	(49)	(50)	(49)
Lymphoma malignant	1 (2%)			1 (2%)
Pheochromocytoma benign	1 (2%)	1 (2%)	2 (4%)	7 (14%)
Pheochromocytoma benign, bilateral	1 (2%)			
Pheochromocytoma complex	1 (2%)			
Pheochromocytoma malignant		1 (2%)		
Islets, pancreatic	(49)	(49)	(50)	(49)
Adenoma	1 (2%)	3 (6%)	1 (2%)	5 (10%)
Carcinoma				1 (2%)
Carcinoma, metastatic, prostate				1 (2%)
Lymphoma malignant	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Parathyroid gland	(47)	(47)	(47)	(47)
Adenoma	1 (2%)			
Lymphoma malignant		1 (2%)		
Pituitary gland	(49)	(46)	(50)	(49)
Adenoma, multiple, pars distalis	1 (2%)			1 (2%)
Adenoma, pars distalis	22 (45%)	14 (30%)	22 (44%)	21 (43%)
Lymphoma malignant	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Thyroid gland	(49)	(47)	(50)	(46)
Adenoma, C-cell	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Carcinoma, C-cell		1 (2%)		1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	
General Body System				
Tissue NOS			(1)	(1)
Carcinoma, metastatic, abdominal, prostate				1 (100%)
Chondrosarcoma			1 (100%)	
Genital System				
Coagulating gland	(47)	(49)	(50)	(45)
Adenocarcinoma, metastatic, prostate	1 (2%)			
Carcinoma, metastatic, prostate				1 (2%)
Lymphoma malignant		1 (2%)		
Lymphoma malignant, adventitia			1 (2%)	
Epididymis	(51)	(48)	(50)	(49)
Carcinoma, metastatic, prostate				1 (2%)
Lymphoma malignant		1 (2%)	1 (2%)	
Mesothelioma malignant			1 (2%)	
Preputial gland	(49)	(48)	(49)	(49)
Lymphoma malignant		2 (4%)	1 (2%)	
Squamous cell carcinoma	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Prostate, dorsal	(48)	(49)	(50)	(49)
Adenocarcinoma	2 (4%)			
Carcinoma				1 (2%)
Lymphoma malignant	1 (2%)	2 (4%)	2 (4%)	1 (2%)

TABLE A1a
Summary of the Incidence of Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Prostate, ventral	(48)	(49)	(50)	(48)
Adenocarcinoma	1 (2%)			
Carcinoma				1 (2%)
Lymphoma malignant		2 (4%)	2 (4%)	1 (2%)
Seminal vesicle	(47)	(48)	(50)	(45)
Adenocarcinoma, metastatic, prostate	2 (4%)			
Carcinoma, metastatic, prostate				1 (2%)
Testes	(51)	(50)	(50)	(49)
Carcinoma, metastatic, capsule, prostate				1 (2%)
Mesothelioma benign	1 (2%)			
Mesothelioma malignant			1 (2%)	
Seminoma benign				1 (2%)
Hematopoietic System				
Bone marrow	(49)	(49)	(50)	(48)
Lymphoma malignant	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Lymph node	(15)	(13)	(16)	(8)
Leukemia granulocytic, deep cervical	1 (7%)			
Leukemia granulocytic, lumbar	1 (7%)			
Leukemia granulocytic, renal	1 (7%)			
Lymphoma malignant, axillary		1 (8%)		1 (13%)
Lymphoma malignant, deep cervical				1 (13%)
Lymphoma malignant, inguinal	1 (7%)	1 (8%)	1 (6%)	
Lymphoma malignant, lumbar	1 (7%)	2 (15%)		1 (13%)
Lymphoma malignant, mediastinal			2 (13%)	1 (13%)
Lymphoma malignant, pancreatic			1 (6%)	
Lymphoma malignant, popliteal				1 (13%)
Lymphoma malignant, renal	1 (7%)			
Lymphoma malignant, thoracic	1 (7%)		2 (13%)	
Lymph node, mandibular	(52)	(50)	(49)	(46)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Lymph node, mesenteric	(48)	(50)	(50)	(46)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Spleen	(52)	(48)	(50)	(48)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (4%)	3 (6%)	3 (6%)	2 (4%)
Sarcoma				1 (2%)
Thymus	(42)	(44)	(45)	(42)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (5%)	2 (5%)	2 (4%)	2 (5%)`

TABLE A1a
Summary of the Incidence of Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Integumentary System				
Mammary gland	(41)	(43)	(40)	(42)
Adenocarcinoma			1 (3%)	
Fibroadenoma		1 (2%)		2 (5%)
Skin	(51)	(49)	(50)	(50)
Basal cell adenoma		1 (2%)		
Fibroma	1 (2%)	1 (2%)		1 (2%)
Fibrosarcoma			1 (2%)	
Keratoacanthoma		1 (2%)		1 (2%)
Lipoma	1 (2%)			2 (4%)
Lymphoma malignant			1 (2%)	
Sarcoma	1 (2%)	1 (2%)	1 (2%)	
Squamous cell papilloma		1 (2%)		
Musculoskeletal System				
Skeletal muscle				(1)
Carcinoma, metastatic, prostate				1 (100%)
Nervous System				
Brain, brain stem	(50)	(48)	(50)	(48)
Lymphoma malignant		1 (2%)	1 (2%)	
Brain, cerebellum	(50)	(48)	(50)	(47)
Granular cell tumor malignant	1 (2%)			
Lymphoma malignant			1 (2%)	
Brain, cerebrum	(50)	(48)	(50)	(48)
Granular cell tumor benign			1 (2%)	
Granular cell tumor malignant		1 (2%)		1 (2%)
Lymphoma malignant		2 (4%)	1 (2%)	
Respiratory System				
Lung	(49)	(47)	(50)	(47)
Adenoma, alveolar epithelium		1 (2%)		
Alveolar/bronchiolar carcinoma	1 (2%)			
Carcinoma, metastatic, prostate				1 (2%)
Chondrosarcoma, metastatic, uncertain primary site			1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)	
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Nose	(48)	(48)	(50)	(48)
Lymphoma malignant	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Squamous cell carcinoma				2 (4%)
Trachea	(47)	(47)	(50)	(46)
Lymphoma malignant	1 (2%)	1 (2%)	1 (2%)	
Special Senses System				
Eye	(37)	(42)	(43)	(35)
Squamous cell carcinoma, adventitia				1 (3%)
Harderian gland	(39)	(42)	(43)	(37)
Adenoma	1 (3%)			
Zymbal's gland		(1)		(1)
Squamous cell carcinoma		1 (100%)		1 (100%)

TABLE A1a
Summary of the Incidence of Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Urinary System				
Kidney	(48)	(48)	(50)	(48)
Adenoma, tubular	1 (2%)			
Fibrosarcoma, metastatic, skin			1 (2%)	
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Urinary bladder	(47)	(48)	(50)	(46)
Carcinoma, metastatic, serosa, prostate				1 (2%)
Lymphoma malignant		1 (2%)		

TABLE A1b
Summary of the Incidence of Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	50	50	50
Early deaths				
Dead	10	7	7	7
Issue other	4			
Missing	1			
Moribund	8	9	11	5
Surplus	38			
Survey/sentinel	31			
Survivors				
Terminal sacrifice	36	34	32	38
Animals examined microscopically	54	50	50	50
Alimentary System				
Intestine large, cecum	(44)	(45)	(42)	(44)
Lymphoma malignant				1 (2%)
Intestine large, colon	(46)	(45)	(43)	(46)
Adenoma				1 (2%)
Lymphoma malignant				1 (2%)
Intestine small, duodenum	(46)	(45)	(43)	(45)
Lymphoma malignant				1 (2%)
Sarcoma				1 (2%)
Intestine small, ileum	(43)	(44)	(42)	(43)
Adenocarcinoma			1 (2%)	
Lymphoma malignant				1 (2%)
Intestine small, jejunum	(44)	(42)	(42)	(42)
Adenocarcinoma	1 (2%)			
Lymphoma malignant				1 (2%)
Liver	(51)	(49)	(47)	(48)
Cholangiocarcinoma			1 (2%)	
Hepatocellular adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Pancreas	(50)	(49)	(46)	(48)
Adenoma, acinar cell				1 (2%)
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Salivary glands	(49)	(49)	(46)	(50)
Lymphoma malignant	2 (4%)			1 (2%)
Neurofibrosarcoma	1 (2%)			
Stomach, glandular	(45)	(46)	(44)	(45)
Lymphoma malignant				1 (2%)
Cardiovascular System				
Blood vessel	(53)	(50)	(48)	(49)
Lymphoma malignant, adventitia			1 (2%)	
Heart	(52)	(48)	(48)	(50)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)			1 (2%)

The footnotes for this table are defined in Table A1a.

TABLE A1b
Summary of the Incidence of Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System				
Adrenal cortex	(49)	(47)	(46)	(46)
Adenoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)			
Adrenal medulla	(47)	(47)	(46)	(45)
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	1 (2%)			
Pheochromocytoma benign	1 (2%)	2 (4%)		4 (9%)
Pheochromocytoma benign, bilateral	1 (2%)	1 (2%)		
Pheochromocytoma complex	1 (2%)			1 (2%)
Pheochromocytoma malignant		1 (2%)	1 (2%)	2 (4%)
Islets, pancreatic	(49)	(49)	(46)	(48)
Adenoma	1 (2%)		1 (2%)	3 (6%)
Lymphoma malignant	2 (4%)		1 (2%)	1 (2%)
Parathyroid gland	(47)	(48)	(47)	(46)
Adenoma	1 (2%)			1 (2%)
Lymphoma malignant				1 (2%)
Pituitary gland	(49)	(49)	(48)	(48)
Adenoma, multiple, pars distalis	1 (2%)			1 (2%)
Adenoma, pars distalis	22 (45%)	18 (37%)	13 (27%)	15 (31%)
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)		1 (2%)	1 (2%)
Thyroid gland	(49)	(46)	(44)	(48)
Adenoma, C-cell	1 (2%)	1 (2%)		1 (2%)
Adenoma, follicular cell		1 (2%)		1 (2%)
Carcinoma, C-cell			1 (2%)	
Lymphoma malignant	1 (2%)			1 (2%)
Genital System				
Coagulating gland	(47)	(45)	(45)	(47)
Adenocarcinoma, metastatic, prostate	1 (2%)		1 (2%)	
Lymphoma malignant				1 (2%)
Epididymis	(51)	(50)	(47)	(49)
Lymphoma malignant				1 (2%)
Preputial gland	(49)	(50)	(48)	(49)
Lymphoma malignant			1 (2%)	1 (2%)
Sarcoma		1 (2%)		
Squamous cell carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Squamous cell carcinoma, adventitia			1 (2%)	
Prostate, dorsal	(48)	(49)	(50)	(49)
Adenocarcinoma	2 (4%)		1 (2%)	
Carcinoma, metastatic, urinary bladder				1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	1 (2%)
Prostate, ventral	(48)	(49)	(48)	(48)
Adenocarcinoma	1 (2%)		1 (2%)	
Adenoma		1 (2%)		
Carcinoma				1 (2%)
Carcinoma, metastatic, urinary bladder				1 (2%)
Lymphoma malignant			1 (2%)	1 (2%)
Seminal vesicle	(47)	(43)	(45)	(47)
Adenocarcinoma, metastatic, prostate	2 (4%)		1 (2%)	
Lymphoma malignant				1 (2%)
Testes	(51)	(50)	(49)	(50)
Mesothelioma benign	1 (2%)			
Seminoma benign				1 (2%)

TABLE A1b
Summary of the Incidence of Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System				
Bone marrow	(49)	(48)	(47)	(49)
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Lymph node	(15)	(14)	(14)	(9)
Leukemia granulocytic, deep cervical	1 (7%)			
Leukemia granulocytic, lumbar	1 (7%)			
Leukemia granulocytic, renal	1 (7%)			
Lymphoma malignant, deep cervical				1 (11%)
Lymphoma malignant, inguinal	1 (7%)			
Lymphoma malignant, lumbar	1 (7%)			
Lymphoma malignant, renal	1 (7%)			1 (11%)
Lymphoma malignant, thoracic	1 (7%)			1 (11%)
Lymph node, mandibular	(52)	(49)	(45)	(48)
Fibrosarcoma, metastatic, skin		1 (2%)		
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Lymph node, mesenteric	(48)	(47)	(45)	(46)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Spleen	(52)	(50)	(47)	(49)
Hemangiosarcoma			1 (2%)	
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Thymus	(42)	(47)	(40)	(45)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (5%)	1 (2%)	2 (5%)	1 (2%)
Integumentary System				
Mammary gland	(41)	(42)	(34)	(45)
Lymphoma malignant				1 (2%)
Skin	(51)	(50)	(50)	(50)
Carcinoma, sebaceous gland		1 (2%)		
Fibroma	1 (2%)	2 (4%)		2 (4%)
Fibrosarcoma		1 (2%)		
Keratoacanthoma			1 (2%)	
Lipoma	1 (2%)	1 (2%)	1 (2%)	
Sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Schwannoma benign			1 (2%)	
Schwannoma malignant		1 (2%)		
Squamous cell carcinoma		1 (2%)	1 (2%)	
Musculoskeletal System				
Bone, cranium			(1)	
Osteoma			1 (100%)	

TABLE A1b
Summary of the Incidence of Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Nervous System				
Brain, brain stem	(50)	(50)	(48)	(48)
Astrocytoma malignant				1 (2%)
Glioma malignant				1 (2%)
Lymphoma malignant			1 (2%)	1 (2%)
Brain, cerebellum	(50)	(49)	(48)	(48)
Astrocytoma malignant			1 (2%)	
Granular cell tumor benign		1 (2%)		
Granular cell tumor malignant	1 (2%)		1 (2%)	
Lymphoma malignant				1 (2%)
Lymphoma malignant, meninges			1 (2%)	
Brain, cerebrum	(50)	(50)	(48)	(48)
Astrocytoma malignant			1 (2%)	1 (2%)
Glioma malignant				1 (2%)
Granular cell tumor benign			1 (2%)	
Granular cell tumor malignant			1 (2%)	
Leukemia mononuclear		1 (2%)		
Lymphoma malignant				1 (2%)
Lymphoma malignant, meninges			1 (2%)	
Respiratory System				
Lung	(49)	(48)	(44)	(49)
Alveolar/bronchiolar carcinoma	1 (2%)			
Fibrosarcoma, metastatic, skin		1 (2%)		
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)	1 (2%)	2 (5%)	1 (2%)
Squamous cell carcinoma, metastatic, preputial gland		1 (2%)		
Nose	(48)	(47)	(45)	(48)
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Squamous cell carcinoma			1 (2%)	
Trachea	(47)	(47)	(46)	(48)
Lymphoma malignant	1 (2%)			1 (2%)
Special Senses System				
Ear				(1)
Neural crest tumor				1 (100%)
Eye	(37)	(37)	(33)	(40)
Lymphoma malignant			1 (3%)	
Harderian gland	(39)	(39)	(33)	(41)
Adenoma	1 (3%)			
Lymphoma malignant			1 (3%)	
Zymbal's gland			(1)	
Carcinoma			1 (100%)	
Urinary System				
Kidney	(48)	(48)	(46)	(49)
Adenoma, tubular	1 (2%)			
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear		1 (2%)		
Lymphoma malignant	2 (4%)		2 (4%)	1 (2%)
Urinary bladder	(47)	(48)	(46)	(47)
Carcinoma, transitional epithelium				1 (2%)
Lymphoma malignant				1 (2%)

TABLE A1c
Summary of the Incidence of Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	66	50	50	50
Early deaths				
Dead	11	7	6	10
Moribund	8	1	11	4
Survey/sentinel	14			
Survivors				
Terminal sacrifice	33	42	33	36
Animals examined microscopically	52	50	49	49
Alimentary System				
Esophagus	(49)	(49)	(48)	(49)
Fibrous histiocytoma, metastatic, adventitia, uncertain primary site	1 (2%)			
Intestine large, cecum	(41)	(43)	(46)	(45)
Leukemia granulocytic				1 (2%)
Intestine large, colon	(41)	(43)	(46)	(45)
Adenocarcinoma	1 (2%)			
Leukemia granulocytic				1 (2%)
Intestine large, rectum	(38)	(42)	(38)	(38)
Leiomyosarcoma	1 (3%)			
Intestine small, duodenum	(41)	(43)	(46)	(43)
Adenocarcinoma	2 (5%)			
Intestine small, ileum	(40)	(42)	(45)	(43)
Leukemia granulocytic				1 (2%)
Intestine small, jejunum	(40)	(43)	(45)	(41)
Adenocarcinoma				1 (2%)
Leukemia granulocytic				1 (2%)
Liver	(49)	(47)	(47)	(48)
Carcinoma, metastatic, pancreas				1 (2%)
Hepatocellular adenoma	1 (2%)			1 (2%)
Hepatocellular carcinoma	1 (2%)	1 (2%)		
Histiocytic sarcoma			1 (2%)	
Leukemia	1 (2%)			
Leukemia granulocytic				1 (2%)
Leukemia mononuclear			1 (2%)	
Lymphoma malignant	2 (4%)			
Pancreas	(45)	(47)	(48)	(47)
Adenoma, acinar cell			2 (4%)	
Carcinoma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Salivary glands	(49)	(47)	(47)	(48)
Carcinoma, metastatic, pancreas				1 (2%)
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)			
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			

The footnotes for this table are defined in Table A1a.

TABLE A1c
Summary of the Incidence of Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Cardiovascular System				
Blood vessel	(51)	(50)	(49)	(47)
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)			
Heart	(51)	(48)	(49)	(47)
Fibrous histiocytoma, metastatic, pericardium, uncertain primary site	1 (2%)			
Leukemia granulocytic				1 (2%)
Lymphoma malignant	1 (2%)			
Endocrine System				
Adrenal cortex	(48)	(47)	(47)	(47)
Adenoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Leukemia mononuclear			1 (2%)	
Lymphoma malignant	1 (2%)			
Adrenal medulla	(48)	(46)	(47)	(45)
Leukemia mononuclear			1 (2%)	
Lymphoma malignant	1 (2%)			
Pheochromocytoma benign	4 (8%)	3 (7%)	4 (9%)	2 (4%)
Pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(45)	(49)	(48)	(48)
Adenoma	3 (7%)	3 (6%)	2 (4%)	
Carcinoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Lymphoma malignant	1 (2%)			
Parathyroid gland	(41)	(46)	(48)	(43)
Adenoma			1 (2%)	
Lymphoma malignant	1 (2%)			
Pituitary gland	(49)	(46)	(48)	(48)
Adenoma, multiple, pars distalis	1 (2%)			1 (2%)
Adenoma, pars distalis	16 (33%)	18 (39%)	17 (35%)	14 (29%)
Lymphoma malignant	2 (4%)			
Thyroid gland	(44)	(46)	(46)	(45)
Adenoma, bilateral, C-cell	1 (2%)			
Adenoma, C-cell	1 (2%)			1 (2%)
Carcinoma, C-cell				1 (2%)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (5%)			
General Body System				
Tissue NOS		(1)		(2)
Sarcoma, abdominal		1 (100%)		
Squamous cell carcinoma				1 (50%)

TABLE A1c
Summary of the Incidence of Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System				
Coagulating gland	(44)	(43)	(47)	(45)
Histiocytic sarcoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Lymphoma malignant	1 (2%)			
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Epididymis	(49)	(48)	(49)	(47)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	1 (2%)			
Mesothelioma malignant		1 (2%)		1 (2%)
Preputial gland	(48)	(48)	(47)	(47)
Carcinoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Squamous cell carcinoma			5 (11%)	3 (6%)
Prostate, dorsal	(51)	(47)	(47)	(48)
Adenocarcinoma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Mesothelioma malignant		1 (2%)		
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Prostate, ventral	(48)	(46)	(48)	(47)
Adenoma			1 (2%)	1 (2%)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Seminal vesicle	(43)	(43)	(47)	(45)
Adenoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant	1 (2%)			
Sarcoma			1 (2%)	
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Testes	(51)	(50)	(48)	(49)
Adenoma, interstitial cell	1 (2%)	1 (2%)		
Mesothelioma malignant		1 (2%)		1 (2%)
Seminoma benign	1 (2%)			
Hematopoietic System				
Bone marrow	(48)	(48)	(48)	(46)
Carcinoma, metastatic, pancreas				1 (2%)
Histiocytic sarcoma			1 (2%)	
Leukemia	1 (2%)			
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Lymph node	(13)	(9)	(18)	(12)
Histiocytic sarcoma, lumbar			1 (6%)	
Histiocytic sarcoma, mediastinal			1 (6%)	
Histiocytic sarcoma, renal			1 (6%)	
Leukemia granulocytic, inguinal				1 (8%)
Leukemia granulocytic, thoracic				1 (8%)
Leukemia, inguinal	1 (8%)			
Lymphoma malignant, axillary	1 (8%)			
Lymphoma malignant, inguinal	1 (8%)			
Lymphoma malignant, lumbar	1 (8%)			
Lymphoma malignant, renal	1 (8%)			
Squamous cell carcinoma, metastatic, lumbar, preputial gland				1 (8%)

TABLE A1c
Summary of the Incidence of Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(48)	(48)	(48)
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Leukemia	1 (2%)			
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Lymph node, mesenteric	(45)	(46)	(47)	(47)
Histiocytic sarcoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Spleen	(50)	(49)	(48)	(47)
Carcinoma, metastatic, pancreas				1 (2%)
Histiocytic sarcoma			1 (2%)	
Leukemia	1 (2%)			
Leukemia granulocytic				1 (2%)
Leukemia mononuclear			1 (2%)	
Lymphoma malignant	2 (4%)			
Sarcoma	1 (2%)	1 (2%)		
Thymus	(46)	(45)	(41)	(44)
Fibrous histiocytoma, metastatic, adventitia, uncertain primary site	1 (2%)			
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Integumentary System				
Mammary gland	(39)	(43)	(41)	(41)
Adenocarcinoma			1 (2%)	
Fibroadenoma				2 (5%)
Fibroma				2 (5%)
Skin	(49)	(50)	(48)	(49)
Basal cell adenoma				1 (2%)
Fibroma		1 (2%)		
Keratoacanthoma	1 (2%)			1 (2%)
Leukemia granulocytic				1 (2%)
Lipoma			1 (2%)	
Neurofibrosarcoma				1 (2%)
Schwannoma malignant	1 (2%)			
Squamous cell carcinoma	1 (2%)		3 (6%)	
Squamous cell papilloma				1 (2%)
Musculoskeletal System				
Bone				(1)
Chordoma				1 (100%)
Skeletal muscle	(1)			(1)
Carcinoma, metastatic, pancreas				1 (100%)
Fibrous histiocytoma, metastatic, uncertain primary site	1 (100%)			

TABLE A1c
Summary of the Incidence of Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Nervous System				
Brain, brain stem	(46)	(46)	(48)	(47)
Lymphoma malignant	1 (2%)			
Reticulosis malignant				1 (2%)
Brain, cerebellum	(46)	(46)	(48)	(46)
Astrocytoma malignant	1 (2%)			
Lymphoma malignant	1 (2%)			
Reticulosis malignant				1 (2%)
Brain, cerebrum	(45)	(46)	(48)	(46)
Astrocytoma malignant	1 (2%)	1 (2%)		
Lymphoma malignant	1 (2%)			
Reticulosis malignant				1 (2%)
Respiratory System				
Lung	(48)	(47)	(47)	(46)
Adenocarcinoma		1 (2%)		
Carcinoma, metastatic, pancreas				1 (2%)
Carcinoma, metastatic, uncertain primary site		1 (2%)		
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Leukemia mononuclear			1 (2%)	
Lymphoma malignant	2 (4%)			
Nose	(46)	(45)	(49)	(45)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)			
Squamous cell carcinoma		1 (2%)	1 (2%)	
Squamous cell carcinoma, adventitia				1 (2%)
Trachea	(45)	(44)	(48)	(44)
Fibrous histiocytoma, metastatic, adventitia, uncertain primary site	1 (2%)			
Lymphoma malignant	2 (4%)			
Special Senses System				
Eye	(37)	(43)	(38)	(39)
Carcinoma, retrobulbar		1 (2%)		
Squamous cell carcinoma, adventitia				1 (3%)
Harderian gland	(38)	(43)	(38)	(39)
Adenoma				1 (3%)
Squamous cell carcinoma, adventitia				1 (3%)
Zymbal's gland			(1)	
Adenoma			1 (100%)	
Urinary System				
Kidney	(46)	(49)	(47)	(47)
Carcinoma, metastatic, adventitia, pancreas				1 (2%)
Histiocytic sarcoma			1 (2%)	
Leukemia granulocytic				1 (2%)
Leukemia mononuclear			1 (2%)	
Lymphoma malignant	2 (4%)			
Papilloma, transitional epithelium				1 (2%)
Urinary bladder	(45)	(43)	(47)	(46)
Lymphoma malignant	1 (2%)			

TABLE A2a
Statistical Analysis of Primary Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/47 (4.3%)	1/49 (2.0%)	2/50 (4.0%)	7/49 (14.3%)
Adjusted rate[b]	2/41.3 (4.8%)	1/44.0 (2.3%)	2/46.1 (4.3%)	7/42.9 (16.3%)
Terminal rate[c]	2/36 (5.6%)	1/41 (2.4%)	2/43 (4.7%)	7/31 (22.6%)
First incidence (days)	742 (T)	749 (T)	737 (T)	741 (T)
Poly-3 test[d]	P=0.006	P=0.478N	P=0.654N	P=0.087
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/47 (6.4%)	2/49 (4.1%)	2/50 (4.0%)	7/49 (14.3%)
Adjusted rate	3/41.3 (7.3%)	2/44.0 (4.5%)	2/46.1 (4.3%)	7/42.9 (16.3%)
Terminal rate	3/36 (8.3%)	2/41 (4.9%)	2/43 (4.7%)	7/31 (22.6%)
First incidence (days)	742 (T)	738 (T)	737 (T)	741 (T)
Poly-3 test	P=0.028	P=0.471N	P=0.450N	P=0.172
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/51 (2.0%)	3/48 (6.3%)	2/50 (4.0%)	0/48 (0.0%)
Adjusted rate	1/42.4 (2.4%)	3/43.4 (6.9%)	2/46.1 (4.3%)	0/42.9 (0.0%)
Terminal rate	1/36 (2.8%)	3/41 (7.3%)	2/43 (4.7%)	0/31 (0.0%)
First incidence (days)	742 (T)	736 (T)	747 (T)	—[e]
Poly-3 test	P=0.155N	P=0.314	P=0.529	P=0.497N
Pancreatic Islets: Adenoma				
Overall rate	1/49 (2.0%)	3/49 (6.1%)	1/50 (2.0%)	5/49 (10.2%)
Adjusted rate	1/41.2 (2.4%)	3/43.7 (6.9%)	1/46.1 (2.2%)	5/43.2 (11.6%)
Terminal rate	1/36 (2.8%)	3/41 (7.3%)	1/43 (2.3%)	3/31 (9.7%)
First incidence (days)	748 (T)	738 (T)	742 (T)	729
Poly-3 test	P=0.077	P=0.327	P=0.735N	P=0.112
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	1/49 (2.0%)	3/49 (6.1%)	1/50 (2.0%)	6/49 (12.2%)
Adjusted rate	1/41.2 (2.4%)	3/43.7 (6.9%)	1/46.1 (2.2%)	6/43.4 (13.8%)
Terminal rate	1/36 (2.8%)	3/41 (7.3%)	1/43 (2.3%)	3/31 (9.7%)
First incidence (days)	748 (T)	738 (T)	742 (T)	710
Poly-3 test	P=0.029	P=0.327	P=0.735N	P=0.064
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	23/49 (46.9%)	14/46 (30.4%)	22/50 (44.0%)	22/49 (44.9%)
Adjusted rate	23/42.5 (54.1%)	14/42.6 (32.8%)	22/47.8 (46.0%)	22/44.0 (49.9%)
Terminal rate	19/35 (54.3%)	12/39 (30.8%)	19/43 (44.2%)	16/31 (51.6%)
First incidence (days)	571	601	473	664
Poly-3 test	P=0.289	P=0.036N	P=0.290N	P=0.432N
Preputial Gland: Squamous Cell Carcinoma				
Overall rate	1/49 (2.0%)	3/48 (6.3%)	1/49 (2.0%)	2/49 (4.1%)
Adjusted rate	1/41.3 (2.4%)	3/43.9 (6.8%)	1/45.1 (2.2%)	2/43.2 (4.6%)
Terminal rate	1/35 (2.9%)	3/41 (7.3%)	1/42 (2.4%)	1/31 (3.2%)
First incidence (days)	743 (T)	738 (T)	746 (T)	704
Poly-3 test	P=0.616	P=0.328	P=0.741N	P=0.515
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Adenoma				
Overall rate	0/51 (0.0%)	3/49 (6.1%)	0/50 (0.0%)	1/50 (2.0%)
Adjusted rate	0/42.7 (0.0%)	3/43.8 (6.9%)	0/46.1 (0.0%)	1/43.9 (2.3%)
Terminal rate	0/35 (0.0%)	3/41 (7.3%)	0/43 (0.0%)	1/31 (3.2%)
First incidence (days)	—	738 (T)	—[f]	742 (T)
Poly-3 test	P=0.598N	P=0.123	—	P=0.506

TABLE A2a
Statistical Analysis of Primary Neoplasms in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Skin: All Neoplastic Morphologies				
Overall rate	3/51 (5.9%)	5/49 (10.2%)	2/50 (4.0%)	4/50 (8.0%)
Adjusted rate	3/43.2 (6.9%)	5/44.6 (11.2%)	2/46.5 (4.3%)	4/44.5 (9.0%)
Terminal rate	2/35 (5.7%)	4/41 (9.8%)	1/43 (2.3%)	3/31 (9.7%)
First incidence (days)	577	452	616	563
Poly-3 test	P=0.555	P=0.374	P=0.466N	P=0.516
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	1/49 (2.0%)	3/47 (6.4%)	1/50 (2.0%)	2/46 (4.3%)
Adjusted rate	1/41.4 (2.4%)	3/43.2 (6.9%)	1/46.1 (2.2%)	2/41.7 (4.8%)
Terminal rate	1/36 (2.8%)	3/41 (7.3%)	1/43 (2.3%)	1/31 (3.2%)
First incidence (days)	741 (T)	742 (T)	748 (T)	664
Poly-3 test	P=0.604	P=0.321	P=0.736N	P=0.503
All Organs: Malignant Lymphoma				
Overall rate	2/54 (3.7%)	3/50 (6.0%)	3/50 (6.0%)	2/50 (4.0%)
Adjusted rate	2/45.5 (4.4%)	3/46.5 (6.4%)	3/48.0 (6.2%)	2/44.6 (4.5%)
Terminal rate	0/36 (0.0%)	0/41 (0.0%)	0/43 (0.0%)	0/31 (0.0%)
First incidence (days)	435	302	212	563
Poly-3 test	P=0.518N	P=0.510	P=0.525	P=0.687
All Organs: Benign Neoplasms				
Overall rate	26/54 (48.1%)	26/50 (52.0%)	26/50 (52.0%)	31/50 (62.0%)
Adjusted rate	26/45.9 (56.6%)	26/45.1 (57.7%)	26/47.8 (54.4%)	31/46.3 (66.9%)
Terminal rate	21/36 (58.3%)	24/41 (58.5%)	23/43 (53.5%)	21/31 (67.7%)
First incidence (days)	571	601	473	527
Poly-3 test	P=0.142	P=0.544	P=0.496N	P=0.207
All Organs: Malignant Neoplasms				
Overall rate	9/54 (16.7%)	9/50 (18.0%)	5/50 (10.0%)	10/50 (20.0%)
Adjusted rate	9/45.0 (20.0%)	9/45.1 (19.9%)	5/46.5 (10.7%)	10/46.4 (21.5%)
Terminal rate	7/36 (19.4%)	8/41 (19.5%)	4/43 (9.3%)	2/31 (6.5%)
First incidence (days)	274	452	616	358
Poly-3 test	P=0.387	P=0.600N	P=0.173N	P=0.531
All Organs: Benign or Malignant Neoplasms				
Overall rate	32/54 (59.3%)	29/50 (58.0%)	28/50 (56.0%)	38/50 (76.0%)
Adjusted rate	32/46.9 (68.2%)	29/45.8 (63.3%)	28/48.2 (58.1%)	38/48.8 (77.9%)
Terminal rate	25/36 (69.4%)	26/41 (63.4%)	24/43 (55.8%)	21/31 (67.7%)
First incidence (days)	274	452	473	358
Poly-3 test	P=0.055	P=0.388N	P=0.206N	P=0.196

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

TABLE A2b
Statistical Analysis of Primary Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/47 (4.3%)	3/47 (6.4%)	0/46 (0.0%)	4/45 (8.9%)
Adjusted rate[b]	2/41.3 (4.8%)	3/43.5 (6.9%)	0/39.4 (0.0%)	4/42.6 (9.4%)
Terminal rate[c]	2/36 (5.6%)	2/34 (5.9%)	0/31 (0.0%)	4/36 (11.1%)
First incidence (days)	742 (T)	712	—[d]	736 (T)
Poly-3 test[e]	P=0.230	P=0.523	P=0.248N	P=0.351
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/47 (6.4%)	3/47 (6.4%)	1/46 (2.2%)	7/45 (15.6%)
Adjusted rate	3/41.3 (7.3%)	3/43.5 (6.9%)	1/39.4 (2.5%)	7/42.6 (16.4%)
Terminal rate	3/36 (8.3%)	2/34 (5.9%)	1/31 (3.2%)	7/36 (19.4%)
First incidence (days)	742 (T)	712	748 (T)	736 (T)
Poly-3 test	P=0.039	P=0.639N	P=0.322N	P=0.169
Pancreatic Islets: Adenoma				
Overall rate	1/49 (2.0%)	0/49 (0.0%)	1/46 (2.2%)	3/48 (6.3%)
Adjusted rate	1/41.2 (2.4%)	0/44.6 (0.0%)	1/39.8 (2.5%)	3/45.2 (6.6%)
Terminal rate	1/36 (2.8%)	0/34 (0.0%)	0/31 (0.0%)	2/38 (5.3%)
First incidence (days)	748 (T)	—	736	710
Poly-3 test	P=0.086	P=0.484N	P=0.753	P=0.339
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	23/49 (46.9%)	18/49 (36.7%)	13/48 (27.1%)	16/48 (33.3%)
Adjusted rate	23/42.5 (54.1%)	18/45.7 (39.4%)	13/41.7 (31.2%)	16/45.5 (35.2%)
Terminal rate	19/35 (54.3%)	13/34 (38.2%)	8/30 (26.7%)	12/37 (32.4%)
First incidence (days)	571	564	455	698
Poly-3 test	P=0.180N	P=0.118N	P=0.025N	P=0.055N
Skin: Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	2/51 (3.9%)	4/50 (8.0%)	1/50 (2.0%)	3/50 (6.0%)
Adjusted rate	2/43.2 (4.6%)	4/45.7 (8.8%)	1/42.5 (2.4%)	3/46.9 (6.4%)
Terminal rate	1/35 (2.9%)	1/34 (2.9%)	1/32 (3.1%)	2/38 (5.3%)
First incidence (days)	577	664	736 (T)	448
Poly-3 test	P=0.597	P=0.363	P=0.505N	P=0.537
Skin: All Neoplastic Morphologies				
Overall rate	3/51 (5.9%)	8/50 (16.0%)	5/50 (10.0%)	3/50 (6.0%)
Adjusted rate	3/43.2 (6.9%)	8/46.4 (17.2%)	5/43.2 (11.6%)	3/46.9 (6.4%)
Terminal rate	2/35 (5.7%)	3/34 (8.8%)	2/32 (6.3%)	2/38 (5.3%)
First incidence (days)	577	485	626	448
Poly-3 test	P=0.186N	P=0.122	P=0.356	P=0.624N

TABLE A2b
Statistical Analysis of Primary Neoplasms in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
All Organs: Benign Neoplasms				
Overall rate	26/54 (48.1%)	27/50 (54.0%)	16/50 (32.0%)	29/50 (58.0%)
Adjusted rate	26/45.9 (56.6%)	27/46.9 (57.6%)	16/44.1 (36.3%)	29/47.5 (61.0%)
Terminal rate	21/36 (58.3%)	19/34 (55.9%)	10/32 (31.3%)	23/38 (60.5%)
First incidence (days)	571	564	455	533
Poly-3 test	P=0.238	P=0.548	P=0.038N	P=0.412
All Organs: Malignant Neoplasms				
Overall rate	9/54 (16.7%)	8/50 (16.0%)	14/50 (28.0%)	9/50 (18.0%)
Adjusted rate	9/45.0 (20.0%)	8/46.5 (17.2%)	14/45.7 (30.6%)	9/48.2 (18.7%)
Terminal rate	7/36 (19.4%)	3/34 (8.8%)	7/32 (21.9%)	5/38 (13.2%)
First incidence (days)	274	485	361	448
Poly-3 test	P=0.459N	P=0.470N	P=0.177	P=0.539N
All Organs: Benign or Malignant Neoplasms				
Overall rate	32/54 (59.3%)	32/50 (64.0%)	29/50 (58.0%)	32/50 (64.0%)
Adjusted rate	32/46.9 (68.2%)	32/48.1 (66.5%)	29/47.3 (61.4%)	32/48.9 (65.5%)
Terminal rate	25/36 (69.4%)	20/34 (58.8%)	16/32 (50.0%)	24/38 (63.2%)
First incidence (days)	274	485	361	448
Poly-3 test	P=0.516N	P=0.520N	P=0.314N	P=0.474N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[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 control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.

TABLE A2c
Statistical Analysis of Primary Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/48 (8.3%)	3/46 (6.5%)	4/47 (8.5%)	2/45 (4.4%)
Adjusted rate[b]	4/41.7 (9.6%)	3/42.4 (7.1%)	4/41.0 (9.7%)	2/40.5 (4.9%)
Terminal rate[c]	4/33 (12.1%)	3/41 (7.3%)	3/33 (9.1%)	1/36 (2.8%)
First incidence (days)	753 (T)	751 (T)	701	712
Poly-3 test[d]	P=0.332N	P=0.492N	P=0.635	P=0.351N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	5/48 (10.4%)	3/46 (6.5%)	4/47 (8.5%)	2/45 (4.4%)
Adjusted rate	5/41.7 (12.0%)	3/42.4 (7.1%)	4/41.0 (9.7%)	2/40.5 (4.9%)
Terminal rate	5/33 (15.2%)	3/41 (7.3%)	3/33 (9.1%)	1/36 (2.8%)
First incidence (days)	753 (T)	751 (T)	701	712
Poly-3 test	P=0.269N	P=0.348N	P=0.511N	P=0.228N
Mammary Gland: Fibroma or Fibroadenoma				
Overall rate	0/39 (0.0%)	0/43 (0.0%)	0/41 (0.0%)	4/41 (9.8%)
Adjusted rate	0/37.1 (0.0%)	0/42.5 (0.0%)	0/37.4 (0.0%)	4/37.4 (10.7%)
Terminal rate	0/33 (0.0%)	0/42 (0.0%)	0/32 (0.0%)	4/34 (11.8%)
First incidence (days)	—[e]	—[f]	—	753 (T)
Poly-3 test	P=0.001	—	—	P=0.060
Pancreatic Islets: Adenoma				
Overall rate	3/45 (6.7%)	3/49 (6.1%)	2/48 (4.2%)	0/48 (0.0%)
Adjusted rate	3/39.8 (7.5%)	3/44.4 (6.8%)	2/42.0 (4.8%)	0/41.4 (0.0%)
Terminal rate	3/32 (9.4%)	3/42 (7.1%)	2/33 (6.1%)	0/36 (0.0%)
First incidence (days)	751 (T)	753 (T)	750 (T)	—
Poly-3 test	P=0.083N	P=0.612N	P=0.476N	P=0.111N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/45 (6.7%)	3/49 (6.1%)	3/48 (6.3%)	0/48 (0.0%)
Adjusted rate	3/39.8 (7.5%)	3/44.4 (6.8%)	3/42.0 (7.1%)	0/41.4 (0.0%)
Terminal rate	3/32 (9.4%)	3/42 (7.1%)	3/33 (9.1%)	0/36 (0.0%)
First incidence (days)	751 (T)	753 (T)	750 (T)	—
Poly-3 test	P=0.083N	P=0.612N	P=0.638N	P=0.111N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	17/49 (34.7%)	18/46 (39.1%)	17/48 (35.4%)	15/48 (31.3%)
Adjusted rate	17/44.8 (38.0%)	18/43.0 (41.8%)	17/42.4 (40.1%)	15/42.7 (35.1%)
Terminal rate	10/33 (30.3%)	17/41 (41.5%)	13/32 (40.6%)	12/36 (33.3%)
First incidence (days)	505	521	549	531
Poly-3 test	P=0.348N	P=0.440	P=0.505	P=0.479N
Preputial Gland: Squamous Cell Carcinoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	5/47 (10.6%)	3/47 (6.4%)
Adjusted rate	0/40.4 (0.0%)	0/43.9 (0.0%)	5/42.7 (11.7%)	3/42.5 (7.1%)
Terminal rate	0/33 (0.0%)	0/42 (0.0%)	1/33 (3.0%)	2/36 (5.6%)
First incidence (days)	—	—	644	600
Poly-3 test	P=0.151	—	P=0.035	P=0.127
Skin: Squamous Cell Carcinoma				
Overall rate	1/49 (2.0%)	0/50 (0.0%)	3/48 (6.3%)	0/49 (0.0%)
Adjusted rate	1/42.2 (2.4%)	0/45.2 (0.0%)	3/42.4 (7.1%)	0/42.0 (0.0%)
Terminal rate	0/33 (0.0%)	0/42 (0.0%)	1/33 (3.0%)	0/36 (0.0%)
First incidence (days)	661	—	644	—
Poly-3 test	P=0.415N	P=0.487N	P=0.307	P=0.501N

TABLE A2c
Statistical Analysis of Primary Neoplasms in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/49 (2.0%)	0/50 (0.0%)	3/48 (6.3%)	1/49 (2.0%)
Adjusted rate	1/42.2 (2.4%)	0/45.2 (0.0%)	3/42.4 (7.1%)	1/42.0 (2.4%)
Terminal rate	0/33 (0.0%)	0/42 (0.0%)	1/33 (3.0%)	1/36 (2.8%)
First incidence (days)	661	—	644	753 (T)
Poly-3 test	P=0.616	P=0.487N	P=0.307	P=0.760
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	2/49 (4.1%)	0/50 (0.0%)	3/48 (6.3%)	2/49 (4.1%)
Adjusted rate	2/42.2 (4.7%)	0/45.2 (0.0%)	3/42.4 (7.1%)	2/42.0 (4.8%)
Terminal rate	1/33 (3.0%)	0/42 (0.0%)	1/33 (3.0%)	2/36 (5.6%)
First incidence (days)	661	—	644	750 (T)
Poly-3 test	P=0.445	P=0.222N	P=0.502	P=0.692
Skin: All Neoplastic Morphologies				
Overall rate	3/49 (6.1%)	1/50 (2.0%)	4/48 (8.3%)	3/49 (6.1%)
Adjusted rate	3/42.3 (7.1%)	1/45.2 (2.2%)	4/42.4 (9.4%)	3/42.6 (7.0%)
Terminal rate	1/33 (3.0%)	1/42 (2.4%)	2/33 (6.1%)	2/36 (5.6%)
First incidence (days)	661	750 (T)	644	553
Poly-3 test	P=0.457	P=0.282N	P=0.502	P=0.660N
All Organs: Benign Neoplasms				
Overall rate	24/52 (46.2%)	21/50 (42.0%)	24/49 (49.0%)	21/49 (42.9%)
Adjusted rate	24/45.7 (52.6%)	21/45.8 (45.8%)	24/44.0 (54.6%)	21/43.0 (48.8%)
Terminal rate	17/33 (51.5%)	20/42 (47.6%)	18/33 (54.5%)	18/36 (50.0%)
First incidence (days)	505	521	549	531
Poly-3 test	P=0.511N	P=0.329N	P=0.510	P=0.443N
All Organs: Malignant Neoplasms				
Overall rate	11/52 (21.2%)	7/50 (14.0%)	12/49 (24.5%)	11/49 (22.4%)
Adjusted rate	11/44.9 (24.5%)	7/45.4 (15.4%)	12/43.6 (27.5%)	11/44.6 (24.6%)
Terminal rate	6/33 (18.2%)	6/42 (14.3%)	6/33 (18.2%)	5/36 (13.9%)
First incidence (days)	493	693	592	528
Poly-3 test	P=0.375	P=0.207N	P=0.468	P=0.591
All Organs: Benign or Malignant Neoplasms				
Overall rate	30/52 (57.7%)	25/50 (50.0%)	35/49 (71.4%)	29/49 (59.2%)
Adjusted rate	30/47.2 (63.6%)	25/46.0 (54.3%)	35/45.5 (76.9%)	29/45.5 (63.7%)
Terminal rate	19/33 (57.6%)	23/42 (54.8%)	24/33 (72.7%)	21/36 (58.3%)
First incidence (days)	493	521	549	528
Poly-3 test	P=0.460	P=0.240N	P=0.114	P=0.581

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

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	78	72	80
Early deaths				
Dead	10	4		7
Dead no CID		1	1	1
Discard		1		
Issue other	4	4	4	4
Missing	1	2	1	
Moribund	8	5	7	12
Surplus	38	20	16	25
Survey/sentinel	31			
Survivors				
Terminal sacrifice	36	41	43	31
Animals examined microscopically	54	50	50	50
Alimentary System				
Esophagus	(53)	(50)	(50)	(50)
Dilatation, marked				1 (2%)
Hyperkeratosis, mild	4 (8%)	1 (2%)		4 (8%)
Hyperkeratosis, minimal				3 (6%)
Intestine large, cecum	(44)	(46)	(50)	(46)
Autolysis, marked				1 (2%)
Hyperplasia, lymphoid, mild	2 (5%)		1 (2%)	1 (2%)
Polyarteritis, marked		1 (2%)		1 (2%)
Intestine large, colon	(46)	(46)	(50)	(46)
Autolysis, marked				1 (2%)
Hyperplasia, lymphoid, mild	1 (2%)		1 (2%)	
Hyperplasia, lymphoid, moderate				1 (2%)
Polyarteritis, moderate				1 (2%)
Intestine small, duodenum	(46)	(45)	(50)	(46)
Autolysis, marked				1 (2%)
Hemorrhage, mild				1 (2%)
Inflammation, suppurative, moderate				1 (2%)
Necrosis, mild				1 (2%)
Polyarteritis, moderate, serosa	1 (2%)			
Intestine small, ileum	(43)	(47)	(50)	(44)
Autolysis, moderate			1 (2%)	
Hyperplasia, lymphoid, mild	1 (2%)	1 (2%)	1 (2%)	
Polyarteritis, marked		1 (2%)		
Polyarteritis, mild				1 (2%)
Intestine small, jejunum	(44)	(45)	(50)	(43)
Autolysis, moderate			1 (2%)	
Hyperplasia, lymphoid, mild	2 (5%)		1 (2%)	
Polyarteritis, marked		1 (2%)		
Polyarteritis, mild				1 (2%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Animals initially in study refers to animals born into the study. Pups were randomly selected for continuation on the study and were necropsied in pathology if they survived to terminal sacrifice or died or became moribund prior to scheduled necropsy. All other pups were allocated to addenda studies or euthanized (Discard, Issue other, Surplus). In some cases, young pups that died were likely cannibalized by the dam and were thus indicated as Missing. Survey/sentinel animals were microbiological sentinels. Animals designated Dead no CID (carcass identification number) were animals that were not selected for continuation on study but died prior to weaning. Only animals processed by pathology received CIDs.

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Alimentary System (continued)				
Liver	(51)	(48)	(50)	(48)
Angiectasis, mild	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Angiectasis, minimal	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Angiectasis, moderate		1 (2%)		
Autolysis, marked	1 (2%)			
Autolysis, mild	2 (4%)			2 (4%)
Autolysis, moderate				1 (2%)
Basophilic focus	3 (6%)	5 (10%)	4 (8%)	5 (10%)
Basophilic focus, multiple		2 (4%)		1 (2%)
Cholangiofibrosis, moderate			1 (2%)	
Clear cell focus	1 (2%)	1 (2%)		
Clear cell focus, multiple		1 (2%)		1 (2%)
Cyst			2 (4%)	1 (2%)
Degeneration, cystic, mild	1 (2%)	3 (6%)	2 (4%)	
Degeneration, cystic, minimal	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Developmental malformation	1 (2%)	1 (2%)		
Eosinophilic focus	1 (2%)	1 (2%)	2 (4%)	
Eosinophilic focus, multiple	3 (6%)	4 (8%)		1 (2%)
Fibrosis, mild, biliary tract	2 (4%)	1 (2%)		1 (2%)
Fibrosis, mild, capsule	1 (2%)		1 (2%)	
Fibrosis, minimal, biliary tract	5 (10%)	12 (25%)	7 (14%)	15 (31%)
Fibrosis, minimal, capsule				1 (2%)
Granuloma, multiple, marked			1 (2%)	
Hematopoietic cell proliferation, minimal	1 (2%)			
Hemorrhage, mild	1 (2%)	1 (2%)		1 (2%)
Hemorrhage, mild, capsule		1 (2%)		
Hemorrhage, moderate		1 (2%)		
Hemorrhage, moderate, adventitia				1 (2%)
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)		3 (6%)
Hyperplasia, mild, bile duct	5 (10%)	3 (6%)	1 (2%)	4 (8%)
Hyperplasia, minimal, bile duct	12 (24%)	10 (21%)	8 (16%)	15 (31%)
Infiltration cellular, lymphocyte, mild	1 (2%)			
Infiltration cellular, lymphocyte, minimal	7 (14%)	2 (4%)	2 (4%)	8 (17%)
Inflammation, chronic active, mild	1 (2%)		1 (2%)	
Inflammation, chronic active, minimal	8 (16%)	7 (15%)	5 (10%)	6 (13%)
Inflammation, chronic, minimal, capsule			1 (2%)	
Mineralization, minimal	1 (2%)			
Necrosis, mild	1 (2%)			
Necrosis, minimal	2 (4%)		2 (4%)	3 (6%)
Necrosis, moderate			1 (2%)	
Pigmentation, minimal		1 (2%)		
Polyarteritis, marked		1 (2%)		1 (2%)
Tension lipidosis, minimal		1 (2%)		
Tension lipidosis, moderate	2 (4%)			1 (2%)
Vacuolization cytoplasmic, mild	3 (6%)	2 (4%)	3 (6%)	1 (2%)
Vacuolization cytoplasmic, minimal	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic, moderate			1 (2%)	
Mesentery	(1)	(1)		(1)
Necrosis, marked, fat		1 (100%)		1 (100%)
Necrosis, moderate, fat	1 (100%)			

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Alimentary System (continued)				
Pancreas	(50)	(49)	(50)	(49)
Autolysis, marked				1 (2%)
Autolysis, mild	1 (2%)			2 (4%)
Autolysis, moderate	2 (4%)			
Basophilic focus	1 (2%)		2 (4%)	
Degeneration, marked, acinar cell	4 (8%)		2 (4%)	2 (4%)
Degeneration, mild, acinar cell	13 (26%)	16 (33%)	16 (32%)	11 (22%)
Degeneration, minimal, acinar cell	11 (22%)	13 (27%)	8 (16%)	10 (20%)
Degeneration, moderate, acinar cell	5 (10%)	4 (8%)	8 (16%)	4 (8%)
Hyperplasia, marked, acinar cell			1 (2%)	
Hyperplasia, mild, acinar cell		1 (2%)		
Hyperplasia, moderate, acinar cell				1 (2%)
Infiltration cellular, lymphocyte, mild				1 (2%)
Infiltration cellular, lymphocyte, minimal	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic active, mild	1 (2%)			
Inflammation, chronic active, minimal	2 (4%)			
Inflammation, chronic, moderate				1 (2%)
Inflammation, granulomatous, mild	1 (2%)			
Pigmentation, mild		1 (2%)		
Pigmentation, minimal	2 (4%)			
Polyarteritis, marked				1 (2%)
Polyarteritis, moderate		1 (2%)		
Salivary glands	(49)	(49)	(50)	(47)
Hyperplasia, mild, acinar cell				1 (2%)
Mineralization, mild			1 (2%)	
Stomach, forestomach	(45)	(46)	(50)	(46)
Cyst, squamous	1 (2%)			
Hyperkeratosis, minimal		1 (2%)		
Hyperplasia, mild	1 (2%)	2 (4%)		
Hyperplasia, mild, epithelium			1 (2%)	
Inflammation, chronic active, mild	1 (2%)			
Keratin cyst			1 (2%)	
Polyarteritis, mild				1 (2%)
Ulcer, moderate		1 (2%)		
Stomach, glandular	(45)	(47)	(50)	(44)
Hyperplasia, marked, epithelium		1 (2%)		
Polyarteritis, mild				1 (2%)
Cardiovascular System				
Blood vessel	(53)	(50)	(50)	(50)
Polyarteritis, marked		1 (2%)		
Thrombosis, marked		1 (2%)		
Heart	(52)	(50)	(50)	(50)
Autolysis, marked	1 (2%)			1 (2%)
Cardiomyopathy, mild	3 (6%)	13 (26%)	11 (22%)	3 (6%)
Cardiomyopathy, minimal	10 (19%)	17 (34%)	17 (34%)	18 (36%)
Cardiomyopathy, moderate			1 (2%)	
Hyperplasia, minimal, epicardium	1 (2%)			
Metaplasia, osseous, minimal	1 (2%)		5 (10%)	
Mineralization, minimal	1 (2%)			
Polyarteritis, marked		1 (2%)		
Polyarteritis, mild				1 (2%)
Polyarteritis, minimal				1 (2%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System				
Adrenal cortex	(49)	(47)	(50)	(48)
Accessory adrenal cortical nodule	2 (4%)	2 (4%)		3 (6%)
Angiectasis, mild	1 (2%)		1 (2%)	1 (2%)
Angiectasis, minimal				1 (2%)
Atrophy, marked			2 (4%)	
Atrophy, moderate			1 (2%)	
Cyst		1 (2%)		1 (2%)
Degeneration, cystic, marked	1 (2%)			
Degeneration, cystic, mild		1 (2%)	1 (2%)	1 (2%)
Degeneration, cystic, minimal	1 (2%)		1 (2%)	1 (2%)
Degeneration, cystic, moderate	1 (2%)			
Fibrosis, mild, capsule			1 (2%)	
Hyperplasia, mild	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, minimal		4 (9%)	1 (2%)	1 (2%)
Hyperplasia, minimal, bilateral		1 (2%)		
Hyperplasia, moderate		1 (2%)		
Hypertrophy, mild		2 (4%)	7 (14%)	1 (2%)
Hypertrophy, minimal	2 (4%)	5 (11%)	1 (2%)	2 (4%)
Infiltration cellular, lymphocyte, mild			1 (2%)	
Pigmentation, mild			1 (2%)	1 (2%)
Vacuolization cytoplasmic, marked			1 (2%)	
Vacuolization cytoplasmic, mild	9 (18%)	7 (15%)	13 (26%)	5 (10%)
Vacuolization cytoplasmic, minimal	5 (10%)	18 (38%)	22 (44%)	8 (17%)
Adrenal medulla	(47)	(49)	(50)	(49)
Cyst	1 (2%)			
Hyperplasia, focal, minimal		1 (2%)		
Hyperplasia, marked		1 (2%)		
Hyperplasia, marked, bilateral	1 (2%)			
Hyperplasia, mild	3 (6%)	4 (8%)	3 (6%)	1 (2%)
Hyperplasia, minimal	2 (4%)	2 (4%)	7 (14%)	4 (8%)
Hyperplasia, minimal, bilateral	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, moderate	1 (2%)	1 (2%)	1 (2%)	
Islets, pancreatic	(49)	(49)	(50)	(49)
Hyperplasia, mild	5 (10%)	8 (16%)	4 (8%)	5 (10%)
Hyperplasia, minimal	16 (33%)	15 (31%)	12 (24%)	16 (33%)
Hyperplasia, moderate	2 (4%)		2 (4%)	
Parathyroid gland	(47)	(47)	(47)	(47)
Hyperplasia, mild	2 (4%)	4 (9%)	2 (4%)	1 (2%)
Hyperplasia, mild, bilateral	2 (4%)	4 (9%)	2 (4%)	
Hyperplasia, minimal	1 (2%)	2 (4%)	5 (11%)	1 (2%)
Hyperplasia, minimal, bilateral		1 (2%)		
Hyperplasia, moderate			1 (2%)	
Pituitary gland	(49)	(46)	(50)	(49)
Autolysis, moderate				1 (2%)
Cyst, multiple, pars distalis	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Cyst, multiple, pars intermedia	1 (2%)	1 (2%)		
Cyst, pars distalis	3 (6%)	6 (13%)	6 (12%)	5 (10%)
Cyst, pars intermedia			1 (2%)	
Hyperplasia, marked, pars distalis		1 (2%)		
Hyperplasia, mild, pars distalis	6 (12%)	7 (15%)	8 (16%)	8 (16%)
Hyperplasia, minimal, pars distalis	4 (8%)	4 (9%)	3 (6%)	4 (8%)
Hyperplasia, moderate, pars distalis	3 (6%)	5 (11%)		1 (2%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System (continued)				
Thyroid gland	(49)	(47)	(50)	(46)
Autolysis, marked				1 (2%)
Autolysis, mild	1 (2%)			
Cyst, squamous	7 (14%)	8 (17%)	4 (8%)	3 (7%)
Hyperplasia, mild, C-cell	2 (4%)			2 (4%)
Hyperplasia, minimal, C-cell	5 (10%)	1 (2%)	1 (2%)	6 (13%)
Hyperplasia, moderate, C-cell				1 (2%)
Infiltration cellular, lymphocyte, minimal	2 (4%)			
Inflammation, chronic, mild	1 (2%)			
Polyarteritis, moderate		1 (2%)		
Genital System				
Coagulating gland	(47)	(49)	(50)	(45)
Atrophy, marked	1 (2%)			
Atrophy, mild				1 (2%)
Atrophy, moderate	1 (2%)		2 (4%)	1 (2%)
Autolysis, moderate		1 (2%)		
Concretion		1 (2%)		
Degeneration, mild	1 (2%)			
Developmental malformation	4 (9%)	4 (8%)	4 (8%)	4 (9%)
Dilatation, moderate			1 (2%)	
Hyperplasia, mild	1 (2%)			
Infiltration cellular, lymphocyte, mild				1 (2%)
Inflammation, chronic, moderate, interstitium		1 (2%)		
Polyarteritis, moderate, adventitia		1 (2%)		
Epididymis	(51)	(48)	(50)	(49)
Atrophy, marked	1 (2%)			
Autolysis, mild	1 (2%)			
Degeneration, marked		1 (2%)		
Degeneration, mild	2 (4%)	1 (2%)	3 (6%)	4 (8%)
Degeneration, minimal		2 (4%)		2 (4%)
Degeneration, moderate			2 (4%)	1 (2%)
Granuloma sperm, marked		1 (2%)		
Hypospermia, marked	6 (12%)	4 (8%)	5 (10%)	4 (8%)
Hypospermia, mild	1 (2%)		1 (2%)	
Infiltration cellular, lymphocyte, minimal	4 (8%)	5 (10%)	1 (2%)	2 (4%)
Inflammation, chronic active, mild			1 (2%)	
Polyarteritis, mild			1 (2%)	
Polyarteritis, mild, adventitia		1 (2%)		
Polyarteritis, moderate				1 (2%)
Penis		(1)		
Concretion		1 (100%)		
Preputial gland	(49)	(48)	(49)	(49)
Abscess, marked			1 (2%)	3 (6%)
Atrophy, mild	1 (2%)			
Autolysis, marked		1 (2%)		
Autolysis, moderate	1 (2%)			1 (2%)
Cyst		1 (2%)		
Degeneration, marked, parenchymal cell	1 (2%)	1 (2%)	3 (6%)	
Degeneration, mild, parenchymal cell	6 (12%)	9 (19%)	14 (29%)	7 (14%)
Degeneration, minimal, parenchymal cell	8 (16%)	9 (19%)	9 (18%)	8 (16%)
Degeneration, moderate, parenchymal cell	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Dilatation, marked, duct	3 (6%)	2 (4%)	7 (14%)	5 (10%)
Dilatation, mild, duct		1 (2%)		

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Preputial gland (continued)	(49)	(48)	(49)	(49)
Dilatation, moderate, duct	1 (2%)	1 (2%)		
Foreign body			1 (2%)	
Infiltration cellular, lymphocyte, mild	6 (12%)	7 (15%)	6 (12%)	3 (6%)
Infiltration cellular, lymphocyte, minimal	13 (27%)	14 (29%)	14 (29%)	7 (14%)
Infiltration cellular, lymphocyte, moderate	2 (4%)		1 (2%)	
Inflammation, suppurative, marked	6 (12%)	4 (8%)	11 (22%)	11 (22%)
Inflammation, suppurative, mild	4 (8%)	4 (8%)	5 (10%)	7 (14%)
Inflammation, suppurative, minimal	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Inflammation, suppurative, moderate	4 (8%)	5 (10%)	3 (6%)	3 (6%)
Keratin cyst				1 (2%)
Necrosis, moderate			1 (2%)	
Prostate, dorsal	(48)	(49)	(50)	(49)
Autolysis, moderate		1 (2%)		1 (2%)
Cyst			2 (4%)	
Degeneration, mild	1 (2%)		4 (8%)	1 (2%)
Degeneration, minimal	1 (2%)			1 (2%)
Fibrosis, marked, interstitium		1 (2%)		
Hyperplasia, mild		1 (2%)		
Infiltration cellular, lymphocyte, mild		1 (2%)		
Infiltration cellular, lymphocyte, minimal	2 (4%)	3 (6%)	2 (4%)	
Inflammation, suppurative, marked	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Inflammation, suppurative, mild	17 (35%)	15 (31%)	23 (46%)	21 (43%)
Inflammation, suppurative, minimal	7 (15%)	10 (20%)	10 (20%)	5 (10%)
Inflammation, suppurative, moderate	6 (13%)	5 (10%)	7 (14%)	12 (24%)
Polyarteritis, marked		1 (2%)		
Polyarteritis, mild				2 (4%)
Prostate, ventral	(48)	(49)	(50)	(48)
Autolysis, moderate				1 (2%)
Degeneration, marked		2 (4%)	1 (2%)	
Degeneration, mild	6 (13%)	4 (8%)	6 (12%)	6 (13%)
Degeneration, minimal	4 (8%)	1 (2%)	2 (4%)	
Degeneration, moderate	3 (6%)	2 (4%)	4 (8%)	1 (2%)
Fibrosis, minimal, interstitium				1 (2%)
Fibrosis, moderate, interstitium		1 (2%)		
Hyperplasia, mild	6 (13%)	2 (4%)	3 (6%)	3 (6%)
Hyperplasia, minimal		2 (4%)	2 (4%)	4 (8%)
Hyperplasia, moderate	1 (2%)		3 (6%)	2 (4%)
Infiltration cellular, lymphocyte, mild	1 (2%)	1 (2%)	1 (2%)	
Infiltration cellular, lymphocyte, minimal	6 (13%)	3 (6%)	5 (10%)	4 (8%)
Inflammation, marked				1 (2%)
Inflammation, suppurative, marked	1 (2%)	1 (2%)	1 (2%)	
Inflammation, suppurative, mild	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, suppurative, minimal	2 (4%)	3 (6%)	2 (4%)	
Inflammation, suppurative, moderate	1 (2%)	1 (2%)		2 (4%)
Polyarteritis, mild				1 (2%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Seminal vesicle	(47)	(48)	(50)	(45)
Atrophy, marked	1 (2%)			1 (2%)
Atrophy, mild		2 (4%)	2 (4%)	2 (4%)
Atrophy, minimal		1 (2%)		
Atrophy, moderate	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Autolysis, marked	1 (2%)			
Autolysis, moderate		1 (2%)		
Dilatation, mild		1 (2%)	2 (4%)	2 (4%)
Dilatation, moderate		1 (2%)		
Fibrosis, mild			1 (2%)	
Hyperplasia, mild		2 (4%)	1 (2%)	
Hyperplasia, moderate		1 (2%)		
Inflammation, chronic, minimal			1 (2%)	
Inflammation, suppurative, mild		1 (2%)		
Testes	(51)	(50)	(50)	(49)
Autolysis, marked	1 (2%)			1 (2%)
Degeneration, marked, seminiferous tubule	11 (22%)	5 (10%)	8 (16%)	5 (10%)
Degeneration, mild, seminiferous tubule	4 (8%)	4 (8%)	3 (6%)	1 (2%)
Degeneration, minimal, seminiferous tubule	15 (29%)	16 (32%)	14 (28%)	11 (22%)
Degeneration, moderate, seminiferous tubule	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, moderate, interstitial cell	1 (2%)			
Mineralization, moderate, artery				1 (2%)
Polyarteritis, mild	2 (4%)			1 (2%)
Testes, rete testes	(44)	(47)	(47)	(44)
Dilatation, marked	1 (2%)			
Dilatation, mild	1 (2%)			1 (2%)
Dilatation, minimal	1 (2%)		2 (4%)	1 (2%)
Dilatation, moderate			1 (2%)	1 (2%)
Fibrosis, mild			1 (2%)	
Fibrosis, moderate	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Spermatocele, marked			1 (2%)	
Hematopoietic System				
Bone marrow	(49)	(49)	(50)	(48)
Autolysis, marked	1 (2%)	1 (2%)		
Hyperplasia, marked, myeloid cell				4 (8%)
Hyperplasia, mild, erythroid cell		2 (4%)	1 (2%)	1 (2%)
Hyperplasia, mild, myeloid cell	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Hyperplasia, minimal, myeloid cell				1 (2%)
Hyperplasia, moderate, erythroid cell				3 (6%)
Hyperplasia, moderate, myeloid cell	1 (2%)			1 (2%)
Hypocellularity, marked			1 (2%)	
Hypocellularity, mild	2 (4%)	1 (2%)		2 (4%)
Hypocellularity, moderate			1 (2%)	1 (2%)
Lymph node	(15)	(13)	(16)	(8)
Autolysis, marked, deep cervical	1 (7%)			
Autolysis, marked, lumbar	1 (7%)			
Autolysis, marked, renal	1 (7%)			
Degeneration, cystic, marked		1 (8%)		
Degeneration, cystic, marked, lumbar	4 (27%)	2 (15%)	5 (31%)	2 (25%)
Degeneration, cystic, mild, lumbar		1 (8%)		1 (13%)
Degeneration, cystic, moderate, lumbar	2 (13%)	1 (8%)	2 (13%)	1 (13%)
Hemorrhage, marked, renal, adventitia	1 (7%)			
Hemorrhage, moderate, lumbar	1 (7%)			

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node (continued)	(15)	(13)	(16)	(8)
Hyperplasia, lymphoid, marked, lumbar	2 (13%)			
Hyperplasia, lymphoid, mild, inguinal			1 (6%)	
Hyperplasia, lymphoid, mild, lumbar		2 (15%)	3 (19%)	
Hyperplasia, lymphoid, mild, pancreatic	1 (7%)	2 (15%)	1 (6%)	1 (13%)
Hyperplasia, lymphoid, mild, popliteal			1 (6%)	
Hyperplasia, lymphoid, mild, renal			1 (6%)	
Hyperplasia, lymphoid, moderate, lumbar	1 (7%)	1 (8%)	1 (6%)	
Hyperplasia, lymphoid, moderate, pancreatic		1 (8%)		
Hyperplasia, lymphoid, moderate, popliteal		1 (8%)		
Infiltration cellular, plasma cell, marked, inguinal			1 (6%)	
Infiltration cellular, plasma cell, marked, lumbar	6 (40%)	1 (8%)	8 (50%)	4 (50%)
Infiltration cellular, plasma cell, marked, mediastinal			1 (6%)	
Infiltration cellular, plasma cell, marked, popliteal		1 (8%)		1 (13%)
Infiltration cellular, plasma cell, marked, renal			1 (6%)	
Infiltration cellular, plasma cell, mild		1 (8%)		
Infiltration cellular, plasma cell, mild, inguinal			1 (6%)	
Infiltration cellular, plasma cell, mild, lumbar			1 (6%)	
Infiltration cellular, plasma cell, mild, pancreatic				1 (13%)
Infiltration cellular, plasma cell, mild, popliteal			1 (6%)	
Infiltration cellular, plasma cell, moderate, lumbar	1 (7%)	4 (31%)		
Infiltration cellular, plasma cell, moderate, mediastinal	1 (7%)	1 (8%)		
Infiltration cellular, plasma cell, moderate, pancreatic			1 (6%)	1 (13%)
Inflammation, granulomatous, mild, pancreatic	1 (7%)	1 (8%)		
Pigmentation, mild, renal	1 (7%)			
Polyarteritis, moderate, pancreatic, adventitia	1 (7%)			
Lymph node, mandibular	(52)	(50)	(49)	(46)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, mild				1 (2%)
Autolysis, moderate	2 (4%)			
Degeneration, cystic, marked	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Degeneration, cystic, mild			4 (8%)	3 (7%)
Degeneration, cystic, minimal	1 (2%)	1 (2%)	1 (2%)	
Degeneration, cystic, moderate	2 (4%)	2 (4%)	3 (6%)	3 (7%)
Hemorrhage, mild				1 (2%)
Hyperplasia, lymphoid, marked				2 (4%)
Hyperplasia, lymphoid, mild	12 (23%)	9 (18%)	8 (16%)	15 (33%)
Hyperplasia, lymphoid, minimal	4 (8%)			
Hyperplasia, lymphoid, moderate	7 (13%)	3 (6%)	5 (10%)	2 (4%)
Infiltration cellular, plasma cell, marked	4 (8%)	1 (2%)	2 (4%)	7 (15%)
Infiltration cellular, plasma cell, mild	14 (27%)	15 (30%)	14 (29%)	13 (28%)
Infiltration cellular, plasma cell, minimal	2 (4%)		2 (4%)	1 (2%)
Infiltration cellular, plasma cell, moderate	10 (19%)	5 (10%)	13 (27%)	12 (26%)
Pigmentation, mild				1 (2%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(50)	(50)	(46)
Autolysis, marked		1 (2%)		
Autolysis, mild				1 (2%)
Autolysis, moderate		1 (2%)		
Degeneration, cystic, marked	3 (6%)	4 (8%)	1 (2%)	3 (7%)
Degeneration, cystic, mild				1 (2%)
Degeneration, cystic, minimal				1 (2%)
Degeneration, cystic, moderate				1 (2%)
Hemorrhage, mild				1 (2%)
Hemorrhage, moderate			1 (2%)	
Hyperplasia, lymphoid, marked			1 (2%)	
Hyperplasia, lymphoid, mild	10 (21%)	3 (6%)	6 (12%)	9 (20%)
Hyperplasia, lymphoid, minimal	3 (6%)			1 (2%)
Hyperplasia, lymphoid, moderate	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Infiltration cellular, mast cell, mild	2 (4%)			2 (4%)
Infiltration cellular, plasma cell, marked		2 (4%)	2 (4%)	
Infiltration cellular, plasma cell, mild	3 (6%)	1 (2%)		1 (2%)
Infiltration cellular, plasma cell, moderate		1 (2%)		3 (7%)
Inflammation, granulomatous, marked	1 (2%)		1 (2%)	
Inflammation, granulomatous, mild	6 (13%)	10 (20%)	12 (24%)	9 (20%)
Inflammation, granulomatous, minimal	7 (15%)	6 (12%)	12 (24%)	6 (13%)
Inflammation, granulomatous, moderate		1 (2%)	2 (4%)	2 (4%)
Pigmentation, minimal	1 (2%)			
Polyarteritis, marked		1 (2%)		1 (2%)
Polyarteritis, mild				1 (2%)
Spleen	(52)	(48)	(50)	(48)
Accessory spleen	1 (2%)			
Autolysis, mild	1 (2%)			3 (6%)
Autolysis, moderate	2 (4%)			
Depletion lymphoid, marked				2 (4%)
Depletion lymphoid, mild			1 (2%)	
Fibrosis, mild, capsule	1 (2%)			1 (2%)
Hematopoietic cell proliferation, marked		1 (2%)		2 (4%)
Hematopoietic cell proliferation, mild	6 (12%)	3 (6%)	7 (14%)	2 (4%)
Hematopoietic cell proliferation, minimal	1 (2%)	4 (8%)		2 (4%)
Hematopoietic cell proliferation, moderate	1 (2%)	4 (8%)	1 (2%)	3 (6%)
Hyperplasia, lymphoid, marked		1 (2%)		
Hyperplasia, lymphoid, mild	1 (2%)		2 (4%)	1 (2%)
Hyperplasia, lymphoid, minimal	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, lymphoid, moderate				1 (2%)
Hyperplasia, marked, red pulp			1 (2%)	
Hyperplasia, stromal, moderate				1 (2%)
Pigmentation, marked	3 (6%)	2 (4%)	4 (8%)	5 (10%)
Pigmentation, mild	14 (27%)	15 (31%)	10 (20%)	16 (33%)
Pigmentation, minimal	6 (12%)	7 (15%)	3 (6%)	2 (4%)
Pigmentation, moderate	7 (13%)	6 (13%)	7 (14%)	8 (17%)
Polyarteritis, moderate, adventitia				1 (2%)
Thymus	(42)	(44)	(45)	(42)
Atrophy, marked	31 (74%)	39 (89%)	39 (87%)	35 (83%)
Atrophy, mild			2 (4%)	2 (5%)
Atrophy, minimal	1 (2%)			
Atrophy, moderate	4 (10%)	2 (5%)	2 (4%)	2 (5%)
Autolysis, marked		1 (2%)		1 (2%)
Hemorrhage, moderate				1 (2%)
Hyperplasia, lymphoid, marked	1 (2%)			
Polyarteritis, moderate, adventitia		1 (2%)		

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Integumentary System				
Mammary gland	(41)	(43)	(40)	(42)
Autolysis, moderate	1 (2%)			
Degeneration, marked	5 (12%)	6 (14%)	3 (8%)	5 (12%)
Degeneration, mild	8 (20%)	7 (16%)	2 (5%)	5 (12%)
Degeneration, minimal	3 (7%)	2 (5%)	2 (5%)	1 (2%)
Degeneration, moderate	5 (12%)	9 (21%)	5 (13%)	3 (7%)
Dilatation, marked, duct	1 (2%)			1 (2%)
Dilatation, mild, duct			1 (3%)	2 (5%)
Dilatation, moderate, duct		2 (5%)	2 (5%)	
Galactocele, marked		1 (2%)	1 (3%)	
Hemorrhage, marked		1 (2%)		
Hyperplasia, mild, alveolus	2 (5%)	1 (2%)	2 (5%)	1 (2%)
Hyperplasia, minimal, alveolus	1 (2%)	1 (2%)	3 (8%)	6 (14%)
Hyperplasia, moderate, alveolus			1 (3%)	1 (2%)
Inflammation, granulomatous, marked		1 (2%)		
Inflammation, suppurative, mild		1 (2%)		
Lactation, mild	3 (7%)	1 (2%)	3 (8%)	7 (17%)
Skin	(51)	(49)	(50)	(50)
Abscess, marked	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Angiectasis, mild			1 (2%)	
Angiectasis, moderate				1 (2%)
Autolysis, moderate	1 (2%)			
Cyst		1 (2%)		
Cyst epithelial inclusion	2 (4%)		2 (4%)	2 (4%)
Fibrosis, marked		1 (2%)		
Fibrosis, moderate	1 (2%)			
Foreign body				1 (2%)
Hemorrhage, mild		1 (2%)	1 (2%)	
Hyperkeratosis, mild	5 (10%)	1 (2%)	1 (2%)	1 (2%)
Hyperkeratosis, moderate		1 (2%)	1 (2%)	
Hyperplasia, mild, epidermis	4 (8%)			1 (2%)
Hyperplasia, moderate, epidermis	1 (2%)	2 (4%)	2 (4%)	
Inflammation, chronic active, marked		3 (6%)	1 (2%)	
Inflammation, chronic active, mild	4 (8%)		3 (6%)	1 (2%)
Inflammation, chronic active, minimal			1 (2%)	
Inflammation, chronic active, moderate	3 (6%)	5 (10%)	2 (4%)	4 (8%)
Inflammation, chronic, mild	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic, minimal	1 (2%)	1 (2%)		
Inflammation, pyogranulomatous, marked	1 (2%)			1 (2%)
Inflammation, suppurative, marked	20 (39%)	19 (39%)	23 (46%)	16 (32%)
Inflammation, suppurative, mild			1 (2%)	1 (2%)
Inflammation, suppurative, moderate	2 (4%)	2 (4%)	5 (10%)	2 (4%)
Necrosis, marked		1 (2%)		1 (2%)
Necrosis, mild	2 (4%)		1 (2%)	3 (6%)
Necrosis, moderate	2 (4%)	1 (2%)		
Ulcer, marked, epidermis	1 (2%)			
Musculoskeletal System				
Bone, femur	(53)	(50)	(50)	(50)
Hyperostosis, mild	1 (2%)			
Necrosis, marked			1 (2%)	

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Nervous System				
Brain, brain stem	(50)	(48)	(50)	(48)
Autolysis, moderate	1 (2%)			
Compression, marked				1 (2%)
Compression, mild	5 (10%)	3 (6%)	4 (8%)	1 (2%)
Compression, minimal	2 (4%)			1 (2%)
Compression, moderate			1 (2%)	2 (4%)
Hemorrhage, mild				1 (2%)
Hemorrhage, minimal	1 (2%)			
Brain, cerebellum	(50)	(48)	(50)	(47)
Autolysis, moderate	1 (2%)			
Gliosis, minimal	1 (2%)			
Hemorrhage, marked				1 (2%)
Hemorrhage, minimal	1 (2%)			
Hemorrhage, moderate				1 (2%)
Hydrocephalus, marked	1 (2%)			
Hydrocephalus, minimal			1 (2%)	
Hydrocephalus, moderate		1 (2%)		
Brain, cerebrum	(50)	(48)	(50)	(48)
Autolysis, moderate	1 (2%)			
Congestion, moderate, meninges	1 (2%)			
Hemorrhage, mild				1 (2%)
Hemorrhage, moderate, meninges	1 (2%)			
Hydrocephalus, marked	1 (2%)			
Hydrocephalus, mild	1 (2%)			2 (4%)
Hydrocephalus, minimal			1 (2%)	1 (2%)
Hydrocephalus, moderate	1 (2%)	1 (2%)		
Infiltration cellular, lymphocyte, mild				1 (2%)
Mineralization, mild				1 (2%)
Respiratory System				
Lung	(49)	(47)	(50)	(47)
Autolysis, marked	1 (2%)			
Autolysis, moderate				2 (4%)
Cyst	1 (2%)			
Edema, moderate	1 (2%)			
Fibrosis, minimal, pleura			1 (2%)	
Hemorrhage, marked	1 (2%)		1 (2%)	
Hemorrhage, mild	1 (2%)			
Hemorrhage, moderate	1 (2%)			
Hyperplasia, lymphoid, mild, peribronchial				1 (2%)
Hyperplasia, marked, alveolar epithelium			2 (4%)	
Hyperplasia, mild, alveolar epithelium		1 (2%)	2 (4%)	
Hyperplasia, minimal, alveolar epithelium	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, minimal, pleura			1 (2%)	
Hyperplasia, moderate, alveolar epithelium	1 (2%)	1 (2%)		
Infiltration cellular, histiocyte, marked			2 (4%)	
Infiltration cellular, histiocyte, mild	5 (10%)	11 (23%)	8 (16%)	5 (11%)
Infiltration cellular, histiocyte, minimal	8 (16%)	6 (13%)	10 (20%)	11 (23%)
Infiltration cellular, histiocyte, moderate	2 (4%)	2 (4%)		
Infiltration cellular, histiocytic, mild		1 (2%)		
Infiltration cellular, lymphocyte, minimal	1 (2%)		1 (2%)	
Inflammation, chronic, mild		1 (2%)		
Inflammation, chronic, minimal, pleura			1 (2%)	
Inflammation, suppurative, moderate				1 (2%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Respiratory System (continued)				
Lung (continued)	(49)	(47)	(50)	(47)
Metaplasia, osseous, mild		1 (2%)		
Metaplasia, osseous, minimal	2 (4%)	2 (4%)	6 (12%)	3 (6%)
Mineralization, mild, artery	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Mineralization, minimal, artery	1 (2%)	5 (11%)	6 (12%)	8 (17%)
Pigmentation, minimal				1 (2%)
Polyarteritis, mild				2 (4%)
Nose	(48)	(48)	(50)	(48)
Autolysis, moderate	1 (2%)			1 (2%)
Foreign body			1 (2%)	
Hemorrhage, moderate	1 (2%)			
Hyperkeratosis, mild	1 (2%)			
Hyperplasia, mild, squamous epithelium	1 (2%)			
Hyperplasia, moderate, squamous epithelium	1 (2%)			
Inflammation, chronic active, mild	1 (2%)		1 (2%)	
Inflammation, chronic active, mild, upper molar	2 (4%)			1 (2%)
Inflammation, chronic active, minimal		1 (2%)		
Inflammation, chronic active, minimal, upper molar				1 (2%)
Inflammation, suppurative, marked				1 (2%)
Inflammation, suppurative, mild	2 (4%)		2 (4%)	2 (4%)
Inflammation, suppurative, minimal		1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative, moderate	1 (2%)			
Keratin cyst	1 (2%)			1 (2%)
Metaplasia, mild, squamous epithelium	1 (2%)			
Metaplasia, osseous, minimal				1 (2%)
Ulcer, moderate	1 (2%)			
Trachea	(47)	(47)	(50)	(46)
Hyperplasia, mild, epithelium				1 (2%)
Special Senses System				
Eye	(37)	(42)	(43)	(35)
Atrophy, mild, bilateral, retina	4 (11%)	4 (10%)	9 (21%)	2 6%)
Atrophy, mild, retina	3 (8%)	2 (5%)	1 (2%)	
Atrophy, minimal, bilateral, retina	1 (3%)		1 (2%)	4 (11%)
Atrophy, minimal, retina	2 (5%)			1 (3%)
Atrophy, moderate, bilateral, retina	1 (3%)			
Cataract, minimal				1 (3%)
Cataract, moderate				1 (3%)
Inflammation, chronic active, mild				1 (3%)
Inflammation, chronic, mild	1 (3%)			
Inflammation, suppurative, marked				1 (3%)
Harderian gland	(39)	(42)	(43)	(37)
Degeneration, mild			1 (2%)	
Degeneration, minimal	1 (3%)	2 (5%)		1 (3%)
Infiltration cellular, lymphocyte, mild	2 (5%)	2 (5%)		
Infiltration cellular, lymphocyte, minimal	3 (8%)	3 (7%)	3 (7%)	4 (11%)
Pigmentation, marked				1 (3%)
Lacrimal gland	(10)	(9)	(10)	(14)
Ectopic harderian	10 (100%)	9 (100%)	10 (100%)	14 (100%)

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Urinary System				
Kidney	(48)	(48)	(50)	(48)
Accumulation, hyaline droplet, marked	1 (2%)			1 (2%)
Autolysis, marked				2 (4%)
Autolysis, mild	1 (2%)			1 (2%)
Autolysis, moderate		1 (2%)		1 (2%)
Bacterium, marked		1 (2%)		
Congestion, mild	1 (2%)			
Cyst, cortex	24 (50%)	26 (54%)	22 (44%)	29 (60%)
Cyst, medulla	1 (2%)			
Dilatation, marked, pelvis				1 (2%)
Dilatation, mild, renal tubule	1 (2%)			2 (4%)
Dilatation, minimal, pelvis	1 (2%)			
Dilatation, minimal, renal tubule	1 (2%)			
Dilatation, moderate, pelvis	1 (2%)			
Dilatation, moderate, renal tubule	1 (2%)			
Fatty change, capsule		1 (2%)	3 (6%)	2 (4%)
Fatty change, mild			1 (2%)	
Fibrosis, mild, capsule		1 (2%)		
Fibrosis, minimal				1 (2%)
Hyperplasia, mild, pelvis	4 (8%)	2 (4%)	4 (8%)	2 (4%)
Hyperplasia, minimal, pelvis	1 (2%)	2 (4%)	2 (4%)	
Hyperplasia, tubular, minimal	1 (2%)			
Hyperplasia, tubular, moderate			2 (4%)	
Infiltration cellular, lymphocyte, mild			1 (2%)	
Infiltration cellular, lymphocyte, minimal			1 (2%)	5 (10%)
Inflammation, chronic, minimal	1 (2%)	1 (2%)		1 (2%)
Inflammation, suppurative, mild, renal tubule	1 (2%)		1 (2%)	1 (2%)
Inflammation, suppurative, moderate		1 (2%)		
Mineralization, mild			1 (2%)	
Mineralization, mild, pelvis		1 (2%)	1 (2%)	
Mineralization, mild, renal tubule				3 (6%)
Mineralization, minimal, renal tubule	1 (2%)			1 (2%)
Nephropathy, chronic, marked	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Nephropathy, chronic, mild	7 (15%)	12 (25%)	14 (28%)	15 (31%)
Nephropathy, chronic, minimal	29 (60%)	26 (54%)	23 (46%)	16 (33%)
Nephropathy, chronic, moderate	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Polyarteritis, mild				1 (2%)
Urinary bladder	(47)	(48)	(50)	(46)
Autolysis, marked				1 (2%)
Dilatation, marked		1 (2%)	1 (2%)	
Hemorrhage, mild	1 (2%)			1 (2%)
Hemorrhage, minimal				1 (2%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	50	50	50
Early deaths				
Dead	10	7	7	7
Issue other	4			
Missing	1			
Moribund	8	9	11	5
Surplus	38			
Survey/sentinel	31			
Survivors				
Terminal sacrifice	36	34	32	38
Animals examined microscopically	54	50	50	50
Alimentary System				
Esophagus	(53)	(50)	(47)	(49)
Hyperkeratosis, mild	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Hyperkeratosis, minimal		1 (2%)		
Hyperkeratosis, moderate				1 (2%)
Intestine large, cecum	(44)	(45)	(42)	(44)
Hyperplasia, lymphoid, mild	2 (5%)		1 (2%)	2 (5%)
Intestine large, colon	(46)	(45)	(43)	(46)
Autolysis, marked				1 (2%)
Hyperplasia, lymphoid, mild	1 (2%)			2 (4%)
Inflammation, suppurative, marked				1 (2%)
Polyarteritis, moderate				1 (2%)
Intestine small, duodenum	(46)	(45)	(43)	(45)
Polyarteritis, moderate, serosa	1 (2%)			
Intestine small, ileum	(43)	(44)	(42)	(43)
Hyperplasia, lymphoid, mild	1 (2%)			2 (5%)
Intestine small, jejunum	(44)	(42)	(42)	(42)
Hyperplasia, lymphoid, mild	2 (5%)			
Liver	(51)	(49)	(47)	(48)
Angiectasis, mild	1 (2%)	4 (8%)	3 (6%)	6 (13%)
Angiectasis, minimal	1 (2%)			1 (2%)
Angiectasis, moderate			1 (2%)	
Autolysis, marked	1 (2%)			
Autolysis, mild	2 (4%)	1 (2%)		
Autolysis, moderate		1 (2%)	1 (2%)	
Basophilic focus	3 (6%)	2 (4%)	4 (9%)	1 (2%)
Clear cell focus	1 (2%)			
Clear cell focus, multiple		1 (2%)	1 (2%)	
Cyst			1 (2%)	1 (2%)
Degeneration, cystic, mild	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Degeneration, cystic, minimal	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Developmental malformation	1 (2%)	1 (2%)		
Eosinophilic focus	1 (2%)		3 (6%)	1 (2%)
Eosinophilic focus, multiple	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Fatty change, mild		1 (2%)		
Fibrosis, mild, biliary tract	2 (4%)	1 (2%)		
Fibrosis, mild, capsule	1 (2%)			1 (2%)
Fibrosis, minimal, biliary tract	5 (10%)	11 (22%)	9 (19%)	9 (19%)
Hematopoietic cell proliferation, minimal	1 (2%)		1 (2%)	2 (4%)
Hemorrhage, mild	1 (2%)			1 (2%)
Hepatodiaphragmatic nodule	2 (4%)		2 (4%)	2 (4%)

The footnotes for this table are defined in Table A3a.

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm		5 ppm		100 ppm		500 ppm	
Alimentary System (continued)								
Liver (continued)	(51)		(49)		(47)		(48)	
Hyperplasia, minimal, bile duct	12	(24%)	12	(24%)	6	(13%)	10	(21%)
Infiltration cellular, lymphocyte, mild	1	(2%)						
Infiltration cellular, lymphocyte, minimal	7	(14%)	1	(2%)	3	(6%)	7	(15%)
Inflammation, chronic active, mild	1	(2%)			1	(2%)		
Inflammation, chronic active, minimal	8	(16%)	6	(12%)	8	(17%)	10	(21%)
Mineralization, minimal	1	(2%)						
Mixed cell focus							1	(2%)
Necrosis, mild	1	(2%)						
Necrosis, minimal	2	(4%)			3	(6%)	4	(8%)
Tension lipidosis, moderate	2	(4%)	1	(2%)	1	(2%)		
Vacuolization cytoplasmic, mild	3	(6%)	1	(2%)	2	(4%)	2	(4%)
Vacuolization cytoplasmic, minimal	2	(4%)	2	(4%)	3	(6%)	2	(4%)
Mesentery	(1)		(1)		(1)		(1)	
Inflammation, chronic, minimal, fat							1	(100%)
Necrosis, marked, fat			1	(100%)				
Necrosis, moderate, fat	1	(100%)			1	(100%)		
Pancreas	(50)		(49)		(46)		(48)	
Accessory spleen					1	(2%)		
Autolysis, marked							1	(2%)
Autolysis, mild	1	(2%)			1	(2%)	1	(2%)
Autolysis, moderate	2	(4%)	2	(4%)				
Basophilic focus	1	(2%)						
Degeneration, marked, acinar cell	4	(8%)					2	(4%)
Degeneration, mild, acinar cell	13	(26%)	14	(29%)	16	(35%)	14	(29%)
Degeneration, minimal, acinar cell	11	(22%)	11	(22%)	11	(24%)	11	(23%)
Degeneration, moderate, acinar cell	5	(10%)	7	(14%)	6	(13%)	3	(6%)
Infiltration cellular, lymphocyte, minimal	1	(2%)						
Inflammation, chronic active, mild	1	(2%)			1	(2%)		
Inflammation, chronic active, minimal	2	(4%)						
Inflammation, chronic, mild					2	(4%)		
Inflammation, granulomatous, mild	1	(2%)						
Pigmentation, mild							1	(2%)
Pigmentation, minimal	2	(4%)	1	(2%)	2	(4%)	1	(2%)
Polyarteritis, marked							1	(2%)
Polyarteritis, mild, adventitia					1	(2%)		
Salivary glands	(49)		(49)		(46)		(50)	
Atrophy, moderate			1	(2%)				
Hyperplasia, lymphoid, marked			1	(2%)				
Hyperplasia, mild, acinar cell			1	(2%)				
Stomach, forestomach	(45)		(47)		(45)		(49)	
Cyst, squamous	1	(2%)						
Edema, moderate, submucosa			1	(2%)				
Hyperplasia, mild	1	(2%)						
Inflammation, chronic active, mild	1	(2%)						

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Cardiovascular System				
Heart	(52)	(48)	(48)	(50)
Autolysis, marked	1 (2%)			
Autolysis, mild			1 (2%)	
Bacterium, marked				1 (2%)
Cardiomyopathy, mild	3 (6%)	3 (6%)	5 (10%)	4 (8%)
Cardiomyopathy, minimal	10 (19%)	18 (38%)	22 (46%)	12 (24%)
Cardiomyopathy, moderate		2 (4%)		
Hyperplasia, mild, endocardium			1 (2%)	
Hyperplasia, minimal, epicardium	1 (2%)			
Inflammation, chronic active, mild, endocardium			1 (2%)	
Inflammation, suppurative, marked				1 (2%)
Metaplasia, osseous, minimal	1 (2%)	2 (4%)		
Mineralization, minimal	1 (2%)			
Necrosis, marked, myocardium				1 (2%)
Polyarteritis, mild		1 (2%)		
Thrombosis			1 (2%)	
Thrombosis, marked				1 (2%)
Endocrine System				
Adrenal cortex	(49)	(47)	(46)	(46)
Accessory adrenal cortical nodule	2 (4%)		3 (7%)	1 (2%)
Angiectasis, mild	1 (2%)	2 (4%)		1 (2%)
Atrophy, marked				1 (2%)
Autolysis, moderate		1 (2%)		
Degeneration, cystic, marked	1 (2%)			1 (2%)
Degeneration, cystic, mild		1 (2%)	5 (11%)	3 (7%)
Degeneration, cystic, minimal	1 (2%)		1 (2%)	2 (4%)
Degeneration, cystic, moderate	1 (2%)			1 (2%)
Fibrosis, minimal, capsule		1 (2%)		
Hyperplasia, mild	2 (4%)	2 (4%)	1 (2%)	
Hyperplasia, minimal		1 (2%)	2 (4%)	1 (2%)
Hyperplasia, moderate		2 (4%)		
Hypertrophy, marked				1 (2%)
Hypertrophy, mild		4 (9%)	4 (9%)	2 (4%)
Hypertrophy, minimal	2 (4%)	2 (4%)	3 (7%)	
Metaplasia, osseous, moderate			1 (2%)	
Pigmentation, mild				1 (2%)
Vacuolization cytoplasmic, marked			1 (2%)	
Vacuolization cytoplasmic, mild	9 (18%)	7 (15%)	13 (28%)	9 (20%)
Vacuolization cytoplasmic, minimal	5 (10%)	19 (40%)	6 (13%)	8 (17%)
Vacuolization cytoplasmic, moderate			2 (4%)	
Adrenal medulla	(47)	(47)	(46)	(45)
Cyst	1 (2%)			
Hemorrhage, marked				1 (2%)
Hyperplasia, marked, bilateral	1 (2%)			
Hyperplasia, mild	3 (6%)	3 (6%)	4 (9%)	1 (2%)
Hyperplasia, minimal	2 (4%)	3 (6%)		1 (2%)
Hyperplasia, minimal, bilateral	1 (2%)		1 (2%)	
Hyperplasia, moderate	1 (2%)		1 (2%)	
Infiltration cellular, lymphocyte, mild			1 (2%)	
Vacuolization cytoplasmic, mild			1 (2%)	

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System (continued)				
Islets, pancreatic	(49)	(49)	(46)	(48)
Autolysis, marked				1 (2%)
Hyperplasia, mild	5 (10%)	3 (6%)	5 (11%)	3 (6%)
Hyperplasia, minimal	16 (33%)	16 (33%)	9 (20%)	19 (40%)
Hyperplasia, moderate	2 (4%)		1 (2%)	1 (2%)
Parathyroid gland	(47)	(48)	(47)	(46)
Hyperplasia, mild	2 (4%)	5 (10%)	2 (4%)	5 (11%)
Hyperplasia, mild, bilateral	2 (4%)		1 (2%)	
Hyperplasia, minimal	1 (2%)	4 (8%)	6 (13%)	
Hyperplasia, minimal, bilateral		1 (2%)		
Hyperplasia, moderate				1 (2%)
Hyperplasia, moderate, bilateral			1 (2%)	
Pituitary gland	(49)	(49)	(48)	(48)
Autolysis, marked		1 (2%)	3 (6%)	
Autolysis, mild		1 (2%)		
Cyst, multiple, pars distalis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Cyst, multiple, pars intermedia	1 (2%)			
Cyst, pars distalis	3 (6%)	6 (12%)	3 (6%)	4 (8%)
Hyperplasia, marked, pars distalis				1 (2%)
Hyperplasia, mild, pars distalis	6 (12%)	8 (16%)	11 (23%)	8 (17%)
Hyperplasia, mild, pars intermedia			1 (2%)	
Hyperplasia, minimal, pars distalis	4 (8%)	8 (16%)	6 (13%)	3 (6%)
Hyperplasia, moderate, pars distalis	3 (6%)	3 (6%)	2 (4%)	8 (17%)
Thyroid gland	(49)	(46)	(44)	(48)
Autolysis, mild	1 (2%)			
Cyst, follicular cell		2 (4%)		
Cyst, squamous	7 (14%)	2 (4%)	4 (9%)	2 (4%)
Hyperplasia, mild, C-cell	2 (4%)	2 (4%)		3 (6%)
Hyperplasia, minimal, C-cell	5 (10%)			2 (4%)
Hyperplasia, moderate, follicular cell		1 (2%)		
Infiltration cellular, lymphocyte, minimal	2 (4%)			
Inflammation, chronic, mild	1 (2%)			
Vacuolization cytoplasmic, moderate			2 (5%)	
Genital System				
Coagulating gland	(47)	(45)	(45)	(47)
Atrophy, marked	1 (2%)			1 (2%)
Atrophy, mild		3 (7%)	3 (7%)	4 (9%)
Atrophy, moderate	1 (2%)			
Autolysis, mild		1 (2%)		1 (2%)
Degeneration, mild	1 (2%)			
Degeneration, moderate				1 (2%)
Developmental malformation	4 (9%)	2 (4%)	4 (9%)	2 (4%)
Hyperplasia, mild	1 (2%)	1 (2%)		
Inflammation, suppurative, marked			1 (2%)	2 (4%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Epididymis	(51)	(50)	(47)	(49)
Atrophy, marked	1 (2%)			
Atrophy, moderate				1 (2%)
Autolysis, mild	1 (2%)			
Degeneration, marked			1 (2%)	
Degeneration, mild	2 (4%)		3 (6%)	3 (6%)
Degeneration, minimal			1 (2%)	1 (2%)
Degeneration, moderate		1 (2%)		1 (2%)
Granuloma sperm, marked				1 (2%)
Hypospermia, marked	6 (12%)	1 (2%)	7 (15%)	4 (8%)
Hypospermia, mild	1 (2%)			
Infiltration cellular, lymphocyte, mild			1 (2%)	
Infiltration cellular, lymphocyte, minimal	4 (8%)	1 (2%)	3 (6%)	1 (2%)
Inflammation, suppurative, marked			1 (2%)	
Polyarteritis, mild				1 (2%)
Penis		(1)		
Concretion		1 (100%)		
Hemorrhage, minimal		1 (100%)		
Preputial gland	(49)	(50)	(48)	(49)
Abscess, marked		1 (2%)	1 (2%)	1 (2%)
Atrophy, mild	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Atrophy, moderate		1 (2%)		
Autolysis, marked			1 (2%)	
Autolysis, moderate	1 (2%)			
Degeneration, marked, parenchymal cell	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Degeneration, mild, parenchymal cell	6 (12%)	10 (20%)	8 (17%)	10 (20%)
Degeneration, minimal, parenchymal cell	8 (16%)	7 (14%)	9 (19%)	4 (8%)
Degeneration, moderate, parenchymal cell	1 (2%)	2 (4%)	3 (6%)	
Dilatation, marked, duct	3 (6%)	4 (8%)	2 (4%)	3 (6%)
Dilatation, mild, duct		1 (2%)		
Dilatation, moderate, duct	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Infiltration cellular, lymphocyte, mild	6 (12%)	8 (16%)	7 (15%)	6 (12%)
Infiltration cellular, lymphocyte, minimal	13 (27%)	7 (14%)	9 (19%)	9 (18%)
Infiltration cellular, lymphocyte, moderate	2 (4%)			
Inflammation, chronic active, minimal				1 (2%)
Inflammation, chronic active, moderate				1 (2%)
Inflammation, chronic, mild			1 (2%)	
Inflammation, suppurative, marked	6 (12%)	9 (18%)	10 (21%)	10 (20%)
Inflammation, suppurative, mild	4 (8%)	5 (10%)	8 (17%)	
Inflammation, suppurative, minimal	1 (2%)		1 (2%)	3 (6%)
Inflammation, suppurative, moderate	4 (8%)	6 (12%)	3 (6%)	3 (6%)
Prostate, dorsal	(48)	(49)	(50)	(49)
Autolysis, marked		1 (2%)	3 (6%)	
Autolysis, mild				1 (2%)
Autolysis, moderate		1 (2%)	1 (2%)	1 (2%)
Cyst				2 (4%)
Degeneration, mild	1 (2%)	1 (2%)	1 (2%)	
Degeneration, minimal	1 (2%)			1 (2%)
Degeneration, moderate			1 (2%)	
Infiltration cellular, lymphocyte, minimal	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative, marked	1 (2%)	2 (4%)	4 (8%)	4 (8%)
Inflammation, suppurative, mild	17 (35%)	17 (35%)	25 (50%)	22 (45%)
Inflammation, suppurative, minimal	7 (15%)	7 (14%)	8 (16%)	9 (18%)
Inflammation, suppurative, moderate	6 (13%)	8 (16%)	3 (6%)	5 (10%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Prostate, ventral	(48)	(49)	(48)	(48)
Autolysis, marked		1 (2%)	2 (4%)	
Autolysis, mild		1 (2%)		1 (2%)
Autolysis, moderate		1 (2%)		1 (2%)
Degeneration, mild	6 (13%)	2 (4%)	4 (8%)	4 (8%)
Degeneration, minimal	4 (8%)	2 (4%)		
Degeneration, moderate	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Hyperplasia, marked		2 (4%)		
Hyperplasia, mild	6 (13%)	4 (8%)	2 (4%)	7 (15%)
Hyperplasia, minimal		2 (4%)	2 (4%)	4 (8%)
Hyperplasia, moderate	1 (2%)	1 (2%)		
Infiltration cellular, lymphocyte, marked			1 (2%)	
Infiltration cellular, lymphocyte, mild	1 (2%)		1 (2%)	
Infiltration cellular, lymphocyte, minimal	6 (13%)	6 (12%)	2 (4%)	4 (8%)
Inflammation, suppurative, marked	1 (2%)	2 (4%)	2 (4%)	
Inflammation, suppurative, mild	2 (4%)		3 (6%)	2 (4%)
Inflammation, suppurative, minimal	2 (4%)	4 (8%)	4 (8%)	5 (10%)
Inflammation, suppurative, moderate	1 (2%)		1 (2%)	
Seminal vesicle	(47)	(43)	(45)	(47)
Atrophy, marked	1 (2%)			1 (2%)
Atrophy, mild		2 (5%)	1 (2%)	5 (11%)
Atrophy, moderate	2 (4%)		2 (4%)	3 (6%)
Autolysis, marked	1 (2%)		1 (2%)	1 (2%)
Dilatation, mild		1 (2%)		1 (2%)
Dilatation, moderate			1 (2%)	
Hyperplasia, mild				1 (2%)
Hyperplasia, moderate			1 (2%)	
Inflammation, chronic active, mild			1 (2%)	
Inflammation, chronic, mild		1 (2%)		
Inflammation, suppurative, marked			1 (2%)	
Inflammation, suppurative, minimal				1 (2%)
Testes	(51)	(50)	(49)	(50)
Autolysis, marked	1 (2%)		3 (6%)	
Autolysis, mild			1 (2%)	
Degeneration, marked, seminiferous tubule	11 (22%)	4 (8%)	7 (14%)	5 (10%)
Degeneration, mild, seminiferous tubule	4 (8%)	4 (8%)	1 (2%)	5 (10%)
Degeneration, minimal, seminiferous tubule	15 (29%)	22 (44%)	14 (29%)	15 (30%)
Degeneration, moderate, seminiferous tubule	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, mild, interstitial cell				1 (2%)
Hyperplasia, moderate, interstitial cell	1 (2%)			
Polyarteritis, mild	2 (4%)		1 (2%)	1 (2%)
Polyarteritis, minimal		1 (2%)		
Testes, rete testes	(44)	(50)	(46)	(49)
Dilatation, marked	1 (2%)			
Dilatation, mild	1 (2%)	1 (2%)	1 (2%)	
Dilatation, minimal	1 (2%)	2 (4%)	1 (2%)	
Dilatation, moderate			1 (2%)	3 (6%)
Fibrosis, mild			1 (2%)	
Fibrosis, moderate	1 (2%)			

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System				
Bone marrow	(49)	(48)	(47)	(49)
Autolysis, marked	1 (2%)			
Autolysis, mild			1 (2%)	
Hyperplasia, marked, erythroid cell				1 (2%)
Hyperplasia, marked, myeloid cell			2 (4%)	
Hyperplasia, mild, erythroid cell		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, mild, myeloid cell	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hyperplasia, moderate, erythroid cell				1 (2%)
Hyperplasia, moderate, myeloid cell	1 (2%)	2 (4%)	1 (2%)	
Hypocellularity, marked			1 (2%)	
Hypocellularity, mild	2 (4%)			1 (2%)
Hypocellularity, moderate				1 (2%)
Lymph node	(15)	(14)	(14)	(9)
Autolysis, marked, deep cervical	1 (7%)			
Autolysis, marked, lumbar	1 (7%)			
Autolysis, marked, renal	1 (7%)			
Degeneration, cystic, marked, lumbar	4 (27%)	3 (21%)	3 (21%)	1 (11%)
Degeneration, cystic, marked, renal			2 (14%)	1 (11%)
Degeneration, cystic, mild, lumbar		3 (21%)	4 (29%)	1 (11%)
Degeneration, cystic, mild, popliteal		1 (7%)		
Degeneration, cystic, moderate, lumbar	2 (13%)	3 (21%)		1 (11%)
Degeneration, cystic, moderate, renal		1 (7%)		
Fibrosis, marked, renal			1 (7%)	
Hemorrhage, marked, renal, adventitia	1 (7%)			
Hemorrhage, minimal, pancreatic			1 (7%)	
Hemorrhage, moderate, lumbar	1 (7%)			
Hemorrhage, moderate, mediastinal				1 (11%)
Hyperplasia, lymphoid, marked, lumbar	2 (13%)		1 (7%)	
Hyperplasia, lymphoid, marked, popliteal		1 (7%)		
Hyperplasia, lymphoid, marked, renal		1 (7%)		
Hyperplasia, lymphoid, mild, lumbar			2 (14%)	
Hyperplasia, lymphoid, mild, mediastinal		1 (7%)		
Hyperplasia, lymphoid, mild, pancreatic	1 (7%)	1 (7%)		
Hyperplasia, lymphoid, mild, popliteal		1 (7%)		
Hyperplasia, lymphoid, moderate, inguinal			2 (14%)	
Hyperplasia, lymphoid, moderate, lumbar	1 (7%)	1 (7%)	4 (29%)	
Hyperplasia, lymphoid, moderate, renal			1 (7%)	
Infiltration cellular, plasma cell, marked				1 (11%)
Infiltration cellular, plasma cell, marked, inguinal			1 (7%)	
Infiltration cellular, plasma cell, marked, lumbar	6 (40%)	5 (36%)	4 (29%)	3 (33%)
Infiltration cellular, plasma cell, marked, popliteal		1 (7%)		
Infiltration cellular, plasma cell, marked, renal		1 (7%)	2 (14%)	
Infiltration cellular, plasma cell, mild, lumbar		1 (7%)		
Infiltration cellular, plasma cell, mild, popliteal		1 (7%)		
Infiltration cellular, plasma cell, moderate, inguinal			1 (7%)	
Infiltration cellular, plasma cell, moderate, lumbar	1 (7%)		6 (43%)	2 (22%)
Infiltration cellular, plasma cell, moderate, mediastinal	1 (7%)			
Infiltration cellular, plasma cell, moderate, pancreatic			1 (7%)	
Infiltration cellular, plasma cell, moderate, renal				1 (11%)
Inflammation, granulomatous, mild, pancreatic	1 (7%)			
Inflammation, granulomatous, minimal, pancreatic		1 (7%)		
Pigmentation, mild, renal	1 (7%)			
Pigmentation, minimal, pancreatic			1 (7%)	
Polyarteritis, moderate, pancreatic, adventitia	1 (7%)			

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(52)	(49)	(45)	(48)
Autolysis, marked	1 (2%)			
Autolysis, moderate	2 (4%)			
Degeneration, cystic, marked	4 (8%)		1 (2%)	1 (2%)
Degeneration, cystic, mild		3 (6%)	2 (4%)	5 (10%)
Degeneration, cystic, minimal	1 (2%)	1 (2%)		
Degeneration, cystic, moderate	2 (4%)	2 (4%)	1 (2%)	
Hyperplasia, lymphoid, mild	12 (23%)	10 (20%)	8 (18%)	12 (25%)
Hyperplasia, lymphoid, minimal	4 (8%)	2 (4%)		3 (6%)
Hyperplasia, lymphoid, moderate	7 (13%)	5 (10%)	3 (7%)	5 (10%)
Infiltration cellular, plasma cell, marked	4 (8%)	2 (4%)	3 (7%)	4 (8%)
Infiltration cellular, plasma cell, mild	14 (27%)	19 (39%)	9 (20%)	12 (25%)
Infiltration cellular, plasma cell, minimal	2 (4%)		1 (2%)	
Infiltration cellular, plasma cell, moderate	10 (19%)	7 (14%)	8 (18%)	12 (25%)
Lymph node, mesenteric	(48)	(47)	(45)	(46)
Autolysis, marked		1 (2%)		
Degeneration, cystic, marked	3 (6%)		1 (2%)	2 (4%)
Degeneration, cystic, mild		1 (2%)		1 (2%)
Degeneration, cystic, minimal			1 (2%)	1 (2%)
Hemorrhage, mild				1 (2%)
Hyperplasia, lymphoid, mild	10 (21%)	7 (15%)	3 (7%)	9 (20%)
Hyperplasia, lymphoid, minimal	3 (6%)		1 (2%)	3 (7%)
Hyperplasia, lymphoid, moderate	1 (2%)			2 (4%)
Infiltration cellular, mast cell, mild	2 (4%)	2 (4%)		4 (9%)
Infiltration cellular, mast cell, moderate				1 (2%)
Infiltration cellular, plasma cell, mild	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Infiltration cellular, plasma cell, moderate				1 (2%)
Inflammation, granulomatous, marked	1 (2%)			
Inflammation, granulomatous, mild	6 (13%)	10 (21%)	8 (18%)	8 (17%)
Inflammation, granulomatous, minimal	7 (15%)	12 (26%)	10 (22%)	8 (17%)
Inflammation, granulomatous, moderate			4 (9%)	
Pigmentation, marked			1 (2%)	
Pigmentation, mild				1 (2%)
Pigmentation, minimal	1 (2%)			
Spleen	(52)	(50)	(47)	(49)
Accessory spleen	1 (2%)			
Autolysis, mild	1 (2%)	1 (2%)	2 (4%)	
Autolysis, moderate	2 (4%)	1 (2%)	1 (2%)	
Depletion lymphoid, marked			1 (2%)	2 (4%)
Depletion lymphoid, moderate				1 (2%)
Fibrosis, mild, capsule	1 (2%)			
Hematopoietic cell proliferation erythrocytic, moderate				1 (2%)
Hematopoietic cell proliferation, mild	6 (12%)	6 (12%)	4 (9%)	5 (10%)
Hematopoietic cell proliferation, minimal	1 (2%)	3 (6%)	9 (19%)	2 (4%)
Hematopoietic cell proliferation, moderate	1 (2%)	3 (6%)		4 (8%)
Hyperplasia, lymphoid, marked			1 (2%)	
Hyperplasia, lymphoid, mild	1 (2%)	2 (4%)		1 (2%)
Hyperplasia, lymphoid, minimal	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, lymphoid, moderate		1 (2%)		
Hyperplasia, stromal, marked				1 (2%)
Inflammation, chronic active, marked			1 (2%)	
Necrosis, marked			1 (2%)	
Pigmentation, marked	3 (6%)	5 (10%)	4 (9%)	6 (12%)
Pigmentation, mild	14 (27%)	15 (30%)	12 (26%)	12 (24%)
Pigmentation, minimal	6 (12%)	9 (18%)	9 (19%)	7 (14%)
Pigmentation, moderate	7 (13%)	6 (12%)	2 (4%)	3 (6%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Thymus	(42)	(47)	(40)	(45)
Atrophy, marked	31 (74%)	37 (79%)	34 (85%)	40 (89%)
Atrophy, mild		2 (4%)	1 (3%)	1 (2%)
Atrophy, minimal	1 (2%)			
Atrophy, moderate	4 (10%)	2 (4%)	3 (8%)	3 (7%)
Autolysis, marked		1 (2%)	1 (3%)	
Hyperplasia, lymphoid, marked	1 (2%)			
Hyperplasia, lymphoid, moderate		1 (2%)		
Hyperplasia, mild, epithelial cell		1 (2%)		
Hyperplasia, moderate, epithelial cell		1 (2%)		
Integumentary System				
Mammary gland	(41)	(42)	(34)	(45)
Autolysis, moderate	1 (2%)			
Degeneration, marked	5 (12%)	6 (14%)	4 (12%)	5 (11%)
Degeneration, mild	8 (20%)	8 (19%)	5 (15%)	7 (16%)
Degeneration, minimal	3 (7%)	2 (5%)	5 (15%)	1 (2%)
Degeneration, moderate	5 (12%)	1 (2%)	4 (12%)	7 (16%)
Dilatation, marked, duct	1 (2%)			1 (2%)
Dilatation, mild, duct		1 (2%)		
Dilatation, moderate, duct		1 (2%)	1 (3%)	
Galactocele, marked				1 (2%)
Hyperplasia, mast cell, mild				1 (2%)
Hyperplasia, mild, alveolus	2 (5%)		1 (3%)	2 (4%)
Hyperplasia, minimal, alveolus	1 (2%)	1 (2%)		6 (13%)
Hyperplasia, moderate, alveolus				1 (2%)
Infiltration cellular, mast cell, mild			1 (3%)	
Inflammation, chronic, marked				1 (2%)
Lactation, mild	3 (7%)	3 (7%)	3 (9%)	3 (7%)
Skin	(51)	(50)	(50)	(50)
Abscess, marked	1 (2%)			
Autolysis, moderate	1 (2%)			
Cyst epithelial inclusion	2 (4%)	3 (6%)		2 (4%)
Fibrosis, marked			1 (2%)	
Fibrosis, marked, dermis				1 (2%)
Fibrosis, moderate	1 (2%)			
Foreign body			1 (2%)	
Hemorrhage, mild			1 (2%)	
Hemorrhage, moderate				1 (2%)
Hyperkeratosis, marked				1 (2%)
Hyperkeratosis, mild	5 (10%)	3 (6%)		2 (4%)
Hyperkeratosis, minimal		1 (2%)		
Hyperkeratosis, moderate		2 (4%)		
Hyperplasia, mild, epidermis	4 (8%)	3 (6%)		2 (4%)
Hyperplasia, moderate, epidermis	1 (2%)	3 (6%)		
Inflammation, chronic active, marked		2 (4%)	3 (6%)	3 (6%)
Inflammation, chronic active, mild	4 (8%)	3 (6%)	3 (6%)	1 (2%)
Inflammation, chronic active, minimal			1 (2%)	
Inflammation, chronic active, moderate	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, chronic, mild	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic, minimal	1 (2%)	1 (2%)		
Inflammation, granulomatous, marked			1 (2%)	
Inflammation, pyogranulomatous, marked	1 (2%)			

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Integumentary System (continued)				
Skin (continued)	(51)	(50)	(50)	(50)
Inflammation, suppurative, marked	20 (39%)	20 (40%)	23 (46%)	20 (40%)
Inflammation, suppurative, mild				1 (2%)
Inflammation, suppurative, moderate	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Necrosis, marked				1 (2%)
Necrosis, mild	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Necrosis, moderate	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Ulcer, marked, epidermis	1 (2%)			
Musculoskeletal System				
Bone, femur	(53)	(49)	(50)	(50)
Hyperostosis, mild	1 (2%)			
Skeletal muscle				(2)
Cyst				1 (50%)
Fibrosis, marked				1 (50%)
Nervous System				
Brain, brain stem	(50)	(50)	(48)	(48)
Autolysis, marked			1 (2%)	
Autolysis, mild		1 (2%)		
Autolysis, moderate	1 (2%)			
Compression, mild	5 (10%)	2 (4%)	3 (6%)	2 (4%)
Compression, minimal	2 (4%)	1 (2%)		
Compression, moderate		1 (2%)	1 (2%)	
Cyst			1 (2%)	
Gliosis, mild		1 (2%)		
Hemorrhage, mild		1 (2%)	1 (2%)	
Hemorrhage, minimal	1 (2%)			
Brain, cerebellum	(50)	(49)	(48)	(48)
Autolysis, mild		1 (2%)		
Autolysis, moderate	1 (2%)			
Gliosis, minimal	1 (2%)			
Hemorrhage, mild		1 (2%)		
Hemorrhage, minimal	1 (2%)			
Hydrocephalus, marked	1 (2%)			
Hydrocephalus, mild		1 (2%)	1 (2%)	
Hydrocephalus, minimal		1 (2%)		
Brain, cerebrum	(50)	(50)	(48)	(48)
Autolysis, mild		1 (2%)		
Autolysis, moderate	1 (2%)			
Compression, mild			1 (2%)	
Congestion, moderate, meninges	1 (2%)			
Developmental malformation			1 (2%)	
Ectopic tissue			1 (2%)	
Fibrosis, mild, meninges				1 (2%)
Gliosis, mild			1 (2%)	
Hemorrhage, mild		2 (4%)	1 (2%)	
Hemorrhage, moderate, meninges	1 (2%)			
Hydrocephalus, marked	1 (2%)			
Hydrocephalus, mild	1 (2%)	1 (2%)	3 (6%)	
Hydrocephalus, minimal		1 (2%)		1 (2%)
Hydrocephalus, moderate	1 (2%)			
Mineralization, mild			1 (2%)	

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Respiratory System				
Lung	(49)	(48)	(44)	(49)
Autolysis, marked	1 (2%)			
Autolysis, mild		1 (2%)		1 (2%)
Autolysis, moderate				2 (4%)
Congestion, marked				1 (2%)
Cyst	1 (2%)			
Edema, moderate	1 (2%)			
Hemorrhage, marked	1 (2%)		1 (2%)	1 (2%)
Hemorrhage, mild	1 (2%)			
Hemorrhage, moderate	1 (2%)			1 (2%)
Hyperplasia, mild, alveolar epithelium		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, minimal, alveolar epithelium	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, moderate, alveolar epithelium	1 (2%)			
Infiltration cellular, histiocyte, mild	5 (10%)	10 (21%)	7 (16%)	13 (27%)
Infiltration cellular, histiocyte, minimal	8 (16%)	11 (23%)	6 (14%)	8 (16%)
Infiltration cellular, histiocyte, moderate	2 (4%)		1 (2%)	
Infiltration cellular, histiocytic, minimal		1 (2%)		
Infiltration cellular, lymphocyte, mild		1 (2%)		
Infiltration cellular, lymphocyte, minimal	1 (2%)			
Inflammation, chronic, mild		1 (2%)		
Metaplasia, osseous, mild		1 (2%)		2 (4%)
Metaplasia, osseous, minimal	2 (4%)	2 (4%)	4 (9%)	1 (2%)
Mineralization, mild, artery	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Mineralization, minimal, artery	1 (2%)	4 (8%)	2 (5%)	3 (6%)
Nose	(48)	(47)	(45)	(48)
Autolysis, mild		1 (2%)		
Autolysis, moderate	1 (2%)			
Cyst				1 (2%)
Foreign body		1 (2%)	1 (2%)	
Fungus		1 (2%)		
Hemorrhage, moderate	1 (2%)			
Hyperkeratosis, mild	1 (2%)			
Hyperplasia, mild, squamous epithelium	1 (2%)			
Hyperplasia, moderate, squamous epithelium	1 (2%)			
Inflammation, chronic active, marked		1 (2%)		
Inflammation, chronic active, mild	1 (2%)	2 (4%)	3 (7%)	
Inflammation, chronic active, mild, upper molar	2 (4%)	2 (4%)		
Inflammation, suppurative, marked			1 (2%)	
Inflammation, suppurative, mild	2 (4%)	2 (4%)	3 (7%)	
Inflammation, suppurative, minimal		3 (6%)	4 (9%)	1 (2%)
Inflammation, suppurative, moderate	1 (2%)			
Keratin cyst	1 (2%)		1 (2%)	
Metaplasia, mild, squamous epithelium	1 (2%)			
Necrosis, marked		1 (2%)		
Necrosis, mild		1 (2%)		
Ulcer, moderate	1 (2%)			
Trachea	(47)	(47)	(46)	(48)
Cyst, squamous				1 (2%)

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Special Senses System				
Eye	(37)	(37)	(33)	(40)
Atrophy, mild, bilateral, retina	4 (11%)	3 (8%)	3 (9%)	
Atrophy, mild, retina	3 (8%)	2 (5%)		1 (3%)
Atrophy, minimal, bilateral, retina	1 (3%)	2 (5%)	1 (3%)	1 (3%)
Atrophy, minimal, retina	2 (5%)			
Atrophy, moderate, bilateral, retina	1 (3%)			
Cataract, minimal		1 (3%)		
Degeneration, marked, cornea			1 (3%)	
Hemorrhage, marked, anterior chamber			1 (3%)	
Inflammation, chronic, mild	1 (3%)			
Inflammation, suppurative, marked, anterior chamber			1 (3%)	
Inflammation, suppurative, marked, cornea			1 (3%)	
Inflammation, suppurative, moderate				1 (3%)
Ulcer, marked, cornea			1 (3%)	
Harderian gland	(39)	(39)	(33)	(41)
Degeneration, mild		1 (3%)		
Degeneration, minimal	1 (3%)			1 (2%)
Hyperplasia, minimal, epithelium		1 (3%)		
Infiltration cellular, lymphocyte, mild	2 (5%)			
Infiltration cellular, lymphocyte, minimal	3 (8%)	1 (3%)	3 (9%)	6 (15%)
Inflammation, chronic, mild		1 (3%)		
Lacrimal gland	(10)	(14)	(12)	(5)
Degeneration, marked			1 (8%)	
Degeneration, mild		1 (7%)		
Ectopic harderian	10 (100%)	13 (93%)	12 (100%)	5 (100%)
Infiltration cellular, lymphocyte, mild		1 (7%)	1 (8%)	
Inflammation, chronic active, moderate		1 (7%)		
Zymbal's gland			(1)	
Inflammation, suppurative, marked			1 (100%)	
Urinary System				
Kidney	(48)	(48)	(46)	(49)
Accumulation, hyaline droplet, marked	1 (2%)		1 (2%)	
Autolysis, marked		3 (6%)	2 (4%)	1 (2%)
Autolysis, mild	1 (2%)			
Autolysis, moderate			1 (2%)	2 (4%)
Congestion, mild	1 (2%)			
Congestion, moderate		1 (2%)		
Cyst, cortex	24 (50%)	27 (56%)	22 (48%)	24 (49%)
Cyst, medulla	1 (2%)			
Dilatation, mild, pelvis		1 (2%)	1 (2%)	
Dilatation, mild, renal tubule	1 (2%)	1 (2%)		
Dilatation, minimal, pelvis	1 (2%)		1 (2%)	
Dilatation, minimal, renal tubule	1 (2%)			
Dilatation, moderate, pelvis	1 (2%)		1 (2%)	1 (2%)
Dilatation, moderate, renal tubule	1 (2%)			
Fatty change, capsule		2 (4%)	4 (9%)	3 (6%)
Fibrosis, mild		1 (2%)		
Fibrosis, minimal			1 (2%)	1 (2%)
Hyperplasia, mild, pelvis	4 (8%)	2 (4%)	3 (7%)	2 (4%)
Hyperplasia, minimal, pelvis	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Hyperplasia, moderate, pelvis			1 (2%)	
Hyperplasia, tubular, minimal	1 (2%)			

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Urinary System (continued)				
Kidney (continued)	(48)	(48)	(46)	(49)
Infiltration cellular, lymphocyte, mild				1 (2%)
Infiltration cellular, lymphocyte, minimal		2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic active, marked			1 (2%)	
Inflammation, chronic, minimal	1 (2%)	1 (2%)	1 (2%)	
Inflammation, suppurative, marked, pelvis			1 (2%)	
Inflammation, suppurative, mild, pelvis		1 (2%)		
Inflammation, suppurative, mild, renal tubule	1 (2%)		1 (2%)	1 (2%)
Inflammation, suppurative, moderate, pelvis			1 (2%)	
Mineralization, mild, pelvis		1 (2%)		
Mineralization, mild, renal tubule			1 (2%)	1 (2%)
Mineralization, minimal, renal tubule	1 (2%)			1 (2%)
Nephropathy, chronic, marked	2 (4%)	1 (2%)	3 (7%)	3 (6%)
Nephropathy, chronic, mild	7 (15%)	12 (25%)	20 (43%)	11 (22%)
Nephropathy, chronic, minimal	29 (60%)	23 (48%)	11 (24%)	23 (47%)
Nephropathy, chronic, moderate	3 (6%)	3 (6%)	4 (9%)	3 (6%)
Polycystic kidney, moderate		1 (2%)		
Urethra		(1)	(1)	(2)
Congestion, mild			1 (100%)	
Urinary bladder	(47)	(48)	(46)	(47)
Autolysis, moderate		1 (2%)	1 (2%)	
Dilatation, marked			1 (2%)	2 (4%)
Hemorrhage, mild	1 (2%)			
Hemorrhage, moderate			1 (2%)	
Hyperplasia, moderate, transitional epithelium		1 (2%)		
Inflammation, chronic active, moderate		1 (2%)		

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	66	50	50	50
Early deaths				
Dead	11	7	6	10
Moribund	8	1	11	4
Survey/sentinel	14			
Survivors				
Terminal sacrifice	33	42	33	36
Animals examined microscopically	52	50	49	49
Alimentary System				
Esophagus	(49)	(49)	(48)	(49)
Dilatation, mild		1 (2%)		
Hyperkeratosis, marked	1 (2%)			
Hyperkeratosis, mild	1 (2%)	1 (2%)		1 (2%)
Intestine large, cecum	(41)	(43)	(46)	(45)
Autolysis, moderate				1 (2%)
Ectasia, marked, lymphatic				1 (2%)
Hyperplasia, lymphoid, mild	1 (2%)			
Inflammation, suppurative, marked				1 (2%)
Polyarteritis, moderate		1 (2%)		
Intestine large, colon	(41)	(43)	(46)	(45)
Hyperplasia, lymphoid, moderate	1 (2%)			
Polyarteritis, moderate		1 (2%)		
Intestine large, rectum	(38)	(42)	(38)	(38)
Polyarteritis, marked		1 (2%)		
Intestine small, duodenum	(41)	(43)	(46)	(43)
Cyst				1 (2%)
Intestine small, ileum	(40)	(42)	(45)	(43)
Hyperplasia, lymphoid, mild	1 (3%)			
Liver	(49)	(47)	(47)	(48)
Angiectasis, marked		1 (2%)		
Angiectasis, mild	3 (6%)	2 (4%)		2 (4%)
Angiectasis, minimal	3 (6%)	1 (2%)	2 (4%)	
Autolysis, marked	2 (4%)			
Autolysis, mild	2 (4%)	2 (4%)		
Autolysis, minimal			1 (2%)	
Autolysis, moderate				1 (2%)
Basophilic focus		4 (9%)	3 (6%)	1 (2%)
Basophilic focus, multiple				1 (2%)
Clear cell focus			2 (4%)	
Congestion, moderate				1 (2%)
Cyst			1 (2%)	
Cyst, biliary tract				1 (2%)
Degeneration, cystic, mild	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Degeneration, cystic, minimal	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Degeneration, cystic, moderate	1 (2%)		1 (2%)	1 (2%)
Developmental malformation	1 (2%)		1 (2%)	
Dilatation, marked, bile duct				1 (2%)
Eosinophilic focus	3 (6%)	2 (4%)	2 (4%)	
Eosinophilic focus, multiple	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Fatty change, marked			1 (2%)	
Fibrosis, marked				1 (2%)
Fibrosis, mild, biliary tract	1 (2%)			1 (2%)
Fibrosis, minimal, biliary tract	7 (14%)	2 (4%)	6 (13%)	9 (19%)

The footnotes for this table are defined in Table A3a.

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Alimentary System (continued)				
Liver (continued)	(49)	(47)	(47)	(48)
Hematopoietic cell proliferation, minimal	2 (4%)	1 (2%)	2 (4%)	
Hemorrhage, mild	1 (2%)			
Hemorrhage, minimal			1 (2%)	
Hemorrhage, moderate, capsule	1 (2%)			
Hepatodiaphragmatic nodule	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia, marked, bile duct				1 (2%)
Hyperplasia, mild, bile duct	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Hyperplasia, minimal, bile duct	12 (24%)	8 (17%)	7 (15%)	19 (40%)
Hyperplasia, minimal, capsule				1 (2%)
Infiltration cellular, lymphocyte, mild	1 (2%)	1 (2%)		
Infiltration cellular, lymphocyte, minimal	6 (12%)	1 (2%)		5 (10%)
Inflammation, chronic active, marked				1 (2%)
Inflammation, chronic active, mild	2 (4%)			1 (2%)
Inflammation, chronic active, minimal	6 (12%)	10 (21%)	5 (11%)	7 (15%)
Inflammation, suppurative, minimal	1 (2%)			
Mixed cell focus			1 (2%)	
Necrosis, mild	2 (4%)			
Necrosis, minimal	2 (4%)		3 (6%)	4 (8%)
Necrosis, moderate				1 (2%)
Tension lipidosis, mild		1 (2%)		2 (4%)
Tension lipidosis, moderate		1 (2%)	1 (2%)	2 (4%)
Vacuolization cytoplasmic, mild	3 (6%)		6 (13%)	
Vacuolization cytoplasmic, minimal	2 (4%)	1 (2%)	1 (2%)	
Vacuolization cytoplasmic, moderate				1 (2%)
Mesentery		(1)		
Necrosis, marked, fat		1 (100%)		
Pancreas	(45)	(47)	(48)	(47)
Autolysis, marked	2 (4%)			
Autolysis, mild	1 (2%)			1 (2%)
Autolysis, moderate		1 (2%)		1 (2%)
Degeneration, marked, acinar cell	3 (7%)	6 (13%)	5 (10%)	5 (11%)
Degeneration, mild, acinar cell	14 (31%)	17 (36%)	18 (38%)	11 (23%)
Degeneration, minimal, acinar cell	10 (22%)	11 (23%)	3 (6%)	11 (23%)
Degeneration, moderate, acinar cell	10 (22%)	4 (9%)	12 (25%)	8 (17%)
Infiltration cellular, lymphocyte, mild				1 (2%)
Infiltration cellular, lymphocyte, minimal	1 (2%)			1 (2%)
Inflammation, chronic active, mild				1 (2%)
Pigmentation, minimal	1 (2%)			
Polyarteritis, marked		1 (2%)		
Salivary glands	(49)	(47)	(47)	(48)
Autolysis, marked	1 (2%)			
Degeneration, marked, acinar cell	1 (2%)			
Degeneration, mild, acinar cell				1 (2%)
Degeneration, minimal, acinar cell	1 (2%)			
Hyperplasia, mild		1 (2%)		
Hypertrophy, marked				1 (2%)
Infiltration cellular, lymphocyte, moderate	1 (2%)			
Mineralization, mild		1 (2%)		
Mineralization, moderate	2 (4%)			
Stomach, forestomach	(44)	(45)	(48)	(47)
Edema, marked, submucosa	1 (2%)			
Infiltration cellular, lymphocyte, moderate	1 (2%)			
Inflammation, suppurative, moderate	1 (2%)			
Keratin cyst				1 (2%)
Ulcer, mild, mucosa	1 (2%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Cardiovascular System				
Heart	(51)	(48)	(49)	(47)
Autolysis, mild	1 (2%)	1 (2%)		
Cardiomyopathy, mild	9 (18%)	12 (25%)	17 (35%)	4 (9%)
Cardiomyopathy, minimal	18 (35%)	17 (35%)	18 (37%)	18 (38%)
Cardiomyopathy, moderate		2 (4%)	2 (4%)	
Congestion, marked		1 (2%)		
Dilatation, marked, atrium	1 (2%)			
Hyperplasia, minimal, endocardium		1 (2%)		
Hyperplasia, minimal, pericardium				1 (2%)
Inflammation, chronic active, minimal, pericardium	1 (2%)			
Metaplasia, osseous, mild		1 (2%)		
Mineralization, mild	2 (4%)			
Mineralization, minimal		1 (2%)	1 (2%)	
Endocrine System				
Adrenal cortex	(48)	(47)	(47)	(47)
Accessory adrenal cortical nodule	2 (4%)	4 (9%)	1 (2%)	2 (4%)
Angiectasis, marked				1 (2%)
Angiectasis, mild	1 (2%)		1 (2%)	3 (6%)
Autolysis, moderate	1 (2%)		1 (2%)	
Cyst	1 (2%)		1 (2%)	
Degeneration, cystic, marked		1 (2%)		1 (2%)
Degeneration, cystic, mild	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Degeneration, cystic, minimal		2 (4%)	1 (2%)	1 (2%)
Degeneration, cystic, moderate	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Fibrosis, mild, capsule	1 (2%)			
Hyperplasia, mild	3 (6%)	1 (2%)	5 (11%)	2 (4%)
Hyperplasia, minimal	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, minimal, bilateral	1 (2%)		1 (2%)	
Hypertrophy, marked		1 (2%)		
Hypertrophy, mild	2 (4%)	4 (9%)	5 (11%)	1 (2%)
Hypertrophy, minimal	2 (4%)		3 (6%)	
Hypertrophy, moderate				1 (2%)
Pigmentation, mild				1 (2%)
Vacuolization cytoplasmic, mild	10 (21%)	17 (36%)	14 (30%)	9 (19%)
Vacuolization cytoplasmic, minimal	18 (38%)	9 (19%)	19 (40%)	16 (34%)
Vacuolization cytoplasmic, moderate			1 (2%)	
Adrenal medulla	(48)	(46)	(47)	(45)
Degeneration, cystic, mild		1 (2%)		
Degeneration, cystic, moderate			1 (2%)	
Hyperplasia, marked		2 (4%)	1 (2%)	
Hyperplasia, mild	4 (8%)	1 (2%)	4 (9%)	2 (4%)
Hyperplasia, mild, bilateral	1 (2%)			1 (2%)
Hyperplasia, minimal	3 (6%)	5 (11%)	5 (11%)	3 (7%)
Hyperplasia, moderate	2 (4%)	1 (2%)		1 (2%)
Hyperplasia, moderate, bilateral	1 (2%)		1 (2%)	
Hypertrophy, mild	1 (2%)			
Islets, pancreatic	(45)	(49)	(48)	(48)
Autolysis, moderate		1 (2%)		
Hyperplasia, mild	5 (11%)	4 (8%)	6 (13%)	9 (19%)
Hyperplasia, minimal	18 (40%)	16 (33%)	15 (31%)	16 (33%)
Hyperplasia, moderate		3 (6%)	1 (2%)	2 (4%)

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System (continued)				
Parathyroid gland	(41)	(46)	(48)	(43)
Hyperplasia, mild	2 (5%)	3 (7%)	4 (8%)	4 (9%)
Hyperplasia, mild, bilateral	1 (2%)	3 (7%)	4 (8%)	2 (5%)
Hyperplasia, minimal	1 (2%)		3 (6%)	2 (5%)
Pituitary gland	(49)	(46)	(48)	(48)
Autolysis, marked	1 (2%)			
Cyst, multiple, pars distalis	2 (4%)			1 (2%)
Cyst, pars distalis	3 (6%)	5 (11%)	5 (10%)	6 (13%)
Cyst, pars intermedia	1 (2%)			
Dysplasia, mild, pars intermedia	1 (2%)			
Hyperplasia, marked, pars distalis		2 (4%)	2 (4%)	
Hyperplasia, mild, pars distalis	10 (20%)	8 (17%)	8 (17%)	7 (15%)
Hyperplasia, minimal, pars distalis	7 (14%)	2 (4%)	2 (4%)	5 (10%)
Hyperplasia, moderate, pars distalis	2 (4%)	4 (9%)	1 (2%)	
Infiltration cellular, lymphocyte, mild, pars nervosa			1 (2%)	
Thyroid gland	(44)	(46)	(46)	(45)
Autolysis, marked	2 (5%)			
Cyst, squamous	6 (14%)	4 (9%)	2 (4%)	4 (9%)
Hyperplasia, marked, follicular cell			1 (2%)	
Hyperplasia, mild, C-cell		2 (4%)		4 (9%)
Hyperplasia, minimal, C-cell	8 (18%)	3 (7%)	3 (7%)	3 (7%)
Hyperplasia, moderate, C-cell	1 (2%)			
Infiltration cellular, lymphocyte, mild	1 (2%)			
Infiltration cellular, lymphocyte, minimal			1 (2%)	
Genital System				
Coagulating gland	(44)	(43)	(47)	(45)
Atrophy, mild	2 (5%)	1 (2%)		4 (9%)
Atrophy, moderate	1 (2%)			2 (4%)
Autolysis, marked	2 (5%)			
Degeneration, mild			1 (2%)	
Developmental malformation	1 (2%)	2 (5%)	2 (4%)	1 (2%)
Fibrosis, marked			1 (2%)	
Inflammation, chronic, mild			1 (2%)	
Inflammation, suppurative, moderate	1 (2%)			
Epididymis	(49)	(48)	(49)	(47)
Atrophy, mild		2 (4%)		
Atrophy, moderate				1 (2%)
Autolysis, marked		1 (2%)		
Autolysis, moderate	1 (2%)			
Degeneration, marked			1 (2%)	
Degeneration, mild	3 (6%)	1 (2%)	2 (4%)	3 (6%)
Degeneration, minimal		2 (4%)	2 (4%)	
Degeneration, moderate	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, mild				1 (2%)
Hypospermia, marked	4 (8%)	9 (19%)	8 (16%)	3 (6%)
Hypospermia, mild		1 (2%)	2 (4%)	1 (2%)
Hypospermia, moderate				1 (2%)
Infiltration cellular, lymphocyte, mild	1 (2%)	1 (2%)		
Infiltration cellular, lymphocyte, minimal	4 (8%)	5 (10%)	6 (12%)	3 (6%)
Inflammation, mild	1 (2%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Preputial gland	(48)	(48)	(47)	(47)
Abscess, marked	1 (2%)		2 (4%)	
Atrophy, mild	1 (2%)			
Autolysis, marked		1 (2%)		
Autolysis, mild	2 (4%)			
Autolysis, moderate	2 (4%)			2 (4%)
Degeneration, marked, parenchymal cell	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Degeneration, mild, parenchymal cell	7 (15%)	4 (8%)	2 (4%)	4 (9%)
Degeneration, minimal, parenchymal cell	7 (15%)	11 (23%)	6 (13%)	6 (13%)
Degeneration, moderate, parenchymal cell	1 (2%)	1 (2%)	4 (9%)	4 (9%)
Dilatation, marked, duct	1 (2%)	3 (6%)	4 (9%)	4 (9%)
Dilatation, mild, duct	1 (2%)	2 (4%)		1 (2%)
Dilatation, moderate, duct	2 (4%)	2 (4%)	3 (6%)	4 (9%)
Infiltration cellular, lymphocyte, marked			2 (4%)	
Infiltration cellular, lymphocyte, mild	9 (19%)	6 (13%)	4 (9%)	5 (11%)
Infiltration cellular, lymphocyte, minimal	10 (21%)	14 (29%)	8 (17%)	4 (9%)
Infiltration cellular, lymphocyte, moderate			1 (2%)	
Inflammation, chronic active, mild		1 (2%)		
Inflammation, suppurative, marked	8 (17%)	1 (2%)	9 (19%)	13 (28%)
Inflammation, suppurative, mild	2 (4%)	8 (17%)	5 (11%)	6 (13%)
Inflammation, suppurative, minimal	4 (8%)	4 (8%)	4 (9%)	2 (4%)
Inflammation, suppurative, moderate	3 (6%)	3 (6%)		5 (11%)
Prostate, dorsal	(51)	(47)	(47)	(48)
Atrophy, mild				1 (2%)
Autolysis, marked	2 (4%)	1 (2%)		
Autolysis, mild	1 (2%)			1 (2%)
Autolysis, moderate	2 (4%)	1 (2%)		1 (2%)
Cyst	3 (6%)	1 (2%)		
Degeneration, mild	1 (2%)			2 (4%)
Degeneration, minimal				1 (2%)
Hyperplasia, marked	2 (4%)			
Infiltration cellular, lymphocyte, mild	1 (2%)			
Infiltration cellular, lymphocyte, minimal	2 (4%)		2 (4%)	2 (4%)
Inflammation, suppurative, marked	4 (8%)		2 (4%)	
Inflammation, suppurative, mild	14 (27%)	12 (26%)	17 (36%)	18 (38%)
Inflammation, suppurative, minimal	13 (25%)	16 (34%)	9 (19%)	15 (31%)
Inflammation, suppurative, moderate	4 (8%)	10 (21%)	7 (15%)	1 (2%)
Polyarteritis, mild		1 (2%)		
Prostate, ventral	(48)	(46)	(48)	(47)
Atrophy, mild				1 (2%)
Autolysis, marked	3 (6%)	1 (2%)		
Autolysis, mild			1 (2%)	
Degeneration, marked				1 (2%)
Degeneration, mild	7 (15%)	2 (4%)	5 (10%)	7 (15%)
Degeneration, minimal	2 (4%)	1 (2%)		1 (2%)
Degeneration, moderate	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, marked			2 (4%)	
Hyperplasia, mild	3 (6%)	4 (9%)		4 (9%)
Hyperplasia, minimal	2 (4%)		1 (2%)	5 (11%)
Hyperplasia, moderate	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Infiltration cellular, lymphocyte, mild	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Infiltration cellular, lymphocyte, minimal	7 (15%)	5 (11%)	12 (25%)	6 (13%)
Infiltration cellular, plasma cell, moderate	1 (2%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Prostate, ventral (continued)	(48)	(46)	(48)	(47)
Inflammation, chronic, marked				1 (2%)
Inflammation, chronic, mild			1 (2%)	
Inflammation, suppurative, marked	2 (4%)		1 (2%)	
Inflammation, suppurative, mild	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Inflammation, suppurative, minimal	2 (4%)	2 (4%)	7 (15%)	5 (11%)
Mineralization, mild				1 (2%)
Seminal vesicle	(43)	(43)	(47)	(45)
Atrophy, marked	1 (2%)			
Atrophy, mild	2 (5%)	2 (5%)	2 (4%)	5 (11%)
Atrophy, minimal			1 (2%)	
Atrophy, moderate	1 (2%)	1 (2%)	2 (4%)	3 (7%)
Autolysis, marked	2 (5%)		1 (2%)	
Degeneration, mild	2 (5%)		1 (2%)	
Dilatation, marked			1 (2%)	
Dilatation, mild				1 (2%)
Dilatation, moderate	1 (2%)		1 (2%)	
Hyperplasia, marked			2 (4%)	
Hyperplasia, moderate			1 (2%)	
Inflammation, chronic active, mild			1 (2%)	
Inflammation, suppurative, marked	1 (2%)			
Inflammation, suppurative, mild	1 (2%)		1 (2%)	
Inflammation, suppurative, minimal				1 (2%)
Testes	(51)	(50)	(48)	(49)
Autolysis, marked	3 (6%)	1 (2%)		
Autolysis, mild				1 (2%)
Autolysis, moderate		1 (2%)		1 (2%)
Degeneration, marked, seminiferous tubule	5 (10%)	13 (26%)	12 (25%)	3 (6%)
Degeneration, mild, seminiferous tubule	3 (6%)		4 (8%)	7 (14%)
Degeneration, minimal, seminiferous tubule	14 (27%)	12 (24%)	12 (25%)	17 (35%)
Degeneration, moderate, seminiferous tubule	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Edema, moderate			1 (2%)	
Fibrosis, moderate			1 (2%)	
Hemorrhage, moderate				1 (2%)
Hyperplasia, moderate, interstitial cell	1 (2%)			
Inflammation, granulomatous, moderate	1 (2%)			
Inflammation, suppurative, marked			1 (2%)	
Mineralization, mild, artery				1 (2%)
Polyarteritis, marked		1 (2%)		
Polyarteritis, mild	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Polyarteritis, moderate	1 (2%)			
Testes, rete testes	(47)	(48)	(46)	(41)
Dilatation, marked		1 (2%)		
Dilatation, mild		6 (13%)	2 (4%)	3 (7%)
Dilatation, minimal	2 (4%)		1 (2%)	1 (2%)
Dilatation, moderate			2 (4%)	
Fibrosis, mild		1 (2%)	1 (2%)	
Fibrosis, moderate		1 (2%)	1 (2%)	

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System				
Bone marrow	(48)	(48)	(48)	(46)
Autolysis, marked	2 (4%)			1 (2%)
Autolysis, mild		1 (2%)		
Depletion cellular, marked				1 (2%)
Hyperplasia, marked, erythroid cell			2 (4%)	
Hyperplasia, marked, myeloid cell	2 (4%)		1 (2%)	1 (2%)
Hyperplasia, mild, erythroid cell	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, mild, myeloid cell	3 (6%)		3 (6%)	2 (4%)
Hyperplasia, minimal, myeloid cell		1 (2%)		
Hyperplasia, moderate, erythroid cell			2 (4%)	1 (2%)
Hyperplasia, moderate, myeloid cell	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Hypocellularity, moderate			1 (2%)	2 (4%)
Lymph node	(13)	(9)	(18)	(12)
Autolysis, marked, inguinal	1 (8%)			
Congestion, moderate, lumbar	1 (8%)			
Congestion, moderate, mediastinal	1 (8%)			
Congestion, moderate, renal	1 (8%)			
Degeneration, cystic, marked, inguinal			1 (6%)	
Degeneration, cystic, marked, lumbar	3 (23%)	2 (22%)	8 (44%)	3 (25%)
Degeneration, cystic, marked, mediastinal		1 (11%)		
Degeneration, cystic, marked, renal	2 (15%)	3 (33%)	1 (6%)	2 (17%)
Degeneration, cystic, mild, lumbar	1 (8%)	1 (11%)	1 (6%)	1 (8%)
Degeneration, cystic, mild, popliteal		1 (11%)		
Degeneration, cystic, mild, renal	1 (8%)	1 (11%)	2 (11%)	1 (8%)
Degeneration, cystic, moderate, lumbar		2 (22%)	2 (11%)	1 (8%)
Hemorrhage, mild, mediastinal				1 (8%)
Hemorrhage, mild, pancreatic			1 (6%)	
Hemorrhage, moderate, renal		1 (11%)		
Hyperplasia, lymphoid, marked, axillary	1 (8%)			
Hyperplasia, lymphoid, marked, popliteal		1 (11%)		
Hyperplasia, lymphoid, mild, lumbar				1 (8%)
Hyperplasia, lymphoid, mild, pancreatic			1 (6%)	
Hyperplasia, lymphoid, mild, renal		2 (22%)	1 (6%)	
Hyperplasia, lymphoid, moderate, lumbar	2 (15%)	2 (22%)	4 (22%)	2 (17%)
Hyperplasia, lymphoid, moderate, popliteal	1 (8%)			
Infiltration cellular, plasma cell, marked, axillary	1 (8%)			
Infiltration cellular, plasma cell, marked, inguinal			1 (6%)	
Infiltration cellular, plasma cell, marked, lumbar	6 (46%)	5 (56%)	6 (33%)	3 (25%)
Infiltration cellular, plasma cell, marked, popliteal		1 (11%)		
Infiltration cellular, plasma cell, marked, renal	1 (8%)	2 (22%)		2 (17%)
Infiltration cellular, plasma cell, mild, lumbar			1 (6%)	
Infiltration cellular, plasma cell, mild, mediastinal	1 (8%)			
Infiltration cellular, plasma cell, moderate, lumbar	1 (8%)	1 (11%)	6 (33%)	2 (17%)
Infiltration cellular, plasma cell, moderate, renal	1 (8%)	1 (11%)	1 (6%)	1 (8%)
Inflammation, suppurative, mild, renal		1 (11%)		
Necrosis, mild, renal		1 (11%)		
Pigmentation, mild, lumbar			1 (6%)	
Pigmentation, mild, mediastinal				1 (8%)
Pigmentation, mild, renal	1 (8%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(48)	(48)	(48)
Autolysis, marked	1 (2%)			1 (2%)
Autolysis, moderate		1 (2%)		1 (2%)
Degeneration, cystic, marked	1 (2%)		3 (6%)	2 (4%)
Degeneration, cystic, mild	3 (6%)	6 (13%)	5 (10%)	5 (10%)
Degeneration, cystic, minimal	1 (2%)			
Degeneration, cystic, moderate		1 (2%)	1 (2%)	
Depletion lymphoid, marked				1 (2%)
Hyperplasia, lymphoid, marked		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid, mild	15 (31%)	7 (15%)	11 (23%)	14 (29%)
Hyperplasia, lymphoid, minimal		1 (2%)		1 (2%)
Hyperplasia, lymphoid, moderate	7 (15%)	5 (10%)	5 (10%)	5 (10%)
Infiltration cellular, plasma cell, marked	8 (17%)	7 (15%)	5 (10%)	7 (15%)
Infiltration cellular, plasma cell, mild	8 (17%)	12 (25%)	13 (27%)	11 (23%)
Infiltration cellular, plasma cell, minimal	2 (4%)			1 (2%)
Infiltration cellular, plasma cell, moderate	13 (27%)	10 (21%)	8 (17%)	17 (35%)
Inflammation, chronic active, mild			1 (2%)	
Lymph node, mesenteric	(45)	(46)	(47)	(47)
Autolysis, mild		1 (2%)		
Autolysis, moderate				1 (2%)
Congestion, moderate	1 (2%)			
Degeneration, cystic, marked	2 (4%)			
Hemorrhage, moderate			1 (2%)	
Hyperplasia, lymphoid, mild	7 (16%)	5 (11%)	5 (11%)	9 (19%)
Hyperplasia, lymphoid, minimal	2 (4%)	1 (2%)		1 (2%)
Infiltration cellular, mast cell, mild	2 (4%)			2 (4%)
Infiltration cellular, plasma cell, mild	2 (4%)		2 (4%)	1 (2%)
Infiltration cellular, plasma cell, moderate	4 (9%)	1 (2%)		2 (4%)
Inflammation, chronic active, marked			1 (2%)	
Inflammation, granulomatous, marked				1 (2%)
Inflammation, granulomatous, mild	11 (24%)	6 (13%)	7 (15%)	13 (28%)
Inflammation, granulomatous, minimal	5 (11%)	13 (28%)	8 (17%)	10 (21%)
Inflammation, granulomatous, moderate		2 (4%)	1 (2%)	1 (2%)
Spleen	(50)	(49)	(48)	(47)
Autolysis, marked	1 (2%)	1 (2%)		1 (2%)
Autolysis, mild	1 (2%)	2 (4%)		
Autolysis, moderate	3 (6%)	1 (2%)		1 (2%)
Congestion, marked		1 (2%)		
Cyst, multiple, capsule			1 (2%)	
Degeneration, cystic, mild, capsule		1 (2%)		
Depletion lymphoid, marked	1 (2%)			1 (2%)
Depletion lymphoid, moderate			1 (2%)	1 (2%)
Fibrosis, mild, capsule	1 (2%)	1 (2%)		1 (2%)
Hematopoietic cell proliferation granulocytic, marked	1 (2%)			
Hematopoietic cell proliferation, marked	2 (4%)		2 (4%)	1 (2%)
Hematopoietic cell proliferation, mild	5 (10%)	2 (4%)	3 (6%)	6 (13%)
Hematopoietic cell proliferation, minimal	2 (4%)	5 (10%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation, moderate			6 (13%)	
Hyperplasia, lymphoid, mild		1 (2%)	1 (2%)	2 (4%)
Hyperplasia, lymphoid, minimal	1 (2%)			1 (2%)
Hyperplasia, lymphoid, moderate	1 (2%)			
Hyperplasia, marked, red pulp		1 (2%)		
Hyperplasia, stromal, mild		2 (4%)	1 (2%)	1 (2%)
Hyperplasia, stromal, minimal				1 (2%)
Necrosis, marked				1 (2%)

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Spleen (continued)	(50)	(49)	(48)	(47)
Pigmentation, marked	6 (12%)	2 (4%)	1 (2%)	1 (2%)
Pigmentation, mild	12 (24%)	19 (39%)	10 (21%)	7 (15%)
Pigmentation, minimal	4 (8%)	1 (2%)	9 (19%)	5 (11%)
Pigmentation, moderate	7 (14%)	5 (10%)	2 (4%)	4 (9%)
Thymus	(46)	(45)	(41)	(44)
Atrophy, marked	38 (83%)	38 (84%)	34 (83%)	39 (89%)
Atrophy, mild			1 (2%)	1 (2%)
Atrophy, moderate	3 (7%)	5 (11%)	6 (15%)	1 (2%)
Autolysis, marked		1 (2%)		
Autolysis, moderate				1 (2%)
Depletion lymphoid, marked				1 (2%)
Hemorrhage, marked	1 (2%)			
Hyperplasia, lymphoid, marked	1 (2%)			
Hyperplasia, marked, epithelial cell	1 (2%)			
Hyperplasia, mild, epithelial cell		1 (2%)	1 (2%)	
Polyarteritis, moderate				1 (2%)
Integumentary System				
Mammary gland	(39)	(43)	(41)	(41)
Degeneration, marked	9 (23%)	13 (30%)	4 (10%)	7 (17%)
Degeneration, mild	4 (10%)	4 (9%)		3 (7%)
Degeneration, minimal	2 (5%)	3 (7%)	2 (5%)	1 (2%)
Degeneration, moderate	1 (3%)	4 (9%)	4 (10%)	1 (2%)
Dilatation, moderate, duct		1 (2%)		1 (2%)
Fibrosis, marked		1 (2%)		
Hyperplasia, mild, alveolus	2 (5%)	1 (2%)	2 (5%)	4 (10%)
Hyperplasia, minimal, alveolus	2 (5%)	4 (9%)	4 (10%)	1 (2%)
Hyperplasia, moderate, alveolus				1 (2%)
Infiltration cellular, lymphocyte, minimal	1 (3%)			
Lactation, mild	2 (5%)	1 (2%)	2 (5%)	4 (10%)
Lactation, minimal			2 (5%)	
Skin	(49)	(50)	(48)	(49)
Angiectasis, marked				1 (2%)
Cyst epithelial inclusion	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Ectasia, moderate, lymphatic			1 (2%)	
Hyperkeratosis, marked	1 (2%)	1 (2%)		
Hyperkeratosis, mild	4 (8%)		2 (4%)	2 (4%)
Hyperkeratosis, minimal	1 (2%)			
Hyperkeratosis, moderate		1 (2%)		
Hyperplasia, mild, epidermis	4 (8%)		1 (2%)	1 (2%)
Hyperplasia, minimal, epidermis	2 (4%)			
Hyperplasia, moderate, epidermis		2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active, marked			2 (4%)	
Inflammation, chronic active, mild	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active, minimal	1 (2%)			1 (2%)
Inflammation, chronic active, moderate	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic, mild				1 (2%)
Inflammation, chronic, minimal				1 (2%)
Inflammation, chronic, moderate				1 (2%)
Inflammation, granulomatous, marked			1 (2%)	
Inflammation, suppurative, marked	18 (37%)	19 (38%)	20 (42%)	18 (37%)
Inflammation, suppurative, mild	1 (2%)	1 (2%)		
Inflammation, suppurative, moderate	2 (4%)	2 (4%)	4 (8%)	3 (6%)
Necrosis, mild	1 (2%)		2 (4%)	1 (2%)
Necrosis, moderate	1 (2%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Musculoskeletal System				
Bone, cranium	(2)			
Hemorrhage, marked	1 (50%)			
Hyperostosis, moderate	1 (50%)			
Nervous System				
Brain, brain stem	(46)	(46)	(48)	(47)
Autolysis, marked				1 (2%)
Autolysis, mild		1 (2%)		
Compression, mild	4 (9%)	1 (2%)	1 (2%)	2 (4%)
Compression, minimal			2 (4%)	2 (4%)
Compression, moderate	2 (4%)			
Hemorrhage, mild	1 (2%)			
Hemorrhage, moderate			1 (2%)	
Brain, cerebellum	(46)	(46)	(48)	(46)
Autolysis, mild		1 (2%)		
Hydrocephalus, mild	2 (4%)			
Brain, cerebrum	(45)	(46)	(48)	(46)
Autolysis, mild		1 (2%)		
Developmental malformation	1 (2%)			
Gliosis, marked			1 (2%)	
Gliosis, mild		1 (2%)		
Hemorrhage, mild	1 (2%)			
Hydrocephalus, mild	1 (2%)			1 (2%)
Hydrocephalus, minimal	1 (2%)			
Hydrocephalus, moderate	1 (2%)			
Infiltration cellular, lymphocyte, mild		1 (2%)		
Vacuolization cytoplasmic, minimal			1 (2%)	
Respiratory System				
Lung	(48)	(47)	(47)	(46)
Autolysis, marked	1 (2%)			
Autolysis, mild	1 (2%)	1 (2%)		1 (2%)
Autolysis, moderate	2 (4%)			
Bacterium, marked, mediastinum	1 (2%)			
Congestion, moderate		1 (2%)		1 (2%)
Foreign body, mediastinum	1 (2%)			
Hemorrhage, marked				1 (2%)
Hemorrhage, marked, mediastinum	1 (2%)			
Hyperplasia, marked, alveolar epithelium		1 (2%)		
Hyperplasia, mild, alveolar epithelium	2 (4%)			
Hyperplasia, minimal, alveolar epithelium	1 (2%)	2 (4%)		
Hyperplasia, moderate, alveolar epithelium	1 (2%)			1 (2%)
Infiltration cellular, histiocyte, marked				1 (2%)
Infiltration cellular, histiocyte, mild	5 (10%)	5 (11%)	3 (6%)	7 (15%)
Infiltration cellular, histiocyte, minimal	8 (17%)	6 (13%)	8 (17%)	9 (20%)
Infiltration cellular, histiocyte, moderate	1 (2%)	1 (2%)	1 (2%)	
Infiltration cellular, lymphocyte, mild			2 (4%)	
Infiltration cellular, lymphocyte, minimal		1 (2%)		
Inflammation, chronic, mild		1 (2%)		1 (2%)
Inflammation, chronic, moderate	1 (2%)			
Inflammation, suppurative, marked, mediastinum	1 (2%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Respiratory System (continued)				
Lung (continued)	(48)	(47)	(47)	(46)
Metaplasia, osseous, minimal	3 (6%)	5 (11%)	5 (11%)	2 (4%)
Mineralization, mild, artery	1 (2%)		2 (4%)	1 (2%)
Mineralization, minimal, artery	2 (4%)	5 (11%)	10 (21%)	5 (11%)
Necrosis, marked, mediastinum	1 (2%)			
Thrombosis, mild	1 (2%)			
Nose	(46)	(45)	(49)	(45)
Autolysis, moderate	1 (2%)			
Foreign body				1 (2%)
Hyperkeratosis, marked	1 (2%)			
Hyperkeratosis, mild	1 (2%)			1 (2%)
Hyperplasia, mild, goblet cell	1 (2%)			
Hyperplasia, mild, respiratory epithelium			1 (2%)	
Inflammation, chronic active, marked, upper molar			1 (2%)	
Inflammation, chronic active, mild	1 (2%)		2 (4%)	
Inflammation, chronic active, minimal	1 (2%)			
Inflammation, chronic, mild				1 (2%)
Inflammation, chronic, minimal	1 (2%)			1 (2%)
Inflammation, suppurative, marked	3 (7%)		2 (4%)	1 (2%)
Inflammation, suppurative, mild	4 (9%)	1 (2%)		
Inflammation, suppurative, minimal		1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative, moderate				1 (2%)
Metaplasia, mild, goblet cell			1 (2%)	
Metaplasia, squamous, moderate			1 (2%)	
Necrosis, moderate, upper molar			1 (2%)	
Special Senses System				
Eye	(37)	(43)	(38)	(39)
Atrophy, mild, bilateral, retina	7 (19%)	7 (16%)	5 (13%)	8 (21%)
Atrophy, mild, retina		2 (5%)		2 (5%)
Atrophy, minimal, bilateral, retina	1 (3%)	4 (9%)		4 (10%)
Atrophy, moderate, bilateral, retina	4 (11%)			
Autolysis, marked		1 (2%)		1 (3%)
Hemorrhage, marked			1 (3%)	
Hyperplasia, mild, cornea		1 (2%)	1 (3%)	
Hyperplasia, moderate, cornea		1 (2%)		
Inflammation, suppurative, marked			1 (3%)	1 (3%)
Harderian gland	(38)	(43)	(38)	(39)
Autolysis, moderate		1 (2%)		
Degeneration, mild				2 (5%)
Degeneration, minimal		1 (2%)		1 (3%)
Hyperplasia, mild		2 (5%)		
Hyperplasia, mild, epithelium		1 (2%)		
Infiltration cellular, lymphocyte, mild	1 (3%)	1 (2%)		
Infiltration cellular, lymphocyte, minimal	5 (13%)	1 (2%)	2 (5%)	7 (18%)
Inflammation, suppurative, marked				1 (3%)
Pigmentation, marked				1 (3%)
Lacrimal gland		(2)	(2)	(1)
Ectopic harderian		2 (100%)	2 (100%)	1 (100%)

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Male Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Urinary System				
Kidney	(46)	(49)	(47)	(47)
Accumulation, hyaline droplet, marked	1 (2%)			
Accumulation, hyaline droplet, minimal	1 (2%)			
Autolysis, marked	1 (2%)	3 (6%)		1 (2%)
Autolysis, mild	2 (4%)		1 (2%)	
Autolysis, moderate		2 (4%)		1 (2%)
Cyst, cortex	23 (50%)	31 (63%)	22 (47%)	21 (45%)
Cyst, medulla		1 (2%)		
Dilatation, mild, pelvis	2 (4%)			
Dilatation, moderate, pelvis		1 (2%)		
Fatty change, capsule		3 (6%)	2 (4%)	
Fibrosis, minimal, capsule	1 (2%)			
Hyperplasia, mild, pelvis	3 (7%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, minimal, pelvis			2 (4%)	3 (6%)
Hyperplasia, tubular, mild			2 (4%)	1 (2%)
Infiltration cellular, lymphocyte, minimal	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, suppurative, marked, pelvis	1 (2%)			
Inflammation, suppurative, mild, renal tubule		1 (2%)		
Mineralization, mild, pelvis		1 (2%)	1 (2%)	1 (2%)
Mineralization, minimal, pelvis				1 (2%)
Nephropathy, chronic, marked	3 (7%)	2 (4%)	1 (2%)	1 (2%)
Nephropathy, chronic, mild	18 (39%)	20 (41%)	17 (36%)	10 (21%)
Nephropathy, chronic, minimal	13 (28%)	18 (37%)	18 (38%)	24 (51%)
Nephropathy, chronic, moderate	5 (11%)	6 (12%)	7 (15%)	4 (9%)
Polycystic kidney, marked	1 (2%)		1 (2%)	
Urinary bladder	(45)	(43)	(47)	(46)
Dilatation, marked	2 (4%)			3 (7%)
Hemorrhage, mild	1 (2%)			
Hemorrhage, minimal				1 (2%)
Hyperplasia, mild, transitional epithelium	1 (2%)			
Hypertrophy, mild, transitional epithelium				1 (2%)
Inflammation, suppurative, minimal	1 (2%)			

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

TABLE B1a Summary of the Incidence of Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein 132
TABLE B1b Summary of the Incidence of Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein 136
TABLE B1c Summary of the Incidence of Neoplasms in F_3T21 Female Rats in the 2-Year Feed Study of Genistein 140
TABLE B2a Statistical Analysis of Primary Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein 143
TABLE B2b Statistical Analysis of Primary Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein 145
TABLE B2c Statistical Analysis of Primary Neoplasms in F_3T21 Female Rats in the 2-Year Feed Study of Genistein 147
TABLE B3a Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein 149
TABLE B3b Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein 156
TABLE B3c Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein 163

TABLE B1a
Summary of the Incidence of Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	77	74	81
Early deaths				
Dead	3	8	7	7
Dead no CID	3		1	3
Issue other	4	4	4	4
Missing		1	2	4
Moribund	25	14	21	21
Surplus	36	22	17	20
Survey/sentinel	31			1
Survivors				
Terminal sacrifice	26	28	22	21
Animals examined microscopically	54	50	50	49
Alimentary System				
Intestine large, cecum	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Intestine large, colon	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Intestine small, duodenum	(53)	(50)	(48)	(48)
Leukemia granulocytic	1 (2%)			
Intestine small, ileum	(53)	(49)	(47)	(45)
Leukemia granulocytic	1 (2%)			
Intestine small, jejunum	(54)	(49)	(47)	(45)
Adenoma		1 (2%)		
Liver	(54)	(50)	(50)	(49)
Cholangioma	1 (2%)			
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Lymphoma malignant	1 (2%)			
Mesentery	(1)	(2)	(1)	(2)
Lipoma	1 (100%)			
Sarcoma		1 (50%)		
Pancreas	(54)	(50)	(50)	(48)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Salivary glands	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Stomach, forestomach	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Cardiovascular System				
Heart	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Animals initially in study refers to animals born into the study. Pups were randomly selected for continuation on the study and were necropsied in pathology if they survived to terminal sacrifice or died or became moribund prior to scheduled necropsy. All other pups were allocated to addenda studies or euthanized (Issue other, Surplus). In some cases, young pups that died were likely cannibalized by the dam and were thus indicated as Missing. Survey/sentinel animals were microbiological sentinels. Animals designated Dead no CID (carcass identification number) were animals that were not selected for continuation on study but died prior to weaning. Only animals processed by pathology received CIDs.

TABLE B1a
Summary of the Incidence of Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System				
Adrenal cortex	(54)	(50)	(50)	(49)
Adenoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Lymphoma malignant	1 (2%)			
Adrenal medulla	(54)	(48)	(50)	(48)
Leukemia mononuclear				1 (2%)
Pheochromocytoma benign		1 (2%)		
Pheochromocytoma complex			1 (2%)	
Islets, pancreatic	(54)	(50)	(50)	(48)
Adenoma	1 (2%)	1 (2%)	2 (4%)	
Carcinoma		1 (2%)		1 (2%)
Parathyroid gland	(46)	(46)	(46)	(44)
Leukemia granulocytic	1 (2%)			
Pituitary gland	(54)	(50)	(50)	(49)
Adenoma, pars distalis	38 (70%)	40 (80%)	33 (66%)	46 (94%)
Carcinoma, pars distalis			1 (2%)	
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Thyroid gland	(54)	(50)	(49)	(49)
Adenoma, C-cell	2 (4%)		2 (4%)	3 (6%)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Genital System				
Clitoral gland	(51)	(49)	(49)	(49)
Carcinoma			1 (2%)	
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Squamous cell papilloma	1 (2%)		1 (2%)	
Ovary	(54)	(50)	(50)	(49)
Granulosa cell tumor benign				1 (2%)
Granulosa cell tumor malignant			2 (4%)	
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Sarcoma stromal			1 (2%)	
Oviduct	(54)	(50)	(49)	(49)
Leukemia mononuclear				1 (2%)
Uterus	(54)	(50)	(50)	(49)
Adenocarcinoma			1 (2%)	
Adenoma				1 (2%)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Polyp stromal	4 (7%)	1 (2%)	3 (6%)	1 (2%)
Sarcoma stromal	1 (2%)		1 (2%)	
Vagina	(54)	(50)	(50)	(48)
Granular cell tumor benign	1 (2%)			
Leukemia granulocytic	1 (2%)			
Sarcoma stromal	1 (2%)		1 (2%)	

TABLE B1a
Summary of the Incidence of Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System				
Bone marrow	(54)	(50)	(50)	(48)
Leukemia granulocytic	1 (2%)			
Lymph node	(11)	(10)	(12)	(5)
Fibrous histiocytoma, metastatic, pancreatic, skin		1 (10%)		
Fibrous histiocytoma, metastatic, renal, skin		1 (10%)		
Leukemia granulocytic, lumbar	1 (9%)			
Lymphoma malignant, lumbar	1 (9%)			
Lymphoma malignant, renal	1 (9%)			
Lymph node, mandibular	(53)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Lymph node, mesenteric	(54)	(50)	(50)	(48)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Lymphoma malignant	1 (2%)			
Spleen	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Lymphoma malignant	1 (2%)			
Thymus	(50)	(43)	(43)	(44)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Lymphoma malignant	1 (2%)			
Thymoma malignant	1 (2%)			
Integumentary System				
Mammary gland	(54)	(50)	(50)	(49)
Adenocarcinoma	7 (13%)	1 (2%)	6 (12%)	10 (20%)
Adenocarcinoma, multiple	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Adenoma	2 (4%)	1 (2%)		5 (10%)
Fibroadenoma	19 (35%)	17 (34%)	20 (40%)	8 (16%)
Fibroadenoma, multiple	13 (24%)	10 (20%)	8 (16%)	4 (8%)
Fibroma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Skin	(54)	(50)	(50)	(49)
Fibroma	1 (2%)			
Fibrous histiocytoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Keratoacanthoma		1 (2%)		
Lipoma	1 (2%)		1 (2%)	
Sarcoma	2 (4%)			
Squamous cell carcinoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle		(1)	(1)	
Hemangiosarcoma			1 (100%)	
Histiocytic sarcoma		1 (100%)		
Sarcoma			1 (100%)	

TABLE B1a
Summary of the Incidence of Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Nervous System				
Brain, cerebellum	(53)	(50)	(50)	(49)
Astrocytoma malignant		1 (2%)		
Granular cell tumor benign				1 (2%)
Brain, cerebrum	(54)	(50)	(50)	(49)
Granular cell tumor benign	1 (2%)			1 (2%)
Granular cell tumor malignant			1 (2%)	
Granular cell tumor NOS				1 (2%)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Meningioma malignant			1 (2%)	
Respiratory System				
Lung	(54)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Lymphoma malignant	1 (2%)			
Squamous cell carcinoma, metastatic, nose				1 (2%)
Nose	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Squamous cell carcinoma			1 (2%)	2 (4%)
Trachea	(54)	(50)	(50)	(49)
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Special Senses System				
Eye	(32)	(32)	(31)	(26)
Leukemia mononuclear				1 (4%)
Harderian gland	(30)	(34)	(30)	(25)
Leukemia mononuclear				1 (4%)
Squamous cell carcinoma, metastatic, nose				1 (4%)
Urinary System				
Kidney	(54)	(50)	(50)	(49)
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Leukemia mononuclear				1 (2%)
Nephroblastoma				1 (2%)
Transitional epithelial carcinoma	1 (2%)			
Urinary bladder	(54)	(49)	(49)	(49)
Leukemia mononuclear				1 (2%)

TABLE B1b
Summary of the Incidence of Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	50	50	50
Early deaths				
Dead	3	7	4	9
Dead no CID	3			
Issue other	4			
Moribund	25	12	14	18
Surplus	36			
Survey/sentinel	31			
Survivors				
Terminal sacrifice	26	31	32	23
Animals examined microscopically	54	50	50	50
Alimentary System				
Intestine large, cecum	(54)	(49)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Intestine large, colon	(54)	(50)	(49)	(50)
Leiomyosarcoma				1 (2%)
Leukemia granulocytic	1 (2%)			
Intestine small, duodenum	(53)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Intestine small, ileum	(53)	(49)	(48)	(47)
Leukemia granulocytic	1 (2%)			
Liver	(54)	(50)	(50)	(50)
Cholangioma	1 (2%)			
Hepatocellular adenoma				1 (2%)
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Mesentery	(1)	(2)		(2)
Lipoma	1 (100%)			
Pancreas	(54)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Salivary glands	(54)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Stomach, forestomach	(54)	(49)	(49)	(50)
Leukemia granulocytic	1 (2%)			
Cardiovascular System				
Heart	(54)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Schwannoma NOS		1 (2%)		

The footnotes for this table are defined in Table B1a.

TABLE B1b
Summary of the Incidence of Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System				
Adrenal cortex	(54)	(50)	(50)	(50)
Adenoma	2 (4%)		2 (4%)	2 (4%)
Carcinoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Adrenal medulla	(54)	(48)	(50)	(48)
Pheochromocytoma benign		2 (4%)		
Islets, pancreatic	(54)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Carcinoma			1 (2%)	
Parathyroid gland	(46)	(47)	(42)	(43)
Leukemia granulocytic	1 (2%)			
Pituitary gland	(54)	(49)	(50)	(50)
Adenoma, pars distalis	38 (70%)	32 (65%)	40 (80%)	43 (86%)
Carcinoma, pars distalis				1 (2%)
Leukemia granulocytic	1 (2%)			
Thyroid gland	(54)	(50)	(50)	(50)
Adenoma, C-cell	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Adenoma, follicular cell				1 (2%)
Carcinoma, C-cell				1 (2%)
Leukemia granulocytic	1 (2%)			
General Body System				
Tissue NOS				(1)
Liposarcoma				1 (100%)
Genital System				
Clitoral gland	(51)	(49)	(49)	(49)
Leukemia granulocytic	1 (2%)			
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	
Ovary	(54)	(50)	(49)	(49)
Granulosa cell tumor benign		1 (2%)		
Granulosa cell tumor malignant		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Sarcoma stromal			1 (2%)	
Uterus	(54)	(50)	(49)	(50)
Leiomyosarcoma				1 (2%)
Leukemia granulocytic	1 (2%)			
Polyp stromal	4 (7%)	1 (2%)	2 (4%)	3 (6%)
Sarcoma stromal	1 (2%)	1 (2%)		
Vagina	(54)	(49)	(48)	(50)
Granular cell tumor benign	1 (2%)		1 (2%)	
Leukemia granulocytic	1 (2%)			
Sarcoma stromal	1 (2%)			1 (2%)

TABLE B1b
Summary of the Incidence of Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System				
Bone marrow	(54)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Lymph node	(11)	(9)	(10)	(9)
Leukemia granulocytic, lumbar	1 (9%)			
Lymphoma malignant, lumbar	1 (9%)			
Lymphoma malignant, renal	1 (9%)			
Lymph node, mandibular	(53)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Lymph node, mesenteric	(54)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Spleen	(54)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Thymus	(50)	(47)	(47)	(47)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Thymoma malignant	1 (2%)			
Integumentary System				
Mammary gland	(54)	(50)	(50)	(50)
Adenocarcinoma	7 (13%)	3 (6%)	3 (6%)	7 (14%)
Adenocarcinoma, multiple	1 (2%)			2 (4%)
Adenoma	2 (4%)		2 (4%)	1 (2%)
Fibroadenoma	19 (35%)	21 (42%)	14 (28%)	18 (36%)
Fibroadenoma, multiple	13 (24%)	9 (18%)	17 (34%)	7 (14%)
Leukemia granulocytic	1 (2%)			
Skin	(54)	(50)	(50)	(50)
Fibroma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Keratoacanthoma		1 (2%)		
Lipoma	1 (2%)		1 (2%)	
Osteosarcoma				1 (2%)
Sarcoma	2 (4%)			1 (2%)
Squamous cell carcinoma	1 (2%)			
Musculoskeletal System				
Bone, mandible		(1)		
Squamous cell carcinoma		1 (100%)		
Skeletal muscle		(1)	(1)	
Granulosa cell tumor malignant, metastatic, ovary		1 (100%)		
Lipoma			1 (100%)	
Nervous System				
Brain, cerebrum	(54)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Granular cell tumor benign	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			

TABLE B1b
Summary of the Incidence of Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Respiratory System				
Lung	(54)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	1 (2%)			
Nose	(54)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia granulocytic	1 (2%)			
Squamous cell carcinoma				1 (2%)
Trachea	(54)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Special Senses System				
Ear		(2)		
Squamous cell papilloma		1 (50%)		
Urinary System				
Kidney	(54)	(50)	(50)	(50)
Adenoma, renal tubule			1 (2%)	
Leukemia granulocytic	1 (2%)			
Transitional epithelial carcinoma	1 (2%)			

TABLE B1c
Summary of the Incidence of Neoplasms in F_3T21 Female Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	66	50	50	50
Early deaths				
Dead	5	6	5	8
Moribund	15	14	16	17
Survey/sentinel	13			
Survivors				
Terminal sacrifice	33	30	29	25
Animals examined microscopically	53	50	50	50
Alimentary System				
Intestine small, duodenum	(52)	(50)	(50)	(49)
Leukemia mononuclear			1 (2%)	
Intestine small, ileum	(51)	(48)	(47)	(48)
Leukemia mononuclear			1 (2%)	
Intestine small, jejunum	(51)	(49)	(49)	(48)
Leiomyosarcoma		1 (2%)		
Leukemia mononuclear			1 (2%)	
Liver	(53)	(50)	(50)	(49)
Cholangiocarcinoma		1 (2%)		
Fibrous histiocytoma, metastatic, skin	1 (2%)			
Hepatocellular adenoma			1 (2%)	
Leukemia mononuclear		1 (2%)	1 (2%)	
Oral mucosa	(1)		(1)	(1)
Sarcoma	1 (100%)			1 (100%)
Stomach, glandular	(53)	(50)	(50)	(49)
Leukemia mononuclear			1 (2%)	
Cardiovascular System				
Heart	(53)	(50)	(50)	(49)
Schwannoma NOS			1 (2%)	
Endocrine System				
Adrenal cortex	(53)	(50)	(50)	(49)
Adenoma		2 (4%)	1 (2%)	1 (2%)
Leukemia mononuclear			1 (2%)	
Adrenal medulla	(53)	(46)	(50)	(48)
Leukemia mononuclear			1 (2%)	
Pheochromocytoma benign	2 (4%)	1 (2%)		2 (4%)
Islets, pancreatic	(52)	(50)	(50)	(49)
Adenoma	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pituitary gland	(53)	(50)	(50)	(50)
Adenoma, pars distalis	41 (77%)	42 (84%)	42 (84%)	40 (80%)
Carcinoma, pars distalis		1 (2%)		
Thyroid gland	(53)	(50)	(50)	(49)
Adenoma, C-cell		1 (2%)		3 (6%)
Carcinoma, C-cell		1 (2%)		
Leukemia mononuclear			1 (2%)	

The footnotes for this table are defined in Table B1a.

TABLE B1c
Summary of the Incidence of Neoplasms in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System				
Clitoral gland	(49)	(47)	(49)	(48)
Adenoma	2 (4%)		1 (2%)	
Carcinoma			1 (2%)	
Fibrous histiocytoma, metastatic, skin	1 (2%)			
Leukemia mononuclear			1 (2%)	
Ovary	(53)	(50)	(49)	(49)
Leukemia mononuclear			1 (2%)	
Tubulostromal carcinoma	1 (2%)			
Yolk sac carcinoma				1 (2%)
Oviduct	(53)	(49)	(49)	(49)
Leukemia mononuclear			1 (2%)	
Uterus	(53)	(50)	(50)	(49)
Adenocarcinoma	1 (2%)		1 (2%)	
Adenoma			1 (2%)	
Leiomyoma		1 (2%)		
Leukemia mononuclear			1 (2%)	
Polyp stromal	5 (9%)		5 (10%)	2 (4%)
Sarcoma stromal			2 (4%)	
Hematopoietic System				
Bone marrow	(53)	(50)	(50)	(49)
Leukemia mononuclear		1 (2%)	1 (2%)	
Lymph node	(18)	(9)	(8)	(12)
Fibrous histiocytoma, metastatic, lumbar, skin	1 (6%)			
Leukemia mononuclear, axillary		1 (11%)		
Leukemia mononuclear, inguinal			1 (13%)	
Leukemia mononuclear, lumbar		1 (11%)		
Leukemia mononuclear, mediastinal			1 (13%)	
Leukemia mononuclear, pancreatic			1 (13%)	
Sarcoma, metastatic, inguinal, skin	1 (6%)			
Sarcoma, metastatic, popliteal, skin	1 (6%)			
Sarcoma, metastatic, skin	1 (6%)			
Yolk sac carcinoma, metastatic, lumbar, ovary				1 (8%)
Yolk sac carcinoma, metastatic, renal, ovary				1 (8%)
Lymph node, mandibular	(53)	(49)	(50)	(49)
Leukemia mononuclear			1 (2%)	
Lymph node, mesenteric	(53)	(50)	(50)	(49)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)		
Leukemia mononuclear			1 (2%)	
Spleen	(53)	(50)	(50)	(49)
Leukemia mononuclear		1 (2%)	1 (2%)	
Thymus	(48)	(45)	(46)	(47)
Sarcoma	1 (2%)			
Thymoma malignant	1 (2%)			1 (2%)

TABLE B1c
Summary of the Incidence of Neoplasms in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Integumentary System				
Mammary gland	(53)	(49)	(50)	(50)
Adenocarcinoma	5 (9%)	6 (12%)	8 (16%)	10 (20%)
Adenocarcinoma, multiple	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Adenoma			1 (2%)	1 (2%)
Fibroadenoma	9 (17%)	9 (18%)	13 (26%)	19 (38%)
Fibroadenoma, multiple	23 (43%)	11 (22%)	20 (40%)	9 (18%)
Leukemia mononuclear			1 (2%)	
Skin	(53)	(50)	(50)	(50)
Fibrous histiocytoma	1 (2%)			
Keratoacanthoma				1 (2%)
Leukemia mononuclear			1 (2%)	
Sarcoma	1 (2%)			1 (2%)
Squamous cell carcinoma	1 (2%)			1 (2%)
Nervous System				
Brain, cerebellum	(53)	(50)	(50)	(49)
Granular cell tumor benign	1 (2%)			
Leukemia mononuclear			1 (2%)	
Brain, cerebrum	(53)	(50)	(50)	(49)
Carcinoma, metastatic, pituitary gland				1 (2%)
Glioma malignant, mixed	1 (2%)			
Granular cell tumor benign				1 (2%)
Respiratory System				
Lung	(53)	(50)	(50)	(49)
Fibrous histiocytoma, metastatic, skin	1 (2%)			
Leukemia mononuclear			1 (2%)	
Squamous cell carcinoma, metastatic, skin				1 (2%)
Nose	(53)	(50)	(50)	(49)
Leukemia mononuclear			1 (2%)	
Squamous cell carcinoma	1 (2%)	1 (2%)		3 (6%)
Trachea	(53)	(50)	(50)	(49)
Leukemia mononuclear			1 (2%)	
Urinary System				
Kidney	(53)	(50)	(50)	(49)
Adenoma, renal tubule	1 (2%)		1 (2%)	
Leukemia mononuclear			1 (2%)	
Urinary bladder	(53)	(47)	(48)	(47)
Leukemia mononuclear			1 (2%)	

TABLE B2a
Statistical Analysis of Primary Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Brain (All Sites): Benign, Malignant, or NOS Granular Cell Tumor				
Overall rate[a]	1/54 (1.9%)	0/50 (0.0%)	1/50 (2.0%)	3/49 (6.1%)
Adjusted rate[b]	1/42.0 (2.4%)	0/41.4 (0.0%)	1/39.6 (2.5%)	3/37.8 (7.9%)
Terminal rate[c]	1/26 (3.8%)	0/28 (0.0%)	0/22 (0.0%)	1/21 (4.8%)
First incidence (days)	743 (T)	—[d]	625	625
Poly-3 test[e]	P=0.061	P=0.503N	P=0.748	P=0.267
Mammary Gland: Fibroadenoma				
Overall rate	32/54 (59.3%)	27/50 (54.0%)	28/50 (56.0%)	12/49 (24.5%)
Adjusted rate	32/47.8 (66.9%)	27/46.1 (58.6%)	28/43.8 (63.9%)	12/39.3 (30.6%)
Terminal rate	17/26 (65.4%)	14/28 (50.0%)	14/22 (63.6%)	7/21 (33.3%)
First incidence (days)	330	527	464	549
Poly-3 test	P=0.001N	P=0.261N	P=0.466N	P=0.001N
Mammary Gland: Fibroma or Fibroadenoma				
Overall rate	32/54 (59.3%)	28/50 (56.0%)	28/50 (56.0%)	12/49 (24.5%)
Adjusted rate	32/47.8 (66.9%)	28/46.1 (60.8%)	28/43.8 (63.9%)	12/39.3 (30.6%)
Terminal rate	17/26 (65.4%)	15/28 (53.6%)	14/22 (63.6%)	7/21 (33.3%)
First incidence (days)	330	527	464	549
Poly-3 test	P=0.001N	P=0.338N	P=0.466N	P=0.001N
Mammary Gland: Adenoma				
Overall rate	2/54 (3.7%)	1/50 (2.0%)	0/50 (0.0%)	5/49 (10.2%)
Adjusted rate	2/42.8 (4.7%)	1/41.4 (2.4%)	0/39.2 (0.0%)	5/38.2 (13.1%)
Terminal rate	0/26 (0.0%)	1/28 (3.6%)	0/22 (0.0%)	2/21 (9.5%)
First incidence (days)	625	742 (T)	—	617
Poly-3 test	P=0.019	P=0.512N	P=0.257N	P=0.171
Mammary Gland: Adenocarcinoma				
Overall rate	8/54 (14.8%)	3/50 (6.0%)	8/50 (16.0%)	13/49 (26.5%)
Adjusted rate	8/44.5 (18.0%)	3/42.4 (7.1%)	8/40.9 (19.6%)	13/40.1 (32.4%)
Terminal rate	2/26 (7.7%)	0/28 (0.0%)	4/22 (18.2%)	5/21 (23.8%)
First incidence (days)	366	604	519	549
Poly-3 test	P=0.007	P=0.112N	P=0.536	P=0.096
Mammary Gland: Adenoma or Adenocarcinoma				
Overall rate	9/54 (16.7%)	4/50 (8.0%)	8/50 (16.0%)	16/49 (32.7%)
Adjusted rate	9/44.8 (20.1%)	4/42.4 (9.4%)	8/40.9 (19.6%)	16/40.4 (39.6%)
Terminal rate	2/26 (7.7%)	1/28 (3.6%)	4/22 (18.2%)	7/21 (33.3%)
First incidence (days)	366	604	519	549
Poly-3 test	P=0.001	P=0.135N	P=0.584N	P=0.037
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	38/54 (70.4%)	40/50 (80.0%)	33/50 (66.0%)	46/49 (93.9%)
Adjusted rate	38/47.9 (79.4%)	40/47.3 (84.5%)	33/44.7 (73.8%)	46/47.2 (97.4%)
Terminal rate	21/26 (80.8%)	22/28 (78.6%)	15/22 (68.2%)	20/21 (95.2%)
First incidence (days)	424	559	485	344
Poly-3 test	P=0.004	P=0.345	P=0.340N	P=0.004
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	38/54 (70.4%)	40/50 (80.0%)	34/50 (68.0%)	46/49 (93.9%)
Adjusted rate	38/47.9 (79.4%)	40/47.3 (84.5%)	34/44.8 (75.8%)	46/47.2 (97.4%)
Terminal rate	21/26 (80.8%)	22/28 (78.6%)	15/22 (68.2%)	20/21 (95.2%)
First incidence (days)	424	559	485	344
Poly-3 test	P=0.004	P=0.345	P=0.430N	P=0.004

TABLE B2a
Statistical Analysis of Primary Neoplasms in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Skin: Fibroma, Fibrous Histiocytoma, or Sarcoma				
Overall rate	3/54 (5.6%)	1/50 (2.0%)	0/50 (0.0%)	0/49 (0.0%)
Adjusted rate	3/43.4 (6.9%)	1/41.4 (2.4%)	0/39.2 (0.0%)	0/37.1 (0.0%)
Terminal rate	1/26 (3.8%)	1/28 (3.6%)	0/22 (0.0%)	0/21 (0.0%)
First incidence (days)	223	744 (T)	—	—
Poly-3 test	P=0.180N	P=0.322N	P=0.137N	P=0.148N
Skin: All Neoplastic Morphologies				
Overall rate	4/54 (7.4%)	3/50 (6.0%)	1/50 (2.0%)	0/49 (0.0%)
Adjusted rate	4/43.5 (9.2%)	3/42.4 (7.1%)	1/39.9 (2.5%)	0/37.1 (0.0%)
Terminal rate	1/26 (3.8%)	1/28 (3.6%)	0/22 (0.0%)	0/21 (0.0%)
First incidence (days)	223	550	485	—
Poly-3 test	P=0.073N	P=0.513N	P=0.205N	P=0.082N
Thyroid Gland (C-Cell): Adenoma				
Overall rate	2/54 (3.7%)	0/50 (0.0%)	2/49 (4.1%)	3/49 (6.1%)
Adjusted rate	2/42.0 (4.8%)	0/41.4 (0.0%)	2/38.8 (5.1%)	3/37.1 (8.1%)
Terminal rate	2/26 (7.7%)	0/28 (0.0%)	1/22 (4.5%)	3/21 (14.3%)
First incidence (days)	742 (T)	—	730	736 (T)
Poly-3 test	P=0.163	P=0.240N	P=0.666	P=0.443
Uterus: Stromal Polyp				
Overall rate	4/54 (7.4%)	1/50 (2.0%)	3/50 (6.0%)	1/49 (2.0%)
Adjusted rate	4/42.5 (9.4%)	1/41.4 (2.4%)	3/39.8 (7.5%)	1/37.1 (2.7%)
Terminal rate	3/26 (11.5%)	1/28 (3.6%)	0/22 (0.0%)	1/21 (4.8%)
First incidence (days)	582	738 (T)	637	736 (T)
Poly-3 test	P=0.332N	P=0.186N	P=0.537N	P=0.221N
All Organs: Benign Neoplasms				
Overall rate	49/54 (90.7%)	45/50 (90.0%)	44/50 (88.0%)	46/49 (93.9%)
Adjusted rate	49/50.7 (96.7%)	45/48.4 (93.0%)	44/48.2 (91.3%)	46/47.2 (97.4%)
Terminal rate	25/26 (96.2%)	25/28 (89.3%)	18/22 (81.8%)	20/21 (95.2%)
First incidence (days)	330	527	464	344
Poly-3 test	P=0.314	P=0.338N	P=0.225N	P=0.678
All Organs: Malignant Neoplasms				
Overall rate	14/54 (25.9%)	7/50 (14.0%)	19/50 (38.0%)	17/49 (34.7%)
Adjusted rate	14/45.9 (30.5%)	7/43.6 (16.1%)	19/42.9 (44.3%)	17/41.7 (40.8%)
Terminal rate	4/26 (15.4%)	2/28 (7.1%)	6/22 (27.3%)	6/21 (28.6%)
First incidence (days)	223	550	519	329
Poly-3 test	P=0.055	P=0.083N	P=0.126	P=0.214
All Organs: Benign or Malignant Neoplasms				
Overall rate	52/54 (96.3%)	47/50 (94.0%)	45/50 (90.0%)	48/49 (98.0%)
Adjusted rate	52/53.2 (97.7%)	47/49.0 (95.9%)	45/48.2 (93.4%)	48/48.2 (99.7%)
Terminal rate	25/26 (96.2%)	26/28 (92.9%)	19/22 (86.4%)	21/21 (100.0%)
First incidence (days)	223	527	464	329
Poly-3 test	P=0.239	P=0.515N	P=0.269N	P=0.512

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[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 control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.

TABLE B2b
Statistical Analysis of Primary Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Mammary Gland: Fibroadenoma				
Overall rate[a]	32/54 (59.3%)	30/50 (60.0%)	31/50 (62.0%)	25/50 (50.0%)
Adjusted rate[b]	32/47.8 (66.9%)	30/45.8 (65.5%)	31/48.3 (64.2%)	25/44.1 (56.8%)
Terminal rate[c]	17/26 (65.4%)	20/31 (64.5%)	19/32 (59.4%)	13/23 (56.5%)
First incidence (days)	330	542	422	375
Poly-3 test[d]	P=0.173N	P=0.530N	P=0.474N	P=0.206N
Mammary Gland: Adenocarcinoma				
Overall rate	8/54 (14.8%)	3/50 (6.0%)	3/50 (6.0%)	9/50 (18.0%)
Adjusted rate	8/44.5 (18.0%)	3/43.7 (6.9%)	3/44.4 (6.8%)	9/41.0 (21.9%)
Terminal rate	2/26 (7.7%)	0/31 (0.0%)	1/32 (3.1%)	2/23 (8.7%)
First incidence (days)	366	580	682	594
Poly-3 test	P=0.074	P=0.102N	P=0.097N	P=0.426
Mammary Gland: Adenoma or Adenocarcinoma				
Overall rate	9/54 (16.7%)	3/50 (6.0%)	5/50 (10.0%)	10/50 (20.0%)
Adjusted rate	9/44.8 (20.1%)	3/43.7 (6.9%)	5/44.4 (11.3%)	10/41.0 (24.4%)
Terminal rate	2/26 (7.7%)	0/31 (0.0%)	3/32 (9.4%)	3/23 (13.0%)
First incidence (days)	366	580	682	594
Poly-3 test	P=0.069	P=0.063N	P=0.196N	P=0.413
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	38/54 (70.4%)	32/49 (65.3%)	40/50 (80.0%)	43/50 (86.0%)
Adjusted rate	38/47.9 (79.4%)	32/46.9 (68.3%)	40/48.4 (82.7%)	43/47.8 (90.0%)
Terminal rate	21/26 (80.8%)	17/31 (54.8%)	26/32 (81.3%)	20/23 (87.0%)
First incidence (days)	424	450	409	417
Poly-3 test	P=0.017	P=0.151N	P=0.439	P=0.106
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	38/54 (70.4%)	32/49 (65.3%)	40/50 (80.0%)	44/50 (88.0%)
Adjusted rate	38/47.9 (79.4%)	32/46.9 (68.3%)	40/48.4 (82.7%)	44/48.1 (91.4%)
Terminal rate	21/26 (80.8%)	17/31 (54.8%)	26/32 (81.3%)	20/23 (87.0%)
First incidence (days)	424	450	409	417
Poly-3 test	P=0.009	P=0.151N	P=0.439	P=0.068
Skin: Fibroma or Sarcoma				
Overall rate	3/54 (5.6%)	1/50 (2.0%)	1/50 (2.0%)	2/50 (4.0%)
Adjusted rate	3/43.4 (6.9%)	1/42.6 (2.4%)	1/44.8 (2.2%)	2/39.5 (5.1%)
Terminal rate	1/26 (3.8%)	1/31 (3.2%)	0/32 (0.0%)	1/23 (4.3%)
First incidence (days)	223	738 (T)	409	601
Poly-3 test	P=0.569	P=0.312N	P=0.294N	P=0.543N
Skin: All Neoplastic Morphologies				
Overall rate	4/54 (7.4%)	2/50 (4.0%)	2/50 (4.0%)	3/50 (6.0%)
Adjusted rate	4/43.5 (9.2%)	2/42.6 (4.7%)	2/45.1 (4.4%)	3/39.5 (7.6%)
Terminal rate	1/26 (3.8%)	2/31 (6.5%)	0/32 (0.0%)	2/23 (8.7%)
First incidence (days)	223	738 (T)	409	601
Poly-3 test	P=0.537	P=0.346N	P=0.320N	P=0.552N
Thyroid Gland (All Sites): Adenoma or Carcinoma				
Overall rate	2/54 (3.7%)	1/50 (2.0%)	1/50 (2.0%)	3/50 (6.0%)
Adjusted rate	2/42.0 (4.8%)	1/42.6 (2.4%)	1/44.0 (2.3%)	3/39.2 (7.6%)
Terminal rate	2/26 (7.7%)	1/31 (3.2%)	1/32 (3.1%)	2/23 (8.7%)
First incidence (days)	742 (T)	748 (T)	752 (T)	694
Poly-3 test	P=0.225	P=0.495N	P=0.484N	P=0.469

TABLE B2b
Statistical Analysis of Primary Neoplasms in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Uterus: Stromal Polyp				
Overall rate	4/54 (7.4%)	1/50 (2.0%)	2/49 (4.1%)	3/50 (6.0%)
Adjusted rate	4/42.5 (9.4%)	1/42.6 (2.4%)	2/43.2 (4.6%)	3/39.4 (7.6%)
Terminal rate	3/26 (11.5%)	1/31 (3.2%)	2/32 (6.3%)	2/23 (8.7%)
First incidence (days)	582	737 (T)	747 (T)	647
Poly-3 test	P=0.452	P=0.177N	P=0.330N	P=0.542N
All Organs: Benign Neoplasms				
Overall rate	49/54 (90.7%)	44/50 (88.0%)	49/50 (98.0%)	50/50 (100.0%)
Adjusted rate	49/50.7 (96.7%)	44/48.2 (91.3%)	49/49.7 (98.6%)	50/50.0 (100.0%)
Terminal rate	25/26 (96.2%)	28/31 (90.3%)	32/32 (100.0%)	23/23 (100.0%)
First incidence (days)	330	450	409	375
Poly-3 test	P=0.067	P=0.223N	P=0.523	P=0.270
All Organs: Malignant Neoplasms				
Overall rate	14/54 (25.9%)	8/50 (16.0%)	6/50 (12.0%)	15/50 (30.0%)
Adjusted rate	14/45.9 (30.5%)	8/44.7 (17.9%)	6/44.4 (13.5%)	15/42.2 (35.5%)
Terminal rate	4/26 (15.4%)	3/31 (9.7%)	4/32 (12.5%)	5/23 (21.7%)
First incidence (days)	223	438	682	506
Poly-3 test	P=0.068	P=0.121N	P=0.042N	P=0.391
All Organs: Benign or Malignant Neoplasms				
Overall rate	52/54 (96.3%)	45/50 (90.0%)	49/50 (98.0%)	50/50 (100.0%)
Adjusted rate	52/53.2 (97.7%)	45/49.0 (91.9%)	49/49.7 (98.6%)	50/50.0 (100.0%)
Terminal rate	25/26 (96.2%)	28/31 (90.3%)	32/32 (100.0%)	23/23 (100.0%)
First incidence (days)	223	438	409	375
Poly-3 test	P=0.102	P=0.176N	P=0.680	P=0.437

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.

TABLE B2c
Statistical Analysis of Primary Neoplasms in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Mammary Gland: Fibroadenoma				
Overall rate[a]	32/53 (60.4%)	20/49 (40.8%)	33/50 (66.0%)	28/50 (56.0%)
Adjusted rate[b]	32/49.1 (65.2%)	20/43.5 (46.0%)	33/45.8 (72.0%)	28/44.2 (63.4%)
Terminal rate[c]	23/33 (69.7%)	15/30 (50.0%)	22/29 (75.9%)	15/25 (60.0%)
First incidence (days)	499	524	558	590
Poly-3 test[d]	P=0.335	P=0.043N	P=0.304	P=0.516N
Mammary Gland: Adenocarcinoma				
Overall rate	7/53 (13.2%)	8/49 (16.3%)	10/50 (20.0%)	12/50 (24.0%)
Adjusted rate	7/47.2 (14.8%)	8/42.9 (18.6%)	10/44.7 (22.4%)	12/43.0 (27.9%)
Terminal rate	3/33 (9.1%)	4/30 (13.3%)	7/29 (24.1%)	6/25 (24.0%)
First incidence (days)	611	574	558	323
Poly-3 test	P=0.103	P=0.421	P=0.254	P=0.101
Mammary Gland: Adenoma or Adenocarcinoma				
Overall rate	7/53 (13.2%)	8/49 (16.3%)	11/50 (22.0%)	13/50 (26.0%)
Adjusted rate	7/47.2 (14.8%)	8/42.9 (18.6%)	11/44.8 (24.6%)	13/43.2 (30.1%)
Terminal rate	3/33 (9.1%)	4/30 (13.3%)	7/29 (24.1%)	6/25 (24.0%)
First incidence (days)	611	574	558	323
Poly-3 test	P=0.067	P=0.421	P=0.180	P=0.065
Nose: Squamous Cell Carcinoma				
Overall rate	1/53 (1.9%)	1/50 (2.0%)	0/50 (0.0%)	3/49 (6.1%)
Adjusted rate	1/46.6 (2.1%)	1/41.8 (2.4%)	0/43.2 (0.0%)	3/39.8 (7.5%)
Terminal rate	0/33 (0.0%)	1/30 (3.3%)	0/29 (0.0%)	2/25 (8.0%)
First incidence (days)	589	750 (T)	—[e]	735
Poly-3 test	P=0.094	P=0.737	P=0.515N	P=0.251
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	41/53 (77.4%)	42/50 (84.0%)	42/50 (84.0%)	40/50 (80.0%)
Adjusted rate	41/50.5 (81.2%)	42/48.0 (87.6%)	42/48.6 (86.5%)	40/47.8 (83.6%)
Terminal rate	25/33 (75.8%)	26/30 (86.7%)	24/29 (82.8%)	20/25 (80.0%)
First incidence (days)	499	495	558	493
Poly-3 test	P=0.516N	P=0.267	P=0.324	P=0.478
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	41/53 (77.4%)	43/50 (86.0%)	42/50 (84.0%)	40/50 (80.0%)
Adjusted rate	41/50.5 (81.2%)	43/48.1 (89.3%)	42/48.6 (86.5%)	40/47.8 (83.6%)
Terminal rate	25/33 (75.8%)	26/30 (86.7%)	24/29 (82.8%)	20/25 (80.0%)
First incidence (days)	499	495	558	493
Poly-3 test	P=0.467N	P=0.187	P=0.324	P=0.478
Skin: Fibrous Histiocytoma or Sarcoma				
Overall rate	2/53 (3.8%)	0/50 (0.0%)	0/50 (0.0%)	1/50 (2.0%)
Adjusted rate	2/46.3 (4.3%)	0/41.8 (0.0%)	0/43.2 (0.0%)	1/40.8 (2.5%)
Terminal rate	1/33 (3.0%)	0/30 (0.0%)	0/29 (0.0%)	0/25 (0.0%)
First incidence (days)	676	—	—	675
Poly-3 test	P=0.656	P=0.260N	P=0.253N	P=0.544N
Skin: All Neoplastic Morphologies				
Overall rate	3/53 (5.7%)	0/50 (0.0%)	0/50 (0.0%)	3/50 (6.0%)
Adjusted rate	3/47.0 (6.4%)	0/41.8 (0.0%)	0/43.2 (0.0%)	3/41.1 (7.3%)
Terminal rate	1/33 (3.0%)	0/30 (0.0%)	0/29 (0.0%)	0/25 (0.0%)
First incidence (days)	485	—	—	668
Poly-3 test	P=0.198	P=0.141N	P=0.134N	P=0.599

TABLE B2c
Statistical Analysis of Primary Neoplasms in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Thyroid Gland (C-Cell): Adenoma				
Overall rate	0/53 (0.0%)	1/50 (2.0%)	0/50 (0.0%)	3/49 (6.1%)
Adjusted rate	0/46.1 (0.0%)	1/41.8 (2.4%)	0/43.2 (0.0%)	3/39.8 (7.5%)
Terminal rate	0/33 (0.0%)	1/30 (3.3%)	0/29 (0.0%)	3/25 (12.0%)
First incidence (days)	—	754 (T)	—	750 (T)
Poly-3 test	P=0.033	P=0.481	—[f]	P=0.094
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	0/53 (0.0%)	1/50 (2.0%)	0/50 (0.0%)	3/49 (6.1%)
Adjusted rate	0/46.1 (0.0%)	1/41.8 (2.4%)	0/43.2 (0.0%)	3/39.8 (7.5%)
Terminal rate	0/33 (0.0%)	1/30 (3.3%)	0/29 (0.0%)	3/25 (12.0%)
First incidence (days)	—	754 (T)	—	750 (T)
Poly-3 test	P=0.033	P=0.481	—	P=0.094
Uterus: Stromal Polyp				
Overall rate	5/53 (9.4%)	0/50 (0.0%)	5/50 (10.0%)	2/49 (4.1%)
Adjusted rate	5/47.1 (10.6%)	0/41.8 (0.0%)	5/43.6 (11.5%)	2/40.0 (5.0%)
Terminal rate	1/33 (3.0%)	0/30 (0.0%)	4/29 (13.8%)	1/25 (4.0%)
First incidence (days)	611	—	640	705
Poly-3 test	P=0.487N	P=0.042N	P=0.580	P=0.288N
All Organs: Benign Neoplasms				
Overall rate	49/53 (92.5%)	48/50 (96.0%)	46/50 (92.0%)	48/50 (96.0%)
Adjusted rate	49/51.6 (95.0%)	48/49.0 (98.0%)	46/48.7 (94.5%)	48/48.4 (99.1%)
Terminal rate	31/33 (93.9%)	29/30 (96.7%)	27/29 (93.1%)	25/25 (100.0%)
First incidence (days)	499	495	558	493
Poly-3 test	P=0.266	P=0.396	P=0.640N	P=0.246
All Organs: Malignant Neoplasms				
Overall rate	16/53 (30.2%)	11/50 (22.0%)	13/50 (26.0%)	17/50 (34.0%)
Adjusted rate	16/49.5 (32.3%)	11/43.1 (25.5%)	13/44.7 (29.1%)	17/43.8 (38.8%)
Terminal rate	7/33 (21.2%)	6/30 (20.0%)	10/29 (34.5%)	7/25 (28.0%)
First incidence (days)	485	574	558	323
Poly-3 test	P=0.159	P=0.312N	P=0.453N	P=0.331
All Organs: Benign or Malignant Neoplasms				
Overall rate	52/53 (98.1%)	48/50 (96.0%)	47/50 (94.0%)	49/50 (98.0%)
Adjusted rate	52/53.0 (98.1%)	48/49.0 (98.0%)	47/49.1 (95.7%)	49/49.3 (99.3%)
Terminal rate	32/33 (97.0%)	29/30 (96.7%)	27/29 (93.1%)	25/25 (100.0%)
First incidence (days)	485	495	558	323
Poly-3 test	P=0.430	P=0.743N	P=0.444N	P=0.646

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

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	77	74	81
Early deaths				
Dead	3	8	7	7
Dead no CID	3		1	3
Issue other	4	4	4	4
Missing		1	2	4
Moribund	25	14	21	21
Surplus	36	22	17	20
Survey/sentinel	31			1
Survivors				
Terminal sacrifice	26	28	22	21
Animals examined microscopically	54	50	50	49
Alimentary System				
Esophagus	(54)	(50)	(49)	(49)
Dilatation, moderate, lumen				1 (2%)
Intestine small, jejunum	(54)	(49)	(47)	(45)
Inflammation, moderate				1 (2%)
Liver	(54)	(50)	(50)	(49)
Angiectasis, mild			1 (2%)	
Angiectasis, minimal		1 (2%)	3 (6%)	2 (4%)
Atypical cells, mild				1 (2%)
Basophilic focus	4 (7%)	7 (14%)	3 (6%)	7 (14%)
Clear cell focus	1 (2%)			
Congestion, mild		1 (2%)		
Cyst			1 (2%)	2 (4%)
Degeneration, cystic, minimal	1 (2%)		2 (4%)	
Developmental malformation		2 (4%)	1 (2%)	
Eosinophilic focus		4 (8%)	4 (8%)	2 (4%)
Fibrosis, mild, biliary tract	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Fibrosis, minimal, biliary tract	3 (6%)		1 (2%)	
Hematopoietic cell proliferation, mild	1 (2%)			
Hematopoietic cell proliferation, minimal	5 (9%)	1 (2%)	2 (4%)	4 (8%)
Hepatodiaphragmatic nodule	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, mild, bile duct	6 (11%)	4 (8%)	5 (10%)	2 (4%)
Hyperplasia, minimal, bile duct	16 (30%)	9 (18%)	9 (18%)	8 (16%)
Hyperplasia, moderate, bile duct			1 (2%)	
Infiltration cellular, lymphocyte, minimal	2 (4%)		4 (8%)	2 (4%)
Inflammation, chronic active, mild			1 (2%)	1 (2%)
Inflammation, chronic active, minimal	4 (7%)	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic active, moderate			1 (2%)	
Mixed cell focus		1 (2%)		1 (2%)
Necrosis, minimal	1 (2%)	2 (4%)		
Polyarteritis, minimal	1 (2%)			
Tension lipidosis, mild	1 (2%)	1 (2%)		
Vacuolization cytoplasmic, focal		2 (4%)		2 (4%)
Vacuolization cytoplasmic, mild	1 (2%)	2 (4%)	1 (2%)	
Vacuolization cytoplasmic, minimal	4 (7%)	1 (2%)	9 (18%)	2 (4%)
Mesentery	(1)	(2)	(1)	(2)
Necrosis, mild, fat		1 (50%)	1 (100%)	2 (100%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Animals initially in study refers to animals born into the study. Pups were randomly selected for continuation on the study and were necropsied in pathology if they survived to terminal sacrifice or died or became moribund prior to scheduled necropsy. All other pups were allocated to addenda studies or euthanized (Issue other, Surplus). In some cases, young pups that died were likely cannibalized by the dam and were thus indicated as Missing. Survey/sentinel animals were microbiological sentinels. Animals designated Dead no CID (carcass identification number) were animals that were not selected for continuation on study but died prior to weaning. Only animals processed by pathology received CIDs.

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Alimentary System (continued)				
Pancreas	(54)	(50)	(50)	(48)
Degeneration, marked, acinar cell	1 (2%)	1 (2%)		
Degeneration, mild, acinar cell	6 (11%)	7 (14%)	7 (14%)	3 (6%)
Degeneration, minimal, acinar cell	14 (26%)	4 (8%)	10 (20%)	6 (13%)
Degeneration, moderate, acinar cell		1 (2%)	3 (6%)	
Hyperplasia, minimal, acinar cell		1 (2%)		
Salivary glands	(54)	(50)	(50)	(49)
Atrophy, mild	1 (2%)			
Inflammation, mild, parotid gland				1 (2%)
Inflammation, minimal, submandibular gland			1 (2%)	
Stomach, forestomach	(54)	(50)	(50)	(49)
Hyperplasia, mild	2 (4%)		1 (2%)	
Hyperplasia, minimal	1 (2%)			
Inflammation, minimal		1 (2%)		
Keratin cyst			1 (2%)	
Ulcer, marked			1 (2%)	
Ulcer, mild	1 (2%)			1 (2%)
Ulcer, moderate				1 (2%)
Stomach, glandular	(54)	(50)	(50)	(49)
Erosion, mild				1 (2%)
Erosion, minimal			1 (2%)	
Cardiovascular System				
Blood vessel	(53)	(50)	(50)	(49)
Mineralization, marked		1 (2%)		
Mineralization, mild			1 (2%)	
Heart	(54)	(50)	(50)	(49)
Cardiomyopathy, mild	1 (2%)	3 (6%)	2 (4%)	8 (16%)
Cardiomyopathy, minimal	25 (46%)	25 (50%)	20 (40%)	18 (37%)
Cardiomyopathy, moderate		2 (4%)	2 (4%)	
Dilatation, moderate, atrium right		1 (2%)		
Inflammation, mild				1 (2%)
Mineralization, moderate			1 (2%)	
Endocrine System				
Adrenal cortex	(54)	(50)	(50)	(49)
Accessory adrenal cortical nodule				1 (2%)
Angiectasis, mild			2 (4%)	
Angiectasis, minimal	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Atrophy, marked			1 (2%)	
Atrophy, mild				1 (2%)
Atrophy, moderate		1 (2%)		
Degeneration, cystic, marked	3 (6%)	1 (2%)		2 (4%)
Degeneration, cystic, mild	22 (41%)	21 (42%)	29 (58%)	22 (45%)
Degeneration, cystic, minimal	14 (26%)	18 (36%)	8 (16%)	9 (18%)
Degeneration, cystic, moderate	6 (11%)	5 (10%)	5 (10%)	9 (18%)
Hematopoietic cell proliferation, mild	1 (2%)			
Hematopoietic cell proliferation, minimal		1 (2%)	1 (2%)	
Hyperplasia, mild	3 (6%)	6 (12%)	4 (8%)	4 (8%)
Hyperplasia, minimal	8 (15%)	12 (24%)	12 (24%)	5 (10%)
Hypertrophy, marked		3 (6%)		
Hypertrophy, mild	9 (17%)	6 (12%)	8 (16%)	5 (10%)
Hypertrophy, minimal	5 (9%)	4 (8%)	9 (18%)	7 (14%)
Hypertrophy, moderate	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Infarct, moderate				1 (2%)
Vacuolization cytoplasmic, minimal				1 (2%)

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System (continued)				
Adrenal medulla	(54)	(48)	(50)	(48)
Hyperplasia, diffuse, moderate			1 (2%)	
Hyperplasia, focal, mild	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, focal, minimal	2 (4%)	2 (4%)	4 (8%)	
Hyperplasia, focal, moderate			1 (2%)	
Infiltration cellular, eosinophilic, moderate		1 (2%)		
Islets, pancreatic	(54)	(50)	(50)	(48)
Hyperplasia, minimal		1 (2%)	2 (4%)	
Parathyroid gland	(46)	(46)	(46)	(44)
Hyperplasia, diffuse, mild	1 (2%)			
Hyperplasia, focal, mild		2 (4%)		
Hyperplasia, focal, minimal	2 (4%)		1 (2%)	
Hyperplasia, focal, moderate				1 (2%)
Pituitary gland	(54)	(50)	(50)	(49)
Angiectasis, moderate	1 (2%)			
Cyst	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia, mild, pars distalis	4 (7%)	3 (6%)	5 (10%)	
Hyperplasia, minimal, pars distalis		3 (6%)	5 (10%)	1 (2%)
Hyperplasia, moderate, pars distalis	1 (2%)		3 (6%)	
Infiltration cellular, histiocyte, moderate			1 (2%)	
Thyroid gland	(54)	(50)	(49)	(49)
Atrophy, mild, follicular cell		2 (4%)		
Cyst, squamous, mild	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Cyst, squamous, minimal	4 (7%)	3 (6%)	8 (16%)	3 (6%)
Hyperplasia, mild, C-cell			1 (2%)	1 (2%)
Hyperplasia, minimal, C-cell	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, minimal, follicular cell		1 (2%)		
Genital System				
Clitoral gland	(51)	(49)	(49)	(49)
Degeneration, marked, parenchymal cell	1 (2%)			1 (2%)
Degeneration, mild, parenchymal cell	1 (2%)	2 (4%)		2 (4%)
Degeneration, minimal, parenchymal cell	1 (2%)		1 (2%)	2 (4%)
Degeneration, moderate, parenchymal cell	2 (4%)	1 (2%)		1 (2%)
Dilatation, marked, duct	1 (2%)	1 (2%)		
Dilatation, mild, duct	2 (4%)	4 (8%)	4 (8%)	2 (4%)
Dilatation, minimal, duct			1 (2%)	1 (2%)
Dilatation, moderate, duct	4 (8%)	4 (8%)	3 (6%)	3 (6%)
Hyperplasia, mild	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, minimal	1 (2%)	1 (2%)		
Inflammation, marked	1 (2%)		2 (4%)	
Inflammation, mild	10 (20%)	15 (31%)	12 (24%)	13 (27%)
Inflammation, minimal	13 (25%)	9 (18%)	5 (10%)	8 (16%)
Inflammation, moderate	8 (16%)	4 (8%)	2 (4%)	2 (4%)
Ovary	(54)	(50)	(50)	(49)
Angiectasis, mild			1 (2%)	
Angiectasis, minimal			1 (2%)	
Atrophy, marked	2 (4%)			1 (2%)
Atrophy, mild	12 (22%)	14 (28%)	16 (32%)	17 (35%)
Atrophy, minimal	3 (6%)	5 (10%)	4 (8%)	4 (8%)
Atrophy, moderate	17 (31%)	13 (26%)	9 (18%)	18 (37%)
Cyst	11 (20%)	12 (24%)	14 (28%)	13 (27%)
Hyperplasia, stromal, marked	1 (2%)			
Hyperplasia, stromal, mild	10 (19%)	8 (16%)	16 (32%)	12 (24%)
Hyperplasia, stromal, minimal	11 (20%)	9 (18%)	7 (14%)	5 (10%)
Hyperplasia, stromal, moderate	3 (6%)	2 (4%)	7 (14%)	2 (4%)

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Uterus	(54)	(50)	(50)	(49)
Angiectasis, mild			1 (2%)	
Angiectasis, minimal			1 (2%)	1 (2%)
Atrophy, moderate			1 (2%)	
Hemorrhage, minimal		1 (2%)		
Hyperplasia, cystic, marked				1 (2%)
Hyperplasia, cystic, mild	9 (17%)	7 (14%)	5 (10%)	10 (20%)
Hyperplasia, cystic, minimal	5 (9%)	12 (24%)	4 (8%)	8 (16%)
Hyperplasia, cystic, moderate	2 (4%)	5 (10%)	7 (14%)	5 (10%)
Hyperplasia, focal, mild				1 (2%)
Hypertrophy, cervix, muscularis	1 (2%)	1 (2%)	2 (4%)	
Inflammation, mild	1 (2%)			
Metaplasia, mild	1 (2%)	4 (8%)	3 (6%)	
Metaplasia, minimal	2 (4%)	1 (2%)	5 (10%)	5 (10%)
Metaplasia, moderate	1 (2%)			
Necrosis, moderate			1 (2%)	
Vagina	(54)	(50)	(50)	(48)
Developmental malformation				1 (2%)
Hyperplasia, mild				1 (2%)
Inflammation, mild	2 (4%)	3 (6%)	1 (2%)	3 (6%)
Inflammation, minimal	2 (4%)		4 (8%)	3 (6%)
Inflammation, moderate				1 (2%)
Keratin cyst, mild	2 (4%)			
Hematopoietic System				
Bone marrow	(54)	(50)	(50)	(48)
Hyperplasia, mild, myeloid cell				2 (4%)
Hypocellularity, mild			2 (4%)	1 (2%)
Hypocellularity, moderate	2 (4%)	1 (2%)		1 (2%)
Lymph node	(11)	(10)	(12)	(5)
Degeneration, cystic, marked, lumbar	1 (9%)		1 (8%)	
Degeneration, cystic, mild, lumbar	2 (18%)	3 (30%)	1 (8%)	3 (60%)
Degeneration, cystic, mild, renal				1 (20%)
Degeneration, cystic, minimal				1 (20%)
Degeneration, cystic, minimal, lumbar		1 (10%)		
Degeneration, cystic, moderate, lumbar	1 (9%)		2 (17%)	
Hemorrhage, mild, pancreatic			1 (8%)	
Hemorrhage, minimal, lumbar			1 (8%)	
Hemorrhage, minimal, pancreatic				1 (20%)
Hyperplasia, lymphoid, minimal, lumbar	1 (9%)			
Hyperplasia, lymphoid, moderate, lumbar		1 (10%)		
Hyperplasia, lymphoid, moderate, popliteal		1 (10%)		
Infiltration cellular, plasma cell, mild				1 (20%)
Infiltration cellular, plasma cell, mild, lumbar	5 (45%)	4 (40%)	3 (25%)	1 (20%)
Infiltration cellular, plasma cell, mild, popliteal			1 (8%)	
Infiltration cellular, plasma cell, mild, renal		1 (10%)		
Infiltration cellular, plasma cell, minimal, lumbar		1 (10%)		
Infiltration cellular, plasma cell, minimal, pancreatic		1 (10%)		
Infiltration cellular, plasma cell, minimal, popliteal		1 (10%)	1 (8%)	

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm		5 ppm		100 ppm		500 ppm	
Hematopoietic System (continued)								
Lymph node (continued)	(11)		(10)		(12)		(5)	
Infiltration cellular, plasma cell, moderate, inguinal	1	(9%)						
Infiltration cellular, plasma cell, moderate, lumbar	1	(9%)	1	(10%)	1	(8%)	2	(40%)
Infiltration cellular, plasma cell, moderate, popliteal			1	(10%)	1	(8%)		
Infiltration cellular, plasma cell, moderate, renal							1	(20%)
Inflammation, granulomatous, mild, pancreatic					1	(8%)		
Pigmentation, moderate, pancreatic					1	(8%)		
Thrombosis, moderate, thoracic					1	(8%)		
Lymph node, mandibular	(53)		(50)		(50)		(49)	
Degeneration, cystic, mild					3	(6%)		
Degeneration, cystic, minimal	1	(2%)						
Degeneration, cystic, moderate			1	(2%)			2	(4%)
Hemorrhage, mild	1	(2%)						
Hemorrhage, minimal							1	(2%)
Hyperplasia, lymphoid, moderate					1	(2%)		
Infiltration cellular, plasma cell, mild	25	(47%)	27	(54%)	24	(48%)	32	(65%)
Infiltration cellular, plasma cell, minimal	12	(23%)	10	(20%)	17	(34%)	9	(18%)
Infiltration cellular, plasma cell, moderate	4	(8%)	3	(6%)	2	(4%)	3	(6%)
Lymph node, mesenteric	(54)		(50)		(50)		(48)	
Degeneration, cystic, marked					1	(2%)		
Degeneration, cystic, mild			1	(2%)				
Hemorrhage, mild							1	(2%)
Hemorrhage, minimal							1	(2%)
Hyperplasia, lymphoid, moderate			2	(4%)				
Inflammation, granulomatous, mild	22	(41%)	22	(44%)	25	(50%)	30	(63%)
Inflammation, granulomatous, minimal	22	(41%)	16	(32%)	16	(32%)	13	(27%)
Inflammation, granulomatous, moderate			4	(8%)	1	(2%)	1	(2%)
Spleen	(54)		(50)		(50)		(49)	
Atrophy, mild, lymphocyte			1	(2%)	4	(8%)	4	(8%)
Atrophy, mild, red pulp					1	(2%)		
Atrophy, minimal, lymphocyte	1	(2%)	1	(2%)			1	(2%)
Atrophy, moderate, lymphocyte					1	(2%)	1	(2%)
Hematopoietic cell proliferation, mild	4	(7%)	3	(6%)	6	(12%)	5	(10%)
Hematopoietic cell proliferation, minimal	5	(9%)	4	(8%)	3	(6%)	5	(10%)
Hematopoietic cell proliferation, moderate	6	(11%)	2	(4%)	3	(6%)	2	(4%)
Inflammation, focal, chronic active, moderate					1	(2%)		
Pigmentation, marked					1	(2%)	2	(4%)
Pigmentation, mild	15	(28%)	11	(22%)	11	(22%)	19	(39%)
Pigmentation, minimal	9	(17%)	12	(24%)	12	(24%)	9	(18%)
Pigmentation, moderate	7	(13%)	3	(6%)	4	(8%)	11	(22%)
Thymus	(50)		(43)		(43)		(44)	
Atrophy, marked					1	(2%)		
Atrophy, mild	3	(6%)	6	(14%)	3	(7%)	9	(20%)
Atrophy, minimal	6	(12%)	1	(2%)	1	(2%)		
Atrophy, moderate					2	(5%)	3	(7%)
Cyst, mild	5	(10%)	4	(9%)	5	(12%)	9	(20%)
Cyst, minimal	10	(20%)	5	(12%)	11	(26%)	6	(14%)
Cyst, moderate			1	(2%)			2	(5%)
Ectopic thyroid					1	(2%)		
Hemorrhage, mild	1	(2%)	1	(2%)	1	(2%)	1	(2%)
Hemorrhage, moderate					1	(2%)		
Hyperplasia, lymphoid, moderate							1	(2%)
Hyperplasia, mild, epithelial cell	1	(2%)					1	(2%)
Hyperplasia, minimal, epithelial cell			1	(2%)	1	(2%)	1	(2%)
Hyperplasia, moderate, epithelial cell							1	(2%)

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Integumentary System				
Mammary gland	(54)	(50)	(50)	(49)
Atypical focus	13 (24%)	4 (8%)	6 (12%)	5 (10%)
Degeneration, mild, alveolus				1 (2%)
Degeneration, moderate, alveolus				1 (2%)
Galactocele, mild				1 (2%)
Galactocele, minimal	1 (2%)			1 (2%)
Galactocele, moderate	2 (4%)	1 (2%)	2 (4%)	
Hyperplasia, marked, alveolus			1 (2%)	
Hyperplasia, mild, alveolus	1 (2%)	3 (6%)	5 (10%)	5 (10%)
Hyperplasia, minimal, alveolus	9 (17%)	7 (14%)	4 (8%)	3 (6%)
Hyperplasia, moderate, alveolus	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Lactation, mild	15 (28%)	11 (22%)	18 (36%)	20 (41%)
Lactation, minimal	14 (26%)	19 (38%)	15 (30%)	21 (43%)
Lactation, moderate	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Skin	(54)	(50)	(50)	(49)
Inflammation, chronic, marked, foot	2 (4%)	4 (8%)	3 (6%)	1 (2%)
Inflammation, chronic, mild, foot	9 (17%)	4 (8%)	11 (22%)	9 (18%)
Inflammation, chronic, minimal, foot	7 (13%)	6 (12%)	6 (12%)	7 (14%)
Inflammation, chronic, moderate, foot	18 (33%)	20 (40%)	12 (24%)	16 (33%)
Musculoskeletal System				
Bone, femur	(54)	(50)	(50)	(49)
Hyperostosis, mild	1 (2%)			
Nervous System				
Brain, brain stem	(54)	(50)	(50)	(49)
Compression, marked		1 (2%)		
Compression, mild	10 (19%)	8 (16%)	16 (32%)	17 (35%)
Compression, minimal	5 (9%)	7 (14%)	4 (8%)	12 (24%)
Compression, moderate	4 (7%)	2 (4%)	4 (8%)	6 (12%)
Brain, cerebrum	(54)	(50)	(50)	(49)
Hydrocephalus, mild	2 (4%)			3 (6%)
Respiratory System				
Lung	(54)	(50)	(50)	(49)
Hemorrhage, moderate		1 (2%)		
Hyperplasia, mild, alveolar epithelium		1 (2%)		
Hyperplasia, minimal, alveolar epithelium			1 (2%)	
Hyperplasia, moderate, alveolar epithelium			1 (2%)	
Infiltration cellular, histiocyte, marked		2 (4%)		
Infiltration cellular, histiocyte, mild	4 (7%)	6 (12%)	4 (8%)	2 (4%)
Infiltration cellular, histiocyte, minimal	5 (9%)	9 (18%)	8 (16%)	14 (29%)
Infiltration cellular, histiocyte, moderate			1 (2%)	1 (2%)
Inflammation, mild			1 (2%)	
Nose	(54)	(50)	(50)	(49)
Foreign body				1 (2%)
Inflammation, mild, nasolacrimal duct	4 (7%)	3 (6%)	4 (8%)	3 (6%)
Inflammation, minimal			3 (6%)	1 (2%)
Inflammation, minimal, nasolacrimal duct	3 (6%)	3 (6%)	2 (4%)	4 (8%)
Inflammation, moderate				1 (2%)
Inflammation, moderate, nasolacrimal duct		1 (2%)		
Inflammation, upper molar	1 (2%)	1 (2%)	5 (10%)	3 (6%)
Keratin cyst				2 (4%)

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in F_1C Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Special Senses System				
Eye	(32)	(32)	(31)	(26)
Cataract, marked, unilateral, lens	1 (3%)			
Cataract, mild, bilateral, lens			2 (6%)	
Cataract, minimal, bilateral, lens		1 (3%)		
Cataract, minimal, lens				1 (4%)
Cataract, moderate, lens				1 (4%)
Degeneration, mild, bilateral, retina	1 (3%)	1 (3%)		
Degeneration, mild, retina	1 (3%)	1 (3%)	2 (6%)	2 (8%)
Degeneration, minimal, bilateral, retina		1 (3%)		
Degeneration, minimal, retina	1 (3%)		1 (3%)	1 (4%)
Degeneration, moderate, bilateral, retina	2 (6%)	1 (3%)	1 (3%)	1 (4%)
Degeneration, moderate, unilateral, retina	1 (3%)			
Phthisis bulbi				1 (4%)
Harderian gland	(30)	(34)	(30)	(25)
Degeneration, mild, epithelium		6 (18%)	4 (13%)	4 (16%)
Degeneration, minimal, epithelium	6 (20%)	14 (41%)	5 (17%)	4 (16%)
Degeneration, moderate, epithelium				2 (8%)
Hypertrophy, mild	1 (3%)		2 (7%)	
Hypertrophy, minimal	2 (7%)	3 (9%)	2 (7%)	3 (12%)
Lacrimal gland		(1)	(1)	(1)
Metaplasia, mild		1 (100%)		
Metaplasia, moderate				1 (100%)
Urinary System				
Kidney	(54)	(50)	(50)	(49)
Accumulation, hyaline droplet, moderate	2 (4%)	1 (2%)		
Cyst	14 (26%)	17 (34%)	13 (26%)	13 (27%)
Hydronephrosis, mild	2 (4%)			
Hyperplasia, mild, pelvis, epithelium	1 (2%)		1 (2%)	
Infarct, mild			1 (2%)	
Infarct, minimal	1 (2%)	3 (6%)		
Inflammation, mild			1 (2%)	1 (2%)
Inflammation, minimal	2 (4%)			
Mineralization, mild, pelvis	3 (6%)	7 (14%)	4 (8%)	6 (12%)
Mineralization, mild, renal tubule	20 (37%)	14 (28%)	16 (32%)	18 (37%)
Mineralization, minimal, pelvis	13 (24%)	13 (26%)	18 (36%)	19 (39%)
Mineralization, minimal, renal tubule	18 (33%)	19 (38%)	14 (28%)	19 (39%)
Mineralization, moderate, pelvis			1 (2%)	
Mineralization, moderate, renal tubule		4 (8%)	6 (12%)	
Nephropathy, marked		1 (2%)		
Nephropathy, mild	2 (4%)	2 (4%)	5 (10%)	4 (8%)
Nephropathy, minimal	11 (20%)	6 (12%)	7 (14%)	12 (24%)
Nephropathy, moderate		1 (2%)		1 (2%)
Pigmentation, mild, renal tubule				1 (2%)
Urinary bladder	(54)	(49)	(49)	(49)
Developmental malformation				1 (2%)
Hyperplasia, minimal		1 (2%)		
Hyperplasia, moderate			1 (2%)	
Inflammation, minimal			1 (2%)	

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	128	50	50	50
Early deaths				
Dead	3	7	4	9
Dead no CID	3			
Issue other	4			
Moribund	25	12	14	18
Surplus	36			
Survey/sentinel	31			
Survivors				
Terminal sacrifice	26	31	32	23
Animals examined microscopically	54	50	50	50
Alimentary System				
Intestine large, cecum	(54)	(49)	(50)	(50)
Inflammation, minimal		2 (4%)		
Intestine small			(1)	
Hyperplasia, lymphoid, minimal			1 (100%)	
Liver	(54)	(50)	(50)	(50)
Angiectasis, mild		5 (10%)	3 (6%)	
Angiectasis, minimal			1 (2%)	2 (4%)
Angiectasis, moderate		1 (2%)		
Basophilic focus	4 (7%)	5 (10%)	7 (14%)	6 (12%)
Clear cell focus	1 (2%)			
Cyst		1 (2%)	1 (2%)	3 (6%)
Degeneration, cystic, minimal	1 (2%)		1 (2%)	1 (2%)
Developmental malformation			2 (4%)	
Eosinophilic focus		2 (4%)	1 (2%)	4 (8%)
Fibrosis, mild, biliary tract	1 (2%)	1 (2%)		1 (2%)
Fibrosis, minimal		1 (2%)		
Fibrosis, minimal, biliary tract	3 (6%)	4 (8%)		1 (2%)
Fibrosis, moderate, biliary tract		1 (2%)		
Hematopoietic cell proliferation, mild	1 (2%)			
Hematopoietic cell proliferation, minimal	5 (9%)	2 (4%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	1 (2%)			2 (4%)
Hyperplasia, mild, bile duct	6 (11%)	3 (6%)	4 (8%)	6 (12%)
Hyperplasia, minimal, bile duct	16 (30%)	12 (24%)	14 (28%)	7 (14%)
Infiltration cellular, lymphocyte, mild		1 (2%)		
Infiltration cellular, lymphocyte, minimal	2 (4%)	3 (6%)		1 (2%)
Inflammation, chronic active, mild			2 (4%)	1 (2%)
Inflammation, chronic active, minimal	4 (7%)	1 (2%)	2 (4%)	1 (2%)
Necrosis, mild			1 (2%)	2 (4%)
Necrosis, minimal	1 (2%)			
Necrosis, moderate			1 (2%)	
Polyarteritis, minimal	1 (2%)			
Tension lipidosis, mild	1 (2%)	1 (2%)		
Vacuolization cytoplasmic, focal		3 (6%)	3 (6%)	
Vacuolization cytoplasmic, mild	1 (2%)	3 (6%)		1 (2%)
Vacuolization cytoplasmic, minimal	4 (7%)	5 (10%)	1 (2%)	2 (4%)
Vacuolization cytoplasmic, moderate			1 (2%)	
Mesentery	(1)	(2)		(2)
Necrosis, mild, fat		2 (100%)		2 (100%)

The footnotes for this table are defined in Table B3a.

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Alimentary System (continued)				
Pancreas	(54)	(50)	(50)	(50)
Degeneration, marked, acinar cell	1 (2%)	2 (4%)	1 (2%)	
Degeneration, mild, acinar cell	6 (11%)	5 (10%)	5 (10%)	3 (6%)
Degeneration, minimal, acinar cell	14 (26%)	10 (20%)	5 (10%)	11 (22%)
Degeneration, moderate, acinar cell		1 (2%)		
Hyperplasia, mild, acinar cell		1 (2%)		
Inflammation, minimal				1 (2%)
Polyarteritis, minimal				1 (2%)
Polyarteritis, moderate		1 (2%)		
Salivary glands	(54)	(50)	(50)	(50)
Atrophy, mild	1 (2%)			
Atrophy, moderate				1 (2%)
Inflammation, mild, parotid gland				1 (2%)
Inflammation, minimal, submandibular gland			1 (2%)	
Inflammation, moderate, parotid gland				1 (2%)
Stomach, forestomach	(54)	(49)	(49)	(50)
Diverticulum, mild		1 (2%)		
Hyperplasia, mild	2 (4%)	1 (2%)		2 (4%)
Hyperplasia, minimal	1 (2%)			
Hyperplasia, moderate		1 (2%)	1 (2%)	
Inflammation, mild		1 (2%)		1 (2%)
Ulcer, mild	1 (2%)	1 (2%)		
Ulcer, minimal				1 (2%)
Ulcer, moderate			1 (2%)	
Cardiovascular System				
Heart	(54)	(50)	(50)	(50)
Cardiomyopathy, mild	1 (2%)	5 (10%)	4 (8%)	5 (10%)
Cardiomyopathy, minimal	25 (46%)	18 (36%)	22 (44%)	23 (46%)
Endocrine System				
Adrenal cortex	(54)	(50)	(50)	(50)
Angiectasis, minimal	3 (6%)		1 (2%)	1 (2%)
Degeneration, cystic, marked	3 (6%)	1 (2%)		1 (2%)
Degeneration, cystic, mild	22 (41%)	25 (50%)	18 (36%)	22 (44%)
Degeneration, cystic, minimal	14 (26%)	17 (34%)	18 (36%)	13 (26%)
Degeneration, cystic, moderate	6 (11%)	3 (6%)	9 (18%)	9 (18%)
Hematopoietic cell proliferation, mild	1 (2%)			
Hyperplasia, mild	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, minimal	8 (15%)	9 (18%)	12 (24%)	8 (16%)
Hyperplasia, moderate			1 (2%)	
Hypertrophy, marked		2 (4%)	2 (4%)	1 (2%)
Hypertrophy, mild	9 (17%)	8 (16%)	8 (16%)	7 (14%)
Hypertrophy, minimal	5 (9%)	13 (26%)	6 (12%)	7 (14%)
Hypertrophy, moderate	2 (4%)	5 (10%)	2 (4%)	3 (6%)
Vacuolization cytoplasmic, mild		1 (2%)		
Vacuolization cytoplasmic, moderate		1 (2%)		1 (2%)
Adrenal medulla	(54)	(48)	(50)	(48)
Hyperplasia, diffuse, moderate			1 (2%)	
Hyperplasia, focal, mild	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, focal, minimal	2 (4%)	4 (8%)	3 (6%)	2 (4%)
Hyperplasia, focal, moderate		1 (2%)		1 (2%)

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System (continued)				
Islets, pancreatic	(54)	(50)	(50)	(50)
Hyperplasia, mild				2 (4%)
Hyperplasia, minimal		2 (4%)		
Parathyroid gland	(46)	(47)	(42)	(43)
Hyperplasia, diffuse, mild	1 (2%)			1 (2%)
Hyperplasia, focal, mild		2 (4%)		1 (2%)
Hyperplasia, focal, minimal	2 (4%)		1 (2%)	
Pituitary gland	(54)	(49)	(50)	(50)
Angiectasis, moderate	1 (2%)			
Cyst	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia, mild, pars distalis	4 (7%)	2 (4%)	4 (8%)	2 (4%)
Hyperplasia, minimal, pars distalis		2 (4%)	2 (4%)	
Hyperplasia, moderate, pars distalis	1 (2%)	2 (4%)		
Thyroid gland	(54)	(50)	(50)	(50)
Atrophy, mild, follicular cell			1 (2%)	1 (2%)
Cyst, squamous, mild	1 (2%)	2 (4%)		
Cyst, squamous, minimal	4 (7%)	5 (10%)	7 (14%)	7 (14%)
Cyst, squamous, moderate				1 (2%)
Hyperplasia, mild, C-cell		1 (2%)		
Hyperplasia, minimal, C-cell	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, minimal, follicular cell				1 (2%)
Genital System				
Clitoral gland	(51)	(49)	(49)	(49)
Degeneration, marked, parenchymal cell	1 (2%)			
Degeneration, mild, parenchymal cell	1 (2%)	1 (2%)		
Degeneration, minimal, parenchymal cell	1 (2%)			1 (2%)
Degeneration, moderate, parenchymal cell	2 (4%)		2 (4%)	1 (2%)
Dilatation, marked, duct	1 (2%)	1 (2%)		2 (4%)
Dilatation, mild, duct	2 (4%)	2 (4%)	3 (6%)	5 (10%)
Dilatation, minimal, duct		1 (2%)		1 (2%)
Dilatation, moderate, duct	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Hyperplasia, mild	1 (2%)			3 (6%)
Hyperplasia, minimal	1 (2%)		3 (6%)	
Inflammation, marked	1 (2%)			1 (2%)
Inflammation, mild	10 (20%)	12 (24%)	10 (20%)	11 (22%)
Inflammation, minimal	13 (25%)	11 (22%)	17 (35%)	6 (12%)
Inflammation, moderate	8 (16%)	1 (2%)	2 (4%)	5 (10%)
Ovary	(54)	(50)	(49)	(49)
Atrophy, marked	2 (4%)	1 (2%)		
Atrophy, mild	12 (22%)	9 (18%)	12 (24%)	23 (47%)
Atrophy, minimal	3 (6%)	8 (16%)	8 (16%)	2 (4%)
Atrophy, moderate	17 (31%)	6 (12%)	8 (16%)	17 (35%)
Cyst	11 (20%)	9 (18%)	16 (33%)	18 (37%)
Hyperplasia, mild, granulosa cell			1 (2%)	
Hyperplasia, minimal, serosa				1 (2%)
Hyperplasia, moderate, granulosa cell			1 (2%)	
Hyperplasia, stromal, marked	1 (2%)	2 (4%)		
Hyperplasia, stromal, mild	10 (19%)	16 (32%)	8 (16%)	8 (16%)
Hyperplasia, stromal, minimal	11 (20%)	5 (10%)	12 (24%)	7 (14%)
Hyperplasia, stromal, moderate	3 (6%)	2 (4%)	1 (2%)	2 (4%)

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Uterus	(54)	(50)	(49)	(50)
Hyperplasia, cystic, marked				1 (2%)
Hyperplasia, cystic, mild	9 (17%)	5 (10%)	6 (12%)	12 (24%)
Hyperplasia, cystic, minimal	5 (9%)	8 (16%)	17 (35%)	9 (18%)
Hyperplasia, cystic, moderate	2 (4%)	2 (4%)	3 (6%)	11 (22%)
Hyperplasia, focal, moderate				1 (2%)
Hypertrophy, cervix, muscularis	1 (2%)			2 (4%)
Inflammation, mild	1 (2%)			
Metaplasia, mild	1 (2%)		4 (8%)	2 (4%)
Metaplasia, minimal	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Metaplasia, moderate	1 (2%)			1 (2%)
Vagina	(54)	(49)	(48)	(50)
Inflammation, mild	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Inflammation, minimal	2 (4%)	1 (2%)		1 (2%)
Inflammation, moderate		1 (2%)	1 (2%)	
Keratin cyst, mild	2 (4%)			
Hematopoietic System				
Bone marrow	(54)	(50)	(50)	(50)
Hyperplasia, mild, myeloid cell				1 (2%)
Hypocellularity, mild		1 (2%)		1 (2%)
Hypocellularity, moderate	2 (4%)			
Lymph node	(11)	(9)	(10)	(9)
Degeneration, cystic, marked, lumbar	1 (9%)			
Degeneration, cystic, mild, axillary			1 (10%)	
Degeneration, cystic, mild, lumbar	2 (18%)	5 (56%)	3 (30%)	2 (22%)
Degeneration, cystic, minimal, lumbar				1 (11%)
Degeneration, cystic, minimal, renal				1 (11%)
Degeneration, cystic, moderate, lumbar	1 (9%)	1 (11%)	1 (10%)	
Degeneration, cystic, moderate, renal			2 (20%)	
Hemorrhage, mild, mediastinal				1 (11%)
Hemorrhage, mild, pancreatic				2 (22%)
Hyperplasia, lymphoid, minimal, lumbar	1 (9%)			
Infiltration cellular, plasma cell, mild, lumbar	5 (45%)	4 (44%)	5 (50%)	4 (44%)
Infiltration cellular, plasma cell, mild, mediastinal				1 (11%)
Infiltration cellular, plasma cell, mild, popliteal		2 (22%)		1 (11%)
Infiltration cellular, plasma cell, mild, renal		1 (11%)		1 (11%)
Infiltration cellular, plasma cell, mild, thoracic		1 (11%)		
Infiltration cellular, plasma cell, minimal, axillary			1 (10%)	
Infiltration cellular, plasma cell, minimal, lumbar				2 (22%)
Infiltration cellular, plasma cell, moderate, inguinal	1 (9%)			
Infiltration cellular, plasma cell, moderate, lumbar	1 (9%)	2 (22%)	2 (20%)	

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(53)	(50)	(50)	(50)
Cyst, mild			1 (2%)	
Degeneration, cystic, mild			1 (2%)	2 (4%)
Degeneration, cystic, minimal	1 (2%)	2 (4%)		
Hemorrhage, mild	1 (2%)	1 (2%)	1 (2%)	
Hemorrhage, minimal				1 (2%)
Infiltration cellular, plasma cell, mild	25 (47%)	21 (42%)	19 (38%)	27 (54%)
Infiltration cellular, plasma cell, minimal	12 (23%)	14 (28%)	21 (42%)	13 (26%)
Infiltration cellular, plasma cell, moderate	4 (8%)	3 (6%)	3 (6%)	5 (10%)
Lymph node, mesenteric	(54)	(50)	(50)	(50)
Degeneration, cystic, minimal				1 (2%)
Degeneration, cystic, moderate			2 (4%)	
Hemorrhage, mild		1 (2%)		
Inflammation, granulomatous, mild	22 (41%)	24 (48%)	28 (56%)	23 (46%)
Inflammation, granulomatous, minimal	22 (41%)	17 (34%)	11 (22%)	21 (42%)
Inflammation, granulomatous, moderate		5 (10%)	8 (16%)	1 (2%)
Spleen	(54)	(50)	(50)	(50)
Atrophy, marked, lymphocyte				1 (2%)
Atrophy, mild, lymphocyte		1 (2%)	1 (2%)	3 (6%)
Atrophy, minimal, lymphocyte	1 (2%)	1 (2%)		
Atrophy, moderate, lymphocyte		1 (2%)	2 (4%)	
Hematopoietic cell proliferation, marked				1 (2%)
Hematopoietic cell proliferation, mild	4 (7%)	2 (4%)	4 (8%)	5 (10%)
Hematopoietic cell proliferation, minimal	5 (9%)	2 (4%)	3 (6%)	2 (4%)
Hematopoietic cell proliferation, moderate	6 (11%)	1 (2%)	1 (2%)	
Hemorrhage, moderate				1 (2%)
Hyperplasia, mild, red pulp				1 (2%)
Pigmentation, mild	15 (28%)	11 (22%)	12 (24%)	20 (40%)
Pigmentation, minimal	9 (17%)	10 (20%)	5 (10%)	8 (16%)
Pigmentation, moderate	7 (13%)	7 (14%)	2 (4%)	6 (12%)
Thymus	(50)	(47)	(47)	(47)
Atrophy, marked		1 (2%)	1 (2%)	1 (2%)
Atrophy, mild	3 (6%)	6 (13%)	3 (6%)	4 (9%)
Atrophy, minimal	6 (12%)	3 (6%)	1 (2%)	4 (9%)
Atrophy, moderate			4 (9%)	
Cyst, mild	5 (10%)	9 (19%)	6 (13%)	9 (19%)
Cyst, minimal	10 (20%)	5 (11%)	7 (15%)	9 (19%)
Cyst, moderate		3 (6%)		2 (4%)
Hemorrhage, mild	1 (2%)			
Hemorrhage, moderate		1 (2%)		
Hyperplasia, mild, epithelial cell	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, minimal, epithelial cell			1 (2%)	
Hyperplasia, moderate, epithelial cell		1 (2%)		1 (2%)
Integumentary System				
Mammary gland	(54)	(50)	(50)	(50)
Atypical focus	13 (24%)	2 (4%)	7 (14%)	11 (22%)
Galactocele, mild		1 (2%)		2 (4%)
Galactocele, minimal	1 (2%)			
Galactocele, moderate	2 (4%)	1 (2%)		
Hyperplasia, mild, alveolus	1 (2%)	4 (8%)	1 (2%)	3 (6%)
Hyperplasia, minimal, alveolus	9 (17%)	9 (18%)	9 (18%)	9 (18%)
Hyperplasia, moderate, alveolus	3 (6%)	1 (2%)		3 (6%)
Hyperplasia, moderate, duct			1 (2%)	
Inflammation, moderate				1 (2%)

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Integumentary System				
Mammary gland (continued)	(54)	(50)	(50)	(50)
Lactation, mild	15 (28%)	9 (18%)	15 (30%)	22 (44%)
Lactation, minimal	14 (26%)	18 (36%)	17 (34%)	17 (34%)
Lactation, moderate	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Skin	(54)	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)		
Inflammation, chronic, marked, foot	2 (4%)	4 (8%)	5 (10%)	2 (4%)
Inflammation, chronic, mild, foot	9 (17%)	9 (18%)	3 (6%)	11 (22%)
Inflammation, chronic, minimal, foot	7 (13%)	4 (8%)	4 (8%)	6 (12%)
Inflammation, chronic, moderate, foot	18 (33%)	18 (36%)	24 (48%)	16 (32%)
Inflammation, chronic, moderate, lip		1 (2%)	1 (2%)	
Inflammation, mild		1 (2%)		
Musculoskeletal System				
Bone, femur	(54)	(50)	(50)	(50)
Hyperostosis, mild	1 (2%)			
Bone, tibia				(1)
Malformation				1 (100%)
Nervous System				
Brain, brain stem	(54)	(50)	(50)	(50)
Compression, marked			1 (2%)	
Compression, mild	10 (19%)	7 (14%)	5 (10%)	20 (40%)
Compression, minimal	5 (9%)	4 (8%)	7 (14%)	7 (14%)
Compression, moderate	4 (7%)	4 (8%)	4 (8%)	4 (8%)
Brain, cerebrum	(54)	(50)	(50)	(50)
Hemorrhage, mild			1 (2%)	
Hemorrhage, moderate			1 (2%)	
Hydrocephalus, mild	2 (4%)	2 (4%)	1 (2%)	
Hydrocephalus, minimal		1 (2%)	1 (2%)	2 (4%)
Respiratory System				
Lung	(54)	(50)	(50)	(50)
Atelectasis, mild		1 (2%)		
Hyperplasia, minimal, alveolar epithelium				1 (2%)
Infiltration cellular, histiocyte, mild	4 (7%)	3 (6%)	5 (10%)	5 (10%)
Infiltration cellular, histiocyte, minimal	5 (9%)	8 (16%)	6 (12%)	11 (22%)
Infiltration cellular, histiocyte, moderate		1 (2%)	1 (2%)	4 (8%)
Inflammation, minimal				1 (2%)
Inflammation, moderate		1 (2%)		
Metaplasia, mild		1 (2%)		
Nose	(54)	(50)	(50)	(50)
Fungus		1 (2%)		
Inflammation, marked			1 (2%)	
Inflammation, mild		2 (4%)		1 (2%)
Inflammation, mild, nasolacrimal duct	4 (7%)			2 (4%)
Inflammation, minimal		1 (2%)		3 (6%)
Inflammation, minimal, nasolacrimal duct	3 (6%)	2 (4%)		2 (4%)
Inflammation, moderate		1 (2%)		
Inflammation, upper molar	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Keratin cyst		1 (2%)		

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in F_1T140 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Special Senses System				
Ear		(2)		
Hemorrhage, mild		1 (50%)		
Eye	(32)	(33)	(37)	(28)
Cataract, marked, unilateral, lens	1 (3%)			
Cataract, mild, bilateral, lens			2 (5%)	
Cataract, minimal, bilateral, lens		1 (3%)		
Cataract, moderate, bilateral, lens			1 (3%)	
Degeneration, mild, bilateral, retina	1 (3%)	1 (3%)	1 (3%)	
Degeneration, mild, retina	1 (3%)			1 (4%)
Degeneration, minimal, retina	1 (3%)	3 (9%)	1 (3%)	
Degeneration, moderate, bilateral, retina	2 (6%)		1 (3%)	
Degeneration, moderate, retina		1 (3%)	4 (11%)	
Degeneration, moderate, unilateral, retina	1 (3%)			
Polyarteritis, minimal			1 (3%)	
Ulcer, marked, cornea				1 (4%)
Harderian gland	(30)	(33)	(36)	(26)
Degeneration, mild, epithelium		9 (27%)	4 (11%)	5 (19%)
Degeneration, minimal, epithelium	6 (20%)	8 (24%)	9 (25%)	7 (27%)
Degeneration, moderate, epithelium		1 (3%)	4 (11%)	1 (4%)
Hypertrophy, mild	1 (3%)	1 (3%)	2 (6%)	
Hypertrophy, minimal	2 (7%)	2 (6%)	2 (6%)	5 (19%)
Lacrimal gland		(1)		(2)
Metaplasia, mild		1 (100%)		
Metaplasia, minimal				1 (50%)
Urinary System				
Kidney	(54)	(50)	(50)	(50)
Accumulation, hyaline droplet, moderate	2 (4%)			
Cyst	14 (26%)	12 (24%)	16 (32%)	19 (38%)
Hydronephrosis, mild	2 (4%)			
Hyperplasia, mild, pelvis, epithelium	1 (2%)	1 (2%)	1 (2%)	
Infarct, minimal	1 (2%)	1 (2%)	1 (2%)	
Infarct, moderate		1 (2%)		
Inflammation, mild			1 (2%)	
Inflammation, minimal	2 (4%)		2 (4%)	1 (2%)
Mineralization, mild, pelvis	3 (6%)	8 (16%)	6 (12%)	5 (10%)
Mineralization, mild, renal tubule	20 (37%)	18 (36%)	14 (28%)	22 (44%)
Mineralization, minimal, pelvis	13 (24%)	11 (22%)	15 (30%)	18 (36%)
Mineralization, minimal, renal tubule	18 (33%)	11 (22%)	15 (30%)	13 (26%)
Mineralization, moderate, pelvis		1 (2%)		
Mineralization, moderate, renal tubule		7 (14%)	4 (8%)	1 (2%)
Nephropathy, mild	2 (4%)	4 (8%)	1 (2%)	3 (6%)
Nephropathy, minimal	11 (20%)	8 (16%)	3 (6%)	5 (10%)
Nephropathy, moderate		1 (2%)	1 (2%)	
Urinary bladder	(54)	(49)	(48)	(49)
Mineralization, moderate			1 (2%)	

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein[a]

	0 ppm	5 ppm	100 ppm	500 ppm
Disposition Summary[b]				
Animals initially in study	66	50	50	50
Early deaths				
Dead	5	6	5	8
Moribund	15	14	16	17
Survey/sentinel	13			
Survivors				
Terminal sacrifice	33	30	29	25
Animals examined microscopically	53	50	50	50
Alimentary System				
Liver	(53)	(50)	(50)	(49)
Angiectasis, mild		1 (2%)		1 (2%)
Angiectasis, minimal	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Angiectasis, moderate				1 (2%)
Atypical cells, moderate				1 (2%)
Basophilic focus	5 (9%)	7 (14%)	6 (12%)	5 (10%)
Clear cell focus	1 (2%)			1 (2%)
Congestion, mild				1 (2%)
Congestion, moderate				1 (2%)
Cyst	1 (2%)		3 (6%)	1 (2%)
Degeneration, cystic, mild		1 (2%)		
Degeneration, cystic, minimal	1 (2%)	2 (4%)		
Degeneration, cystic, moderate				1 (2%)
Developmental malformation		1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus			1 (2%)	4 (8%)
Fibrosis, mild, biliary tract	1 (2%)	6 (12%)	3 (6%)	
Fibrosis, minimal, biliary tract	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation, mild		1 (2%)	1 (2%)	
Hematopoietic cell proliferation, minimal	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Hemorrhage, minimal			1 (2%)	
Hepatodiaphragmatic nodule	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Hyperplasia, mild, bile duct	6 (11%)	4 (8%)	8 (16%)	4 (8%)
Hyperplasia, minimal, bile duct	10 (19%)	14 (28%)	6 (12%)	12 (24%)
Hyperplasia, moderate, oval cell				1 (2%)
Infiltration cellular, lymphocyte, mild	1 (2%)			
Infiltration cellular, lymphocyte, minimal	3 (6%)	2 (4%)	3 (6%)	3 (6%)
Infiltration cellular, lymphocyte, moderate			1 (2%)	
Inflammation, chronic active, mild	1 (2%)	1 (2%)		2 (4%)
Inflammation, chronic active, minimal	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic active, moderate	1 (2%)		1 (2%)	
Mixed cell focus			1 (2%)	
Necrosis, mild				2 (4%)
Necrosis, minimal	2 (4%)	1 (2%)		
Pigmentation, mild			1 (2%)	
Vacuolization cytoplasmic, focal	4 (8%)		1 (2%)	
Vacuolization cytoplasmic, mild	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Vacuolization cytoplasmic, minimal	3 (6%)	2 (4%)	4 (8%)	1 (2%)
Vacuolization cytoplasmic, moderate	1 (2%)		1 (2%)	2 (4%)
Mesentery		(1)	(1)	
Necrosis, mild, fat			1 (100%)	
Polyarteritis, mild		1 (100%)		
Oral mucosa	(1)		(1)	(1)
Keratin cyst			1 (100%)	

The footnotes for this table are defined in Table B3a.

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Alimentary System (continued)				
Pancreas	(52)	(50)	(50)	(49)
Degeneration, marked, acinar cell	1 (2%)	2 (4%)		
Degeneration, mild, acinar cell	10 (19%)	9 (18%)	7 (14%)	2 (4%)
Degeneration, minimal, acinar cell	14 (27%)	10 (20%)	11 (22%)	12 (24%)
Degeneration, moderate, acinar cell		2 (4%)	1 (2%)	4 (8%)
Polyarteritis, minimal				1 (2%)
Polyarteritis, moderate	1 (2%)			
Salivary glands	(53)	(49)	(50)	(49)
Atrophy, mild				1 (2%)
Atrophy, moderate			1 (2%)	1 (2%)
Stomach		(1)		
Dilatation		1 (100%)		
Stomach, forestomach	(52)	(49)	(49)	(49)
Hyperplasia, mild	1 (2%)	1 (2%)		
Hyperplasia, minimal		2 (4%)		1 (2%)
Hyperplasia, moderate			1 (2%)	
Inflammation, mild		1 (2%)		
Inflammation, minimal	2 (4%)			
Keratin cyst		1 (2%)		
Ulcer, marked			1 (2%)	
Ulcer, moderate			2 (4%)	
Stomach, glandular	(53)	(50)	(50)	(49)
Erosion, mild	1 (2%)			1 (2%)
Mineralization, mild	1 (2%)		1 (2%)	
Cardiovascular System				
Blood vessel	(53)	(50)	(50)	(49)
Mineralization, mild	1 (2%)		1 (2%)	1 (2%)
Mineralization, minimal			1 (2%)	
Heart	(53)	(50)	(50)	(49)
Cardiomyopathy, mild	4 (8%)	6 (12%)	6 (12%)	3 (6%)
Cardiomyopathy, minimal	34 (64%)	26 (52%)	18 (36%)	23 (47%)
Cardiomyopathy, moderate			1 (2%)	
Dilatation, mild, atrium right				1 (2%)
Mineralization, minimal			1 (2%)	
Mineralization, moderate			1 (2%)	
Thrombosis, atrium left	1 (2%)			1 (2%)
Endocrine System				
Adrenal cortex	(53)	(50)	(50)	(49)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)		
Angiectasis, mild			1 (2%)	
Angiectasis, minimal	2 (4%)			
Atrophy, marked		1 (2%)		
Atrophy, moderate				1 (2%)
Degeneration, cystic, marked	1 (2%)	1 (2%)		
Degeneration, cystic, mild	21 (40%)	24 (48%)	30 (60%)	21 (43%)
Degeneration, cystic, minimal	16 (30%)	14 (28%)	11 (22%)	9 (18%)
Degeneration, cystic, moderate	10 (19%)	9 (18%)	4 (8%)	17 (35%)
Hematopoietic cell proliferation, minimal			1 (2%)	
Hyperplasia, mild	4 (8%)	4 (8%)	7 (14%)	5 (10%)
Hyperplasia, minimal	10 (19%)	9 (18%)	6 (12%)	10 (20%)
Hyperplasia, moderate		1 (2%)		1 (2%)

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Endocrine System (continued)				
Adrenal cortex (continued)	(53)	(50)	(50)	(49)
Hypertrophy, marked	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Hypertrophy, mild	7 (13%)	6 (12%)	7 (14%)	3 (6%)
Hypertrophy, minimal	6 (11%)	8 (16%)	5 (10%)	11 (22%)
Hypertrophy, moderate	5 (9%)	6 (12%)	9 (18%)	8 (16%)
Vacuolization cytoplasmic, marked				1 (2%)
Vacuolization cytoplasmic, mild	3 (6%)			
Vacuolization cytoplasmic, minimal	1 (2%)			
Vacuolization cytoplasmic, moderate	2 (4%)			1 (2%)
Adrenal medulla	(53)	(46)	(50)	(48)
Hyperplasia, focal, mild	7 (13%)	1 (2%)	4 (8%)	4 (8%)
Hyperplasia, focal, minimal	3 (6%)		3 (6%)	2 (4%)
Hyperplasia, focal, moderate				1 (2%)
Islets, pancreatic	(52)	(50)	(50)	(49)
Hyperplasia, mild	1 (2%)	2 (4%)		
Hyperplasia, minimal	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Parathyroid gland	(53)	(41)	(47)	(46)
Hyperplasia, diffuse, mild	1 (2%)			
Hyperplasia, diffuse, moderate			1 (2%)	
Hyperplasia, focal, mild			1 (2%)	
Hyperplasia, focal, minimal	1 (2%)		1 (2%)	
Pituitary gland	(53)	(50)	(50)	(50)
Cyst	1 (2%)		2 (4%)	
Hyperplasia, marked, pars distalis				1 (2%)
Hyperplasia, mild, pars distalis	5 (9%)	2 (4%)	2 (4%)	3 (6%)
Hyperplasia, minimal, pars distalis	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, moderate, pars distalis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, histiocyte, minimal				1 (2%)
Thyroid gland	(53)	(50)	(50)	(49)
Cyst, squamous, mild	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Cyst, squamous, minimal	7 (13%)	6 (12%)	6 (12%)	2 (4%)
Hyperplasia, mild, C-cell				2 (4%)
Hyperplasia, minimal, C-cell	2 (4%)			1 (2%)
Genital System				
Clitoral gland	(49)	(47)	(49)	(48)
Degeneration, mild, parenchymal cell	4 (8%)	1 (2%)	1 (2%)	5 (10%)
Degeneration, minimal, parenchymal cell				1 (2%)
Degeneration, moderate, parenchymal cell				2 (4%)
Dilatation, mild, duct	5 (10%)	3 (6%)	4 (8%)	5 (10%)
Dilatation, minimal, duct			1 (2%)	1 (2%)
Dilatation, moderate, duct	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Hyperplasia, mild		1 (2%)		1 (2%)
Hyperplasia, minimal			2 (4%)	2 (4%)
Inflammation, marked		1 (2%)		1 (2%)
Inflammation, mild	9 (18%)	7 (15%)	9 (18%)	8 (17%)
Inflammation, minimal	11 (22%)	9 (19%)	17 (35%)	16 (33%)
Inflammation, moderate	4 (8%)	1 (2%)	3 (6%)	7 (15%)
Vacuolization cytoplasmic, moderate				1 (2%)

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Genital System (continued)				
Ovary	(53)	(50)	(49)	(49)
Atrophy, marked		1 (2%)		1 (2%)
Atrophy, mild	14 (26%)	17 (34%)	26 (53%)	20 (41%)
Atrophy, minimal	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Atrophy, moderate	11 (21%)	14 (28%)	3 (6%)	16 (33%)
Cyst	9 (17%)	15 (30%)	16 (33%)	16 (33%)
Hyperplasia, stromal, marked		2 (4%)		
Hyperplasia, stromal, mild	10 (19%)	11 (22%)	11 (22%)	12 (24%)
Hyperplasia, stromal, minimal	7 (13%)	11 (22%)	15 (31%)	10 (20%)
Hyperplasia, stromal, moderate	4 (8%)	6 (12%)	1 (2%)	2 (4%)
Oviduct	(53)	(49)	(49)	(49)
Atrophy, mild			1 (2%)	
Cyst		1 (2%)		
Hyperplasia, stromal, minimal			1 (2%)	
Uterus	(53)	(50)	(50)	(49)
Adenomyosis, mild		1 (2%)	1 (2%)	1 (2%)
Adenomyosis, minimal				1 (2%)
Adenomyosis, moderate		1 (2%)		
Angiectasis, moderate	1 (2%)			
Hemorrhage, mild			1 (2%)	
Hyperplasia, cystic, marked		1 (2%)		
Hyperplasia, cystic, mild	3 (6%)	5 (10%)	9 (18%)	8 (16%)
Hyperplasia, cystic, minimal	11 (21%)	11 (22%)	7 (14%)	11 (22%)
Hyperplasia, cystic, moderate	2 (4%)	7 (14%)	8 (16%)	5 (10%)
Hyperplasia, focal, marked	1 (2%)			
Hyperplasia, focal, mild	2 (4%)			
Metaplasia, mild	1 (2%)	4 (8%)		2 (4%)
Metaplasia, minimal		2 (4%)	4 (8%)	3 (6%)
Metaplasia, moderate			1 (2%)	1 (2%)
Vagina	(52)	(49)	(49)	(48)
Inflammation, mild	6 (12%)	1 (2%)	1 (2%)	3 (6%)
Inflammation, minimal	2 (4%)	3 (6%)	3 (6%)	3 (6%)
Inflammation, moderate	1 (2%)		1 (2%)	1 (2%)
Hematopoietic System				
Bone marrow	(53)	(50)	(50)	(49)
Hyperplasia, mild, myeloid cell		1 (2%)	1 (2%)	
Hyperplasia, moderate, myeloid cell				1 (2%)
Hypocellularity, mild				3 (6%)
Hypocellularity, moderate			1 (2%)	1 (2%)
Lymph node	(18)	(9)	(8)	(12)
Degeneration, cystic, marked, lumbar	1 (6%)	1 (11%)		
Degeneration, cystic, mild, lumbar	7 (39%)	1 (11%)	2 (25%)	1 (8%)
Degeneration, cystic, mild, popliteal	1 (6%)			
Degeneration, cystic, mild, renal		1 (11%)	1 (13%)	
Degeneration, cystic, minimal, lumbar		1 (11%)		1 (8%)
Degeneration, cystic, moderate, lumbar	1 (6%)	2 (22%)	2 (25%)	2 (17%)
Hemorrhage, mild, mediastinal				1 (8%)
Hemorrhage, mild, pancreatic		1 (11%)		2 (17%)
Hyperplasia, lymphoid, mild, lumbar	1 (6%)			
Hyperplasia, lymphoid, mild, renal	1 (6%)			

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node (continued)	(18)	(9)	(8)	(12)
Infiltration cellular, plasma cell, marked, popliteal	1 (6%)			
Infiltration cellular, plasma cell, mild, lumbar	9 (50%)	5 (56%)	6 (75%)	9 (75%)
Infiltration cellular, plasma cell, mild, mediastinal				2 (17%)
Infiltration cellular, plasma cell, mild, renal	1 (6%)	1 (11%)	1 (13%)	
Infiltration cellular, plasma cell, minimal, lumbar	1 (6%)	1 (11%)		
Infiltration cellular, plasma cell, minimal, renal				1 (8%)
Infiltration cellular, plasma cell, moderate, lumbar	1 (6%)	1 (11%)		1 (8%)
Infiltration cellular, plasma cell, moderate, mediastinal	1 (6%)			
Infiltration cellular, plasma cell, moderate, popliteal				1 (8%)
Lymph node, mandibular	(53)	(49)	(50)	(49)
Cyst, mild		1 (2%)		
Degeneration, cystic, mild	2 (4%)			1 (2%)
Degeneration, cystic, minimal				2 (4%)
Hemorrhage, minimal	1 (2%)		1 (2%)	
Infiltration cellular, plasma cell, mild	28 (53%)	27 (55%)	26 (52%)	29 (59%)
Infiltration cellular, plasma cell, minimal	13 (25%)	12 (24%)	16 (32%)	9 (18%)
Infiltration cellular, plasma cell, moderate	2 (4%)	1 (2%)		4 (8%)
Lymph node, mesenteric	(53)	(50)	(50)	(49)
Degeneration, cystic, mild				1 (2%)
Degeneration, cystic, moderate			1 (2%)	
Hemorrhage, mild	1 (2%)			
Hemorrhage, minimal		1 (2%)		
Hemorrhage, moderate				1 (2%)
Infiltration cellular, plasma cell, mild	1 (2%)			1 (2%)
Inflammation, granulomatous, mild	27 (51%)	22 (44%)	33 (66%)	34 (69%)
Inflammation, granulomatous, minimal	17 (32%)	14 (28%)	9 (18%)	7 (14%)
Inflammation, granulomatous, moderate	4 (8%)	11 (22%)	3 (6%)	3 (6%)
Spleen	(53)	(50)	(50)	(49)
Atrophy, mild, lymphocyte	2 (4%)		1 (2%)	2 (4%)
Atrophy, mild, red pulp				1 (2%)
Atrophy, moderate, lymphocyte	1 (2%)		1 (2%)	1 (2%)
Hematopoietic cell proliferation, marked	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation, mild	7 (13%)	2 (4%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation, minimal	8 (15%)	3 (6%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation, moderate	1 (2%)	2 (4%)		1 (2%)
Pigmentation, marked				1 (2%)
Pigmentation, mild	5 (9%)	8 (16%)	13 (26%)	13 (27%)
Pigmentation, minimal	10 (19%)	18 (36%)	12 (24%)	10 (20%)
Pigmentation, moderate	6 (11%)	6 (12%)	7 (14%)	6 (12%)

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Hematopoietic System (continued)				
Thymus	(48)	(45)	(46)	(47)
Atrophy, marked			1 (2%)	1 (2%)
Atrophy, mild	4 (8%)	3 (7%)	5 (11%)	4 (9%)
Atrophy, minimal	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Atrophy, moderate	4 (8%)	2 (4%)	2 (4%)	3 (6%)
Cyst, marked			1 (2%)	
Cyst, mild	12 (25%)	8 (18%)	6 (13%)	12 (26%)
Cyst, minimal	4 (8%)	4 (9%)	6 (13%)	4 (9%)
Cyst, moderate	2 (4%)	3 (7%)		1 (2%)
Ectopic thyroid			1 (2%)	
Hemorrhage, mild		1 (2%)		1 (2%)
Hemorrhage, moderate				1 (2%)
Hyperplasia, mild, epithelial cell		1 (2%)		2 (4%)
Hyperplasia, minimal, epithelial cell	1 (2%)	1 (2%)		
Hyperplasia, moderate, epithelial cell	1 (2%)	2 (4%)		
Integumentary System				
Mammary gland	(53)	(49)	(50)	(50)
Atypical focus	6 (11%)	7 (14%)	4 (8%)	5 (10%)
Degeneration, mild, alveolus		1 (2%)	1 (2%)	2 (4%)
Degeneration, minimal, alveolus				2 (4%)
Degeneration, moderate, alveolus	3 (6%)			1 (2%)
Galactocele, mild	1 (2%)	4 (8%)		
Galactocele, minimal		1 (2%)		
Galactocele, moderate		1 (2%)	1 (2%)	3 (6%)
Hyperplasia, marked, alveolus		1 (2%)		1 (2%)
Hyperplasia, mild				1 (2%)
Hyperplasia, mild, alveolus	7 (13%)	1 (2%)	5 (10%)	3 (6%)
Hyperplasia, minimal, alveolus	12 (23%)	11 (22%)	11 (22%)	12 (24%)
Hyperplasia, moderate	1 (2%)			
Hyperplasia, moderate, alveolus		1 (2%)	2 (4%)	1 (2%)
Lactation, mild	14 (26%)	20 (41%)	26 (52%)	13 (26%)
Lactation, minimal	16 (30%)	18 (37%)	14 (28%)	19 (38%)
Lactation, moderate	2 (4%)		3 (6%)	1 (2%)
Skin	(53)	(50)	(50)	(50)
Angiectasis, mild	1 (2%)			
Cyst epithelial inclusion			1 (2%)	1 (2%)
Inflammation, chronic, marked, foot	6 (11%)	4 (8%)	3 (6%)	4 (8%)
Inflammation, chronic, mild, foot	8 (15%)	6 (12%)	12 (24%)	12 (24%)
Inflammation, chronic, minimal, foot	4 (8%)	5 (10%)	4 (8%)	4 (8%)
Inflammation, chronic, moderate, foot	21 (40%)	21 (42%)	18 (36%)	15 (30%)
Musculoskeletal System				
Bone, femur	(53)	(50)	(50)	(49)
Fibrous osteodystrophy			1 (2%)	
Bone, joint	(1)			
Inflammation, moderate	1 (100%)			
Skeletal muscle	(1)			
Cyst	1 (100%)			

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Nervous System				
Brain, brain stem	(53)	(50)	(50)	(49)
Compression, mild	11 (21%)	16 (32%)	18 (36%)	15 (31%)
Compression, minimal	9 (17%)	8 (16%)	6 (12%)	8 (16%)
Compression, moderate	3 (6%)	2 (4%)	4 (8%)	6 (12%)
Brain, cerebrum	(53)	(50)	(50)	(49)
Hydrocephalus, mild	1 (2%)			2 (4%)
Hydrocephalus, minimal			1 (2%)	1 (2%)
Respiratory System				
Lung	(53)	(50)	(50)	(49)
Atelectasis, mild		1 (2%)		
Hemorrhage, mild			1 (2%)	
Hyperplasia, mild, alveolar epithelium		1 (2%)	1 (2%)	
Infiltration cellular, histiocyte, marked	1 (2%)			
Infiltration cellular, histiocyte, mild	4 (8%)	1 (2%)	2 (4%)	6 (12%)
Infiltration cellular, histiocyte, minimal	9 (17%)	9 (18%)	10 (20%)	8 (16%)
Infiltration cellular, histiocyte, moderate	2 (4%)		1 (2%)	
Inflammation, mild		3 (6%)	2 (4%)	
Inflammation, minimal	1 (2%)		1 (2%)	
Inflammation, moderate				1 (2%)
Mineralization, mild	1 (2%)			
Polyarteritis, mild	1 (2%)			
Nose	(53)	(50)	(50)	(49)
Inflammation, marked, nasolacrimal duct	1 (2%)			
Inflammation, mild		1 (2%)	2 (4%)	3 (6%)
Inflammation, mild, nasolacrimal duct	2 (4%)	1 (2%)		2 (4%)
Inflammation, minimal	2 (4%)	1 (2%)		
Inflammation, minimal, nasolacrimal duct	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, moderate	1 (2%)		1 (2%)	
Inflammation, upper molar	2 (4%)	6 (12%)		1 (2%)
Keratin cyst			1 (2%)	
Special Senses System				
Eye	(43)	(41)	(40)	(38)
Cataract, mild, bilateral, lens	1 (2%)			
Cataract, mild, lens				1 (3%)
Cataract, minimal, bilateral, lens				1 (3%)
Degeneration, mild, bilateral, retina		2 (5%)	1 (3%)	
Degeneration, mild, retina	1 (2%)	2 (5%)		2 (5%)
Degeneration, minimal, bilateral, retina	1 (2%)	1 (2%)		1 (3%)
Degeneration, minimal, retina	2 (5%)	1 (2%)		1 (3%)
Degeneration, moderate, bilateral, retina	4 (9%)	6 (15%)	5 (13%)	2 (5%)
Degeneration, moderate, retina	3 (7%)	1 (2%)	1 (3%)	2 (5%)
Harderian gland	(43)	(40)	(40)	(38)
Degeneration, mild, epithelium	4 (9%)	7 (18%)	2 (5%)	4 (11%)
Degeneration, minimal, epithelium	12 (28%)	9 (23%)	7 (18%)	17 (45%)
Degeneration, moderate, epithelium		1 (3%)	1 (3%)	
Hypertrophy, mild		2 (5%)		1 (3%)
Hypertrophy, minimal	3 (7%)	3 (8%)	5 (13%)	1 (3%)
Inflammation, mild	1 (2%)			
Lacrimal gland		(1)		
Metaplasia, minimal		1 (100%)		

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in F_3T21 Female Rats in the 2-Year Feed Study of Genistein

	0 ppm	5 ppm	100 ppm	500 ppm
Urinary System				
Kidney	(53)	(50)	(50)	(49)
Accumulation, hyaline droplet, marked	1 (2%)			
Cyst	19 (36%)	17 (34%)	19 (38%)	12 (24%)
Hydronephrosis, marked				1 (2%)
Hydronephrosis, mild		1 (2%)		
Hydronephrosis, moderate			1 (2%)	
Hyperplasia, mild, pelvis, epithelium				1 (2%)
Infarct, minimal			1 (2%)	1 (2%)
Inflammation, mild				1 (2%)
Inflammation, minimal	2 (4%)	1 (2%)		4 (8%)
Mineralization, mild, pelvis	5 (9%)	5 (10%)	12 (24%)	3 (6%)
Mineralization, mild, renal tubule	24 (45%)	14 (28%)	25 (50%)	19 (39%)
Mineralization, minimal, pelvis	11 (21%)	13 (26%)	14 (28%)	21 (43%)
Mineralization, minimal, renal tubule	17 (32%)	17 (34%)	16 (32%)	7 (14%)
Mineralization, moderate, pelvis	1 (2%)	1 (2%)	2 (4%)	
Mineralization, moderate, renal tubule	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Nephropathy, marked	1 (2%)		1 (2%)	1 (2%)
Nephropathy, mild	3 (6%)	5 (10%)	6 (12%)	6 (12%)
Nephropathy, minimal	12 (23%)	9 (18%)	14 (28%)	10 (20%)
Nephropathy, moderate	3 (6%)			1 (2%)
Urinary bladder	(53)	(47)	(48)	(47)
Hyperplasia, moderate	2 (4%)			1 (2%)
Inflammation, mild				1 (2%)

APPENDIX C
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF GENISTEIN 172
BACKGROUND ISOFLAVONE CONTENT OF BASE DIET 173
PREPARATION AND ANALYSIS OF DOSE FORMULATIONS 173
FIGURE C1 Proton Nuclear Magnetic Resonance Spectrum of Genistein 174
TABLE C1 Preparation and Storage of Dose Formulations in the 2-Year Feed Study of Genistein 175
TABLE C2 Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Genistein 176
TABLE C3 Results of Analyses of Animal Room Samples of Dose Formulations Administered to Rats in the 2-Year Feed Study of Genistein 180

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization of Genistein

Genistein was obtained from Toronto Research Chemicals, Inc. (North York, Ontario, Canada), in two lots (2-BP-136-6 and 1-SOP-59-3). Identity and purity analyses were conducted by the study laboratory at the National Center for Toxicological Research (NCTR; Jefferson, AR). Reports on analyses performed in support of the genistein study are on file at the NCTR.

Lots 2-BP-136-6 and 1-SOP-59-3 of the chemical, a pale yellow crystalline solid, were identified as genistein by proton nuclear magnetic resonance (NMR) spectroscopy. NMR spectra were in agreement with the structure of genistein and spectra obtained from other lots of genistein. A representative proton NMR spectrum is presented in Figure C1.

The purities of lots 2-BP-136-6 and 1-SOP-59-3 were determined by high-performance liquid chromatography (HPLC) with ultraviolet (UV) and mass spectrophotometric (MS) detection, by gas chromatography (GC) with MS detection, and by probe/MS methods. The detailed methods for these analyses are described below.

System A (HPLC/UV): HPLC instrument (Waters, Milford, MA) with UV detection (photodiode array)(PDA); 230-400 nm scan, genistein monitored at 260 nm), a Phenomenex ODS(3) (250 mm × 4.6 mm), 5 µm particle size column (Phenomenex, Torrance, CA), a mobile phase of 30% acetonitrile:70% 0.1% formic acid (pH 3.0), at a flow rate of 1 mL/minute.

System B (HPLC/MS): HPLC instrument (Hewlett-Packard, Palo Alto, CA) with MS detection (electrospray) (ESI) mode; the single quadrupole in full scan mode from *m/z* 50 to *m/z* 450 in 0.5 seconds (Hewlett-Packard), a Prodigy ODS (3) (250 mm × 2.0 mm), 5µm particle size column (Phenomenex; Torrance, CA), a mobile phase of A) acetonitrile and B) 3 mM ammonium formate, beginning with 20% A:80% B then linear to 80% A:20% B in 40 minutes, held 20 minutes, at a flow rate of 0.2 mL/minute.

System C (HPLC/MS/MS): HPLC instrument (Hewlett-Packard, Palo Alto, CA) with TSQ MS/MS detection in ESI mode (ThermoFinnigan Corp., San Jose, CA), with the first quadrupole scanned from *m/z* 150 to *m/z* 600 in 1 second, a Polaris C18-A (250 mm × 2.0 mm), 5 µm particle size column (MetaChem, Torrance, CA) or a Prodigy ODS (3) (250 mm × 2.0 mm), 5 µm particle size column (Phenomenex), a mobile phase of A) acetonitrile and B) 0.1% formic acid, beginning with either 5% A:95% B or 10% A:90% B, held 1 minute at 5% or 10%, then linear to 95% A:5% B in 30 minutes, held 9 minutes.

GC/Electron Ionization (EI)-MS: Varian GC instrument (Varian, Inc., Sunnyvale, CA) with TSQ MS detection in EI mode (ThermoFinnigan Corp.), a DB-5ms (30 m × 0.25 mm), 0.25 µm film thickness capillary column (J&W Scientific, Folsom, CA). The oven temperature was linearly increased from 80° to 280° C at 20° C per minute. The carrier gas was helium delivered at a constant pressure of 15 psig. The first quadrupole was scanned from *m/z* 50 to *m/z* 550 with a 0.5 second cycle time.

Direct Exposure Probe/EI-MS: Direct exposure probe, with TSQ MS detection (ThermoFinnigan Corp.). The samples, in methanol, were applied to the wire of the direct exposure probe, the solvent allowed to evaporate, then the probe was inserted into the MS, heated at 5 mA/second and ionized with electron ionization at 70 eV. The first quadrupole was scanned from *m/z* 50 to *m/z* 650 with a 0.5 second cycle time.

HPLC/UV and HPLC/MS spectra agreed with the structure of genistein and matched the spectra obtained from a purchased standard of genistein, indicating a purity of essentially 100% for each lot. GC/mass spectrometry spectra indicated one major peak and minor impurities with a purity greater than 99%. Probe/Mass spectrometry testing indicated one major component with two minor components, suggesting little to no impurities. The overall purity of each lot was determined to be greater than 99%.

To ensure stability, the bulk chemical was stored at –70° C, protected from light in the original shipping containers. Purity was periodically measured during the study using the methods described above; no degradation of the bulk chemical was detected.

Background Isoflavone Content of Base Diet

The base diet used for the current study was an irradiated soy- and alfalfa-free rodent feed, designated 5K96, obtained from Purina Mills, Inc. (Richmond, IN), in an attempt to maintain consistently low background exposure to phytoestrogens. In some associated publications resulting from this study (Appendix J), this feed is referred to as NIH-31C because it maintains the nutritional specifications of the NIH-31 feed and contains casein. The composition of this diet and the results of the routine monitoring of the diet conducted throughout the study are presented in Appendix H. The control feed was routinely assayed for total isoflavone content after acid hydrolysis by the study laboratory using HPLC/MS methods.

HPLC/MS was performed using Systems B and C described previously, with the exceptions that for System B, the first quadrupole was operated in specific ion monitoring mode, using *m/z* 253 for daidzein and *m/z* 269 for genistein, and for System C, the first quadrupole was scanned from *m/z* 140 to *m/z* 450 over 1 second. Analyses of 10 consecutive lots of 5K96 feed by these methods indicated 0.417 ± 0.213 ppm genistein and 0.271 ± 0.161 ppm daidzein. These results were consistent with an earlier study of four lots of 5K96 feed assayed at the study laboratory using liquid chromatography-tandem mass spectrometry that yielded concentrations of 0.54 ± 0.31 ppm genistein and 0.48 ± 0.21 ppm daidzein (Doerge *et al.,* 2000). Animals consuming control feed were ingesting a concentration of genistein approximately 10-fold lower than that of the groups exposed to the lowest experimental exposure concentration, a concentration consistent with the isoflavone intake of individuals consuming typical Western diets.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared every 5 weeks or as needed by mixing genistein with feed (Table C1). A premix of genistein and feed ground to a fine white powder using a mortar and pestle was layered with preweighed diet in a neoprene jar. The jar was capped and shaken, and the contents were dry mixed for 45 minutes with the remainder of the preweighed feed in a Patterson-Kelley twin-shell blender using an intensifier bar. Formulations were stored in stainless steel cans at 4° ± 2° C for up to 9 weeks.

Homogeneity (analysis of three samples each from the top, middle, and bottom of a blend) and stability studies of a 5 ppm dose formulation using lot 1-BP-118-3 were conducted by the study laboratory as part of the reproductive dose range-finding study (NTP, 2007) using the HPLC/UV system described previously. Homogeneity was confirmed, and stability in stainless steel cans was confirmed for up to 17 days at ambient temperature and for up to 32 weeks at 2° to 8° C.

Periodic analyses of the dose formulations of genistein (analysis of one sample each from the top, middle, and bottom of a blend) were conducted by the study laboratory using the HPLC/UV system described previously. The dose formulations were analyzed at intervals of 1 to 4 weeks; 124 of the 125 dose formulations analyzed and used in the study were within 10% of the target concentrations (Table C2). Animal room samples of these dose formulations were also periodically analyzed to confirm that the correct exposure concentrations were being fed (Table C3).

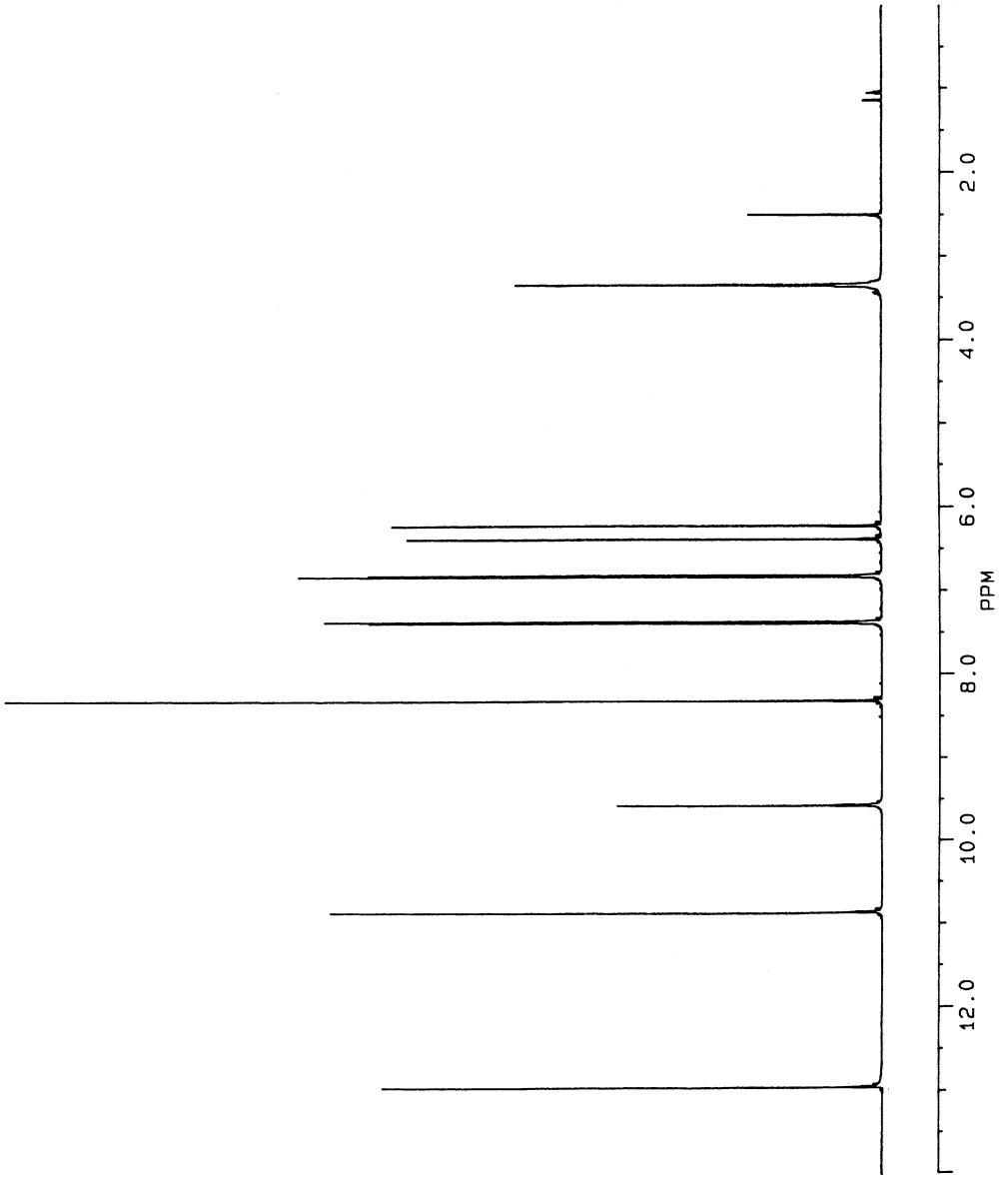


FIGURE C1
Proton Nuclear Magnetic Resonance Spectrum of Genistein

TABLE C1
Preparation and Storage of Dose Formulations in the 2-Year Feed Study of Genistein

Preparation
A premix of feed and genistein ground to a fine powder using a mortar and pestle was layered with preweighed feed in a neoprene jar. The jar was capped and shaken for 2 minutes, and the contents were dry mixed with the remainder of the preweighed feed in a Patterson-Kelley twin-shell blender with the intensifier bar on for 45 minutes. The dose formulations were prepared every 5 weeks or as needed.

Chemical Lot Numbers
2-BP-136-6
1-SOP-59-3

Maximum Storage Time
9 weeks

Storage Conditions
Dose formulations were stored in stainless steel cans secured with tie-downs at 4° ± 2° C.

Study Laboratory
National Center for Toxicological Research (Jefferson, AR)

TABLE C2
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Genistein

Date Prepared	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
December 4, 1998	5	4.73 ± 0.10	–5
	100	95.5 ± 1.7	–5
	500	425.0 ± 8.0	–15
December 7, 1998	5	4.75 ± 0.15	–5
	100	91.4 ± 1.9	–9
December 11, 1998	500	501.0 ± 13.0	0
December 30, 1998	5	4.89 ± 0.17	–2
	5	4.98 ± 0.32	0
January 29, 1999	5	4.70 ± 0.07	–6
	5	4.94 ± 0.16	–1
	100	98.5 ± 1.4	–2
	500	479.0 ± 14.2	–4
February 12, 1999	5	4.99 ± 0.29	0
	5	5.34 ± 0.50	+7
	500	494.0 ± 4.5	–1
February 19, 1999	5	4.95 ± 0.17	–1
	5	5.17 ± 0.08	+3
February 25, 1999	100	91.0 ± 2.4	–9
	100	90.9 ± 3.0	–9
March 18, 1999	5	5.12 ± 0.32	+2
	500	498.0 ± 5.5	0
March 24, 1999	5	5.09 ± 0.06	+2
	100	91.1 ± 2.1	–9
April 7, 1999	5	4.67 ± 0.13	–7
	5	4.84 ± 0.07	–3
	5	4.80 ± 0.09	–4
	100	102.0 ± 0.2	+2
	500	479.0 ± 1.0	–4
April 16, 1999	5	4.83 ± 0.14	–3
April 27, 1999	5	4.66 ± 0.05	–7
	5	4.62 ± 0.04	–8
April 28, 1999	100	91.4 ± 2.0	–9
May 11, 1999	5	5.44 ± 0.16	+9
	500	465.0 ± 1.7	–7
May 20, 1999	5	4.97 ± 0.05	–1
	5	4.61 ± 0.40	–8
	100	94.8 ± 0.2	–5
	100	104.6 ± 1.3	+5

TABLE C2
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Genistein

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
June 4, 1999	5	4.84 ± 0.26	–3
	5	5.09 ± 0.09	+2
	500	493.0 ± 14.7	–1
June 23, 1999	5	5.28 ± 0.29	+6
	5	5.55 ± 0.05[b]	+11
	100	105.0 ± 6.8	+5
	500	495.0 ± 4.0	–1
June 30, 1999	5	4.51 ± 0.19[c]	–10
July 20, 1999	5	4.87 ± 0.14	–3
	5	4.71 ± 0.08	–6
	100	95.6 ± 0.1	–4
	100	96.8 ± 0.9	–3
	500	463.0 ± 0.0	–7
	500	473.0 ± 5.7	–5
August 20, 1999	5	4.89 ± 0.02	–2
	100	98.1 ± 0.2	–2
	500	465.0 ± 6.1	–7
September 16, 1999	100	96.4 ± 0.3	–4
	100	90.0 ± 0.2	–10
	500	518.0 ± 2.0	+4
	500	505.0 ± 2.0	+1
October 5, 1999	5	5.08 ± 0.42	+2
	5	4.55 ± 0.15	–9
November 3, 1999	100	96.2 ± 3.6	–4
	500	532.0 ± 15.0	+6
November 10, 1999	5	4.67 ± 0.11	–7
	5	4.65 ± 0.04	–7
	100	95.2 ± 0.5	–5
December 2, 1999	500	503.0 ± 2.3	+1
	500	513.0 ± 5.0	+3
December 15, 1999	100	99.8 ± 1.6	0
	100	99.8 ± 2.1	0
January 6, 2000	5	5.12 ± 0.12	+2
	5	4.68 ± 0.07	–6
January 11, 2000	500	473.0 ± 0.0	–5
	500	478.0 ± 4.4	–4
January 19, 2000	100	104.4 ± 0.4	+4
	100	105.7 ± 0.4	+6
February 10, 2000	5	4.62 ± 0.18	–8
	5	4.73 ± 0.05	–5

TABLE C2
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Genistein

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
February 25, 2000	500	484.0 ± 3.6	–3
	500	509.0 ± 1.2	+2
March 7, 2000	100	91.8 ± 0.7	–8
	100	93.1 ± 0.4	–7
April 3, 2000	5	4.62 ± 0.08	–8
April 4, 2000	5	4.64 ± 0.01	–7
	500	455.0 ± 0.6	–9
	500	463.0 ± 1.5	–7
April 20, 2000	100	97.2 ± 2.1	–3
	100	95.2 ± 1.2	–5
May 11, 2000	5	5.00 ± 0.23	0
	5	5.05 ± 0.02	+1
	500	509.0 ± 1.2	+2
	500	476.0 ± 1.0	–5
June 14, 2000	100	92.3 ± 0.4	–8
	100	94.0 ± 0.2	–6
July 6, 2000	5	5.12 ± 0.42	+2
	5	5.24 ± 0.17	+5
	500	468.0 ± 1.7	–6
	500	532.0 ± 0.6	+6
July 18, 2000	100	93.2 ± 0.1	–7
August 18, 2000	5	4.86 ± 0.12	–3
	100	95.3 ± 1.5	–5
	500	482.0 ± 5.7	–4
August 30, 2000	5	4.67 ± 0.18	–7
	100	94.1 ± 4.0	–6
	500	458.0 ± 17.3	–8
October 4, 2000	5	5.40 ± 0.16	+8
	100	108.3 ± 1.4	+8
	500	527.4 ± 5.4	+5
October 19, 2000	5	5.30 ± 0.17	+6
	100	108.0 ± 3.4	+8
	500	536.5 ± 13.5	+7
October 27, 2000	5	5.40 ± 0.20	+8
	100	107.3 ± 2.6	+7
	500	526.0 ± 11.2	+5
November 22, 2000	5	4.85 ± 0.02	–3
	100	101.0 ± 1.0	+1
	500	501.7 ± 2.9	0

TABLE C2
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Genistein

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
December 20, 2000	5	4.79 ± 0.12	–4
December 21, 2000	100	105.8 ± 1.4	+6
	500	518.0 ± 6.6	+4
January 11, 2001	5	5.10 ± 0.20	+2
	100	101.8 ± 1.1	+2
	500	506.4 ± 11.8	+1
February 7, 2001	5	5.56[d]	+11
	100	99.2 ± 0.5	–1
	500	522.0 ± 12.0	+4
February 16, 2001	5	5.17 ± 0.55[e]	+3

[a] Results of triplicate analyses (mean ± standard deviation)
[b] Remixed; not used in study
[c] Results of remix
[d] Rejected; reanalyzed
[e] Results of reanalysis

TABLE C3
Results of Analyses of Animal Room Samples of Dose Formulations Administered to Rats in the 2-Year Feed Study of Genistein

Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
July 26, 1999	5	4.54 ± 0.16	–9
	100	91.3 ± 3.5	–9
	500	494.0 ± 35.0	–1
September 20, 1999	5	4.01 ± 0.34	–20
	100	110.0 ± 33.0	+10
	500	409.0 ± 16.0	–18
November 15, 1999	5	3.97 ± 0.13	–21
	100	81.3 ± 2.0	–19
	500	433.0 ± 26.0	–13
February 7, 2000	5	4.32 ± 0.09	–14
	100	82.3 ± 0.6	–18
	500	466.0 ± 9.9	–7
April 17, 2000	5	3.74 ± 0.18	–25
	100	76.7 ± 2.9	–23
	500	446.0 ± 14.2	–11
June 12, 2000	5	4.09 ± 0.15	–18
	100	75.3 ± 2.1	–25
	500	505.0 ± 17.6	+1
August 10, 2000	5	3.09 ± 0.18	–38
	100	76.8 ± 3.3	–23
	500	398.0 ± 10.0	–20
October 2, 2000	5	4.37 ± 0.09	–13
	100	91.2 ± 2.1	–9
	500	447.0 ± 6.0	–11
November 27, 2000	5	4.70 ± 0.30	–6
	100	94.5 ± 2.6	–6
	500	476.0 ± 8.5	–5
January 22, 2001	5	5.08 ± 0.87	+2
	100	91.8 ± 3.4	–8
	500	456.0 ± 9.0	–9

[a] Results of quadruplicate analyses (mean ± standard deviation)

APPENDIX D
BODY WEIGHTS

TABLE D1 Mean Body Weights of F_1C Male Rats in the 2-Year Feed Study of Genistein 182
TABLE D2 Mean Body Weights of F_1C Female Rats in the 2-Year Feed Study of Genistein 184
TABLE D3 Mean Body Weights of F_1T140 Male Rats in the 2-Year Feed Study of Genistein 186
TABLE D4 Mean Body Weights of F_1T140 Female Rats in the 2-Year Feed Study of Genistein 188
TABLE D5 Mean Body Weights of F_3T21 Male Rats in the 2-Year Feed Study of Genistein 190
TABLE D6 Mean Body Weights of F_3T21 Female Rats in the 2-Year Feed Study of Genistein 192

TABLE D1
Mean Body Weights of F_1C Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
1	13.2 ± 0.2 (54)	13.4 ± 0.2 (50)	14.1 ± 0.2* (50)	13.2 ± 0.2 (50)	-	**
5	132.3 ± 1.8 (54)	127.9 ± 2.3 (50)	132.3 ± 2.2 (50)	121.6 ± 2.2** (50)	***	-
9	323.4 ± 3.1 (53)	317.2 ± 3.8 (50)	322.4 ± 3.4 (50)	312.4 ± 3.3 (50)	-	-
13	426.7 ± 3.8 (53)	421.7 ± 5.2 (50)	428.2 ± 4.7 (50)	405.8 ± 4.2** (50)	***	-
17	479.4 ± 5.3 (53)	474.1 ± 6.0 (50)	483.6 ± 5.7 (50)	454.5 ± 5.2** (50)	***	-
21	524.5 ± 5.8 (52)	512.4 ± 6.6 (50)	517.1 ± 6.1 (49)	494.9 ± 5.8** (50)	**	-
25	547.4 ± 6.3 (52)	539.2 ± 6.9 (50)	543.8 ± 7.2 (49)	520.1 ± 6.5* (50)	**	-
29	557.6 ± 7.4 (51)	555.5 ± 7.7 (50)	556.9 ± 7.1 (48)	537.7 ± 7.0 (49)	*	-
33	564.7 ± 7.3 (51)	556.0 ± 7.7 (50)	562.8 ± 7.5 (48)	542.3 ± 7.4* (49)	-	-
37	570.5 ± 7.9 (50)	557.8 ± 8.1 (50)	568.3 ± 8.4 (48)	546.6 ± 7.7 (49)	-	-
41	575.0 ± 7.5 (50)	556.7 ± 8.4 (47)	570.3 ± 8.7 (48)	548.9 ± 7.7 (49)	-	-
45	585.3 ± 8.3 (50)	565.4 ± 9.3 (48)	580.0 ± 8.7 (48)	554.7 ± 7.9 (49)	*	-
49	592.9 ± 8.7 (49)	565.4 ± 9.9 (48)	588.6 ± 8.4 (48)	562.2 ± 8.4* (48)	-	-
53	602.9 ± 9.3 (49)	590.2 ± 10.0 (48)	588.9 ± 8.1 (48)	581.1 ± 7.8 (48)	-	-
57	601.9 ± 9.6 (49)	594.3 ± 10.6 (48)	593.8 ± 9.2 (48)	591.7 ± 8.1 (48)	-	-
61	617.4 ± 10.5 (47)	603.5 ± 10.5 (47)	603.1 ± 7.7 (48)	595.9 ± 8.3 (48)	-	-

TABLE D1
Mean Body Weights of F_1C Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
65	630.6 ± 11.1 (46)	611.5 ± 11.0 (46)	613.4 ± 8.0 (47)	600.1 ± 8.1 (48)	-	-
69	640.9 ± 10.7 (45)	614.8 ± 11.1 (46)	622.2 ± 8.0 (47)	603.2 ± 8.4 (48)	-	-
73	641.4 ± 10.6 (45)	621.9 ± 10.6 (45)	627.9 ± 9.1 (46)	613.7 ± 8.5 (47)	-	-
77	646.2 ± 10.6 (45)	628.7 ± 11.0 (45)	631.7 ± 9.8 (47)	618.9 ± 8.0 (47)	-	-
81	644.9 ± 10.3 (42)	635.5 ± 10.4 (45)	634.6 ± 10.2 (46)	620.1 ± 7.7 (45)	-	-
85	638.1 ± 10.3 (41)	629.4 ± 11.4 (43)	630.5 ± 9.9 (43)	613.4 ± 7.6 (45)	-	-
89	615.8 ± 9.2 (42)	621.3 ± 11.9 (42)	614.9 ± 10.7 (43)	604.5 ± 7.1 (45)	-	-
93	608.5 ± 9.6 (40)	613.1 ± 11.7 (42)	605.3 ± 10.1 (42)	600.4 ± 7.8 (42)	-	-
97	606.9 ± 9.7 (38)	610.4 ± 11.0 (41)	605.1 ± 11.0 (42)	589.9 ± 8.8 (39)	-	-
101	597.5 ± 10.0 (36)	607.1 ± 10.6 (41)	593.0 ± 10.5 (42)	577.2 ± 8.9 (34)	*	-

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean body weight in grams ± standard error at each indicated time point. Numbers in parentheses are the number of animals. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE D2
Mean Body Weights of F_1C Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
1	12.3 ± 0.2 (54)	12.0 ± 0.2 (50)	12.8 ± 0.3 (50)	11.7 ± 0.2 (49)	-	**
5	109.7 ± 1.5 (54)	105.5 ± 1.7 (50)	110.5 ± 1.7 (50)	101.8 ± 1.4*** (49)	***	*
9	211.6 ± 2.5 (53)	211.0 ± 2.6 (50)	214.5 ± 2.4 (50)	193.9 ± 1.3*** (49)	***	**
13	258.0 ± 3.5 (54)	258.9 ± 2.9 (49)	260.6 ± 2.9 (50)	230.4 ± 1.5*** (49)	***	*
17	284.6 ± 4.2 (54)	282.9 ± 3.6 (49)	288.0 ± 3.7 (50)	250.4 ± 1.8*** (49)	***	**
21	305.1 ± 4.7 (53)	301.7 ± 4.0 (49)	306.2 ± 4.1 (49)	263.1 ± 2.0*** (49)	***	*
25	318.2 ± 5.1 (53)	317.5 ± 4.1 (49)	319.6 ± 4.6 (49)	271.3 ± 2.1*** (49)	***	*
29	326.2 ± 5.2 (52)	330.2 ± 4.6 (49)	329.8 ± 5.0 (49)	284.4 ± 2.5*** (49)	***	*
33	330.7 ± 5.3 (52)	340.1 ± 4.9 (49)	340.4 ± 5.4 (49)	291.2 ± 2.7*** (49)	***	*
37	339.8 ± 5.6 (52)	350.6 ± 5.2 (49)	351.5 ± 5.7 (48)	298.7 ± 3.1*** (49)	***	**
41	346.5 ± 6.1 (52)	352.7 ± 5.1 (49)	359.5 ± 6.0 (48)	305.7 ± 3.4*** (49)	***	**
45	354.6 ± 6.4 (51)	362.7 ± 5.6 (49)	367.6 ± 6.4 (48)	312.4 ± 3.6*** (48)	***	**
49	361.2 ± 7.1 (50)	373.0 ± 6.0 (49)	379.0 ± 6.6 (48)	322.0 ± 3.8*** (46)	***	**
53	373.8 ± 7.6 (50)	386.7 ± 6.4 (49)	388.8 ± 6.9 (48)	333.6 ± 4.3*** (46)	***	*
57	379.2 ± 8.0 (50)	393.0 ± 6.9 (49)	398.5 ± 7.6 (47)	337.3 ± 4.7*** (45)	***	**
61	389.0 ± 8.3 (48)	401.1 ± 7.5 (49)	410.3 ± 8.5 (47)	342.7 ± 5.0*** (45)	***	**

TABLE D2
Mean Body Weights of F_1C Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
65	399.5 ± 8.4 (48)	408.0 ± 7.6 (49)	415.6 ± 9.1 (46)	346.0 ± 5.3*** (45)	***	**
69	415.1 ± 9.9 (48)	418.4 ± 8.3 (49)	431.8 ± 9.4 (45)	347.5 ± 6.0*** (45)	***	**
73	420.3 ± 9.6 (46)	422.6 ± 8.7 (48)	444.2 ± 10.4 (43)	356.6 ± 6.5*** (44)	***	**
77	423.9 ± 9.8 (46)	429.9 ± 8.9 (46)	443.1 ± 10.7 (42)	354.2 ± 6.3*** (43)	***	*
81	434.8 ± 10.3 (45)	437.3 ± 9.5 (44)	447.0 ± 11.9 (41)	362.9 ± 6.1*** (41)	***	*
85	431.5 ± 10.6 (44)	432.4 ± 9.8 (42)	437.7 ± 12.7 (39)	360.1 ± 7.0*** (38)	***	-
89	420.7 ± 10.4 (36)	428.6 ± 9.9 (37)	435.7 ± 13.6 (35)	366.6 ± 7.8*** (33)	***	-
93	420.4 ± 10.4 (33)	418.6 ± 11.3 (35)	433.5 ± 14.7 (29)	369.2 ± 10.0*** (29)	***	-
97	420.1 ± 11.1 (30)	428.0 ± 12.2 (33)	432.0 ± 15.4 (28)	385.0 ± 9.8*** (24)	***	-
101	422.5 ± 11.2 (26)	435.2 ± 14.5 (28)	430.5 ± 17.5 (25)	383.7 ± 11.5*** (23)	***	-

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean body weight in grams ± standard error at each indicated time point. Numbers in parentheses are the number of animals. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE D3
Mean Body Weights of F_1T140 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
1	13.2 ± 0.2 (54)	13.7 ± 0.3 (50)	14.3 ± 0.2** (50)	13.0 ± 0.2 (50)	*	***
5	132.3 ± 1.8 (54)	135.4 ± 1.8 (50)	139.5 ± 2.1* (50)	128.6 ± 2.0 (50)	**	**
9	323.4 ± 3.1 (53)	322.4 ± 3.3 (50)	329.4 ± 3.6 (50)	311.1 ± 3.6 (50)	**	*
13	426.7 ± 3.8 (53)	416.9 ± 4.5 (50)	427.9 ± 5.9 (50)	402.6 ± 4.3** (50)	***	-
17	479.4 ± 5.3 (53)	472.2 ± 5.5 (50)	490.6 ± 5.4 (50)	457.3 ± 5.1* (50)	***	**
21	524.5 ± 5.8 (52)	520.0 ± 5.3 (50)	539.0 ± 5.6* (49)	505.1 ± 5.4 (50)	**	***
25	547.4 ± 6.3 (52)	541.2 ± 5.8 (50)	556.5 ± 6.2 (49)	516.2 ± 6.4** (50)	***	**
29	557.6 ± 7.4 (51)	544.0 ± 7.1 (50)	569.8 ± 6.5 (49)	521.7 ± 6.5** (50)	***	***
33	564.7 ± 7.3 (51)	556.6 ± 6.9 (50)	578.0 ± 7.5 (49)	540.0 ± 6.4 (50)	**	**
37	570.5 ± 7.9 (50)	560.2 ± 7.5 (50)	584.2 ± 7.4 (48)	546.4 ± 6.4 (50)	*	**
41	575.0 ± 7.5 (50)	560.1 ± 8.5 (50)	588.1 ± 7.8 (48)	542.2 ± 7.7* (50)	**	**
45	585.3 ± 8.3 (50)	570.8 ± 8.1 (50)	589.7 ± 8.6 (48)	552.6 ± 7.0* (50)	**	-
49	592.9 ± 8.7 (49)	569.4 ± 7.8 (50)	595.7 ± 7.8 (46)	552.9 ± 8.1** (50)	**	-
53	602.9 ± 9.3 (49)	583.5 ± 8.7 (50)	604.5 ± 8.5 (46)	567.9 ± 8.1* (50)	**	-
57	601.9 ± 9.6 (49)	589.3 ± 9.3 (49)	619.9 ± 8.5 (46)	571.0 ± 7.9* (50)	**	**
61	617.4 ± 10.5 (47)	606.5 ± 9.4 (49)	631.4 ± 9.1 (46)	581.5 ± 8.0 (49)	**	*

TABLE D3
Mean Body Weights of F_1T140 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
65	630.6 ± 11.1 (46)	617.1 ± 9.7 (49)	640.0 ± 9.4 (45)	595.8 ± 8.1 (49)	*	*
69	640.9 ± 10.7 (45)	624.8 ± 10.4 (48)	640.6 ± 10.7 (45)	600.6 ± 8.3 (49)	*	-
73	641.4 ± 10.6 (45)	629.8 ± 10.8 (48)	647.8 ± 9.9 (45)	599.2 ± 9.7 (48)	**	-
77	646.2 ± 10.6 (45)	635.4 ± 11.2 (48)	656.8 ± 9.8 (45)	601.3 ± 9.8* (48)	***	*
81	644.9 ± 10.3 (42)	631.2 ± 10.8 (46)	649.1 ± 9.9 (45)	598.2 ± 9.0** (46)	***	-
85	638.1 ± 10.3 (41)	611.3 ± 11.2 (46)	645.2 ± 10.1 (42)	587.0 ± 9.7** (46)	***	*
89	615.8 ± 9.2 (42)	607.6 ± 11.3 (45)	632.7 ± 12.1 (39)	575.4 ± 11.3 (46)	**	*
93	608.5 ± 9.6 (40)	607.7 ± 11.7 (42)	628.0 ± 12.8 (37)	570.1 ± 11.6 (45)	**	*
97	606.9 ± 9.7 (38)	602.6 ± 12.1 (41)	617.3 ± 12.4 (35)	566.8 ± 11.9* (42)	***	-
101	597.5 ± 10.0 (36)	601.5 ± 13.8 (37)	624.2 ± 12.6 (33)	553.0 ± 12.2* (38)	***	*

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean body weight in grams ± standard error at each indicated time point. Numbers in parentheses are the number of animals. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE D4
Mean Body Weights of F_1T140 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
1	12.3 ± 0.2 (54)	12.4 ± 0.3 (50)	13.1 ± 0.2 (50)	12.0 ± 0.3 (50)	-	**
5	109.7 ± 1.5 (54)	113.6 ± 1.5 (50)	117.2 ± 1.3** (50)	107.1 ± 1.7 (50)	**	***
9	211.6 ± 2.5 (53)	213.1 ± 2.6 (50)	215.1 ± 2.5 (50)	197.0 ± 2.4*** (50)	***	*
13	258.0 ± 3.5 (54)	260.3 ± 3.5 (50)	263.5 ± 3.4 (50)	233.1 ± 2.5*** (50)	***	*
17	284.6 ± 4.2 (54)	285.1 ± 4.0 (50)	291.8 ± 4.2 (50)	252.9 ± 2.8*** (50)	***	**
21	305.1 ± 4.7 (53)	308.3 ± 4.6 (50)	314.7 ± 4.9 (49)	272.8 ± 3.2*** (50)	***	**
25	318.2 ± 5.1 (53)	319.1 ± 5.1 (50)	328.7 ± 5.3 (49)	288.2 ± 3.4*** (50)	***	**
29	326.2 ± 5.2 (52)	330.2 ± 5.2 (50)	340.0 ± 5.6 (49)	300.1 ± 4.1*** (50)	***	**
33	330.7 ± 5.3 (52)	334.6 ± 5.3 (50)	344.6 ± 5.8 (49)	307.9 ± 4.1** (50)	***	**
37	339.8 ± 5.6 (52)	340.4 ± 5.3 (50)	352.6 ± 6.0 (49)	315.4 ± 4.4** (50)	***	**
41	346.5 ± 6.1 (52)	350.9 ± 5.9 (50)	363.2 ± 6.5 (49)	325.5 ± 4.5* (50)	***	**
45	354.6 ± 6.4 (51)	363.0 ± 6.8 (49)	374.0 ± 7.0 (49)	335.9 ± 4.7* (50)	***	**
49	361.2 ± 7.1 (50)	371.2 ± 7.1 (49)	383.5 ± 7.7 (49)	346.0 ± 5.3 (50)	**	*
53	373.8 ± 7.6 (50)	381.9 ± 8.0 (49)	394.6 ± 7.9 (49)	353.3 ± 5.6 (49)	**	*
57	379.2 ± 8.0 (50)	385.6 ± 8.1 (49)	405.2 ± 8.3 (47)	361.6 ± 5.5 (48)	**	**
61	389.0 ± 8.3 (48)	394.5 ± 9.1 (48)	415.2 ± 8.6 (47)	369.8 ± 5.7 (48)	**	**

TABLE D4
Mean Body Weights of F_1T140 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
65	399.5 ± 8.4 (48)	410.8 ± 9.3 (47)	428.6 ± 9.0* (47)	380.9 ± 6.2 (48)	**	**
69	415.1 ± 9.9 (48)	421.7 ± 10.1 (47)	436.3 ± 9.2 (47)	386.0 ± 6.8* (47)	**	*
73	420.3 ± 9.6 (46)	429.0 ± 9.7 (47)	444.4 ± 9.5 (47)	392.5 ± 7.0* (45)	***	**
77	423.9 ± 9.8 (46)	430.9 ± 9.7 (46)	453.8 ± 10.7 (46)	401.4 ± 7.3* (44)	***	**
81	434.8 ± 10.3 (45)	431.8 ± 11.1 (45)	452.8 ± 10.8 (45)	408.8 ± 8.0* (43)	**	*
85	431.5 ± 10.6 (44)	427.3 ± 10.6 (45)	447.2 ± 11.9 (45)	398.2 ± 7.7* (39)	***	*
89	420.7 ± 10.4 (36)	437.9 ± 11.0 (41)	453.0 ± 9.8 (43)	395.8 ± 7.7** (36)	***	**
93	420.4 ± 10.4 (33)	435.8 ± 10.8 (36)	445.5 ± 9.5 (39)	394.0 ± 8.7* (29)	***	**
97	420.1 ± 11.1 (30)	446.1 ± 10.5 (34)	449.5 ± 9.3 (35)	389.6 ± 10.3* (26)	***	*
101	422.5 ± 11.2 (26)	442.0 ± 11.5 (32)	440.9 ± 9.6 (33)	392.0 ± 13.1 (23)	*	-

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean body weight in grams ± standard error at each indicated time point. Numbers in parentheses are the number of animals. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE D5
Mean Body Weights of F_3T21 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
3	83.1 ± 2.6 (51)	84.8 ± 2.9 (50)	76.3 ± 1.8 (49)	79.7 ± 2.8 (49)	-	*
7	237.1 ± 4.4 (51)	235.3 ± 4.9 (4.9)	235.8 ± 3.1 (49)	235.8 ± 4.5 (49)	-	-
11	379.7 ± 5.1 (51)	377.4 ± 5.7 (49)	383.2 ± 4.8 (49)	375.0 ± 5.2 (48)	-	-
15	461.0 ± 6.9 (33)	460.0 ± 10.8 (27)	471.2 ± 5.7 (46)	454.6 ± 8.4 (30)	-	-
19	511.5 ± 6.3 (51)	503.5 ± 7.2 (48)	517.3 ± 6.4 (48)	497.9 ± 6.1 (48)	-	-
23	534.7 ± 7.2 (51)	531.1 ± 7.8 (48)	546.4 ± 6.9 (49)	521.5 ± 7.1 (48)	-	-
27	547.4 ± 7.0 (51)	547.3 ± 8.5 (48)	559.5 ± 7.1 (49)	533.4 ± 7.8 (48)	-	-
31	552.4 ± 7.1 (51)	559.8 ± 8.7 (48)	573.4 ± 6.9 (49)	550.4 ± 7.9 (48)	-	*
35	560.5 ± 7.3 (50)	564.2 ± 8.9 (48)	583.3 ± 7.7 (49)	552.8 ± 9.0 (48)	-	*
39	568.4 ± 8.0 (50)	576.0 ± 9.4 (48)	593.6 ± 7.9 (49)	559.6 ± 8.4 (48)	-	*
43	580.5 ± 7.8 (50)	592.0 ± 9.3 (47)	601.8 ± 8.2 (49)	569.1 ± 9.0 (48)	*	-
47	593.0 ± 7.4 (50)	604.8 ± 9.9 (47)	611.3 ± 8.6 (48)	585.0 ± 8.8 (48)	-	-
51	601.5 ± 7.7 (50)	615.2 ± 10.1 (47)	619.7 ± 8.5 (48)	588.3 ± 9.3 (48)	*	-
55	609.8 ± 7.9 (49)	625.8 ± 10.3 (47)	632.9 ± 8.6 (48)	602.4 ± 8.8 (48)	-	-
59	619.9 ± 8.1 (49)	636.2 ± 10.8 (47)	640.2 ± 8.5 (48)	610.1 ± 9.1 (48)	-	-
63	620.5 ± 8.5 (49)	640.5 ± 10.6 (47)	648.1 ± 8.9 (48)	610.7 ± 8.9 (48)	*	*

TABLE D5
Mean Body Weights of F_3T21 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
67	615.4 ± 8.5 (48)	643.7 ± 11.2 (47)	652.0 ± 9.3* (48)	612.0 ± 9.3 (48)	*	*
71	628.5 ± 8.9 (44)	648.2 ± 11.7 (47)	658.4 ± 9.7* (48)	621.9 ± 9.7 (47)	-	*
75	633.0 ± 8.5 (44)	656.9 ± 11.3 (46)	659.8 ± 10.1 (46)	622.8 ± 9.9 (45)	*	*
79	617.0 ± 8.5 (43)	643.3 ± 12.5 (45)	647.1 ± 10.5 (43)	609.5 ± 11.1 (44)	*	-
83	604.5 ± 9.4 (42)	635.2 ± 11.9 (44)	639.4 ± 10.1 (42)	594.4 ± 11.7 (43)	*	*
87	599.1 ± 9.8 (40)	617.1 ± 9.6 (43)	631.6 ± 9.8* (42)	584.2 ± 11.8 (40)	*	*
91	597.6 ± 9.0 (38)	612.4 ± 9.8 (43)	626.4 ± 10.5* (40)	583.8 ± 11.4 (38)	*	*
95	600.8 ± 8.6 (36)	604.5 ± 11.1 (43)	619.9 ± 9.8 (36)	580.9 ± 12.2 (37)	*	-
99	586.6 ± 9.5 (35)	604.2 ± 11.8 (42)	620.0 ± 10.6 (34)	582.1 ± 13.0 (36)	-	*
103	578.0 ± 10.3 (33)	600.9 ± 11.0 (42)	615.4 ± 10.9 (33)	561.0 ± 13.7 (36)	**	*

* $P \leq 0.05$
** $P \leq 0.01$
[a] Mean body weight in grams ± standard error at each indicated time point. Numbers in parentheses are the number of animals. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE D6
Mean Body Weights of F_3T21 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
3	65.7 ± 1.8 (53)	57.4 ± 1.8 (50)	68.3 ± 1.4 (50)	63.7 ± 1.7 (50)	-	-
7	177.2 ± 2.7 (53)	167.0 ± 2.6 (49)	177.8 ± 2.4 (50)	177.8 ± 2.4 (50)	-	-
11	247.2 ± 4.0 (53)	236.6± 28*** (49)	244.2 ± 2.9* (50)	247.7 ± 3.0 (50)	-	***
15	285.7 ± 7.0 (10)	268.2 ± 3.7*** (29)	267.9 ± 4.1*** (12)	283.6 ± 7.2 (17)	-	***
19	304.3 ± 4.7 (52)	294.4 ± 3.6** (49)	296.8 ± 3.5 (50)	303.8 ± 4.5 (50)	-	***
23	316.0 ± 5.5 (52)	306.7 ± 4.1* (49)	310.9 ± 3.9 (50)	314.1 ± 5.1 (50)	-	**
27	325.6 ± 5.7 (52)	313.4 ± 4.4 (49)	320.5 ± 4.4 (50)	322.4 ± 5.5 (50)	-	*
31	334.5 ± 5.9 (52)	323.3 ± 4.3 (49)	329.9 ± 4.9 (50)	332.8 ± 5.9 (50)	-	*
35	344.2 ± 6.3 (52)	334.2 ± 4.7 (49)	339.9 ± 5.1 (50)	341.5 ± 6.8 (50)	-	*
39	353.8 ± 6.9 (52)	342.9 ± 4.9 (49)	348.8 ± 5.6 (50)	350.2 ± 6.8 (50)	-	-
43	364.0 ± 7.3 (52)	353.5 ± 5.3 (49)	357.9 ± 5.8 (50)	360.7 ± 7.3 (49)	-	-
47	378.0 ± 8.1 (52)	363.6 ± 5.5 (49)	368.8 ± 6.1 (50)	374.6 ± 8.0 (49)	-	*
51	385.6 ± 8.7 (52)	372.6 ± 5.9 (49)	376.2 ± 6.4 (49)	381.9 ± 8.3 (49)	-	-
55	393.1 ± 8.9 (52)	384.6 ± 6.4 (49)	386.9 ± 6.4 (49)	389.9 ± 8.7 (49)	-	-
59	406.0 ± 9.3 (52)	397.5 ± 6.9 (49)	398.5 ± 6.9 (49)	402.1 ± 8.7 (49)	-	-
63	420.3 ± 10.3 (52)	410.8 ± 8.1 (49)	410.2 ± 7.0 (49)	414.1 ± 8.9 (49)	-	-

TABLE D6
Mean Body Weights of F_3T21 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
67	431.6 ± 11.1 (50)	417.9 ± 8.8 (49)	417.6 ± 7.4 (49)	419.0 ± 8.9 (49)	-	-
71	441.5 ± 11.3 (49)	425.4 ± 10.5 (47)	423.5 ± 7.6 (49)	417.5 ± 8.9 (47)	-	-
75	450.4 ± 12.1 (49)	437.1 ± 9.0 (42)	430.8 ± 7.8 (49)	418.2 ± 10.3 (45)	*	-
79	443.8 ± 12.3 (49)	436.2 ± 9.8 (42)	421.4 ± 8.6 (48)	415.5 ± 10.8 (42)	*	-
83	444.0 ± 13.1 (45)	440.9 ± 11.3 (36)	421.8 ± 10.3 (41)	417.2 ± 10.7 (40)	*	*
87	433.1 ± 13.1 (45)	442.0 ± 10.8 (40)	415.2 ± 9.7 (43)	413.3 ± 10.6 (41)	*	**
91	430.1 ± 12.8 (43)	445.4 ± 11.3 (40)	422.2 ± 9.5 (39)	412.7 ± 10.7 (37)	*	*
95	432.0 ± 15.2 (41)	443.1 ± 12.4 (38)	423.1 ± 9.7 (35)	406.8 ± 12.3 (32)	*	*
99	439.4 ± 15.0 (36)	461.7 ± 13.8 (33)	431.4 ± 10.7 (33)	416.2 ± 13.9 (28)	**	*
103	436.8 ± 14.9 (33)	450.5 ± 15.0 (31)	419.0 ± 11.7 (30)	417.5 ± 15.8 (26)	-	*

* $P \leq 0.05$
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Mean body weight in grams ± standard error at each indicated time point. Numbers in parentheses are the number of animals. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

APPENDIX E
FEED CONSUMPTION
IN THE 2-YEAR FEED STUDY OF GENISTEIN

TABLE E1	Feed Consumption by F_1C Male Rats in the 2-Year Feed Study of Genistein	196
TABLE E2	Feed Consumption by F_1C Female Rats in the 2-Year Feed Study of Genistein	198
TABLE E3	Feed Consumption by F_1T140 Male Rats in the 2-Year Feed Study of Genistein	200
TABLE E4	Feed Consumption by F_1T140 Female Rats in the 2-Year Feed Study of Genistein	202
TABLE E5	Feed Consumption by F_3T21 Male Rats in the 2-Year Feed Study of Genistein	204
TABLE E6	Feed Consumption by F_3T21 Female Rats in the 2-Year Feed Study of Genistein	206

TABLE E1
Feed Consumption by F_1C Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
6	19.7 ± 0.3 (53)	19.4 ± 0.3 (50)	20.0 ± 0.3 (50)	19.2 ± 0.3 (50)	-	-
10	24.0 ± 0.3 (53)	24.0 ± 0.4 (50)	24.1 ± 0.4 (50)	23.1 ± 0.3 (50)	-	-
14	24.6 ± 0.4 (53)	24.1 ± 0.4 (50)	24.9 ± 0.4 (50)	23.9 ± 0.4 (50)	-	-
18	24.1 ± 0.4 (52)	23.8 ± 0.4 (50)	23.8 ± 0.5 (50)	23.6 ± 0.4 (50)	-	-
22	23.5 ± 0.5 (52)	25.5 ± 0.8 (50)	25.6 ± 0.5* (49)	23.8 ± 0.3 (50)	-	-
26	24.5 ± 0.5 (52)	23.7 ± 0.4 (50)	25.0 ± 0.4 (49)	24.7 ± 0.5 (50)	-	-
30	22.3 ± 0.5 (51)	22.0 ± 0.5 (50)	23.1 ± 0.6 (48)	22.0 ± 0.5 (49)	-	-
34	23.3 ± 0.5 (51)	24.4 ± 0.6 (50)	24.1 ± 0.5 (48)	25.1 ± 0.4* (49)	*	-
38	23.8 ± 0.5 (50)	24.0 ± 0.4 (50)	23.6 ± 0.4 (48)	23.8 ± 0.5 (49)	-	-
42	23.5 ± 0.6 (50)	22.3 ± 0.5 (48)	22.7 ± 0.5 (48)	22.2 ± 0.6 (49)	-	-
46	20.7 ± 0.5 (50)	21.4 ± 0.5 (47)	22.1 ± 0.5 (48)	21.3 ± 0.5 (49)	-	-
50	22.5 ± 0.5 (49)	23.6 ± 0.5 (48)	21.9 ± 0.5 (47)	22.6 ± 0.5 (48)	-	-
54	21.1 ± 0.4 (49)	21.5 ± 0.6 (48)	22.3 ± 0.5 (48)	21.4 ± 0.5 (48)	-	-
58	23.8 ± 0.6 (49)	23.8 ± 0.6 (48)	23.2 ± 0.5 (48)	23.7 ± 0.7 (48)	-	-
62	24.5 ± 0.5 (47)	24.4 ± 0.6 (46)	23.4 ± 0.5 (48)	24.2 ± 0.6 (48)	-	-
66	23.5 ± 0.8 (46)	25.3 ± 0.5 (46)	26.3 ± 0.4** (47)	25.3 ± 0.4 (48)	-	**

TABLE E1
Feed Consumption by F_1C Male Rats in the 2-Year Feed Studies of Genistein

Weeks	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
70	26.3 ± 0.6 (45)	25.6 ± 0.6 (46)	26.3 ± 0.6 (47)	26.7 ± 0.5 (48)	-	-
74	24.2 ± 0.6 (45)	23.6 ± 0.6 (45)	22.9 ± 0.7 (47)	23.2 ± 0.6 (47)	-	-
78	24.5 ± 0.8 (45)	25.9 ± 0.5 (45)	26.2 ± 0.5 (47)	25.1 ± 0.7 (46)	-	-
82	20.1 ± 0.5 (42)	21.1 ± 0.5 (45)	20.0 ± 0.5 (45)	21.7 ± 0.5 (45)	*	-
86	23.3 ± 0.8 (37)	22.5 ± 0.6 (41)	23.5 ± 0.5 (38)	23.1 ± 0.5 (40)	-	-
90	21.3 ± 0.6 (41)	22.8 ± 0.6 (42)	21.5 ± 0.7 (43)	20.7 ± 0.6 (45)	-	-
94	22.3 ± 0.7 (40)	22.7 ± 0.7 (42)	22.8 ± 0.6 (42)	21.5 ± 0.5 (41)	-	-
98	22.9 ± 1.1 (38)	22.9 ± 0.6 (41)	21.9 ± 0.6 (42)	23.9 ± 1.6 (38)	-	-
102	22.4 ± 0.9 (36)	21.5 ± 0.6 (41)	21.9 ± 0.6 (40)	22.6 ± 1.0 (31)	-	-

* $P \leq 0.05$
** $P \leq 0.01$
[a] Mean daily feed consumption in grams/day ± standard error at each indicated time point. Numbers in parentheses are the number of samples. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE E2
Feed Consumption by F_1C Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
6	15.9 ± 0.3 (54)	15.5 ± 0.2** (50)	16.0 ± 0.3 (50)	15.1 ± 0.2** (49)	*	*
10	18.4 ± 0.3 (54)	18.2 ± 0.3 (50)	18.4 ± 0.3 (50)	16.9 ± 0.3*** (49)	***	-
14	18.7 ± 0.3 (54)	18.2 ± 0.4* (49)	18.8 ± 0.3 (50)	17.5 ± 0.3** (49)	*	-
18	18.6 ± 0.3 (54)	18.7 ± 0.3 (49)	18.5 ± 0.3 (50)	17.2 ± 0.2*** (49)	***	-
22	19.9 ± 0.4 (53)	19.8 ± 0.3 (49)	20.2 ± 0.4 (49)	18.4 ± 0.4** (49)	***	*
26	19.3 ± 0.3 (53)	19.4 ± 0.2 (49)	19.5 ± 0.3 (49)	19.2 ± 0.3 (48)	-	-
30	18.4 ± 0.3 (52)	19.1 ± 0.3 (49)	19.0 ± 0.2 (49)	18.4 ± 0.3 (49)	-	-
34	19.4 ± 0.3 (52)	19.8 ± 0.3 (49)	20.0 ± 0.3 (49)	19.1 ± 0.3 (49)	-	*
38	18.6 ± 0.3 (52)	18.6 ± 0.3 (49)	18.4 ± 0.4 (48)	18.2 ± 0.3 (49)	-	-
42	18.5 ± 0.3 (52)	18.4 ± 0.3 (49)	18.7 ± 0.3 (48)	18.3 ± 0.4 (49)	-	-
46	18.0 ± 0.4 (50)	18.6 ± 0.3 (49)	19.4 ± 0.6 (48)	18.1 ± 0.4 (48)	-	*
50	19.7 ± 0.4 (50)	20.2 ± 0.6 (49)	20.5 ± 0.4 (48)	19.2 ± 0.4 (46)	-	-
54	18.3 ± 0.2 (50)	19.1 ± 0.3 (49)	18.4 ± 0.4 (48)	17.9 ± 0.4 (46)	-	-
58	19.9 ± 0.3 (49)	19.9 ± 0.4 (49)	20.2 ± 0.3 (47)	19.1 ± 0.5 (45)	-	-
62	20.1 ± 0.3 (48)	20.6 ± 0.4 (48)	20.8 ± 0.4 (47)	19.7 ± 0.3 (45)	-	-
66	21.2 ± 0.4 (48)	21.8 ± 0.4 (49)	22.4 ± 0.6 (46)	21.0 ± 0.4 (45)	-	*

TABLE E2
Feed Consumption by F_1C Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
70	21.4 ± 0.4 (48)	21.5 ± 0.3 (49)	21.2 ± 0.5 (45)	20.6 ± 0.4 (45)	-	-
74	19.9 ± 0.3 (46)	20.5 ± 0.3 (48)	20.3 ± 0.5 (43)	19.2 ± 0.3 (44)	*	-
78	21.0 ± 0.4 (46)	21.0 ± 0.4 (45)	20.3 ± 0.6 (41)	20.1 ± 0.3 (42)	-	-
82	19.0 ± 0.4 (45)	20.3 ± 0.5 (44)	19.0 ± 0.5 (41)	18.3 ± 0.5 (41)	-	-
86	20.4 ± 0.5 (43)	20.1 ± 0.5 (41)	20.2 ± 0.7 (39)	18.8 ± 0.4 (36)	*	-
90	19.2 ± 0.6 (36)	19.5 ± 1.0 (37)	20.0 ± 1.0 (35)	21.4 ± 1.3 (33)	-	-
94	20.6 ± 0.6 (32)	19.4 ± 0.4 (35)	19.7 ± 0.6 (29)	20.4 ± 1.4 (27)	-	-
98	18.4 ± 0.5 (30)	18.4 ± 0.6 (33)	18.4 ± 0.6 (28)	18.2 ± 0.6 (24)	-	-
102	20.1 ± 0.6 (25)	19.4 ± 0.7 (27)	19.6 ± 0.9 (24)	16.8 ± 1.2 (23)	**	-

* P≤0.05
** P≤0.01
***P≤0.001
[a] Mean daily feed consumption in grams/day ± standard error at each indicated time point. Numbers in parentheses are the number of samples. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE E3
Feed Consumption by F_1T140 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
6	19.7 ± 0.3 (53)	20.5 ± 0.2 (50)	20.7 ± 0.3 (50)	19.8 ± 0.3 (50)	-	*
10	24.0 ± 0.3 (53)	23.7 ± 0.4 (50)	24.5 ± 0.5 (50)	23.5 ± 0.5 (50)	-	-
14	24.6 ± 0.4 (53)	24.6 ± 0.3 (50)	25.8 ± 0.4 (50)	24.4 ± 0.3 (50)	-	**
18	24.1 ± 0.4 (52)	24.6 ± 0.3 (50)	25.8 ± 0.5 (50)	24.7 ± 0.4 (50)	-	**
22	23.5 ± 0.5 (52)	23.8 ± 0.4 (50)	24.2 ± 0.5 (49)	22.7 ± 0.4 (50)	-	-
26	24.5 ± 0.5 (52)	24.0 ± 0.5 (50)	24.9 ± 0.4 (49)	23.6 ± 0.4 (50)	-	-
30	22.3 ± 0.5 (51)	22.7 ± 0.6 (50)	23.3 ± 0.6 (49)	22.3 ± 0.5 (50)	-	-
34	23.3 ± 0.5 (51)	22.5 ± 0.5 (50)	23.8 ± 0.5 (49)	23.0 ± 0.4 (50)	-	-
38	23.8 ± 0.5 (50)	23.3 ± 0.4 (50)	24.4 ± 0.5 (47)	22.5 ± 0.4 (50)	*	-
42	23.5 ± 0.6 (50)	23.3 ± 0.5 (50)	24.2 ± 0.5 (48)	23.1 ± 0.5 (50)	-	-
46	20.7 ± 0.5 (50)	20.2 ± 0.5 (50)	20.7 ± 0.6 (48)	20.1 ± 0.5 (50)	-	-
50	22.5 ± 0.5 (49)	23.1 ± 0.5 (50)	23.7 ± 0.6 (46)	22.2 ± 0.5 (50)	-	-
54	21.1 ± 0.4 (49)	21.5 ± 0.5 (50)	22.9 ± 0.6* (46)	21.6 ± 0.4 (50)	-	**
58	23.8 ± 0.6 (49)	23.6 ± 0.5 (49)	24.4 ± 0.5 (46)	24.4 ± 0.4 (50)	-	-
62	24.5 ± 0.5 (47)	23.9 ± 0.4 (49)	23.9 ± 0.7 (46)	23.6 ± 0.4 (49)	-	-
66	23.5 ± 0.8 (46)	22.1 ± 0.6 (49)	23.9 ± 0.6 (45)	22.2 ± 0.6 (49)	-	-

TABLE E3
Feed Consumption by F_1T140 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
70	26.3 ± 0.6 (45)	25.9 ± 0.5 (48)	26.5 ± 0.7 (45)	24.7 ± 0.4 (49)	*	-
74	24.2 ± 0.6 (45)	23.8 ± 0.6 (48)	24.4 ± 0.6 (45)	22.4 ± 0.6 (47)	*	-
78	24.5 ± 0.8 (45)	24.6 ± 0.5 (47)	24.6 ± 0.5 (45)	23.4 ± 0.5 (48)	-	-
82	20.1 ± 0.5 (42)	19.7 ± 0.6 (46)	20.2 ± 0.8 (45)	19.8 ± 0.6 (46)	-	-
86	23.3 ± 0.8 (37)	24.4 ± 1.3 (41)	23.6 ± 0.9 (39)	22.8 ± 1.0 (40)	-	-
90	21.3 ± 0.6 (41)	22.3 ± 0.7 (45)	23.1 ± 0.8 (45)	22.0 ± 0.8 (46)	-	-
94	22.3 ± 0.7 (40)	21.8 ± 0.6 (42)	21.4 ± 0.7 (36)	20.5 ± 0.6 (44)	*	-
98	22.9 ± 1.1 (38)	21.5 ± 0.6 (41)	23.1 ± 0.9 (34)	21.3 ± 0.6 (41)	-	-
102	22.4 ± 0.9 (36)	22.9 ± 0.9 (36)	22.7 ± 0.7 (33)	23.7 ± 1.0 (38)	-	-

* $P \leq 0.05$
** $P \leq 0.01$
[a] Mean daily feed consumption in grams/day ± standard error at each indicated time point. Numbers in parentheses are the number of samples. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE E4
Feed Consumption by F_1T140 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
6	15.9 ± 0.3 (54)	16.1 ± 0.2 (50)	16.6 ± 0.2 (49)	15.6 ± 0.2 (50)	*	-
10	18.4 ± 0.3 (54)	17.8 ± 0.3* (50)	18.6 ± 0.3 (50)	17.3 ± 0.3** (50)	**	-
14	18.7 ± 0.3 (54)	18.4 ± 0.2 (50)	19.5 ± 0.3 (50)	17.4 ± 0.3*** (50)	***	***
18	18.6 ± 0.3 (54)	18.7 ± 0.2 (50)	19.0 ± 0.3 (50)	17.9 ± 0.3* (50)	**	-
22	19.9 ± 0.4 (53)	19.5 ± 0.3 (50)	20.1 ± 0.3 (49)	19.7 ± 0.2 (50)	-	-
26	19.3 ± 0.3 (53)	19.6 ± 0.3 (50)	19.8 ± 0.3 (49)	19.9 ± 0.3 (50)	-	-
30	18.4 ± 0.3 (52)	18.4 ± 0.3 (50)	18.5 ± 0.3 (49)	18.5 ± 0.3 (50)	-	-
34	19.4 ± 0.3 (52)	19.5 ± 0.3 (50)	19.9 ± 0.3 (49)	19.7 ± 0.4 (50)	-	-
38	18.6 ± 0.3 (52)	19.3 ± 0.3 (50)	19.4 ± 0.4 (49)	19.1 ± 0.4 (50)	-	-
42	18.5 ± 0.3 (52)	18.6 ± 0.3 (50)	19.0 ± 0.3 (49)	19.1 ± 0.5 (50)	-	-
46	18.0 ± 0.4 (50)	18.2 ± 0.3 (49)	18.3 ± 0.3 (49)	18.5 ± 0.3 (50)	-	-
50	19.7 ± 0.4 (50)	19.4 ± 0.4 (49)	20.3 ± 0.3 (49)	19.5 ± 0.3 (50)	-	-
54	18.3 ± 0.2 (50)	18.4 ± 0.3 (49)	18.8 ± 0.3 (49)	18.7 ± 0.3 (49)	-	-
58	19.9 ± 0.3 (49)	19.6 ± 0.4 (49)	20.4 ± 0.4 (47)	19.8 ± 0.3 (48)	-	-
62	20.1 ± 0.3 (48)	20.5 ± 0.4 (47)	20.5 ± 0.3 (47)	19.6 ± 0.3 (48)	*	-
66	21.2 ± 0.4 (48)	20.9 ± 0.5 (47)	21.4 ± 0.4 (47)	21.0 ± 0.5 (48)	-	-

TABLE E4
Feed Consumption by F_1T140 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
70	21.4 ± 0.4 (48)	20.9 ± 0.4 (47)	21.5 ± 0.4 (47)	21.0 ± 0.3 (46)	-	-
74	19.9 ± 0.3 (46)	20.6 ± 0.4 (47)	20.3 ± 0.3 (46)	19.8 ± 0.5 (45)	-	-
78	21.0 ± 0.4 (46)	20.6 ± 0.5 (46)	21.7 ± 0.4 (46)	21.0 ± 0.3 (44)	-	-
82	19.0 ± 0.4 (45)	18.6 ± 0.6 (45)	19.4 ± 0.4 (45)	19.0 ± 0.5 (42)	-	-
86	20.4 ± 0.5 (43)	20.3 ± 0.5 (44)	21.2 ± 0.5 (44)	20.5 ± 0.4 (39)	-	-
90	19.2 ± 0.6 (36)	20.4 ± 0.5 (41)	20.5 ± 0.3 (43)	19.3 ± 0.5 (35)	-	-
94	20.6 ± 0.6 (32)	19.9 ± 0.4 (36)	19.7 ± 0.6 (39)	19.5 ± 0.5 (29)	-	-
98	18.4 ± 0.5 (30)	19.9 ± 0.4 (33)	20.1 ± 0.5 (35)	19.9 ± 0.6 (24)	-	-
102	20.1 ± 0.6 (25)	19.4 ± 0.8 (32)	19.8 ± 0.9 (31)	20.7 ± 0.6 (23)	-	-

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean daily feed consumption in grams/day ± standard error at each indicated time point. Numbers in parentheses are the number of samples. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE E5
Feed Consumption by F_3T21 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
4	12.3 ± 0.3 (51)	12.0 ± 0.4 (50)	11.4 ± 0.3 (50)	12.2 ± 0.3 (50)	-	*
8	23.4 ± 0.4 (51)	23.0 ± 0.4 (50)	23.6 ± 0.3 (49)	22.6 ± 0.4 (49)	*	-
12	25.2 ± 0.5 (51)	24.6 ± 0.4 (49)	24.5 ± 0.4 (49)	25.0 ± 0.4 (48)	-	-
16	25.7 ± 0.8 (37)	25.5 ± 0.5 (31)	25.2 ± 0.4 (47)	24.2 ± 0.4 (33)	*	-
20	25.4 ± 0.5 (51)	24.9 ± 0.4 (48)	25.5 ± 0.4 (49)	24.5 ± 0.5 (48)	*	-
24	23.4 ± 0.5 (51)	23.5 ± 0.4 (48)	23.8 ± 0.5 (49)	23.3 ± 0.6 (48)	-	-
28	23.4 ± 0.5 (50)	24.3 ± 0.5 (48)	24.6 ± 0.5 (49)	24.1 ± 0.5 (48)	-	-
32	22.6 ± 0.4 (50)	24.0 ± 0.7 (48)	23.3 ± 0.5 (49)	22.5 ± 0.5 (48)	-	-
36	23.4 ± 0.6 (50)	23.9 ± 0.4 (46)	23.8 ± 0.5 (48)	22.4 ± 0.5 (48)	**	-
40	22.4 ± 0.5 (50)	22.1 ± 0.4 (48)	22.4 ± 0.5 (49)	21.7 ± 0.5 (48)	-	-
44	23.4 ± 0.4 (50)	24.0 ± 0.5 (47)	23.4 ± 0.4 (49)	23.3 ± 0.4 (48)	-	-
48	22.7 ± 0.6 (50)	22.2 ± 0.5 (47)	22.2 ± 0.5 (48)	22.1 ± 0.5 (48)	-	-
52	23.8 ± 0.4 (49)	23.7 ± 0.4 (47)	24.0 ± 0.6 (48)	24.2 ± 0.6 (48)	-	-
56	24.1 ± 0.5 (49)	24.2 ± 0.4 (47)	23.5 ± 0.5 (48)	23.2 ± 0.4 (48)	*	-
60	23.6 ± 0.4 (49)	23.3 ± 0.7 (47)	24.3 ± 0.5 (48)	24.3 ± 0.6 (48)	-	-
64	24.7 ± 0.4 (48)	25.0 ± 0.5 (47)	25.1 ± 0.4 (48)	24.4 ± 0.4 (47)	-	-

TABLE E5
Feed Consumption by F_3T21 Male Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
68	23.3 ± 0.6 (45)	23.7 ± 0.6 (47)	24.0 ± 0.6 (48)	23.2 ± 0.5 (48)	-	-
72	24.4 ± 0.5 (44)	24.2 ± 0.4 (47)	24.2 ± 0.3 (48)	23.8 ± 0.7 (47)	-	-
76	25.2 ± 1.3 (43)	22.2 ± 1.1 (46)	24.3 ± 1.0 (44)	24.2 ± 1.1 (45)	-	-
80	22.3 ± 0.8 (42)	23.1 ± 1.1 (45)	22.9 ± 0.7 (43)	23.5 ± 0.8 (44)	-	-
84	20.6 ± 0.7 (41)	20.3 ± 0.5 (44)	21.7 ± 0.5 (42)	20.6 ± 0.5 (43)	-	-
88	20.6 ± 0.6 (39)	21.1 ± 0.4 (43)	20.9 ± 0.5 (42)	20.0 ± 0.5 (40)	-	-
92	22.1 ± 0.6 (35)	22.0 ± 0.5 (43)	21.8 ± 0.7 (39)	22.0 ± 0.6 (38)	-	-
96	20.4 ± 0.7 (36)	21.5 ± 0.6 (43)	21.1 ± 0.9 (36)	20.3 ± 0.6 (37)	-	-
100	23.1 ± 1.6 (34)	23.1 ± 1.3 (41)	22.2 ± 2.1 (33)	21.6 ± 1.5 (36)	-	-
104	21.9 ± 1.0 (33)	22.3 ± 0.7 (42)	21.9 ± 0.9 (33)	21.9 ± 0.6 (36)	-	-

* P≤0.05
** P≤0.01
[a] Mean daily feed consumption in grams/day ± standard error at each indicated time point. Numbers in parentheses are the number of samples. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

TABLE E6
Feed Consumption by F_3T21 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
4	13.1 ± 0.3 (38)	11.8 ± 0.5** (18)	13.1 ± 0.3 (37)	12.3 ± 0.4 (30)	-	*
8	17.6 ± 0.3 (53)	17.5 ± 0.3 (49)	17.5 ± 0.3 (50)	17.2 ± 0.3 (50)	-	-
12	19.8 ± 0.4 (53)	19.1 ± 0.4 (49)	19.2 ± 0.3 (50)	19.5 ± 0.3 (50)	-	-
16	19.5 ± 0.3 (16)	18.5 ± 0.4 (31)	18.3 ± 0.4 (12)	19.1 ± 0.5 (20)	-	-
20	18.9 ± 0.3 (52)	18.8 ± 0.3 (49)	18.3 ± 0.3 (50)	18.8 ± 0.3 (50)	-	*
24	18.9 ± 0.3 (51)	17.9 ± 0.2 (47)	18.0 ± 0.3* (50)	18.8 ± 0.3 (50)	-	*
28	19.3 ± 0.4 (52)	18.1 ± 0.4 (49)	19.0 ± 0.4 (50)	19.1 ± 0.4 (50)	-	-
32	19.5 ± 0.4 (52)	19.4 ± 0.3 (49)	18.7 ± 0.3 (50)	19.6 ± 0.4 (50)	-	**
36	19.4 ± 0.4 (52)	19.0 ± 0.3 (49)	18.8 ± 0.3 (50)	19.2 ± 0.3 (50)	-	-
40	18.1 ± 0.3 (52)	18.6 ± 0.3 (49)	18.0 ± 0.3 (50)	18.3 ± 0.4 (50)	-	-
44	18.8 ± 0.4 (52)	19.0 ± 0.3 (49)	19.0 ± 0.3 (50)	19.9 ± 0.4 (49)	-	-
48	19.5 ± 0.3 (52)	19.1 ± 0.4 (49)	18.7 ± 0.3 (50)	19.8 ± 0.4 (48)	-	*
52	20.1 ± 0.4 (52)	20.0 ± 0.4 (49)	19.8 ± 0.3 (49)	20.2 ± 0.4 (49)	-	-
56	20.9 ± 0.4 (52)	21.2 ± 0.3 (49)	20.1 ± 0.4 (49)	21.1 ± 0.4 (49)	-	**
60	22.5 ± 0.5 (52)	22.5 ± 0.5 (49)	21.8 ± 0.3 (49)	22.7 ± 0.5 (49)	-	*
64	20.6 ± 0.4 (52)	20.6 ± 0.5 (49)	20.6 ± 0.3 (49)	20.8 ± 0.3 (49)	-	-

TABLE E6
Feed Consumption by F_3T21 Female Rats in the 2-Year Feed Study of Genistein

Weeks	Dietary genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
68	20.3 ± 0.3 (50)	19.6 ± 0.4 (46)	19.9 ± 0.4 (47)	19.6 ± 0.4 (48)	-	-
72	22.7 ± 0.4 (49)	20.5 ± 0.6* (47)	21.7 ± 0.4 (49)	20.4 ± 0.6** (46)	*	-
76	20.4 ± 0.4 (49)	19.9 ± 0.4 (42)	19.6 ± 0.5 (49)	18.9 ± 0.5* (45)	*	-
80	20.8 ± 0.4 (49)	20.7 ± 0.4 (41)	20.2 ± 0.4 (48)	21.0 ± 0.5 (42)	-	-
84	20.8 ± 0.7 (47)	20.4 ± 0.5 (40)	18.2 ± 0.6*** (45)	19.8 ± 0.5 (41)	-	***
88	20.3 ± 0.6 (44)	19.9 ± 0.4 (40)	18.8 ± 0.6* (43)	19.1 ± 0.6 (39)	-	*
92	19.2 ± 0.8 (42)	19.9 ± 0.4 (38)	18.6 ± 0.6 (38)	19.9 ± 0.7 (37)	-	*
96	19.9 ± 0.7 (41)	19.3 ± 0.7 (38)	19.5 ± 0.6 (35)	19.3 ± 0.7 (31)	-	-
100	20.5 ± 0.7 (36)	20.5 ± 0.6 (33)	18.7 ± 0.9 (32)	19.1 ± 1.0 (28)	-	*
104	19.8 ± 0.7 (33)	20.3 ± 0.8 (30)	20.2 ± 0.7 (29)	18.9 ± 1.2 (26)	-	-

* $P \leq 0.05$
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Mean daily feed consumption in grams/day ± standard error at each indicated time point. Numbers in parentheses are the number of samples. Shaded cells in an exposed group column indicate that the value is significantly different from the control value in the same measurement week by Dunnett's (1955) test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests for each measurement week. Dashes indicate no significant trend.

APPENDIX F
ONSET OF ABERRANT ESTROUS CYCLES

METHODS AND RESULTS 210
TABLE F1 Estrous Cycle Stage in Monitored Female Rats at Onset of Aberrant Estrous Cycles in the 2-Year Feed Study of Genistein 211
TABLE F2 Analysis of Time to Onset of Aberrant Estrous Cycles in Monitored Female Rats in the 2-Year Feed Study of Genistein 212
FIGURE F1 Kaplan-Meier Curves with Generalized Gamma Distribution Indicating Time to Onset of Aberrant Estrous Cycles in F_1C Female Rats in the 2-Year Feed Study of Genistein 213
FIGURE F2 Kaplan-Meier Curves with Generalized Gamma Distribution Indicating Time to Onset of Aberrant Estrous Cycles in F_1T140 Female Rats in the 2-Year Feed Study of Genistein 214
FIGURE F3 Kaplan-Meier Curves with Generalized Gamma Distribution Indicating Time to Onset of Aberrant Estrous Cycles in F_3T21 Female Rats in the 2-Year Feed Study of Genistein 215

ONSET OF ABERRANT ESTROUS CYCLES

METHODS AND RESULTS

During the 2-year feed study of genistein, data were collected for the first occurrence of abnormal estrous cycling in female rats in the F_1C, F_1T140, and F_3T21 treatment arms of the study. Beginning at month 5, swabbing was conducted for 5 consecutive days each month (a run). The swabs were analyzed to determine the current estrous stage (estrus, diestrus, or proestrus) for each day within the run. An abnormal cycle was deemed to be a run with 4 or more consecutive days in diestrus or a run with 3 or more consecutive days in estrus. Onset of aberrant cycling was deemed to have begun at the first of 2 consecutive months with abnormal cycling. In all exposure groups in all arms of the study, the stage that most commonly caused the judgment of aberrant cycling was estrus (Table F1).

Many animals had begun aberrant cycling before data collection began at month 5. Because normal cycling ceased by month 5, data for these animals were left censored. In addition, some animals died or reached the end of the study without clear onset of abnormal cycling, and data for these animals were right censored. Finally, because observations were a month apart, the precise onset time could not be determined, and interval censoring occurred.

The presence of all three classical types of censoring (left, right, and interval) in this study presents a statistical problem. Moreover, of the three types of censoring, the least important in this study is the right censoring, which is the type most commonly modeled in practice. In this study, most animals began aberrant cycling prior to becoming lost to follow-up, so right censoring was somewhat rare. On the other hand, a great many animals began aberrant cycling before data collection began at 5 months, making left censoring relatively common. Data for all animals were interval censored. These factors make it imperative that the censoring be accommodated by the statistical model selected. Because of the simplicity of accommodating data showing all types of censoring, an accelerated failure time Kaplan-Meier model was used.

Because the distributional form can affect the conclusions of such models, several distributional models were tested and the probability plots of the residuals, and the fitted models were examined to determine goodness-of-fit. The Weibull, exponential, generalized gamma, normal, logistic, lognormal, and log-logistic distributions were tested. Statistical analysis indicated that the Weibull, lognormal, log-logistic, and generalized gamma distributions fit the data reasonably well and gave similar results. The models were parameterized so that comparisons to the controls were effectively generated by the fits. Independent analyses were conducted for each of the three arms of the study, and exposure concentration was found to be statistically significant ("Overall" P value in Table F2) for all three arms. Comparisons to the controls showed that exposure to 500 ppm genistein resulted in the greatest acceleration of the onset of aberrant cycling within all arms of the study with significance of 1% or greater. Kaplan-Meier curves and generalized gamma model fits are shown in Figures F1 through F3 as examples.

TABLE F1
Estrous Cycle Stage in Monitored Female Rats at Onset of Aberrant Estrous Cycles in the 2-Year Feed Study of Genistein

Exposure Concentration (ppm)	Diestrus	Estrus	Metestrus	Total[a]
F_1C				
0	5 (22%)	18 (78%)	0	23
5	4 (16%)	20 (80%)	1 (4%)	25
100	4 (17%)	19 (79%)	1 (4%)	24
500	1 (4%)	24 (96%)	0	25
F_1T140				
0	5 (22%)	18 (78%)	0	23
5	6 (24%)	17 (68%)	2 (8%)	25
100	5 (20%)	17 (68%)	3 (12%)	25
500	2 (8%)	23 (92%)	0	25
F_3T21				
0	8 (32%)	17 (68%)	0	25
5	2 (8%)	23 (92%)	0	25
100	6 (24%)	19 (76%)	0	25
500	5 (20%)	20 (80%)	0	25

[a] Number of females with complete vaginal cytology data. Five females that died early or became moribund were not included in the tabulation (two females in the 0 ppm F_1C group; one female in the 100 ppm F_1C group; and two females in the 0 ppm F_1T140 group).

TABLE F2
Analysis of Time to Onset of Aberrant Estrous Cycles in Monitored Female Rats in the 2-Year Feed Study of Genistein

	Generalized Gamma Distribution P Values[a]
F_1C	
Overall	<0.001
5 ppm vs control	0.237
100 ppm vs control	0.205
500 ppm vs control	<0.001
F_1T140	
Overall	<0.001
5 ppm vs control	0.850
100 ppm vs control	0.645
500 ppm vs control	<0.001
F_3T21	
Overall	0.019
5 ppm vs control	0.037
100 ppm vs control	0.016
500 ppm vs control	0.006

[a] P values by Wald chi-square test (Kalbfleisch and Prentice, 2002) are unadjusted for multiple comparisons.

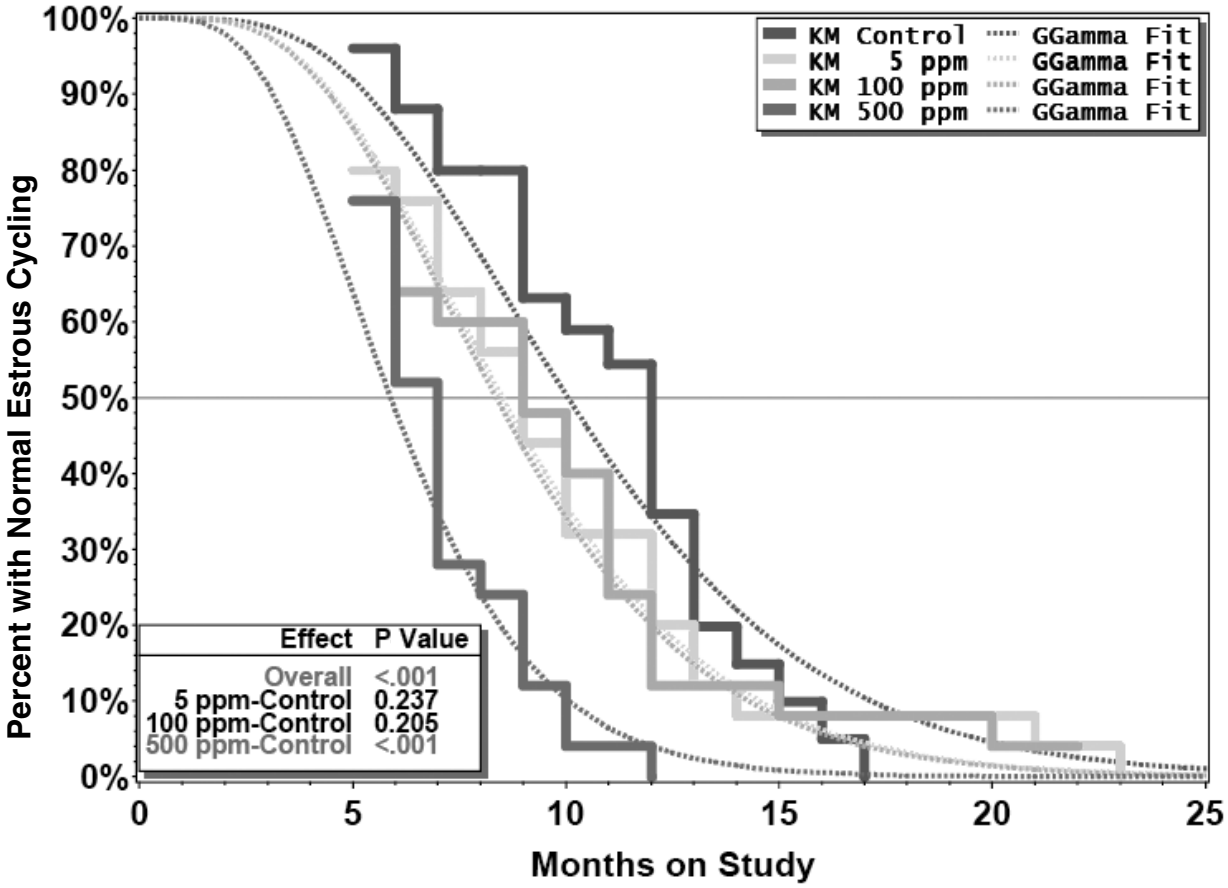


FIGURE F1

Kaplan-Meier Curves with Generalized Gamma Distribution Indicating Time to Onset of Aberrant Estrous Cycles in F_1C Female Rats in the 2-Year Feed Study of Genistein

No data were collected before month 5, causing the curves to be discontinuous. Broken lines show the curves fitted for the generalized gamma distribution. Inset shows the overall P value (Wald chi-square test) as well as comparisons of each exposed group curve to the control group curve.

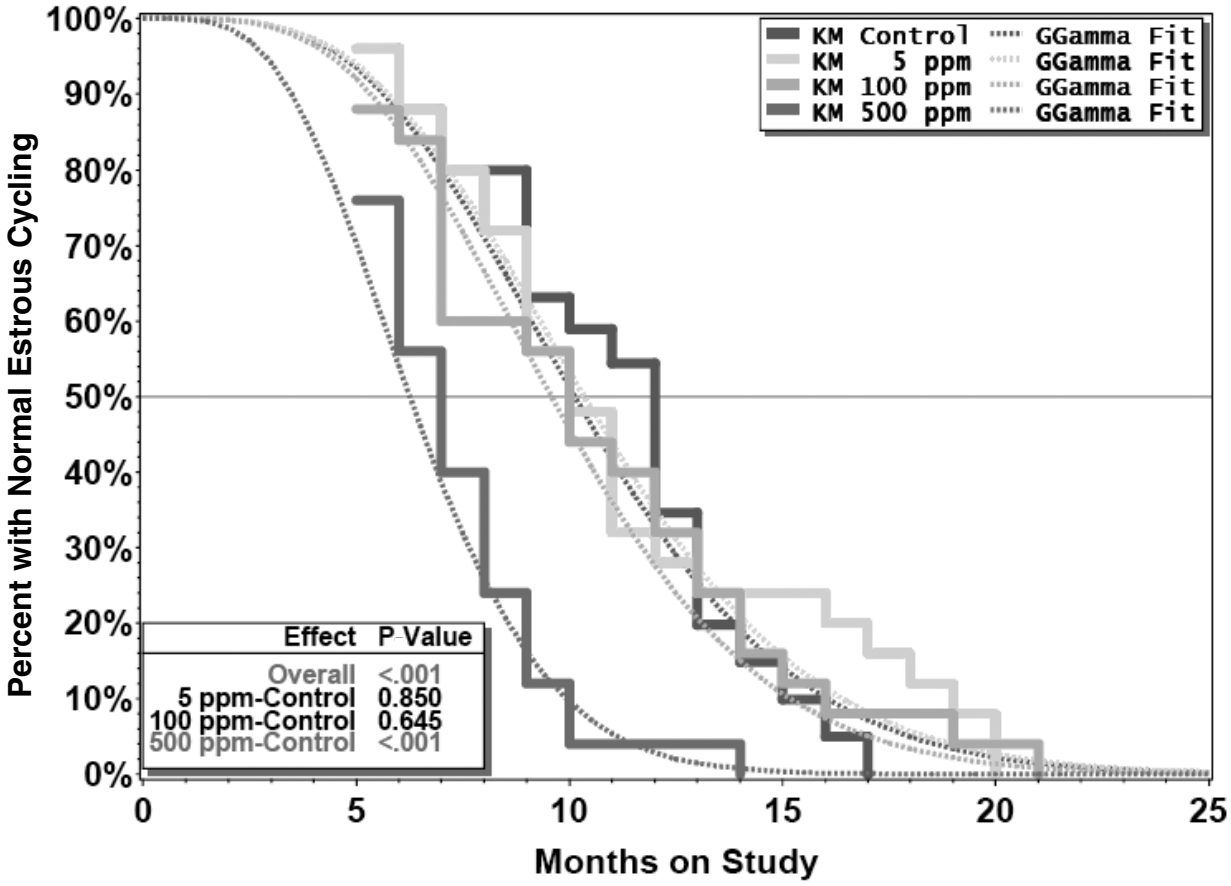


FIGURE F2
Kaplan-Meier Curves with Generalized Gamma Distribution Indicating Time to Onset of Aberrant Estrous Cycles in F_1T140 Female Rats in the 2-Year Feed Study of Genistein
No data were collected before month 5, causing the curves to be discontinuous. Broken lines show the curves fitted for the generalized gamma distribution. Inset shows the overall P value (Wald chi-square test) as well as comparisons of each exposed group curve to the control group curve.

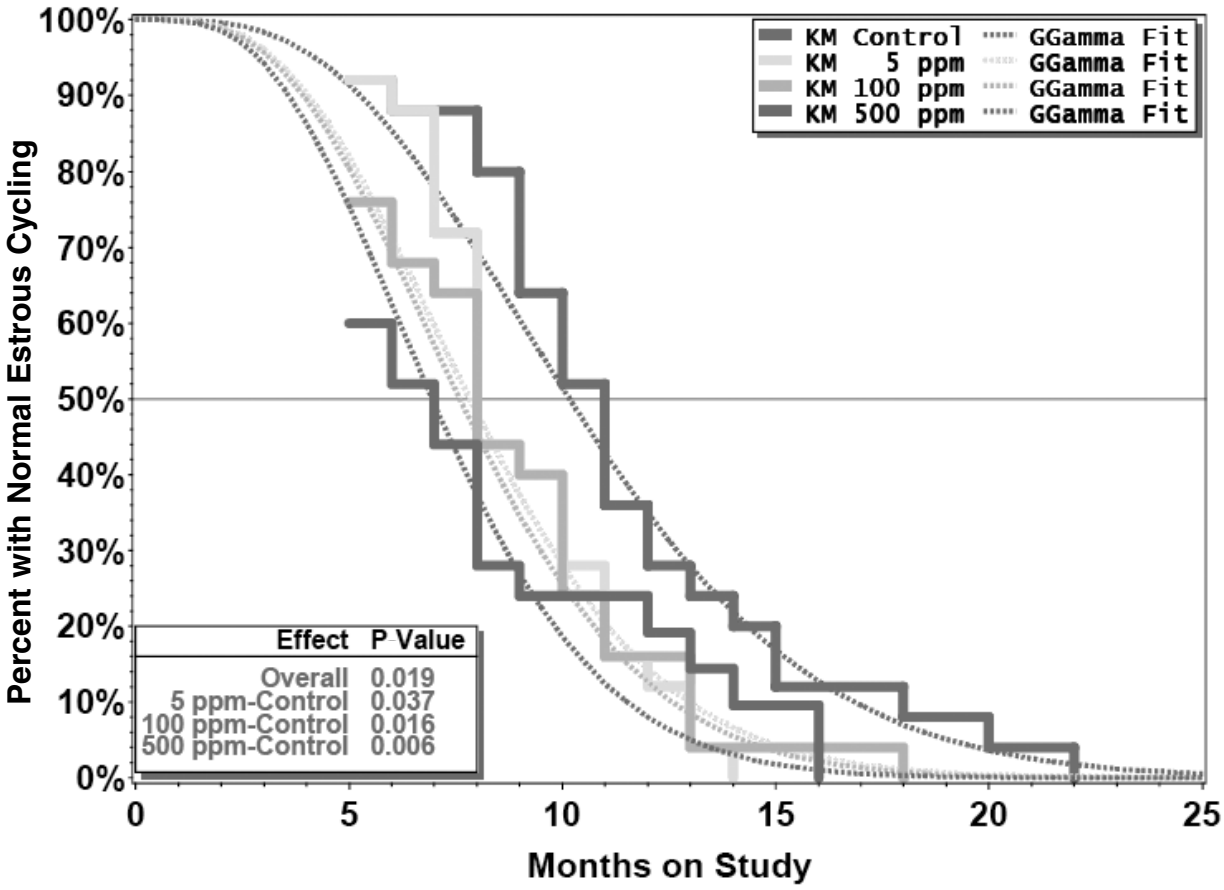


FIGURE F3
Kaplan-Meier Curves with Generalized Gamma Distribution Indicating Time to Onset of Aberrant Estrous Cycles in F_3T21 Female Rats in the 2-Year Feed Study of Genistein
No data were collected before month 5, causing the curves to be discontinuous. Broken lines show the curves fitted for the generalized gamma distribution. Inset shows the overall P value (Wald chi-square test) as well as comparisons of each exposed group curve to the control group curve.

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

TABLE G1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1C Male Rats in the 2-Year Feed Study of Genistein 218
TABLE G2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1C Female Rats in the 2-Year Feed Study of Genistein 221
TABLE G3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1T140 Male Rats in the 2-Year Feed Study of Genistein 223
TABLE G4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1T140 Female Rats in the 2-Year Feed Study of Genistein 226
TABLE G5 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_3T21 Male Rats in the 2-Year Feed Study of Genistein 228
TABLE G6 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_3T21 Female Rats in the 2-Year Feed Study of Genistein 231

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1C Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
Final Mean Body Weight (g)	581.12 ± 10.509 (36)	586.63 ± 10.650 (41)	578.40 ± 10.896 (43)	567.35 ± 8.371 (31)	-	-
Adrenal Gland (both)						
Absolute	0.059 ± 0.003 (36)	0.062 ± 0.002 (40)	0.060 ± 0.002 (43)	0.065 ± 0.003 (31)	-	-
Relative	0.101 ± 0.004 (36)	0.107 ± 0.004 (40)	0.105 ± 0.004 (43)	0.114 ± 0.005 (31)	-	-
ANCOVA[c]		-	-	-	-	-
Brain						
Absolute	2.296 ± 0.020 (36)	2.293 ± 0.018 (41)	2.303 ± 0.019 (43)	2.275 ± 0.028 (31)	-	-
Relative	3.991 ± 0.071 (36)	3.963 ± 0.084 (41)	4.047 ± 0.090 (43)	4.031 ± 0.066 (31)	-	-
ANCOVA		-	-	-	-	-
Dorsal Prostate Gland						
Absolute	0.216 ± 0.009 (33)	0.230 ± 0.011 (41)	0.243 ± 0.015 (42)	0.265 ± 0.022 (30)	* (*)	-
Relative	0.373 ± 0.014 (33)	0.398 ± 0.021 (41)	0.422 ± 0.024 (42)	0.467 ± 0.039* (30)	* (*)	-
ANCOVA		-	-	-	* (*)	-
Epididymis						
Absolute	1.166 ± 0.037 (35)	1.246 ± 0.046 (41)	1.195 ± 0.034 (42)	1.283 ± 0.076 (30)	-	-
Relative	2.036 ± 0.076 (35)	2.142 ± 0.074 (41)	2.071 ± 0.055 (42)	2.276 ± 0.137 (30)	-	-
ANCOVA		-	-	-	-	-

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1C Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Kidneys (both)						
Absolute	3.713 ± 0.099 (36)	3.704 ± 0.072 (41)	3.833 ± 0.083 (43)	3.803 ± 0.139 (31)	-	-
Relative	6.401 ± 0.135 (36)	6.363 ± 0.134 (41)	6.681 ± 0.163 (43)	6.698 ± 0.210 (31)	-	-
ANCOVA		-	-	-	-	-
Lateral Prostate Gland						
Absolute	0.282 ± 0.019 (34)	0.266 ± 0.011 (40)	0.285 ± 0.015 (41)	0.353 ± 0.023* (30)	*** (**)	(*)
Relative	0.486 ± 0.031 (34)	0.460 ± 0.023 (40)	0.496 ± 0.024 (41)	0.617 ± 0.037** (30)	*** (**)	(*)
ANCOVA		-	-	**	*** (**)	(**)
Liver						
Absolute	15.171 ± 0.370 (36)	15.572 ± 0.260 (40)	15.479 ± 0.365 (43)	15.907 ± 0.355 (29)	-	-
Relative	26.162 ± 0.522 (36)	26.734 ± 0.471 (40)	26.885 ± 0.596 (43)	28.154 ± 0.486* (29)	* (*)	-
ANCOVA		-	-	*	* (*)	-
Pituitary Gland						
Absolute	0.021 ± 0.006 (35)	0.016 ± 0.002 (40)	0.032 ± 0.010 (41)	0.022 ± 0.004 (30)	-	-
Relative	0.037 ± 0.010 (35)	0.028 ± 0.004 (40)	0.057 ± 0.019 (41)	0.039 ± 0.008 (30)	-	-
ANCOVA		-	-	-	-	-
Seminal Vesicle/ Coagulating Gland						
Absolute	1.099 ± 0.090 (30)	1.107 ± 0.044 (37)	1.152 ± 0.050 (39)	1.225 ± 0.074 (25)	-	-
Relative	1.930 ± 0.171 (30)	1.907 ± 0.075 (37)	2.015 ± 0.099 (39)	2.187 ± 0.130 (25)	-	-
ANCOVA		-	-	-	-	-

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1C Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Spleen						
Absolute	0.946 ± 0.033 (36)	0.964 ± 0.030 (41)	0.969 ± 0.028 (43)	0.993 ± 0.034 (31)	-	-
Relative	1.632 ± 0.053 (36)	1.660 ± 0.055 (41)	1.677 ± 0.036 (43)	1.752 ± 0.058 (31)	-	-
ANCOVA		-	-	-	-	-
Testis (both)						
Absolute	2.969 ± 0.109 (36)	3.204 ± 0.090 (41)	3.159 ± 0.088 (43)	3.213 ± 0.071 (31)	-	-
Relative	5.201 ± 0.231 (36)	5.521 ± 0.171 (41)	5.491 ± 0.150 (43)	5.686 ± 0.130 (31)	-	-
ANCOVA		-	-	-	-	-
Thymus						
Absolute	0.267 ± 0.015 (35)	0.271 ± 0.022 (41)	0.271 ± 0.017 (43)	0.266 ± 0.022 (31)	-	-
Relative	0.462 ± 0.024 (35)	0.458 ± 0.035 (41)	0.467 ± 0.028 (43)	0.470 ± 0.039 (31)	-	-
ANCOVA		-	-	-	-	-
Thyroid Gland						
Absolute	0.040 ± 0.002 (35)	0.041 ± 0.002 (41)	0.041 ± 0.002 (41)	0.044 ± 0.002 (29)	-	-
Relative	0.070 ± 0.003 (35)	0.070 ± 0.003 (41)	0.072 ± 0.003 (41)	0.077 ± 0.003 (29)	-	-
ANCOVA		-	-	-	-	-
Ventral Prostate Gland						
Absolute	0.505 ± 0.035 (33)	0.487 ± 0.023 (41)	0.518 ± 0.023 (42)	0.581 ± 0.038 (29)	*	-
Relative	0.877 ± 0.061 (33)	0.835 ± 0.038 (41)	0.902 ± 0.040 (42)	1.030 ± 0.067 (29)	* (*)	-
ANCOVA		-	-	-	* (*)	-

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean organ weights ± standard error. Absolute organ weights are given in grams; relative weights are in g/kg body weight. Numbers in parentheses are the numbers of animals or organs included in the calculations. Outliers were excluded from the analyses. Asterisks in shaded cells indicate values that are significantly different from controls by Dunnett's test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests. Asterisks not in parentheses indicate results of dose trend tests; asterisks in parentheses indicate results of ln(dose + 1) trend tests. Dashes indicate no significant trend.
[c] Results of Dunnett's tests from an analysis of covariance (ANCOVA) with body weight as the covariate; dashes indicate no significant difference from controls.

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1C Female Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
Final Mean Body Weight (g)	409.32 ± 10.693 (26)	414.12 ± 13.447 (28)	412.31 ± 20.059 (22)	381.40 ± 12.848 (21)	*	-
Adrenal Gland (both)						
Absolute	0.087 ± 0.007 (26)	0.100 ± 0.006 (28)	0.102 ± 0.008 (22)	0.092 ± 0.008 (21)	-	-
Relative	0.218 ± 0.019 (26)	0.245 ± 0.014 (28)	0.257 ± 0.024 (22)	0.252 ± 0.030 (21)	-	-
ANCOVA[c]		-	-	-	-	-
Brain						
Absolute	2.019 ± 0.030 (26)	2.087 ± 0.023 (28)	2.128 ± 0.021** (22)	2.002 ± 0.028 (21)	-	** (***)
Relative	5.031 ± 0.169 (26)	5.160 ± 0.145 (28)	5.424 ± 0.265 (22)	5.385 ± 0.218 (21)	-	-
ANCOVA		-	**	-	-	** (***)
Kidney (both)						
Absolute	2.494 ± 0.067 (26)	2.539 ± 0.063 (28)	2.514 ± 0.086 (22)	2.424 ± 0.055 (21)	-	-
Relative	6.160 ± 0.188 (26)	6.263 ± 0.206 (28)	6.296 ± 0.283 (22)	6.457 ± 0.193 (21)	-	-
ANCOVA		-	-	-	-	-
Liver						
Absolute	11.514 ± 0.457 (26)	12.546 ± 0.674 (28)	11.828 ± 0.691 (22)	10.973 ± 0.688 (21)	-	-
Relative	28.254 ± 0.902 (26)	30.125 ± 1.127 (28)	28.697 ± 1.001 (22)	28.931 ± 1.561 (21)	-	-
ANCOVA		-	-	-	-	-

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1C Female Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Ovary (both)						
Absolute	0.170 ± 0.011 (26)	0.186 ± 0.019 (28)	0.223 ± 0.030 (22)	0.181 ± 0.023 (21)	-	-
Relative	0.417 ± 0.025 (26)	0.465 ± 0.048 (28)	0.545 ± 0.067 (22)	0.497 ± 0.072 (21)	-	-
ANCOVA		-	-	-	-	-
Pituitary Gland						
Absolute	0.043 ± 0.009 (26)	0.039 ± 0.005 (28)	0.069 ± 0.017 (22)	0.087 ± 0.017* (21)	** (**)	-
Relative	0.106 ± 0.021 (26)	0.101 ± 0.017 (28)	0.196 ± 0.058 (22)	0.238 ± 0.049* (21)	** (**)	-
ANCOVA		-	-	-	* (**)	-
Spleen						
Absolute	0.732 ± 0.033 (26)	0.776 ± 0.035 (28)	0.871 ± 0.082 (22)	0.700 ± 0.033 (21)	-	*
Relative	1.789 ± 0.065 (26)	1.890 ± 0.080 (28)	2.151 ± 0.209 (22)	1.872 ± 0.098 (21)	-	-
ANCOVA		-	-	-	-	*
Thymus						
Absolute	0.263 ± 0.028 (26)	0.235 ± 0.018 (28)	0.312 ± 0.045 (22)	0.190 ± 0.020 (21)	-	*
Relative	0.647 ± 0.071 (26)	0.581 ± 0.045 (28)	0.737 ± 0.091 (22)	0.502 ± 0.050 (21)	-	-
ANCOVA		-	-	-	-	*
Thyroid Gland						
Absolute	0.036 ± 0.002 (26)	0.035 ± 0.002 (28)	0.037 ± 0.003 (22)	0.034 ± 0.002 (21)	-	-
Relative	0.088 ± 0.004 (26)	0.087 ± 0.004 (28)	0.091 ± 0.006 (22)	0.090 ± 0.006 (21)	-	-
ANCOVA		-	-	-	-	-
Uterus						
Absolute	0.908 ± 0.065 (26)	0.950 ± 0.092 (28)	0.875 ± 0.068 (22)	0.957 ± 0.077 (21)	-	-
Relative	2.303 ± 0.192 (26)	2.416 ± 0.268 (28)	2.258 ± 0.234 (22)	2.581 ± 0.234 (21)	-	-
ANCOVA		-	-	-	-	-

* $P \leq 0.05$
** $P \leq 0.01$
*** $P \leq 0.001$
[a] Mean organ weights ± standard error. Absolute organ weights are given in grams; relative weights are in g/kg body weight. Numbers in parentheses are the numbers of animals or organs included in the calculations. Outliers were excluded from the analyses. Asterisks in shaded cells indicate values that are significantly different from controls by Dunnett's test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests. Asterisks not in parentheses indicate results of dose trend tests; asterisks in parentheses indicate results of ln(dose + 1) trend tests. Dashes indicate no significant trend.
[c] Results of Dunnett's tests from an analysis of covariance (ANCOVA) with body weight as the covariate; dashes indicate no significant difference from controls.

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1T140 Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
Final Mean Body Weight (g)	581.12 ± 10.509 (36)	592.51 ± 12.459 (34)	598.21 ± 12.685 (32)	542.17 ± 12.674 ** (37)	**	(*)
Adrenal Gland (both)						
Absolute	0.059 ± 0.003 (36)	0.063 ± 0.002 (32)	0.072 ± 0.008 (31)	0.068 ± 0.007 (38)	-	-
Relative	0.101 ± 0.004 (36)	0.107 ± 0.004 (32)	0.121 ± 0.015 (31)	0.128 ± 0.012 (38)	(*)	-
ANCOVA[c]		-	-	-	-	-
Brain						
Absolute	2.296 ± 0.020 (36)	2.285 ± 0.017 (34)	2.335 ± 0.021 (32)	2.248 ± 0.026 (38)	*	*
Relative	3.991 ± 0.071 (36)	3.912 ± 0.086 (34)	3.959 ± 0.094 (32)	4.312 ± 0.144 (38)	** (*)	-
ANCOVA		-	-	-	-	-
Dorsal Prostate Gland						
Absolute	0.216 ± 0.009 (33)	0.236 ± 0.017 (34)	0.197 ± 0.011 (31)	0.194 ± 0.010 (38)	(*)	-
Relative	0.373 ± 0.014 (33)	0.401 ± 0.028 (34)	0.331 ± 0.018 (31)	0.361 ± 0.015 (38)	-	*
ANCOVA		-	-	-	-	*
Epididymis						
Absolute	1.166 ± 0.037 (35)	1.278 ± 0.024 (34)	1.239 ± 0.037 (32)	1.171 ± 0.036 (38)	-	(**)
Relative	2.036 ± 0.076 (35)	2.192 ± 0.066 (34)	2.079 ± 0.054 (32)	2.205 ± 0.062 (38)	-	-
ANCOVA		-	-	-	-	-
Kidney (both)						
Absolute	3.713 ± 0.099 (36)	3.835 ± 0.088 (34)	3.857 ± 0.119 (32)	3.619 ± 0.101 (37)	-	-
Relative	6.401 ± 0.135 (36)	6.496 ± 0.107 (34)	6.474 ± 0.176 (32)	6.826 ± 0.171 (37)	*	-
ANCOVA		-	-	-	-	-

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1T140 Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Lateral Prostate Gland						
Absolute	0.282 ± 0.019 (34)	0.295 ± 0.018 (34)	0.270 ± 0.014 (31)	0.274 ± 0.016 (38)	-	-
Relative	0.486 ± 0.031 (34)	0.500 ± 0.030 (34)	0.453 ± 0.024 (31)	0.514 ± 0.029 (38)	-	-
ANCOVA		-	-	-	-	-
Liver						
Absolute	15.171 ± 0.370 (36)	15.848 ± 0.350 (34)	15.840 ± 0.451 (32)	14.680 ± 0.472 (38)	-	-
Relative	26.162 ± 0.522 (36)	26.838 ± 0.430 (34)	26.476 ± 0.520 (32)	27.340 ± 0.533 (38)	-	-
ANCOVA		-	-	-	-	-
Pituitary Gland						
Absolute	0.021 ± 0.006 (35)	0.020 ± 0.003 (34)	0.025 ± 0.008 (32)	0.016 ± 0.002 (37)	-	-
Relative	0.037 ± 0.010 (35)	0.033 ± 0.004 (34)	0.043 ± 0.013 (32)	0.031 ± 0.004 (37)	-	-
ANCOVA		-	-	-	-	-
Seminal Vesicle/ Coagulating Gland						
Absolute	1.099 ± 0.090 (30)	1.218 ± 0.080 (33)	1.172 ± 0.082 (28)	0.993 ± 0.077 (34)	-	-
Relative	1.930 ± 0.171 (30)	2.090 ± 0.147 (33)	1.954 ± 0.128 (28)	1.870 ± 0.135 (34)	-	-
ANCOVA		-	-	-	-	-
Spleen						
Absolute	0.946 ± 0.033 (36)	0.967 ± 0.027 (34)	1.068 ± 0.074 (30)	0.946 ± 0.037 (37)	-	*
Relative	1.632 ± 0.053 (36)	1.643 ± 0.046 (34)	1.796 ± 0.114 (30)	1.770 ± 0.055 (37)	-	-
ANCOVA		-	-	-	-	-

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1T140 Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Testis (both)						
Absolute	2.969 ± 0.109 (36)	3.271 ± 0.076 (34)	3.288 ± 0.125 (32)	3.076 ± 0.064 (38)	-	(*)
Relative	5.201 ± 0.231 (36)	5.591 ± 0.165 (34)	5.505 ± 0.185 (32)	5.845 ± 0.164 (38)	(*)	-
ANCOVA		-	-	-	-	-
Thymus						
Absolute (g)	0.267 ± 0.015 (35)	0.280 ± 0.020 (34)	0.286 ± 0.030 (32)	0.268 ± 0.028 (38)	-	-
Relative	0.462 ± 0.024 (35)	0.470 ± 0.030 (34)	0.475 ± 0.049 (32)	0.497 ± 0.046 (38)	-	-
ANCOVA		-	-	-	-	-
Thyroid Gland						
Absolute (g)	0.040 ± 0.002 (35)	0.038 ± 0.001 (34)	0.037 ± 0.002 (32)	0.036 ± 0.002 (38)	-	-
Relative	0.070 ± 0.003 (35)	0.064 ± 0.003 (34)	0.062 ± 0.003 (32)	0.069 ± 0.003 (38)	-	-
ANCOVA		-	-	-	-	-
Ventral Prostate Gland						
Absolute	0.505 ± 0.035 (33)	0.532 ± 0.033 (34)	0.435 ± 0.024 (30)	0.493 ± 0.028 (38)	-	*
Relative	0.877 ± 0.061 (33)	0.904 ± 0.055 (34)	0.732 ± 0.042 (30)	0.918 ± 0.046 (38)	-	**
ANCOVA		-	-	-	-	*

* $P \leq 0.05$
** $P \leq 0.01$
[a] Mean organ weights ± standard error. Absolute organ weights are given in grams; relative weights are in g/kg body weight. Numbers in parentheses are the numbers of animals or organs included in the calculations. Outliers were excluded from the analyses. Asterisks in shaded cells indicate values that are significantly different from controls by Dunnett's test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests. Asterisks not in parentheses indicate results of dose trend tests; asterisks in parentheses indicate results of ln(dose + 1) trend tests. Dashes indicate no significant trend.
[c] Results of Dunnett's tests from an analysis of covariance (ANCOVA) with body weight as the covariate; dashes indicate no significant difference from controls.

TABLE G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1T140 Female Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
Final Mean Body Weight (g)	409.32 ± 10.693 (26)	428.49 ± 11.741 (31)	426.70 ± 10.119 (32)	381.24 ± 13.857 (23)	*	-
Adrenal Gland (both)						
Absolute	0.087 ± 0.007 (26)	0.092 ± 0.006 (31)	0.098 ± 0.006 (32)	0.103 ± 0.007 (22)	* (*)	-
Relative	0.218 ± 0.019 (26)	0.219 ± 0.015 (31)	0.236 ± 0.016 (32)	0.281 ± 0.023* (22)	*** (**)	-
ANCOVA[c]		-	-	-	* (*)	-
Brain						
Absolute	2.019 ± 0.030 (26)	2.098 ± 0.026 (30)	2.088 ± 0.018 (32)	2.019 ± 0.025 (23)		
Relative	5.031 ± 0.169 (26)	4.999 ± 0.164 (30)	4.977 ± 0.121 (32)	5.447 ± 0.199 (23)		
ANCOVA		-	-	-		
Kidney (both)						
Absolute	2.494 ± 0.067 (26)	2.465 ± 0.062 (31)	2.581 ± 0.057 (32)	2.425 ± 0.066 (23)	-	-
Relative	6.160 ± 0.188 (26)	5.835 ± 0.164 (31)	6.106 ± 0.137 (32)	6.476 ± 0.202 (23)	** (*)	(*)
ANCOVA		-	-	-	-	-
Liver						
Absolute	11.514 ± 0.457 (26)	11.595 ± 0.461 (31)	12.129 ± 0.420 (32)	11.703 ± 0.574 (23)	-	-
Relative	28.254 ± 0.902 (26)	27.164 ± 0.828 (31)	28.532 ± 0.793 (32)	30.610 ± 0.837 (23)	** (*)	-
ANCOVA		-	-	-	* (*)	-

TABLE G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_1T140 Female Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Ovary (both)						
Absolute	0.170 ± 0.011 (26)	0.186 ± 0.017 (30)	0.182 ± 0.014 (32)	0.228 ± 0.031 (23)	-	-
Relative	0.417 ± 0.025 (26)	0.436 ± 0.037 (30)	0.433 ± 0.036 (32)	0.626 ± 0.100 (23)	-	-
ANCOVA		-	-	-	* (*)	-
Pituitary Gland						
Absolute	0.043 ± 0.009 (26)	0.051 ± 0.017 (29)	0.058 ± 0.010 (31)	0.120 ± 0.028** (23)	*** (**)	-
Relative	0.106 ± 0.021 (26)	0.152 ± 0.070 (29)	0.146 ± 0.029 (31)	0.346 ± 0.085* (23)	** (**)	-
ANCOVA		-	-	*	** (**)	-
Spleen						
Absolute	0.732 ± 0.033 (26)	0.764 ± 0.026 (31)	0.794 ± 0.035 (32)	0.772 ± 0.037 (23)	-	-
Relative	1.789 ± 0.065 (26)	1.811 ± 0.069 (31)	1.865 ± 0.068 (32)	2.074 ± 0.125 (23)	* (*)	-
ANCOVA		-	-	-	-	-
Thymus						
Absolute	0.263 ± 0.028 (26)	0.305 ± 0.031 (31)	0.242 ± 0.016 (32)	0.230 ± 0.026 (23)	-	-
Relative	0.647 ± 0.071 (26)	0.697 ± 0.066 (31)	0.570 ± 0.037 (32)	0.601 ± 0.062 (23)	-	-
ANCOVA		-	-	-	-	-
Thyroid Gland						
Absolute	0.036 ± 0.002 (26)	0.039 ± 0.002 (29)	0.042 ± 0.003 (31)	0.035 ± 0.002 (23)	-	* (*)
Relative	0.088 ± 0.004 (26)	0.091 ± 0.005 (29)	0.098 ± 0.006 (31)	0.095 ± 0.006 (23)	-	-
ANCOVA		-	-	-	-	-
Uterus						
Absolute	0.908 ± 0.065 (26)	0.735 ± 0.048 (30)	0.866 ± 0.057 (32)	0.975 ± 0.093 (20)	-	-
Relative	2.303 ± 0.192 (26)	1.730 ± 0.128 (30)	2.095 ± 0.158 (32)	2.697 ± 0.288 (20)	** (*)	(**)
ANCOVA		-	-	-	-	-

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean organ weights ± standard error. Absolute organ weights are given in grams; relative weights are in g/kg body weight. Numbers in parentheses are the numbers of animals or organs included in the calculations. Outliers were excluded from the analyses. Asterisks in shaded cells indicate values that are significantly different from controls by Dunnett's test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests. Asterisks not in parentheses indicate results of dose trend tests; asterisks in parentheses indicate results of ln(dose + 1) trend tests. Dashes indicate no significant trend.
[c] Results of Dunnett's tests from an analysis of covariance (ANCOVA) with body weight as the covariate; dashes indicate no significant difference from controls.

TABLE G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_3T21 Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
Final Mean Body Weight (g)	563.63 ± 9.718 (33)	581.69 ± 10.912 (42)	590.52 ± 11.339 (33)	550.61 ± 12.170 (36)	-	-
Adrenal Gland (both)						
Absolute	0.074 ± 0.006 (31)	0.069 ± 0.002 (42)	0.068 ± 0.002 (33)	0.067 ± 0.004 (36)	-	-
Relative	0.133 ± 0.011 (31)	0.120 ± 0.005 (42)	0.116 ± 0.004 (33)	0.124 ± 0.009 (36)	-	-
ANCOVA[c]		-	-	-	-	-
Brain						
Absolute	2.306 ± 0.029 (33)	2.231 ± 0.019 (42)	2.303 ± 0.021 (33)	2.273 ± 0.030 (36)	-	-
Relative	4.137 ± 0.098 (33)	3.887 ± 0.075 (42)	3.949 ± 0.089 (33)	4.241 ± 0.161 (36)	-	(*)
ANCOVA		-	-	-	-	-
Dorsal Prostate Gland						
Absolute	0.219 ± 0.011 (33)	0.247 ± 0.011 (42)	0.259 ± 0.015 (33)	0.229 ± 0.012 (36)	-	-
Relative	0.387 ± 0.017 (33)	0.432 ± 0.022 (42)	0.442 ± 0.027 (33)	0.414 ± 0.020 (36)	-	-
ANCOVA		-	-	-	-	-
Epididymis						
Absolute	1.258 ± 0.030 (33)	1.340 ± 0.075 (41)	1.242 ± 0.031 (33)	1.206 ± 0.075 (36)	-	-
Relative	2.243 ± 0.055 (33)	2.312 ± 0.138 (41)	2.116 ± 0.052 (33)	2.200 ± 0.127 (36)	-	-
ANCOVA		-	-	-	-	-
Kidney (both)						
Absolute	3.879 ± 0.125 (33)	3.982 ± 0.117 (42)	4.076 ± 0.164 (33)	3.705 ± 0.078 (36)	-	-
Relative	6.895 ± 0.195 (33)	6.916 ± 0.247 (42)	6.902 ± 0.228 (33)	6.787 ± 0.133 (36)	-	-
ANCOVA		-	-	-	-	-

TABLE G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_3T21 Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Lateral Prostate Gland						
Absolute	0.239 ± 0.014 (33)	0.250 ± 0.015 (42)	0.252 ± 0.014 (33)	0.225 ± 0.012 (36)	-	-
Relative	0.421 ± 0.023 (33)	0.434 ± 0.025 (42)	0.429 ± 0.025 (33)	0.406 ± 0.020 (36)	-	-
ANCOVA		-	-	-	-	-
Liver						
Absolute	16.103 ± 0.575 (33)	15.532 ± 0.360 (42)	15.385 ± 0.449 (32)	14.021 ± 0.397** (35)	** (**)	-
Relative	28.432 ± 0.727 (33)	26.866 ± 0.602 (42)	26.212 ± 0.564* (32)	25.429 ± 0.543** (35)	* (**)	-
ANCOVA		-	*	**	** (***)	-
Pituitary Gland						
Absolute	0.017 ± 0.003 (32)	0.019 ± 0.004 (42)	0.020 ± 0.002 (32)	0.021 ± 0.005 (36)	-	-
Relative	0.031 ± 0.004 (32)	0.033 ± 0.006 (42)	0.034 ± 0.004 (32)	0.038 ± 0.009 (36)	-	-
ANCOVA		-	-	-	-	-
Seminal Vesicle/ Coagulating Gland						
Absolute	1.012 ± 0.057 (33)	0.988 ± 0.051 (42)	1.095 ± 0.069 (33)	0.947 ± 0.046 (36)	-	-
Relative	1.787 ± 0.094 (33)	1.719 ± 0.092 (42)	1.839 ± 0.101 (33)	1.714 ± 0.076 (36)	-	-
ANCOVA		-	-	-	-	-
Spleen						
Absolute	1.078 ± 0.050 (32)	1.175 ± 0.062 (41)	1.175 ± 0.074 (33)	0.966 ± 0.038 (36)	*	(*)
Relative	1.920 ± 0.081 (32)	2.041 ± 0.113 (41)	1.993 ± 0.110 (33)	1.781 ± 0.077 (36)	-	-
ANCOVA		-	-	-	-	-

TABLE G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_3T21 Male Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Testis (both)						
Absolute	3.203 ± 0.098 (33)	3.201 ± 0.096 (42)	3.175 ± 0.093 (33)	3.018 ± 0.093 (35)	-	-
Relative	5.725 ± 0.190 (33)	5.523 ± 0.161 (42)	5.429 ± 0.182 (33)	5.533 ± 0.167 (35)	-	-
ANCOVA		-	-	-	-	-
Thymus						
Absolute	0.262 ± 0.019 (33)	0.249 ± 0.013 (42)	0.278 ± 0.025 (33)	0.246 ± 0.018 (36)	-	-
Relative	0.462 ± 0.033 (33)	0.427 ± 0.022 (42)	0.463 ± 0.035 (33)	0.444 ± 0.028 (36)	-	-
ANCOVA		-	-	-	-	-
Thyroid Gland						
Absolute	0.044 ± 0.002 (32)	0.040 ± 0.002 (42)	0.044 ± 0.003 (33)	0.038 ± 0.002 (35)	-	-
Relative	0.080 ± 0.004 (32)	0.070 ± 0.003 (42)	0.076 ± 0.005 (33)	0.070 ± 0.004 (35)	-	-
ANCOVA		-	-	-	-	-
Ventral Prostate Gland						
Absolute	0.487 ± 0.027 (33)	0.489 ± 0.025 (42)	0.452 ± 0.022 (33)	0.450 ± 0.025 (36)	-	-
Relative	0.858 ± 0.042 (33)	0.853 ± 0.047 (42)	0.774 ± 0.040 (33)	0.819 ± 0.043 (36)	-	-
ANCOVA		-	-	-	-	-

* P≤0.05
** P≤0.01
*** P≤0.001
[a] Mean organ weights ± standard error. Absolute organ weights are given in grams; relative weights are in g/kg body weight. Numbers in parentheses are the numbers of animals or organs included in the calculations. Outliers were excluded from the analyses. Asterisks in shaded cells indicate values that are significantly different from controls by Dunnett's test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests. Asterisks not in parentheses indicate results of dose trend tests; asterisks in parentheses indicate results of ln(dose + 1) trend tests. Dashes indicate no significant trend.
[c] Results of Dunnett's tests from an analysis of covariance (ANCOVA) with body weight as the covariate; dashes indicate no significant difference from controls.

TABLE G6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_3T21 Female Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)[a]				Trends[b]	
	0	5	100	500	Linear	Quad
Final Mean Body Weight (g)	412.93 ± 14.571 (33)	432.32 ± 15.800 (30)	403.88 ± 12.520 (29)	397.28 ± 17.824 (25)	-	-
Adrenal Gland (both)						
Absolute	0.111 ± 0.008 (33)	0.115 ± 0.010 (30)	0.125 ± 0.009 (29)	0.129 ± 0.018 (25)	-	-
Relative	0.278 ± 0.022 (33)	0.273 ± 0.023 (30)	0.318 ± 0.023 (29)	0.335 ± 0.046 (25)	-	-
ANCOVA[c]		-	-	-	-	-
Brain						
Absolute	2.038 ± 0.022 (33)	2.058 ± 0.026 (30)	2.081 ± 0.027 (29)	2.030 ± 0.030 (25)	-	-
Relative	5.132 ± 0.184 (33)	4.945 ± 0.191 (30)	5.295 ± 0.181 (29)	5.325 ± 0.223 (25)	-	-
ANCOVA		-	-	-	-	-
Kidney (both)						
Absolute	2.581 ± 0.083 (33)	2.669 ± 0.059 (30)	2.750 ± 0.054 (29)	2.643 ± 0.125 (24)	-	-
Relative	6.445 ± 0.294 (33)	6.362 ± 0.215 (30)	6.961 ± 0.217 (29)	6.798 ± 0.299 (24)	-	-
ANCOVA		-	-	-	-	-
Liver						
Absolute	12.714 ± 0.676 (33)	12.642 ± 0.470 (30)	12.677 ± 0.500 (29)	11.995 ± 0.691 (25)	-	-
Relative	30.691 ± 1.141 (33)	29.584 ± 0.817 (30)	31.548 ± 0.986 (29)	30.392 ± 1.298 (25)	-	-
ANCOVA		-	-	-	-	-

TABLE G6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F_3T21 Female Rats in the 2-Year Feed Study of Genistein

Organ	Dietary Genistein (ppm)				Trends	
	0	5	100	500	Linear	Quad
Ovary (both)						
Absolute	0.192 ± 0.015 (32)	0.308 ± 0.046 (30)	0.357 ± 0.100 (28)	0.194 ± 0.026 (25)	-	(*)
Relative	0.486 ± 0.040 (32)	0.731 ± 0.111 (30)	0.879 ± 0.237 (28)	0.513 ± 0.073 (25)	-	(*)
ANCOVA		-	-	-	-	(*)
Pituitary Gland						
Absolute	0.042 ± 0.005 (33)	0.073 ± 0.016 (30)	0.101 ± 0.020* (29)	0.091 ± 0.021 (25)	(*)	* (*)
Relative	0.103 ± 0.013 (33)	0.188 ± 0.045 (30)	0.268 ± 0.052* (29)	0.247 ± 0.063 (25)	(*)	-
ANCOVA		-	*	-	(*)	(*)
Spleen						
Absolute	0.756 ± 0.030 (32)	0.990 ± 0.090* (30)	0.900 ± 0.074 (29)	0.734 ± 0.043 (24)	-	(**)
Relative	1.864 ± 0.066 (32)	2.325 ± 0.205 (30)	2.254 ± 0.187 (29)	1.901 ± 0.108 (24)	-	(*)
ANCOVA		*	-	-	-	(**)
Thymus						
Absolute	0.250 ± 0.030 (33)	0.267 ± 0.027 (30)	0.193 ± 0.016 (29)	0.211 ± 0.018 (25)	-	-
Relative	0.598 ± 0.060 (33)	0.609 ± 0.058 (30)	0.478 ± 0.037 (29)	0.555 ± 0.057 (25)	-	-
ANCOVA		-	-	-	-	-
Thyroid Gland						
Absolute	0.037 ± 0.002 (33)	0.043 ± 0.002 (29)	0.036 ± 0.002 (29)	0.036 ± 0.002 (25)	-	-
Relative	0.090 ± 0.004 (33)	0.102 ± 0.006 (29)	0.091 ± 0.004 (29)	0.093 ± 0.006 (25)	-	-
ANCOVA		-	-	-	-	-
Uterus						
Absolute	0.818 ± 0.043 (33)	1.147 ± 0.109** (30)	0.995 ± 0.061 (27)	0.938 ± 0.059 (25)	-	(**)
Relative	2.114 ± 0.163 (33)	2.749 ± 0.282 (30)	2.556 ± 0.183 (27)	2.497 ± 0.205 (25)	-	-
ANCOVA		**	-	-	-	(**)

* P≤0.05
** P≤0.01
[a] Mean organ weights ± standard error. Absolute organ weights are given in grams; relative weights are in g/kg body weight. Numbers in parentheses are the numbers of animals or organs included in the calculations. Outliers were excluded from the analyses. Asterisks in shaded cells indicate values that are significantly different from controls by Dunnett's test.
[b] Results of linear and quadratic (Quad) exposure concentration trend tests. Asterisks not in parentheses indicate results of dose trend tests; asterisks in parentheses indicate results of ln(dose + 1) trend tests. Dashes indicate no significant trend.
[c] Results of Dunnett's tests from an analysis of covariance (ANCOVA) with body weight as the covariate; dashes indicate no significant difference from controls.

APPENDIX H
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN PURINA 5K96 RAT RATION

INGREDIENTS OF PURINA 5K96 RAT RATION 234
TABLE H1 Vitamins and Minerals in Purina 5K96 Rat Ration 234
TABLE H2 Nutrient Composition of Purina 5K96 Rat Ration 235
TABLE H3 Contaminant Levels in Purina 5K96 Rat Ration 235

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN PURINA 5K96 RAT RATION

Ground wheat, ground corn, wheat middlings, ground oats, fish meal, casein, corn gluten meal, corn oil, dicalcium phosphate, brewers dried yeast, calcium carbonate, and salt

TABLE H1
Vitamins and Minerals in Purina 5K96 Rat Ration

Vitamins	Amount	Source
Carotene	1.6 ppm	multiple sources
Vitamin K	7.1 ppm	menadione sodium bisulfate
Thiamin Hydrochloride	26 ppm	thiamine mononitrate
Riboflavin	8.6 ppm	riboflavin
Niacin	91 ppm	nicotinic acid
Pantothenic acid	29 ppm	calcium pantothenate
Choline chloride	1,800 ppm	choline chloride
Folic acid	2.7 ppm	folic acid
Pyridoxine	10 ppm	pyridoxine hydrochloride
Biotin	0.3 ppm	
Vitamin B_{12}	44 mcg/kg	cyanocobalamin
Vitamin A	25 IU/gm	vitamin A acetate
Vitamin E	93 IU/kg	dl-alpha tocopheryl acetate
Minerals	**Amount**	**Source**
Magnesium	0.20 %	magnesium oxide
Manganese	130 ppm	manganese oxide
Iron	170 ppm	ferrous carbonate
Zinc	85 ppm	zinc sulfate
Copper	10 ppm	copper sulfate
Iodine	0.88 ppm	calcium iodate
Cobalt	0.28 ppm	cobalt carbonate
Selenium	0.28 ppm	multiple sources
Ash	5.8 %	multiple sources
Calcium	1.15 %	multiple sources
Phosphorus	0.89 %	dicalcium phosphate
Potassium	0.44 %	multiple sources
Sulfur	0.17 %	multiple sources
Sodium	0.28 %	salt
Chlorine	0.49 %	salt
Fluorine	14 ppm	multiple sources
Chromium	1.01 ppm	multiple sources

TABLE H2
Nutrient Composition of Purina 5K96 Rat Ration

Nutrient	Mean ± Standard Deviation	Number of Lots
Total Protein, %	18.2 ± 1.0	37
Total Fat, %	5.1 ± 1.0	39
Volatiles, %	6.7 ± 1.9	39
Vitamin A, ppm	8.5 ± 1.7	39
Vitamin B_1, mg/gm	0.05 ± 0.07	39
Vitamin E, ppm	87.7 ± 1.9	39
Selenium, ppm	0.39 ± 0.11	39

TABLE H3
Contaminant Levels in Purina 5K96 Rat Ration

Contaminant	Mean ± Standard Deviation	# Lots / # Lots Positive
Arsenic, ppm	0.125 ± 0.06	39 / 30
Cadmium, ppb	0.085 ± 0.03	39 / 16
Lead, ppm	0.37 ± 0.18	39 / 38
Fumonisin B_1, ppb	36.1 ± 19.6	27 / 27[a]
Total Fumonisin, ppb	53.5 ± 26.4	39 / 39
Aflatoxin B_1, ppb	< MDL	39 / 0
Aflatoxin B_2, ppb	< MDL	39 / 0
Aflatoxin G_1, ppb	< MDL	39 / 0
Aflatoxin G_2, ppb	< MDL	39 / 0

[a] Fumonisin B_1 routine analysis discontinued after initial 27 feed lots.

APPENDIX I
SENTINEL ANIMAL PROGRAM

METHODS 238
RESULTS 238

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 during the 2-year study. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately at the Surveillance/Diagnostic Program, Division of Microbiology, at the National Center for Toxicological Research (Jefferson, AR) for determination of antibody titers. In addition to the serology tests, sentinel animals were examined for ectoparasites, endoparasites, and bacterial pathogens. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the study are also listed.

Method and Test	Time of Analysis
ELISA	
H-1 (Toolan's H-1 virus)	28, 32, 54, 57, 58, 62, 65, 80, 84, 95, and 106 weeks, study termination
KRV (Kilham Rat Virus)	28, 32, 54, 57, 58, 62, 65, 80, 84, 95, and 106 weeks, study termination
Mycoplasma pulmonis	28, 32, 54, 57, 58, 62, 65, 80, 84, 95, and 106 weeks, study termination
PVM (pneumonia virus of mice)	28, 32, 54, 57, 58, 62, 65, 80, 84, 95, and 106 weeks, study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	28, 32, 54, 57, 58, 62, 65, 80, 84, 95, and 106 weeks, study termination
Sendai	28, 32, 54, 57, 58, 62, 65, 80, 84, 95, and 106 weeks, study termination

RESULTS

All serology tests were negative.

APPENDIX J
ASSOCIATED PUBLICATIONS

The following publications relate to the current study in that the studies reported in these publications either used extra animals from the study described in this Technical Report or were conducted with similarly treated animals to provide data relevant to the interpretation of the 2-year study. The results from these studies are discussed in the Discussion section of this Technical Report as appropriate.

Doerge, D.R., Churchwell, M.I., Chang, H.C., Newbold, R.R., and Delclos, K.B. (2001). Placental transfer of the soy isoflavone genistein following dietary and gavage administration to Sprague Dawley rats. *Reprod. Toxicol.* **15**, 105-110.

Doerge, D.R., Twaddle, N.C., Churchwell, M.I., Newbold, R.R., and Delclos, K.B. (2006). Lactational transfer of the soy isoflavone, genistein, in Sprague-Dawley rats consuming dietary genistein. *Reprod. Toxicol.* **21**, 307-312.