NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 409

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

QUERCETIN

(CAS NO. 117-39-5)

IN F344/N RATS

(FEED STUDIES)

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

FOREWORD

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

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

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

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

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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NATIONAL TOXICOLOGY PROGRAM
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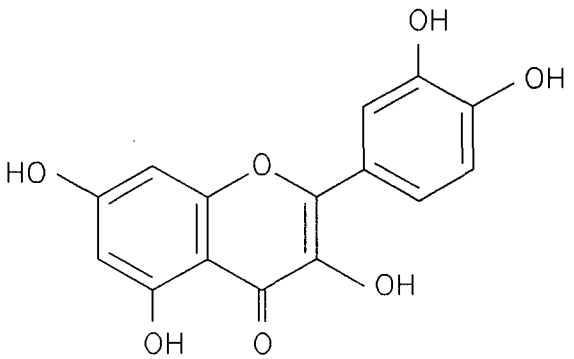
ABSTRACT



QUERCETIN

CAS No. 117-39-5

Chemical Formula: $C_{15}H_{10}O_7$ Molecular Weight: 302.23

Synonyms: C.I. Natural Yellow 10; C.I. 75670; Cyanidelonon 1522; Flavin Meletin; Quercetine; Quercetol; Quertin; Quertine; Sophoretin; Xanthaurine; 3,3′,4′,5,7-Pentahydroxyflavone; 3,5,7,3′,4′-Pentahydroxyflavone; 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one

Quercetin is a member of a group of naturally occurring compounds, the flavonoids, which have a common flavone nucleus composed of two benzene rings linked through a heterocyclicpyrone ring. Quercetin is found in various plants, food products, and dyes of natural origin. The estimated average daily intake of quercetin by an individual in the United States is 25 mg. The Food and Drug Administration nominated quercetin for toxicity and carcinogenicity studies in the rat because it is a chemical that is widely distributed in foods. Quercetin was administered to rats by dosed feed since human exposure is by dietary consumption.

Information in the literature showed that quercetin administered in the diet to rats at levels up to approximately 4% caused a minor body weight effect, whereas higher dose levels produced greater than 10% reduction in body weight gains relative to controls. Based on this information, the NTP 2-year studies were conducted by administering 0, 1,000, 10,000, or 40,000 ppm quercetin (>95% pure) in feed to groups of 50 male and female rats for 104 weeks. Ten additional animals per dose group were evaluated at 6 and 15 months.

Body Weight, Survival, and Clinical Findings in the 2-Year Studies

Body weights of exposed male and female rats given 1,000 and 10,000 ppm were within 5% of controls throughout the studies. Reduced body weight gain in male and female rats receiving 40,000 ppm was observed by week 15 and the final mean body weights were 87% of controls at week 104. Survival and feed consumption were similar among exposed and control groups throughout the studies. The average amounts of quercetin consumed per day by the 1,000, 10,000 and 40,000 ppm dose groups after week 52 were 40, 400, and 1,900 mg/kg of body weight.

Nonneoplastic and Neoplastic Effects in the 2-Year Studies

In male rats, the principal toxic effects associated with the dietary administration of quercetin for 2 years were observed in the kidney. There were dose-related increases in the severity of chronic nephropathy (control, 2.7; low-dose, 2.7; mid-dose, 3.0; high-dose, 3.2) and a slight increased incidence in focal hyperplasia of the renal tubule epithelium (1/50; 2/50; 3/50; 4/50). Parathyroid hyperplasia, indicative of renal secondary hyperparathyroidism, also increased incidence in dosed male rats (1/43, 6/45, 6/43, 17/43).

The evaluation of single sections from the left and right kidneys revealed renal tubule adenomas in three male rats and adenocarcinomas in another male rat receiving 40,000 ppm quercetin; none were seen in the controls. Examination of additional step sections of the male rat kidney identified additional hyperplasia and adenomas in all dose groups (hyperplasia: 2/50, 2/50, 6/50, 8/50; adenoma: 1/50, 2/50, 7/50, 6/50). The overall incidence of renal tubule adenoma or adenocarcinoma combined in male rats was 1/50 in controls and 9/50 in the high-dose group.

There was no apparent effect of quercetin on the kidney of female rats. A single renal tubule adenoma was seen in a female receiving 10,000 ppm; this neoplasm was not considered biologically significant.

There was a statistically significant, dose-related decrease in the incidence of mammary gland fibroadenomas in exposed female rats (29/50, 27/50, 16/50, 9/50), which may in part be attributed to lower body weight gains.

There was a treatment-related accumulation of yellow-brown granular pigment adsorbed to or absorbed by the epithelial cells of the glandular stomach, ileum, jejunum, and, to a lesser extent, the duodenum and colon. The severity of the pigmentation in these tissues increased with increased length of exposure. There were no other lesions considered to be related to chemical administration.

Genetic Toxicology

Quercetin induced gene mutations in *Salmonella typhimurium* strains TA100 and TA98 with and without exogenous metabolic activation (S9). Positive results were also obtained in tests with and without S9 for induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells.

Conclusions

Under the conditions of these 2-year feed studies there was *some evidence of carcinogenic activity** of quercetin in male F344/N rats based on an increased incidence of renal tubule cell adenomas. There was *no evidence of carcinogenic activity* of quercetin in female F344/N rats receiving 1,000, 10,000 or 40,000 ppm. The incidence of renal tubule hyperplasia and the severity of nephropathy were increased in exposed male rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appear on page 10.

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

	Male F344/N Rats	Female F344/N Rats
Doses	0, 1,000, 10,000, or 40,000 ppm in feed	0, 1,000, 10,000, or 40,000 ppm in feed
Final body weights (% of controls)	97%, 95%, 87%	101%, 98%, 87%
2-Year survival rates	26/50, 29/50, 25/50, 25/50	30/50, 28/50, 35/50, 28/50
Nonneoplastic effects	Kidney: renal tubule hyperplasia (single sections): 1/50, 2/50, 3/50, 4/50; (step sections): 2/50, 2/50, 6/50, 8/50; chronic nephropathy (severity grades: 2.7, 2.7, 3.0, 3.2)	None
Neoplastic effects	Kidney (single sections): adenoma - 0/50, 0/50, 0/50, 3/50; adenocarcinoma - 0/50, 0/50, 0/50, 1/50; (step sections): adenoma - 1/50, 2/50, 7/50, 6/50	None
Level of evidence of carcinogenic activity	Some evidence	No evidence
Genetic toxicology		
Salmonella typhimurium (gene mutation):	Positive with and without S9 in strains TA100 and TA98	
Sister chromatid exchanges		
Chinese hamster ovary cells *in vitro*:	Positive with and without S9	
Chromosomal aberrations		
Chinese hamster ovary cells *in vitro*:	Positive with and without S9	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

PEER REVIEW PANEL

The members of the Technical Reports Review Subcommittee who evaluated the NTP draft Technical Report on quercetin on March 11, 1991 are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS

On March 11, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of quercetin received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of quercetin by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on neoplasms and nonneoplastic lesions of the kidneys in male and female rats. The proposed conclusions were *some evidence of carcinogenic activity* in male rats and *no evidence of carcinogenic activity* in female rats. Dr. Dunnick added that because of the low but slightly increased number of renal neoplasms in male rats, additional step sections of residual kidneys from all control and high-dose rats were cut and evaluated.

Dr. Garman, a principal reviewer, agreed with the proposed conclusions. He thought the conclusions in male rats were quite reasonable based both on the frequencies of hyperplasia and of benign and malignant renal tubule epithelial neoplasms and on the morphology of these neoplasms. Dr. Garman asked whether the induction of neoplasms was related to hyaline droplet nephropathy, and if so, he thought this might imply a decreased level of concern with regard to human exposure to quercetin. Dr. J.R. Hailey, NIEHS, said there was no evidence for the hyaline droplet nephropathy in this study and also no evidence of kidney lesions from interim evaluations at 6 and 15 months. Dr. Garman asked for clarification of the identity and tissue location of the pigment found in the gastrointestinal tract. Dr. Hailey said the identity was not determined.

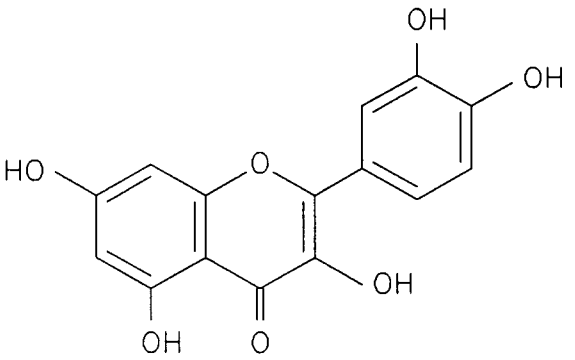
Dr. Goodman, the second principal reviewer, agreed with the proposed conclusions. He inquired what effect the procedure of step sectioning of the kidneys has on the incidence of kidney neoplasms in control and treated animals. Dr. J. Haseman, NIEHS, said that for the eight NTP studies for which step sections have been evaluated, the control rate of renal tubule neoplasms in male rats is 3.7%, or slightly more than double the rate in the current historical control database of 1.6%. Dr. Dunnick reported that the findings from the step sections in other studies have been supportive of the original diagnoses. Dr. Goodman suggested that specific references of studies on chemically induced α_{2u}-globulin nephropathy in male rats should be considered for inclusion in the discussion. Dr. Dunnick said they would be added.

Mr. Beliczky, the third principal reviewer, agreed with the proposed conclusions. He commented that the increased sensitivity of detection for renal neoplasms and preneoplastic lesions resulting from step sectioning was impressive. He asked whether studies on quercetin had been done in mice. Dr. Dunnick responded that several previous studies by others in mice had shown no evidence of carcinogenic effects.

Dr. Carlson said he was not convinced that two squamous cell carcinomas of the tongue in high-dose female rats were unrelated to chemical administration. Dr. Dunnick said the number was within the historical control range and microscopic analysis indicated no supporting preneoplastic lesions.

Dr. Garman moved that the Technical Report on quercetin be accepted with the revisions discussed and the conclusions as written for male rats, *some evidence of carcinogenic activity*, and for female rats, *no evidence of carcinogenic activity*. Dr. Goodman seconded the motion, which was accepted unanimously with 10 votes.

INTRODUCTION



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PHYSICAL AND CHEMICAL PROPERTIES, PRODUCTION, OCCURRENCE, AND USE

Quercetin is a yellow, crystalline solid with a bitter taste, which is insoluble in water, slightly soluble in alcohol, and soluble in glacial acetic acid and aqueous alkaline solutions (Weast, 1979; *Merck Index*, 1983). Quercetin is a member of a group of naturally occurring compounds, the flavonoids, which have a common flavone nucleus composed of two benzene rings linked through a heterocylicpyrone ring. Animals are unable to synthesize the flavone nucleus; thus, flavonoids are found exclusively in the plant kingdom. Quercetin and more than 2,000 other flavonoids occur as condensation products of β-glycosides (Herrmann, 1976; Kuhnau, 1976; Brown, 1980; IARC, 1983). Quercetin is found in various food products and plants, including fruits, seeds, vegetables, tea, coffee, bracken fern, and natural dyes. Quercetin is usually obtained from the hydrolysis of rutin (quercetin-3-rutinoside), a naturally occurring flavonoid glycoside (Griffith *et al.*, 1955), although it can also be synthesized (Shakhova *et al.*, 1962).

Flavonoids, including quercetin, were once thought to have therapeutic applications, including induction of smooth muscle relaxation, reduction of capillary fragility, and as anti-inflammatory agents. However, in 1970, the Food and Drug Administration withdrew its approval of drugs containing rutin or quercetin because there was insufficient evidence to support the reported pharmacologic effects (Brown, 1980; IARC, 1983). The total flavonoid intake in the U.S. is estimated at 1 g per person per day, with an average daily intake of the individual flavonoid, quercetin, of approximately 25 mg per person (Kuhnau, 1976).

METABOLISM AND DISTRIBUTION

Quercetin glycosides are relatively poorly absorbed by the small intestine. Microflora of the lower bowel hydrolyze the flavonide-glycoside to quercetin and the sugar, and quercetin is then absorbed into the enterohepatic system (Brown, 1980; Tamura *et al.*, 1980; Bokkenheuser *et al.*, 1987). After oral administration of quercetin to rabbits (Booth *et al.*, 1956) or rats (Petrakis *et al.*, 1959), three metabolites of quercetin were identified in the urine: 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid), and *m*-hydroxyphenylacetic acid. These metabolites are thought to be formed in the liver after fusion of the heterocylicpyrone ring. When Brown and Griffiths (1983) administered quercetin to rats by intraperitoneal injection, they identified the 3′-*o*-methyl-ether of quercetin (isorhamnetin) as a metabolite in bile.

The distribution, metabolism and excretion of 4-[^{14}C] quercetin in male ACI rats were studied by autoradiography and quantitation of radioactivity (Ueno *et al.*, 1983). After oral administration, 20% of the dose was absorbed from the digestive tract and then excreted into the bile and urine within 48 hours as glucuronide or sulfate conjugates. Autoradiographic analysis of a rat 3 hours after receiving a single 2.3 mg/kg oral dose of quercetin showed that most of the radioactivity remained in the digestive tract with low levels seen in the blood, liver, kidney, lung, and rib.

In five human volunteers, no quercetin was detected in the plasma or urine after oral administration of 4 g of quercetin (Gugler *et al.*, 1975).

TOXICITY

The oral LD_{50} of quercetin was reported as 160 mg/kg in the mouse and 161 mg/kg in the rat; the LD_{50} in the mouse by the subcutaneous route was reported as 97 mg/kg (Sullivan *et al.*, 1951). The purity of the compound used in this study was not specified. Subsequent studies have shown that rodents tolerate much higher doses of quercetin. Rats fed diets containing up to 1% quercetin for 410 days showed no decrease in body weight gain and no compound-related histopathologic lesions (Ambrose *et al.*, 1952).

REPRODUCTIVE TOXICOLOGY

The reproductive toxicity of quercetin was studied in male and female F344 rats fed diets containing 0.1% or 0.2% quercetin from birth to breeding during week 12 or 13. During gestation and lactation, animals were fed diets without quercetin. Quercetin had no effect on mean viable litter size, live birth index, 3-day survival of pups, lactation index, or weight of pups at birth or at 21 days (Stoewsand *et al.*, 1984). When 0, 20, 200, or 2,000 mg/kg quercetin was administered to Sprague-Dawley rats from days 6 through 15 of gestation, no overt signs of toxicity were seen in the dams even at the highest dose, but average fetal weight of the 2,000 mg/kg group was reduced relative to control fetal weight. No fetal abnormalities attributable to chemical administration were observed (Willhite, 1982).

CARCINOGENICITY

Quercetin has been studied in a variety of test systems for carcinogenicity and in the majority of these studies there was no evidence of neoplasms related to chemical administration (Table 1). In a 2-year study of F344 rats, 0%, 1.25% or 5% quercetin was administered in the diet for 104 weeks, followed by an additional 8-week recovery period (Ito *et al.*, 1989). Major tissues and organ systems were examined histopathologically. Hyperplastic polyps of the cecum were found in males and females fed diets containing 5% quercetin. An adenoma and two adenocarcinomas of the cecum were observed in high-dose males, while two adenomas of the colon were observed in the high-dose females. The incidences of these neoplasms were not considered statistically significant and the authors concluded that there was no evidence for any clear carcinogenic effect.

TABLE 1
Quercetin Rodent Carcinogenicity Studies

Strain of Rodent	Route of Administration and Dose[a]	Length of Dosing	Histopathologic Findings[b]	Reference
Male and female F344/DuCrj rats	Diet 0, 1.25, 5.0%	104 weeks	Negative	Ito *et al.*, 1989
Male and female albino rats	Diet 0, 0.1% quercetin	58 weeks	Intestinal and urinary bladder neoplasms in treated groups	Pamukcu *et al.*, 1980
Male and female ACI rats	Diet 1, 5, 10%	850 days	Negative	Hirono *et al.*, 1981
Male and female F344 rats	Diet 0, 0.1%	540 days	Negative	Takanashi *et al.*, 1983
Male and female ddY mice	Diet 0, 2%	842 days	Negative	Saito *et al.*, 1980
Male and female golden hamsters	Diet 0, 1, 4%	351 to 709 days	Negative	Morino *et al.*, 1982
Female ICR/Ha Swiss mice	DMBA as initiator on skin, 25 mg quercetin applied to the skin 3 times per week for 25 weeks	368 days	Negative (no skin neoplasm induction)	Van Duuren and Goldschmidt, 1976
Male F344 rats (effects on initiation/ promotion in urinary bladder)	Diet 0, 5%	a) Quercetin given for 25 weeks after initiation with 0.01% BHBN, b) 5% quercetin given as an initiator for 4 weeks followed by 0.001% BHBN for 29 weeks	No effects on initiation/ promotion in urinary bladder	Hirose *et al.*, 1983
Female ICR mice	Skin initiated with DMBA, promoted with telocidin twice per week, quercetin (30 μmol) treatment applied topically with telocidin	20 weeks	Suppressed skin neoplasm formation	Nishino *et al.*, 1984a

(continued)

TABLE 1
Quercetin Rodent Carcinogenicity Studies (continued)

Strain of Rodent	Route of Administration and Dose	Length of Dosing	Histopathologic Findings[a]	Reference
Male and female A(A/JJms) mice[c]	Diet 0, 5%	23 weeks	Negative (no increase or decrease in lung neoplasms)	Hosaka and Hirono, 1981
Female CD-1 mice	Skin-initiated with DMBA, promoted with TPA, quercetin (30 μmol) applied topically after each TPA treatment	18 weeks	Suppressed skin neoplasm formation	Kato *et al.*, 1983

[a] DMBA = 7,12-dimethyl[a]anthracene; TPA = 12-*o*-tetradecanoylphorbol-13-acetate; BHBN = N-butyl-N-(4-hydroxylbutyl)nitrosamine
[b] Negative = no evidence for neoplasms related to administration of quercetin
[c] This strain develops lung neoplasms at a low incidence by week 23.

Quercetin has been shown to inhibit the promotion of skin neoplasms in the mouse (Kato *et al.*, 1983; Nishino *et al.*, 1984a) and to suppress the formation of urinary bladder neoplasms (Hirose *et al.*, 1983). Quercetin had no effect on the formation of lung neoplasms in strain A mice (Hosaka and Hirono, 1981) and did not induce preneoplastic glutathione S-transferase placental form-positive foci in F344 rats (Ito *et al.*, 1988). When quercetin was given intraperitoneally for 6 days at a dose of 500 mg/kg per day to hepatectomized rats followed by phenobarbital treatment, there was no increase in liver neoplasms compared to rats treated in the same manner without quercetin (Kato *et al.*, 1985).

Pamukcu *et al.* (1980) reported that albino rats (Norwegian strain) fed a diet containing 0.1% quercetin for 58 weeks showed an increased incidence of intestinal and urinary bladder neoplasms in dosed animals. Other long-term rat studies have not confirmed this carcinogenic effect (Hirono *et al.*, 1981; Takanashi *et al.*, 1983; Ito *et al.*, 1989). Long-term studies in mice also showed no carcinogenic effects from quercetin (Saito *et al.*, 1980). Some of these animal studies showed that quercetin can inhibit the promotion of neoplasms (Kato *et al.*, 1983). Follow-up studies *in vitro* suggest that quercetin can inhibit cell proliferation. Quercetin has been shown to have pleiotropic effects on the transformation of BALB 3T3 cells. At a concentration of 0.5 μg/mL, quercetin suppresses the promoting action of 12-*o*-tetradecanoylphorbol-13-acetate on cells initiated with 20-methylcholanthrene (MCA), but at higher concentrations (5.0 μg/mL), quercetin enhanced cell transformation by MCA (Tanaka *et al.*, 1987).

Quercetin has been shown to inhibit cell proliferation in Ehrlich ascites neoplasms cells and to inhibit thymidine incorporation (Graziani and Chayoth, 1979). Quercetin also inhibits the growth of squamous cell carcinoma lines *in vitro* (Castillo *et al.*, 1989).

Bracken fern, which contains quercetin and many other chemicals, causes mononuclear cell leukemia, intestinal neoplasms, urinary bladder carcinomas, and mammary adenocarcinomas in rats; urinary bladder neoplasms in guinea pigs; alimentary tract and urinary bladder cancers in cattle; and intestinal

carcinomas and hepatomas in toads (IARC, 1986, 1987). The neoplasms appear to be caused by known carcinogens, such as shikimic acid and tannin, also found in bracken fern (Evans, 1984; Hirono, 1986).

GENETIC TOXICITY

The mutagenicity of quercetin and other flavonoids has been reviewed by Sugimura *et al.* (1977), Brown (1980), and Nagao *et al.* (1981). Structural requirements for mutagenic activity of flavonoids in *Salmonella* are discussed in detail by MacGregor and Jurd (1978) and Nagao *et al.* (1981). Mutagenic flavonoids (primarily the 3-hydroxyflavones) generally contain a free hydroxyl group at the 3 position, a double bond between positions 2 and 3, and a keto group at the 4 position. The presence of exogenous metabolic activating systems may render some of these structural requirements nonessential. Of the flavonoids, quercetin exhibits the strongest mutagenic activity. Quercetin induces gene mutations in base substitution as well as frameshift strains of *Salmonella typhimurium*, with and without exogenous metabolic activation, although activation increases the magnitude of the mutagenic response (Bjeldanes and Chang, 1977; Hardigree and Epler, 1978; Brown and Dietrich, 1979; Bartholomew and Ryan, 1980; McCoy *et al.*, 1983; Stoewsand *et al.*, 1984; Kuroda, K. *et al.*, 1985; Kuroda, M. *et al.*, 1985; Busch *et al.*, 1986; Löfroth *et al.*, 1986; Rueff *et al.*, 1986; Brams *et al.*, 1987; Marzin *et al.*, 1987; MacGregor and Wilson, 1988). It has also been reported to induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Watson, 1982). Tests for chromosomal effects in mammalian cell cultures have also been positive with quercetin: it induced chromosomal aberrations and sister chromatid exchanges, in the absence of S9 metabolic activation, in Chinese hamster Don-6 and B-131 fibroblasts (Yoshida *et al.*, 1980), in Chinese hamster ovary cells (Stich *et al.*, 1981; Carver *et al.*, 1983), and in human HE2144 fibroblasts and leukocytes (Yoshida *et al.*, 1980). In addition, sister chromatid exchanges (Rueff *et al.*, 1986) and chromosomal aberrations (Marzin *et al.*, 1987) were induced by quercetin in the presence, as well as the absence, of S9 in human peripheral lymphocyte cultures. Despite the consistently positive results for quercetin in *vitro* assays for genotoxic activity, most of the *in vivo* test data were negative.

Quercetin (maximum dose of 1,000 mg/kg) did not induce micronuclei in bone marrow erythrocytes of mice exposed either by intraperitoneal injection or gavage (Aeschbacher *et al.*, 1982; MacGregor *et al.*, 1983); feed studies (5% and 10% in chow for 8 days) also yielded negative results for micronucleus induction (MacGregor *et al.*, 1983). No increase in the frequency of sister chromatid exchanges in rabbit lymphocytes was observed 1 or 7 days after intraperitoneal (i.p.) injection of 250 to 1,000 mg/kg quercetin (MacGregor *et al.*, 1983). Results of dominant lethal assays with quercetin in male Swiss mice (200 to 400 mg/kg i.p.) and Wistar rats (200 and 300 mg/kg i.p.) were also negative (Aravindakshan *et al.*, 1985).

Feces or fecal extracts from laboratory rats fed quercetin showed mutagenic activity in *Salmonella typhimurium* and urine from treated rats showed a small amount of mutagenic activity (in proportion to administered dose) (Stoewsand *et al.*, 1984; Crebelli *et al.*, 1987). Bacterial-mediated degradation of quercetin in the gut and lack of absorption may be contributing factors to the observed lack of *in vivo* genetic effects. Additionally, bacterial gene mutation studies with known metabolites of quercetin have shown little effect: 3-hydroxyphenylacetic acid, 3,4-dihydroxyphenylacetic acid, homovanillic acid, and phloroglucinol carboxylic acid were all negative for gene reversion induction in *S. typhimurium* strains TA98 and TA100 (Bjeldanes and Chang, 1977; MacGregor and Jurd, 1978; Hatcher *et al.*, 1981). However, positive results were obtained in *S. typhimurium* with dihydroquercetin (TA98) and isorhamnetin (TA98, TA100) (MacGregor and Jurd, 1978; Nagao *et al.*, 1981). 3,4-Dihydroxyphenylacetic acid (100 μg/mL) caused chromosomal aberrations in Chinese hamster ovary cells treated for 3 hours with or without S9 activation (Stich *et al.*, 1981).

STUDY RATIONALE

Quercetin was nominated by The Food and Drug Administration for toxicity and carcinogenicity studies in the rat because it is widely distributed in natural foods, and although long-term studies had been conducted previously in both rats and mice, there was conflicting information on the carcinogenicity of quercetin in the rat. Quercetin was administered to rats by dosed feed because human exposure is by dietary consumption.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Quercetin was obtained from Freeman Industries (Tuckahoe, NY) in two lots. It was prepared by hydrolyzing rutin (quercetin-3-rutinoside), a naturally occurring flavonoid glycoside. Both lots (lot no. 969-3790-05, anhydrous form, and lot no. 969-0483-18BL, dihydrate form) were used throughout the studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, Missouri) (Appendix F). The study chemical, a yellow crystalline powder, was identified as quercetin by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

Both lots were greater than 95% pure, as determined by titration, Karl Fischer water analysis, weight loss on drying, chromatographic analysis, nuclear magnetic resonance spectroscopy, and elemental analyses. The largest impurity was identified by spectroscopy and mass spectrometry as ellagic acid (2.6% in lot 969-3790-05 and 1.1% in lot 969-0483-18BL). Stability studies performed by high-performance liquid chromatography indicated that quercetin was stable as a bulk chemical for at least 2 weeks at temperatures to 60° C when protected from light in a nitrogen atmosphere.

Based on the results of a stability study, the bulk chemical was stored at 0° ± 5° C throughout the study period. The bulk chemical was monitored periodically by the study laboratory using high-performance liquid chromatography and infrared spectroscopy. No change in the study material was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate amounts of quercetin and feed (Table F1). Studies were conducted by the analytical chemistry laboratory to determine the homogeneity and stability of 10,000 ppm quercetin in feed. Homogeneity was confirmed by ultraviolet spectroscopy. Stability of dose formulations stored at temperatures up to 25° C for at least 14 days was confirmed by high-performance liquid chromatography. During the studies, the dose formulations were stored in opaque plastic bags (because of reported light sensitivity) at approximately 4° C for no longer than 2 weeks.

The study laboratory conducted periodic analyses of the quercetin dose formulations using ultraviolet spectrophotometry (Appendix F). During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals and all formulations were within 10% of the target concentrations (Table F2). Results of periodic referee analyses of the dose formulations performed by the analytical chemistry laboratory were in agreement with the results from the study laboratory (Table F3).

2-YEAR STUDIES

Study Design

Groups of 70 rats of each sex were administered 0, 1,000, 10,000, or 40,000 ppm quercetin. These doses were selected based on the literature reports which showed that quercetin administered in the diet at levels up to approximately 4% (40,000 ppm) caused a minor body weight decrement, and that this effect was more severe at doses higher than 4%. Since 1,000 ppm was the dose level used in the one study reporting carcinogenic results in rats, this concentration was selected as the low dose for these studies. Ten male and ten female rats per dose group were randomly selected and necropsied for interim evaluation after 6 months and 15 months of chemical administration.

Source and Specification of Animals

Male and female F344/N rats were obtained at 4 to 5 weeks of age from Charles River Breeding Laboratories (Portage, MI) for use in the 2-year

studies. Males were quarantined for 15 days and females were quarantined for 21 days. Five animals of each sex were randomly selected and killed for parasite evaluation and gross observation of disease. The rats were placed on study at about 7 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix I).

Animal Maintenance

Rats were housed five per cage. Feed and water were available *ad libitum*. Racks were rotated in the room every 2 weeks, and cages were rotated from top to bottom within each group every 2 weeks. Further details of animal maintenance are given in Table 2.

Clinical Examinations and Pathology

All animals were observed twice daily and clinical findings were recorded weekly for 13 weeks and monthly thereafter. Rats were weighed at study initiation, once per week for 14 weeks, and once every 4 weeks thereafter. Feed consumption was measured weekly.

After 6 months, 10 male and 10 female rats from each dose group were killed for interim evaluations. An additional 10 rats from each dose group were randomly selected and killed for 15-month interim evaluations. Blood was drawn from the tails of rats to measure the following hematology parameters: erythrocytes, total leukocyte count, leukocyte differential counts, and nucleated erythrocytes. Blood collected from the jugular vein was analyzed for concentrations of blood urea nitrogen, creatinine, sodium, potassium, chloride, alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase. One week prior to the 6- or 15-month interim evaluations, urine was collected over a 24-hour period, the volume was measured and the concentrations of chloride, potassium, and sodium were determined. The brain, liver, and right kidney of each animal were weighed at necropsy. Further details of the interim evaluations are presented in Table 2.

Animals found moribund, selected for the 6- or 15-month interim evaluations, or surviving to the end of the 2-year studies were killed. Necropsy was performed on all animals. At necropsy, all organs and tissues were examined for gross lesions. All major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathology examinations of the tissues were performed according to an "inverse pyramid" design (McConnell, 1983a,b). Complete histopathologic examinations were performed on all grossly visible lesions in all dose groups, on all control animals, and on animals receiving 40,000 ppm. Selected histopathology examinations were performed on 1,000 and 10,000 ppm dose group animals dying before the end of the study period. The tissues, tissue groups, and organs examined are listed in Table 2.

Upon completion of the microscopic evaluation by the laboratory pathologist, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slide and tissue counts were verified, and histotechnique was evaluated. The kidney from all male rats and the kidney, uterus, and thyroid gland from all female rats were reevaluated microscopically by a quality assessment pathologist. Additionally, the duodenum, ileum, jejunum, and glandular stomach were reviewed from all animals in all groups for pigmentation. All diagnoses of primary mammary gland tumor and squamous cell carcinoma of the tongue in females were examined. Since the urinary bladder had been affected in a previous study, 20% of the control and 40,000 ppm dose groups were randomly selected for microscopic review of the urinary bladder.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed all kidneys and all segments of duodenum, ileum, jejunum and glandular stomach with a diagnosis of pigmentation. All uteri and mammary glands with a tumor diagnosis and all tongues with the diagnosis of squamous cell carcinoma from female rats were also reviewed. Representative examples of potential chemical-related nonneoplastic lesions and

neoplasms, lesions for which there was a difference in diagnosis between the study pathologist and reviewing pathologist, and lesions of general interest were selected by the chair for review by the PWG. All renal neoplasms and hyperplasias were examined by the PWG. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses.

When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

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

Calculation of Incidence

Tables A1 and B1 summarize the incidence of neoplasms in male and female rats. Tables A5 and B5 summarize the incidence of nonneoplastic lesions in male and female rats. The incidence of neoplasms or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histopathologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary gland neoplasms) prior to histologic sampling, or when lesions had multiple potential sites of occurrence (e.g., mononuclear cell leukemia), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalence also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one sided. The procedures described above were also used to evaluate selected nonneoplastic lesions. (For further

discussion of these statistical methods, see Haseman, 1984).

Historical Control Data

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

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Clinical chemistry, urinalysis, and hematology data, which typically have skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's or Dunn's test). Average nephropathy severity values for the 2-year studies were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Quality Assurance Methods

The 2-year studies were conducted in compliance with FDA Good Laboratory Practice Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicity

The genetic toxicity of quercetin was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and to induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The protocols for these studies and tabular presentations of their findings are given in Appendix C.

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Feed Studies of Quercetin

Study Laboratory
EG&G Mason Research Institute, Worcester, MA

Strain and Species
F344/N rats

Animal Source
Charles River Breeding Laboratories, Portage, MI

Date of Birth
Males: 3 - 10 May 1982
Females: 10 - 17 May 1982

Time Held Before Study
Males: 15 days
Females: 21 days

Average Age When Placed on Study
7 weeks

Date of First Dose
Males: 23 June 1982
Females: 6 July 1982

Duration of Dosing
104 weeks (7 days/week)

Date of Last Dose
Males: 15 - 21 June 1984
Females: 27 June - 6 July 1984

Necropsy Dates
6-month interim evaluation: Males: 28 - 30 December 1982; Females: 12 - 14 January 1983
15-month interim evaluation: Males: 28 - 30 September 1983; Females: 12 - 14 October 1983
2-year studies: Males: 15 - 21 June 1984; Females: 28 June - 5 July 1984

Average Age When Killed
111 weeks

Size of Study Groups
70 males and 70 females

Method of Animal Distribution
Animals of each sex randomized into cage groups, and then cages randomized to treatment groups using appropriate table of random numbers.

Animals per Cage
5

Method of Animal Identification
Ear punch

Diet
NIH-07 Rat and Mouse Ration, Open formula, pellets (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Feed Studies of Quercetin (continued)

Feeders
Stainless steel, gang style (Scientific Cages, Inc., Bryan, TX), changed once weekly

Water
Tap water (City of Worcester Water Supply) via outside-the-cage automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*

Cages
Solid-bottom polycarbonate (Lab Products, Inc., Rochelle Park, NJ)

Bedding
Aspen bed, heat-treated hardwood chips (American Excelsior Co., Baltimore, MD), changed twice weekly

Cage Filters
Non-woven fiber filters (Snow Filtration, Cincinnati, OH)

Animal Room Environment
Temperature: 22.5° ± 1.5° C
Relative humidity: 47.6% ± 5.8%
Fluorescent light: 12 hours/day
Room air changes: 12/hour

Doses
0, 1,000, 10,000, or 40,000 ppm quercetin in feed

Type and Frequency of Observation
Observed twice/day; body weight initially, once/week for 14 weeks, once/month thereafter; clinical observations once/week for 13 weeks, once/month thereafter; feed consumption measured once/week.

Necropsy and Histopathology

Organ weights:	Recorded for brain, right kidney, and liver of all animals sacrificed at 6 and 15 months
Necropsy:	Performed on all animals
Histopathology:	Complete histopathologic examinations performed on all grossly visible lesions in all dose groups and on all control and 40,000 ppm dose animals; histopathologic examinations performed on the following tissues: At 6 months: 10,000 ppm dose groups (large intestine, small intestine, and uterus) At 15 months: 1,000 ppm dose groups (large intestine); 10,000 ppm dose group (large intestine, small intestine, and stomach) Animals dying early and at study termination (for 1,000 and 10,000 ppm groups): (kidney, liver, pancreas, parathyroid gland, pituitary gland, small intestine, tongue, urinary bladder, and uterus)

Clinical Pathology

	Blood and urine samples were collected from males and females at the 6- and 15-month interim evaluations.
Hematology:	Erythrocytes, leukocytes, leukocyte differential count, and nucleated erythrocytes
Clinical chemistry:	Blood urea nitrogen, creatinine, sodium, potassium, chloride, alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase
Urinalysis:	Urinary sodium, urinary potassium, and urinary chloride

RESULTS

2-YEAR STUDIES

6- and 15-Month Interim Evaluations

The relative kidney and liver weights of male and female rats that received 40,000 ppm were significantly greater than those of the controls at both 6 and 15 months (Tables D1 and D2). For females these differences primarily reflected the reduced body weights observed in high-dose animals. No biologically significant changes in hematology or clinical chemistry parameters were observed (Tables E1 and E2). The only abnormality noted in the urinalyses was the presence of calcium oxalate crystals in 7 of 10 high-dose males at 15 months.

Yellow-brown pigmentation occurred in several tissues and was most prevalent in the glandular stomach and the distal segments of the small intestine. The incidence and severity of pigmentation increased with dose concentration and duration. At 15 months all high-dose males had pigmentation in the glandular stomach, as did 5 of 10 high-dose females. Epithelial staining of the small intestine was present in all high-dose males and in nine high-dose females at 15 months. One high-dose male also had pigmentation in the lamina propria of the jejunum and ileum and two mid-dose females had pigmentation in the jejunal and ileal submucosa. Furthermore, at 15 months eight high-dose males and four high-dose females had pigmentation of the skulls or teeth. There were no neoplasms or nonneoplastic lesions related to quercetin administration in male or female rats at 6 or 15 months.

Survival

Estimates of the probabilities of survival for male and female rats are shown in Table 3 and in the Kaplan-Meier survival curves in Figure 1. Exposure to quercetin had no significant effect on survival.

Body Weights, Feed Consumption, and Clinical Findings in the 2-Year Studies

Male and female rats given 40,000 ppm quercetin had lower body weight gains than those of the controls. In males, the difference was 5% at week 25, and in females, 10% at week 25 (Tables 4 and 5 and Figure 2). From 65 weeks to the end of the study, the difference among males ranged from 6% to 13%; in females, the difference ranged from 13% to 15%. Feed consumption by exposed males and females was similar to that of the controls (Tables G1 and G2). The decreased body weight gains relative to controls were attributed to quercetin toxicity. A yellowish discoloration of the hair coat, especially in the perineal area, was present in all mid- and high-dose animals, presumably due to the urinary and/or fecal excretion of quercetin and/or its metabolites.

TABLE 3
Survival of Rats in the 2-Year Feed Studies of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Male				
Animals initially in study	70	70	70	70
6-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	10	10	10
Natural deaths	3	7	3	6
Moribund kills	21	15	22	21
Animals surviving until end of the study	26	28	25	23
Percent survival at end of study[b]	52	56	50	47
Mean survival (days)[c]	576	581	577	576
Survival analyses[d]	P=0.603	P=0.838N	P=0.940	P=0.824
Female				
Animals initially in study	70	70	70	70
6-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	10	10	10
Natural deaths	1	4	2	3
Moribund kills	19	18	13	19
Animals surviving until end of the study	30	28	35	28
Percent survival at end of study[b]	60	56	71	56
Mean survival (days)[c]	590	574	586	576
Survival analyses[d]	P=0.709	P=0.612	P=0.445N	P=0.656

[a] Censored from survival analyses
[b] Kaplan-Meier determinations. Survival rates adjusted for interim evaluations.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A lower mortality in a dose group is indicated by N.

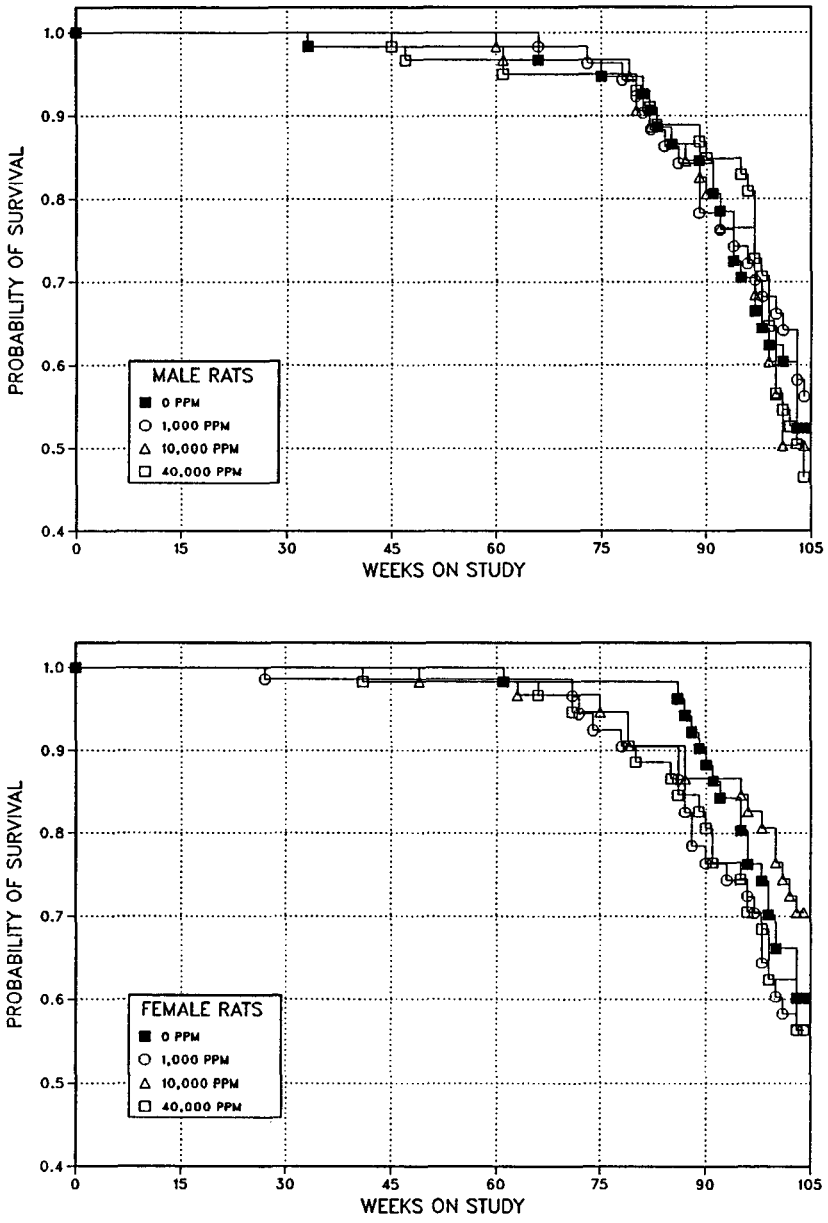

FIGURE 1
Kaplan-Meier Survival Curves for Rats Administered Quercetin in Feed for 2 Years

TABLE 4
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Quercetin

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	1,000 ppm Av. Wt. (g)	1,000 ppm Wt. (% of controls)	1,000 ppm No. of Survivors	10,000 ppm Av. Wt. (g)	10,000 ppm Wt. (% of controls)	10,000 ppm No. of Survivors	40,000 ppm Av. Wt. (g)	40,000 ppm Wt. (% of controls)	40,000 ppm No. of Survivors
1	162	70	160	99	70	165	102	70	167	103	70
2	195	70	196	101	70	203	104	70	198	102	70
3	225	70	230	102	70	233	103	70	228	101	70
4	253	70	255	101	70	257	102	70	252	99	70
5	271	70	272	100	70	272	100	70	259	95	70
6	284	70	278	98	70	287	101	70	282	99	70
7	300	70	298	100	70	304	102	70	300	100	70
8	310	70	304	98	70	312	101	70	309	100	70
9	322	70	321	100	70	325	101	70	320	99	70
10	319	70	323	101	70	336	106	70	332	104	70
11	342	70	343	100	70	346	101	70	339	99	70
12	340	70	337	99	70	334	98	70	328	97	70
13	354	70	350	99	70	343	97	70	343	97	70
14	364	70	363	100	70	359	99	70	355	97	70
17	376	70	375	100	70	373	99	70	364	97	70
21	399	70	399	100	70	395	99	70	382	96	70
25	416	70	412	99	70	409	98	70	393	95	70
29[a]	434	60	438	101	60	430	99	60	413	95	60
30	445	60	438	98	60	435	98	60	409	92	60
33	456	60	456	100	60	448	98	60	426	93	60
37	457	59	460	101	60	458	100	60	432	95	60
41	464	59	466	101	60	464	100	60	439	95	60
45	469	59	470	100	60	464	99	60	442	94	60
49	481	59	486	101	60	482	100	60	453	94	58
53	484	59	487	101	60	481	100	60	453	94	58
57	487	59	491	101	60	488	100	60	460	95	58
61	478	59	487	102	60	484	101	59	457	96	58
65	485	59	491	101	60	483	100	58	453	94	57
68[a]	486	58	493	102	49	490	101	48	458	94	47
73	492	48	497	101	49	491	100	48	458	93	47
81	492	47	492	100	46	483	98	45	451	92	46
85	485	44	488	101	43	480	99	44	444	92	44
89	476	43	477	100	42	473	99	41	436	92	43
93	473	39	482	102	38	465	98	38	426	90	42
97	479	35	485	101	36	450	94	38	418	87	40
101	447	31	451	101	33	427	96	28	402	90	28
104	464	26	451	97	29	440	95	25	403	87	25
Terminal sacrifice		26			29			25			25
Mean for weeks											
1-13	283		282	100		286	101		281	100	
14-52	433		433	100		429	99		410	95	
53-104	479		482	101		472	99		440	92	

[a] Interim evaluation occurred.

TABLE 5
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Quercetin

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	1,000 ppm Av. Wt. (g)	1,000 ppm Wt. (% of controls)	1,000 ppm No. of Survivors	10,000 ppm Av. Wt. (g)	10,000 ppm Wt. (% of controls)	10,000 ppm No. of Survivors	40,000 ppm Av. Wt. (g)	40,000 ppm Wt. (% of controls)	40,000 ppm No. of Survivors
1	138	70	141	102	70	139	101	70	141	102	70
2	153	70	155	102	70	152	99	70	152	100	70
3	163	70	165	101	70	162	100	70	162	99	70
4	165	70	167	101	70	167	101	70	165	100	70
5	177	70	178	101	70	177	100	70	176	100	70
6	187	70	186	100	70	183	98	70	181	97	70
7	191	70	193	101	70	189	99	70	186	97	70
8	199	70	199	100	70	194	98	70	190	96	70
9	200	70	204	102	70	198	99	70	194	97	70
10	208	70	210	101	70	203	98	70	197	95	70
11	210	70	211	101	70	205	98	70	198	94	70
12	215	70	214	100	70	202	94	70	195	91	70
13	215	70	219	102	70	207	96	70	192	89	70
14	216	70	218	101	70	212	98	70	200	93	70
17	225	70	226	101	70	217	97	70	203	91	70
21	233	70	233	100	70	222	95	70	209	90	70
25	244	70	246	101	70	232	95	70	220	90	70
29[a]	255	60	257	101	60	237	93	60	220	86	60
33	257	60	263	102	60	242	94	60	225	88	60
37	268	60	276	103	60	252	94	60	231	86	60
41	279	60	288	103	60	261	94	60	239	86	60
45	292	60	299	102	60	273	94	60	246	84	59
49	301	60	305	102	60	279	93	60	248	82	59
53	311	60	317	102	60	290	93	59	256	83	59
57	319	60	329	103	60	299	94	59	265	83	59
61	327	60	337	103	60	310	95	59	277	85	59
65	336	59	344	103	60	320	95	58	285	85	59
69[a]	343	49	349	102	50	331	96	48	291	85	48
73	350	49	355	102	48	335	96	48	296	85	47
77	355	49	364	102	47	340	96	47	303	85	47
81	362	49	368	102	45	345	95	45	308	85	44
85	365	49	367	101	45	348	95	45	311	85	44
89	369	46	371	101	39	352	95	43	314	85	42
93	369	42	376	102	38	355	96	43	318	86	38
97	360	38	367	102	36	340	94	41	312	87	35
101	365	33	368	101	30	351	96	38	317	87	31
104	357	30	360	101	28	349	98	35	311	87	28
Terminal sacrifice		30			28			35			28
Mean for weeks											
1-13	186		188	101		183	99		179	97	
14-52	257		261	103		243	95		224	88	
53-104	349		355	102		333	95		297	85	

[a] Interim evaluation occurred.

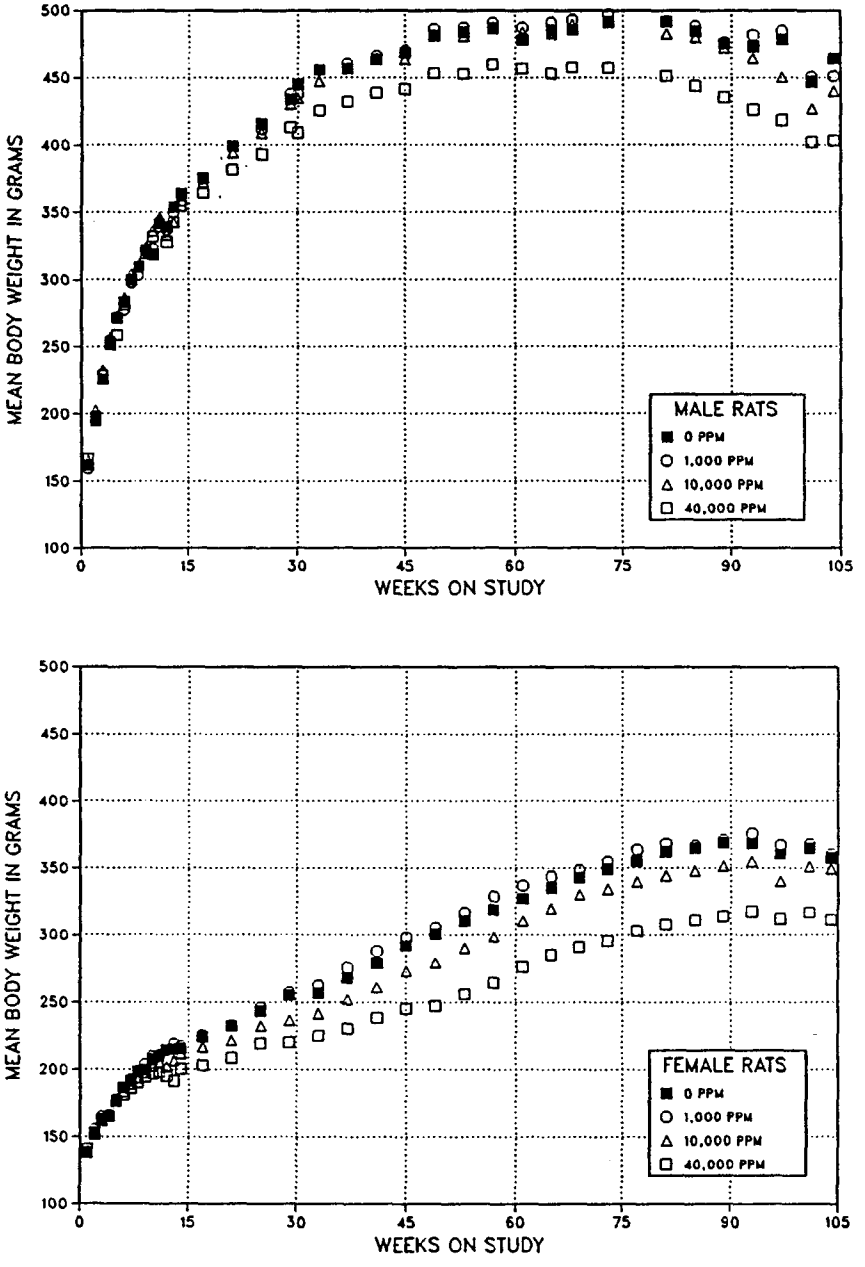

FIGURE 2
Growth Curves for Rats Administered Quercetin in Feed for 2 Years

Pathology and Statistical Analyses of Results of the 2-Year Studies

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the biologically significant neoplasms mentioned in this section are presented in Appendixes A for male rats and B for female rats.

Kidney: Initially, single sections of the left and right kidneys from each rat were examined microscopically. Renal tubule neoplasms were seen in four high-dose male rats, whereas none were observed in controls (Table 6). Three of these neoplasms were adenomas, and one was an adenocarcinoma. Renal tubule neoplasms are relatively uncommon in aged rats. The combined incidence of these neoplasms in the study laboratory historical control males for feed studies is 3/99 (3%, range 0%-6%). The combined incidence in control male rats is 8/499 (1.6%, range 0%-6%) in all NTP feed studies (Table A4). Additionally, there was a slight dose-related increase in the incidence of renal tubule hyperplasia in males.

Because of the low number of neoplasms in the high-dose males, the residual halves of the formalin-fixed kidneys from all males and females were step sectioned to provide approximately eight additional sections per rat for microscopic examination.

During this reevaluation, renal tubule focal hyperplasia was observed in eight high-dose males (one of these animals had been identified in the initial evaluation), and renal tubule adenomas were observed in six high-dose males (one of these animals had been identified in the initial evaluation) (Table 6). Focal hyperplasia was seen in two additional control males and a renal tubule adenoma was observed in one control male. The increased incidences of renal tubule hyperplasia and renal tubule neoplasms in high-dose males is supportive of some evidence of carcinogenicity.

In the initial evaluation, a renal tubule adenoma was seen in one mid-dose female rat, and an adenoma was found in one control female during the evaluation of the step sections. Thus, there was no evidence of a chemical-related increased incidence in kidney neoplasms in females (Table 7).

Renal tubule cell hyperplasias in male rats were focal lesions characterized by increased numbers of tubule epithelial cells forming multiple layers which partially or totally filled the lumen and usually caused slight tubule dilation (Plate 1). The appearance of the hyperplastic cells ranged from those of normal tubule epithelial cells to enlarged polygonal cells resembling cells of the adenomas (Plate 2).

In general, the adenomas were small (400-800 μm) and were distinguished from tubule hyperplasia by larger size and lack of a definite tubular structure. Many adenomas had a prominent microtubular pattern (Plates 3 and 4). Adenomas were expansile and frequently compressed surrounding parenchyma (Plate 5). The neoplasms consisted of large polygonal cells with abundant eosinophilic cytoplasm and large, pale-staining nuclei. The adenocarcinoma was 0.7 cm in diameter, expansile, and was composed of variably sized tubule-like structures which were filled with cells and often contained necrotic centers (Plate 6). Adenocarcinoma cells were clearly more anaplastic and were often characterized by marked pleomorphism, large nuclei, large nucleoli, and atypical mitotic figures (Plate 7).

The nephropathy was significantly more severe in male rats receiving 40,000 ppm than in the controls (Table 8). There was no significant increase in the severity of nephropathy in dosed female rats. Nephropathy was typical of the spontaneously occurring kidney lesion in aging F344/N rats. Severity grades were based upon the extent of nephropathy and the amount of renal parenchyma affected. Nephropathy consisted of a spectrum of lesions, including varying degrees of tubule dilation, distortion with occasional cyst formation, proteinaceous casts, atrophy, regeneration and hypertrophy of tubule epithelium, thickening of tubular and glomerular basement membranes, interstitial fibrosis, scattered foci of suppurative inflammation (primarily within degenerating tubules), and a scattering of varying numbers and aggregates of mononuclear inflammatory cells within the interstitium. Regenerating tubule epithelial cells had basophilic nuclei, scant cytoplasm, and usually formed a single cell layer. There was also a dose-related increase in the incidence of renal pelvic transitional epithelial hyperplasia in males. This change is associated with severe nephropathy.

TABLE 6
Selected Kidney Lesions in Male Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Initial Evaluation (Single Sections)				
Renal Tubule: Hyperplasia				
Overall rates[a]	1/50 (2%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Logistic regression[b]	P=0.079	P=0.752N	P=0.492	P=0.182
Renal Tubule: Adenoma				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates[c]	0.0%	0.0%	0.0%	11.1%
Terminal rates[d]	0/26 (0%)	0/28 (0%)	0/25 (0%)	2/23 (9%)
First incidence (days)	-[e]	-	-	676
Logistic regression	P=0.042	-	-	P=0.122
Renal Tubule: Adenocarcinoma				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Renal Tubule: Adenoma or Adenocarcinoma[f]				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rates	0.0%	0.0%	0.0%	15.3%
Terminal rates	0/26 (0%)	0/28 (0%)	0/25 (0%)	3/23 (13%)
First incidence (days)	-	-	-	676
Logistic regression	P=0.002	-	-	P=0.064
Evaluation of Step Sections				
Renal Tubule: Hyperplasia				
Overall rates	2/50 (4%)	2/50 (4%)	6/50 (12%)	8/50 (16%)
Renal Tubule: Adenoma				
Overall rates	1/50 (2%)	2/50 (4%)	7/50 (14%)	6/50 (12%)
Single and Step Sections Combined				
Renal Tubule: Hyperplasia				
Overall rates	3/50 (6%)	3/50 (6%)	8/50 (16%)	11/50 (22%)
Logistic regression	P=0.006	P=0.655N	P=0.099	P=0.022
Renal Tubule: Adenoma				
Overall rates	1/50 (2%)	2/50 (4%)	7/50 (14%)	8/50 (16%)
Logistic regression	P=0.012	P=0.526	P=0.032	P=0.018
Renal Tubule: Adenoma or Adenocarcinoma				
Overall rates	1/50 (2%)	2/50 (4%)	7/50 (14%)	9/50 (18%)
Logistic regression	P=0.005	P=0.526	P=0.032	P=0.010

[a] Number of lesion-bearing animals/number of animals examined at site
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. A lower incidence in a dose group is indicated by N.
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Not applicable; no neoplasms in animal group
[f] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 4/499 (0.8% ± 1.1%, range 0%-4%)

TABLE 7
Selected Kidney Lesions in Female Rats in the 2-Year Feed Study of Quercetin[a]

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Initial Evaluation (Single Sections)				
Renal Tubule: Hyperplasia				
Overall rates	1/49 (2%)	1/49 (2%)	3/50 (6%)	1/50 (2%)
Renal Tubule: Adenoma[b]				
Overall rates	0/49 (0%)	0/49 (0%)	1/50 (2%)	0/50 (0%)
Evaluation of Step Sections				
Renal Tubule: Hyperplasia				
Overall rates	1/49 (2%)	-	-	3/50 (6%)
Renal Tubule: Adenoma				
Overall rates	1/49 (2%)	-	-	0/50 (0%)
Single and Step Sections Combined				
Renal Tubule: Hyperplasia				
Overall rates	2/49 (4%)	-	-	4/50 (8%)
Renal Tubule: Adenoma				
Overall rates	1/49 (2%)	-	-	0/50 (0%)

[a] Step sections were not evaluated in the 1,000 ppm and 10,000 ppm dose groups.
[b] Historical incidence for 2-year NTP feed studies of untreated control groups (mean ± standard deviation): 1/499 (0.2% ± 0.6%), range 0%-2%

TABLE 8
Incidences and Severity of Nephropathy in Male and Female Rats in the 2-Year Feed Studies of Quercetin[a]

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Male				
Minimal (grade 1)	1/48	2/50	1/50	2/49
Mild (grade 2)	18/48	19/50	13/50	7/49
Moderate (grade 3)	19/48	20/50	23/50	16/49
Marked (grade 4)	10/48	9/50	13/50	24/49
Average severity grade	2.7 ± 0.14	2.7 ± 0.11	3.0 ± 0.11	3.2 ± 0.14**
Female				
Minimal (grade 1)	12/48	7/48	9/50	8/48
Mild (grade 2)	20/48	25/48	30/50	21/48
Moderate (grade 3)	13/48	12/48	10/50	14/48
Marked (grade 4)	3/48	4/48	1/50	5/48
Average severity grade	2.1 ± 0.13	2.2 ± 0.12	2.1 ± 0.10	2.2 ± 0.14

** Statistically significant ($P \leq 0.01$) from the control group by the Mann-Whitney U test
[a] Number of animals with severity grade/number of animals with nephropathy. Severity grade was based on the percentage of parenchyma involved: Minimal - usually less than 25% of cortex; mild - 25% to 50% of cortex; moderate - 50% to 75% of cortex; marked -greater than 75% of cortex. Average severity grade given as the mean ± standard error.

Parathyroid gland: Hyperplasia of the parathyroid glands, characterized by bilateral diffuse enlargement of the glands, occurred with a dose-related increased incidence in male rats (0 ppm, 1/43; 1,000 ppm, 6/45; 10,000 ppm, 6/43; 40,000 ppm, 17/43) (Table A5). Typically, the hyperplasias occurred with greater frequency and severity in animals with marked nephropathy. This is characteristic of renal secondary hyperparathyroidism.

Tongue: A single squamous cell papilloma of the tongue was present in a high-dose male (Table A1). Two squamous cell carcinomas were present in high-dose females (Table B1). The historical control incidence of oral cavity neoplasms for female rats is 4/500 (0.8%, range 0%-2%) for all NTP studies (Table B4b).

Mammary gland: Fibroadenomas of the mammary gland occurred with a highly significant, dose-related, negative trend in female rats (Table 9). The incidences of fibroadenoma in the mid- and high-dose female groups were significantly lower than that in the controls. Fibroadenoma is the most common neoplasm of the mammary gland in female rats, occurring in 178/500 (35.6%, range 8%-56%) of NTP untreated historical controls (Table B4c). Although the incidence of fibroadenoma in the controls of this study (58%) slightly exceeds the range for historical controls, the incidence in the high-dose group is about one-half of the mean rate of historical controls. The lower number of female rats with fibroadenomas in the high-dose group is considered chemically related, and may be associated with the lower body weights in this group.

Uterus: Uterine stromal polyps occurred more frequently in mid-dose female rats than in controls (7/50, 9/50, 16/50, 11/50) (Table B1). The incidence of stromal polyps in the high-dose group, however, was similar to controls. A uterine stromal sarcoma occurred in one female rat in the mid-dose group as well. Due to the marginal increased incidence in stromal polyps, the lack of a dose response, and because only the incidence in the mid-dose group exceeded the range in untreated NTP historical controls (Table B4d), these neoplasms were not considered related to quercetin administration.

Gastrointestinal tract: There was a significant dose-related accumulation of a fine granular yellow to light brown pigment in the epithelial cells lining the glandular stomach, jejunum, ileum, and, to a lesser extent, the duodenum and colon (Table 10). Special stains to further characterize the pigment were not used, but the pigment was believed to be quercetin or one of its metabolites.

Other organs/tissues: Other nonneoplastic lesions occurred with statistically significant increased incidence, but the biological significance of their occurrence is uncertain. High-dose female rats had a marginally increased incidence of chronic inflammation involving the liver (Table B5). However, all male groups had higher incidence than the high-dose females. High-dose male rats had a reduced incidence of bile duct hyperplasia, an increased incidence of lymphatic ectasia within mesenteric lymph nodes, and a marginal dose-related increased incidence in testicular interstitial cell hyperplasia (Table A5).

TABLE 9
Mammary Gland Neoplasms in Female Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Fibroadenoma[a]				
Overall rates[b]	29/50 (58%)	27/50 (54%)	16/50 (32%)	9/50 (18%)
Adjusted rates[c]	66.4%	72.3%	38.4%	30.1%
Terminal rates[d]	16/30 (53%)	18/28 (64%)	10/35 (29%)	8/28 (29%)
First incidence (days)	597	597	605	549
Logistic regression tests[e]	P<0.001N	P=0.553N	P=0.008N	P<0.001N

[a] Historical incidence for 2-year NTP feed studies of untreated control groups (mean ± standard deviation): 178/500 (35.6% ± 15.0%), range 8%-56%
[b] Number of neoplasm-bearing animals/number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE 10
Gastrointestinal Pigmentation in Rats in the 2-Year Feed Studies of Quercetin[a]

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Male				
Glandular Stomach				
Epithelium	0/50	0/50	3/49	34/48**
Large Intestine				
Colon, epithelium	0/49	0/12	0/11	1/47
Small Intestine				
Duodenum, epithelium	0/48	0/47	0/48	3/46
Ilium, epithelium	0/47	1/47	15/48**	28/45**
Jejunum, epithelium	0/48	0/44	2/42	19/44**
Female				
Glandular Stomach				
Epithelium	0/50	0/49	8/50**	38/50**
Small Intestine				
Duodenum, epithelium	0/50	0/48	0/50	1/49
Ileum, epithelium	0/49	0/48	19/49**	32/49**
Jejunum, epithelium	0/50	0/47	3/49	20/49**

** Significantly different (P≤0.01) from the control group by the logistic regression test
[a] Number of lesion-bearing animals/number of tissues examined

GENETIC TOXICOLOGY

Exposure to quercetin (0.3-1,000 μg/plate) produced a strong, dose-related increase in gene mutations in *Salmonella typhimurium* strains TA100 and TA98 both in the presence and in the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table C1). In cytogenetic tests with Chinese hamster ovary cells, quercetin induced marked increases in both sister chromatid exchanges and chromosomal aberrations, with and without metabolic activation (Tables C2 and C3). In the sister chromatid exchange test without S9, positive responses were observed over a dose range of 0.67 to 20 μg/mL quercetin; with S9, effective doses ranged from 2 to 45 μg/mL. In the chromosomal aberration test, the trials conducted in the absence of S9 activation employed a delayed harvest protocol to offset quercetin toxicity; positive responses occurred with 10 to 50 μg/mL quercetin. With S9, standard harvest times were employed and strong increases in aberrations were observed with 25 to 75 μg/mL quercetin. At the highest dose (75 μg/mL), all cells scored contained aberrations.

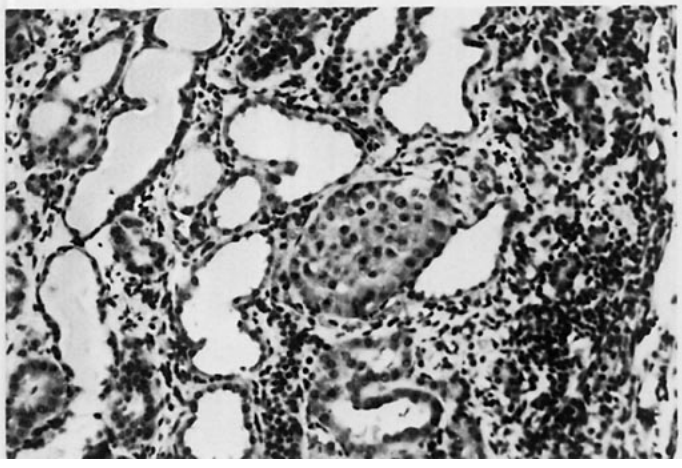

PLATE 1
Renal tubule hyperplasia with hyperplastic cells filling the lumen in the kidney of a male F344/N rat administered 40,000 ppm quercetin in feed for 2 years. H&E, 50X.

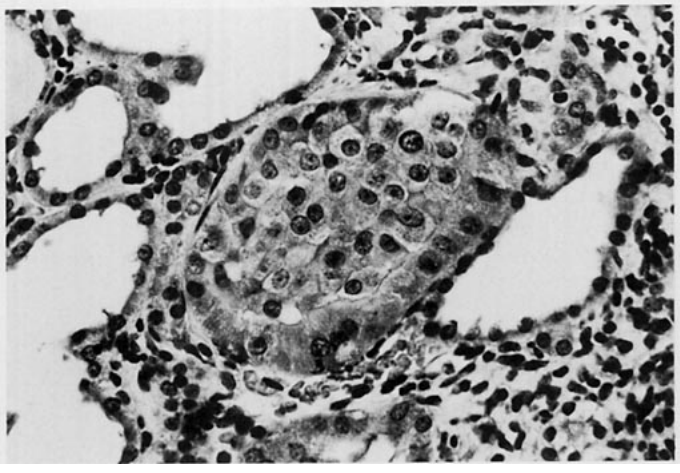

PLATE 2
Higher magnification of Plate 1 demonstrating cellular morphology typical of hyperplasia. H&E, 100X.

PLATE 3
Renal tubule adenoma with microtubular pattern in the kidney of a male F344/N rat administered 40,000 ppm quercetin in feed for 2 years. H&E, 50X.

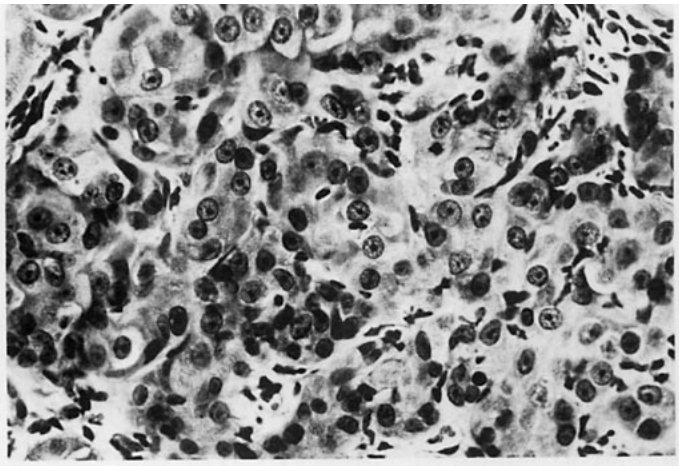

PLATE 4
Higher magnification of Plate 3 demonstrating cellular morphology typical of the adenomas. H&E, 100X.

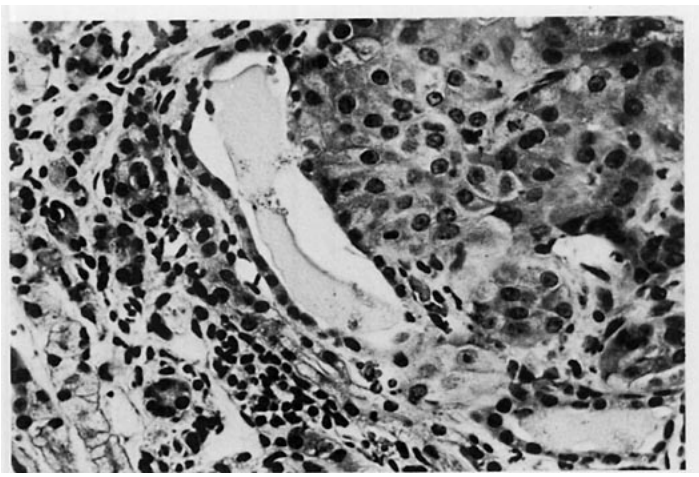

PLATE 5
Expansile renal tubule adenoma with compression of an adjacent tubule in the kidney of a male F344/N rat administered 40,000 ppm quercetin in feed for 2 years. H&E, 100X.

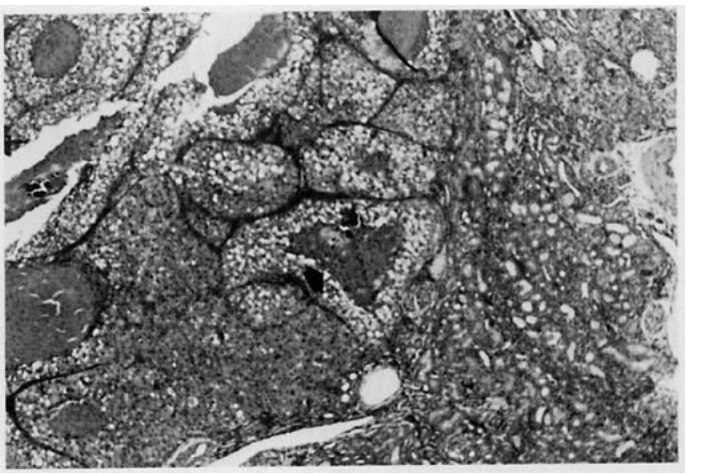

PLATE 6
Renal tubule adenocarcinoma with variably sized tubular structures in the kidney of a male F344/N rat administered 40,000 ppm quercetin in feed for 2 years. Tubular structures often had necrotic centers. H&E, 10X.

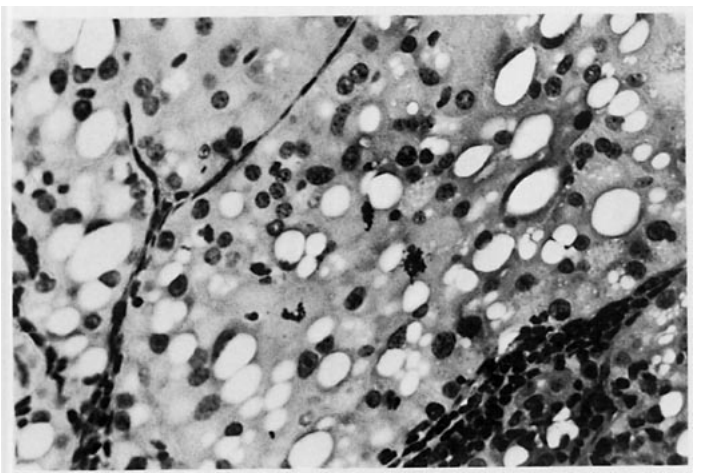

PLATE 7
Higher magnification of Plate 6 demonstrating cellular anaplasia and atypical mitotic figures. H&E, 100X.

DISCUSSION AND CONCLUSIONS

Quercetin, a flavonoid, is found in many food plants including citrus fruits, berries, leafy vegetables, roots, herbs and spices, legumes, cereal grains, tea, and cocoa (Brown, 1980). The flavonoids as a group are reported to have a wide range of possible uses in medicine. To date, though, there have been no reported controlled clinical trials or toxicity testing of these compounds to demonstrate efficacy as antiviral or anticancer agents. Thus, flavonoids are not approved for drug use in the United States (Havsteen, 1983; Cody, 1988; Gilman *et al.*, 1990). Interest in the toxicity and carcinogenicity of the flavonoids began in the mid-1970's when it was shown that some of these naturally occurring chemicals were mutagenic in the *Salmonella typhimurium* assay system. Quercetin is one of the most common flavonoids in plants and is also a component of bracken fern, a plant shown to cause toxicity and death in cattle. Quercetin was nominated by the Food and Drug Administration for toxicity and carcinogenicity studies in the rat because it is widely distributed in natural foods and because of conflicting information in the literature regarding the carcinogenicity of quercetin in previous animal studies.

Previous studies have shown that quercetin administered in feed to rodents at levels up to 5% (the maximum dose usually used in feed studies without adverse effects on nutrition) caused little organ toxicity and had no effect on mortality. Rutin, a glycoside conjugate of quercetin, has also been tested and found to be negative for carcinogenicity when fed in the diet to rats for up to 850 days (Hirono *et al.*, 1981). However, long-term administration of quercetin in feed has resulted in gradually decreased body weights of dosed animals. Hirono *et al.* (1981) observed that male rats fed 5% quercetin in the diet for more than 100 days had an approximate 15% decrease in body weight from that of the control animals. Ito *et al.* (1989) reported that F344/DuCrj rats fed 1.25% or 5.0% quercetin in CRF-1 diet for 104 weeks had final body weights that were 91% and 93% of those of the controls for males and females.

In the present NTP studies, quercetin administered at 4% (40,000 ppm) in the diet also caused a gradual reduction in body weight gain; final mean body weights of male and female rats were 87% of those of the controls. The depressed weight gain observed in the high-dose rats in these studies demonstrates that the doses were sufficient to elicit general toxicity. The high dose (4%) also approached the maximum level of quercetin that could be given in the diet (5%) without adverse nutritional effects. Experience with 2-year rodent studies has shown that control and treated animals must have body weight differences within approximately 10% to 15% to maintain similar rates of background tumors. Thus, these 2-year studies of quercetin were considered adequate for assessing toxicity and carcinogenic activity because the differences in body weights between the high-dose and control groups were within this limit.

The principal lesions associated with the administration of quercetin occurred in the kidney of dosed male rats and included severe chronic nephropathy, renal tubule hyperplasia, and renal tubule adenomas. Chronic nephropathy, a common condition in aging rats, showed a treatment-related increased severity. Hyperplasia of the renal pelvic epithelium (transitional epithelium overlying the renal papilla) is a component of severe nephropathy and occurred in males with a similar treatment-related positive trend. This transitional hyperplasia is characteristic of chemical-related toxicity and is not considered to be a preneoplastic lesion. The dose-related increased incidence of parathyroid hyperplasia in male rats is an indication that nephropathy was severe enough to compromise renal function. Hyperparathyroidism frequently accompanies severe nephropathy in rats because the progressive loss of renal function disrupts calcium and phosphorus homeostasis, which leads to prolonged parathyroid gland stimulation. This results in hyperplasia and elevated levels of parathyroid hormone. An associated mineralization was present in vascular walls and several organs. Severe nephropathy induced by chemical exposure may be life-threatening and has been the cause of

reduced survival among chemical-exposed rats in several NTP 2-year studies. However, the survival rates of exposed rats in the quercetin studies were similar to that of the controls.

The treatment-related increase in the severity of nephropathy was seen only in males. This greater sensitivity to quercetin toxicity is apparently due to a greater susceptibility of male rats to spontaneous nephropathy during aging and the exacerbation of this disease by chemical administration. Changes in glomerular permeability, resulting in proteinuria, progressive glomerular sclerosis, tubule damage, inflammation, and interstitial fibrosis, are associated with the process of aging in rats.

One factor that may contribute in part to the greater severity of tubule damage in male rats than in female rats is their production of more α_{2u}-globulin, a low molecular weight protein. Vandoren *et al.* (1983) showed that female rats excrete less than 1% of the amount of α_{2u}-globulin excreted by male rats. Further, in males, approximately 60% of the α_{2u}-globulin is reabsorbed by epithelial cells of the proximal convoluted tubule, primarily in the P_2 segment, where it is slowly or poorly hydrolyzed and accumulates in lysosomes (Charbonneau *et al.*, 1988). Short *et al.* (1987) showed that cells containing the α_{2u}-globulin undergo degeneration, necrosis, and a higher rate of cell turnover in the P_2 segment compared with other segments of the proximal convoluted tubule.

Histopathologically, the cell turnover is normally cellular regeneration, but under conditions not fully understood, hyperplasia results. Several authors suggest that this hyperplastic response of renal tubules in spontaneous nephropathy may be similar to those of tubules responding to chemical toxins. Konishi and Ward (1989) observed increased ^{3}H-thymidine labeling indices in the tubule epithelium with corresponding increased severity of nephropathy. Short *et al.* (1987) also showed increased cell necrosis and regeneration associated with an accumulation of α_{2u}-globulin induced by chemical administration.

In the initial evaluation of single sections from each left and right kidney, three renal tubule adenomas and one adenocarcinoma were seen in the high-dose male rats with a concomitant slight dose-related increase in the incidence of renal tubule hyperplasia. Although the incidence of renal neoplasms in the high-dose group was not significantly greater than in the controls by pairwise comparisons, the trend test was significant. Even though renal neoplasms are relatively uncommon in NTP untreated historical control male rats (8/499, mean 1.6%, range 0%-6%; Table A4a), the low number of neoplasms was difficult to interpret.

The NTP and Kurokawa *et al.* (1983) have found that multiple sectioning of the kidney may enable a more precise evaluation of the potential chemical-related induction of renal tubule neoplasms compared with observations from single-section sampling. The majority of renal neoplasms in these studies are microscopic (i.e., not observed by macroscopic examination at necropsy), thus, multiple sections might be expected to increase the number of neoplasms observed and allow for a more rigorous statistical evaluation. The residual halves of the formalin-fixed kidneys from all the rats were step sectioned to provide approximately eight additional tissue sections for microscopic examination. Renal tubule focal hyperplasia was observed in eight high-dose males (one of these animals had been identified in the initial evaluation), and renal tubule adenomas were observed in six high-dose males (one of these animals had been identified in the initial evaluation). Focal renal tubule hyperplasia was seen in two additional control males and a renal tubule adenoma was observed in one control male.

The renal tubule hyperplasia observed in these studies was distinguished from background regenerative hyperplasia, which commonly accompanies the degenerative tubule changes of age-related or chemical-induced nephropathy, on the basis of cellular atypia and prominent stratification of the epithelium. These cytological features suggest a loss of cell growth regulation and failure of cellular differentiation. This lesion is similar to those induced by potent renal carcinogens and appears to represent the early stages of renal tubule adenoma and adenocarcinoma development (Hard, 1986; Tsuda *et al.*, 1986). Although focal hyperplasia, adenoma, and adenocarcinoma constitute a morphological continuum, the rates of possible progression or regression of hyperplasia or adenoma are not known and likely vary with the inducing agent and the

mechanism of induction. It has been postulated that increases in cellular proliferation secondary to chemical-related cytotoxicity may create the appropriate environment for the development of neoplasia, perhaps by increasing the frequency of spontaneous mutations through clonal expansion of initiated cells or by other means (Farber, 1980; Pitot and Sirica, 1980; Stott *et al.*, 1981; Butterworth, 1989; Cohen and Ellwein, 1990). An increase in chemical-related accumulation of α_{2u}-globulin in the P_2 segment of the nephron has been associated with the development of renal neoplasms (Goldsworthy and Popp, 1987; Goldsworthy *et al.*, 1988). This syndrome, also known as hyaline droplet nephropathy or α_{2u}-globulin nephropathy, is best identified in 13-week studies; such studies were not conducted by the NTP with quercetin. However, the linear tubule mineralization within the papilla, which is commonly seen in the 2-year studies of chemicals producing this syndrome, was not seen in the quercetin studies.

Previous rodent toxicity and carcinogenicity studies of quercetin did not identify the kidney as a target organ (Saito *et al.*, 1980; Hirono *et al.*, 1981; Takanashi *et al.*, 1983; Ito *et al.*, 1989). However, in the NTP 2-year studies of quercetin, the renal tubule cell neoplasms observed in male rats were judged to show some evidence for carcinogenicity due to supportive evidence for this neoplastic response by an increase in renal tubule hyperplasia. Step-sectioned kidneys showed an increase in the incidence of kidney neoplasms, which supported the original findings of only a few neoplasms at this site. Since most of the neoplasms were adenomas, this effect was judged to be some evidence rather than clear evidence for carcinogenic activity.

In a series of NCI/NTP long-term rodent carcinogenicity studies of chemicals, treatment-related kidney neoplasms were found more frequently in male rats (23) than in female rats (8), male mice (3), or female mice (1) (Table 11). Based on this information, the kidneys of male rats appear to be more sensitive to chemical-induced formation than are the kidneys of female rats or mice of either sex. The reasons for the susceptibility of the male rat kidney to chemical toxicity or carcinogenicity may vary from chemical to chemical. There is no one particular chemical structure that is associated with the induction of kidney neoplasms in male rats and some of the chemicals causing kidney tumors demonstrate genetic toxicity in *in vitro* tests while others do not. An increase in chemical concentration in the kidney of male F344/N rats, an animal with a significant age-related background of kidney disease, may make this animal particularly susceptible to the induction of renal tubule cell neoplasms.

The two squamous cell carcinomas of the tongue observed in the high-dose female rats were not considered to be related to treatment. Squamous cell papillomas or carcinomas have been observed sporadically in NTP study animals in both treated and control groups, occurring with a historical mean incidence of 0.8% in untreated controls (4/500, range 0%-2%; Table B4b). Due to the occurrence of these oral cavity neoplasms, a complete histopathologic examination was performed on the tongue. There was no supportive evidence for hyperplasia or other neoplasms at this site. Chemicals which have been shown to cause oral cavity neoplasms, such as benzidine congeners or dyes, are generally characterized as potent genotoxic agents and cause neoplasms at a variety of other sites. In summary, the oral cavity neoplasms observed in the high-dose female rats were not considered to be related to chemical administration because of the low incidence, lack of supportive nonneoplastic lesions at this site, and lack of supportive evidence of neoplasms in related tissues of epidermal origin.

There was a dose-related decrease in mammary gland fibroadenomas in female rats. Previous studies showed that decreases in some naturally occurring benign neoplasms, especially neoplasms of the mammary gland and reproductive organs, are associated with decreased body weight relative to controls (Rao *et al.*, 1987). Some investigators have reported that quercetin may have some undefined antitumor activity (Hirose *et al.*, 1983; Kato *et al.*, 1983; Nishino *et al.*, 1984b).

While most rat studies of quercetin have shown no evidence of carcinogenicity, Pamukcu *et al.* (1980) reported that 0.1% quercetin administered in the diet to Norwegian rats for 58 weeks caused an 80% increase in the incidence of intestinal neoplasms and a 20% increase in the incidence of urinary bladder neoplasms. The mechanism for this increase could not be explained based on the information given but

may be due to different experimental conditions, study animals, or chemical preparations. The NTP quercetin studies showed no evidence of chemical-induced neoplasms of the urinary bladder or intestine.

Quercetin has a marked ability to cause mutations in various genetic toxicity tests including the *Salmonella typhimurium* assay systems. Due to these results, the chemical might be expected to cause neoplasms at a variety of sites in male rats besides the kidney. The mutagenic flavonoids generally contain a free hydroxy group at the 3 position. Brown and Griffiths (1983) have shown that rats are capable of metabolizing quercetin and other 3-hydroxyl flavonoids to the 3′-*o*-methyl ethers. The 3′-*o*-methyl ether of quercetin is considerably less mutagenic in the *Salmonella* assay than the parent compound (MacGregor and Jurd, 1978). This ability of rats to form 3′-*o*-methyl ethers may be important in protecting against the carcinogenic action of quercetin at various sites in the body.

CONCLUSIONS

Under the conditions of these 2-year feed studies there was *some evidence of carcinogenic activity** of quercetin in male F344/N rats based on an increased incidence of renal tubule cell adenomas. There was *no evidence of carcinogenic activity* of quercetin in female F344/N rats receiving 1,000, 10,000 or 40,000 ppm. Incidence of renal tubule hyperplasia and the severity of nephropathy were increased in exposed male rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appear on page 10.

TABLE 11
Evidence of Kidney Neoplasms and *Salmonella* Mutagenicity in Rats and Mice for Selected Chemicals Tested by the National Toxicology Program

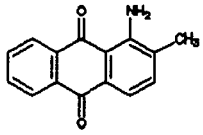
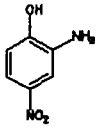
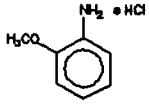
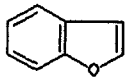
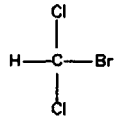
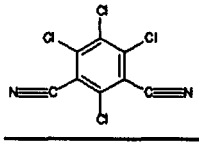
Chemical Name and Structure	Technical Report Number	Kidney Neoplasms[a]				NTP *Salmonella* Results
		♂ Rats	♀ Rats	♂ Mice	♀ Mice	
1-Amino-2-Methylanthraquinone 	111	+				+
2-Amino-4-Nitrophenol 	339	+				+
o-Anisidine 	89	+[b]				+
Benzofuran 	370		+			-
Bromodichloromethane 	321	+	+	+		-
Chlorinated Paraffins $CH_3(CH_2CHClCH_2CHClCH_2)_2CH_2Cl$ (approximation)	308	+				-
Chlorothalonil 	41	+	+			-

TABLE 11
Evidence of Kidney Neoplasms and *Salmonella* Mutagenicity in Rats and Mice for Selected Chemicals Tested by the National Toxicology Program (continued)

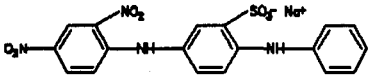
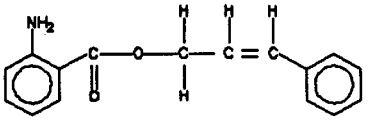
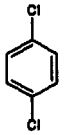
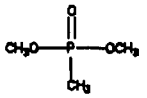
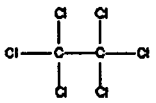
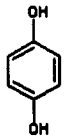
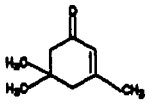
Chemical Name and Structure	Technical Report Number	Kidney Neoplasms				NTP *Salmonella* Results
		♂ Rats	♀ Rats	♂ Mice	♀ Mice	
C.I. Acid Orange 3 	335		+[b]			+
Cinnamyl Anthranilate 	196	+				-
1,4-Dichlorobenzene 	319	+				-
Dimethyl Methylphosphonate 	323	+[c]				-
Hexachloroethane 	361	+		NT	NT	-
Hydroquinone 	366	+				-
Isophorone 	291	+				-

TABLE 11
Evidence of Kidney Neoplasms and *Salmonella* Mutagenicity in Rats and Mice for Selected Chemicals Tested by the National Toxicology Program (continued)

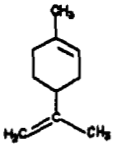
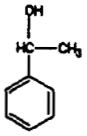
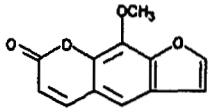
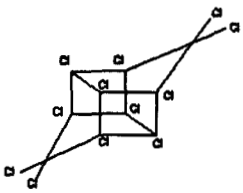
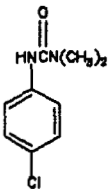
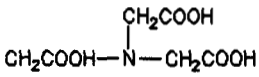
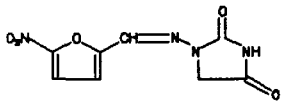
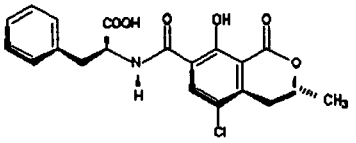
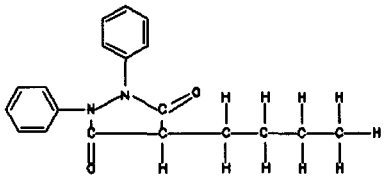
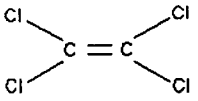
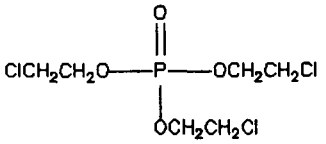
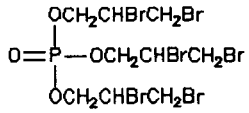
Chemical Name and Structure	Technical Report Number	Kidney Neoplasms				NTP *Salmonella* Results
		♂ Rats	♀ Rats	♂ Mice	♀ Mice	
d-Limonene 	347	+				-
α-Methylbenzyl Alcohol 	369	+				-
8-Methyoxypsoralen 	359	+		NT	NT	+
Mirex 	313	+[b]				-
Monuron 	266	+				-
Nitrilotriacetic Acid 	6	+		+	+	-

TABLE 11
Evidence of Kidney Neoplasms and *Salmonella* Mutagenicity in Rats and Mice for Selected Chemicals Tested by the National Toxicology Program (continued)

Chemical Name and Structure	Technical Report Number	Kidney Neoplasms ♂ Rats	Kidney Neoplasms ♀ Rats	Kidney Neoplasms ♂ Mice	Kidney Neoplasms ♀ Mice	NTP *Salmonella* Results
Nitrofurantoin 	341	+				+
Ochratoxin 	358	+	+	NT	NT	-
Phenylbutazone 	367		+			-
Tetrachloroethylene 	311	+				-
Tris(2-Chloroethyl) Phosphate 	391	+[b]	+			-
Tris(2,3-Dibromopropyl) Phosphate 	76	+	+	+		+

[a] Primarily renal tubule cell neoplasms observed unless otherwise noted; + = present, NT = species not tested.
[b] Transitional cell neoplasms
[c] Transitional cell neoplasms and renal tubule cell neoplasms

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

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
6-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	3	7	3	6
Moribund	21	15	22	21
Survivors				
Moribund			1	1
Terminal sacrifice	25	27	22	19
Died last week of study	1	1	2	3
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(11)	(13)	(46)
Intestine large, colon	(49)	(12)	(11)	(47)
Intestine small, duodenum	(48)	(47)	(48)	(46)
Intestine small, ileum	(47)	(47)	(48)	(45)
Adenoma				1 (2%)
Intestine small, jejunum	(48)	(44)	(42)	(44)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma			1 (2%)	
Hemangiosarcoma			1 (2%)	
Hepatocellular carcinoma		1 (2%)		1 (2%)
Hepatocellular adenoma	3 (6%)	1 (2%)		
Hepatocellular adenoma, multiple			1 (2%)	
Neoplastic nodule		1 (2%)	2 (4%)	
Neoplastic nodule, multiple		1 (2%)	1 (2%)	
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Mesentery	(7)	(6)	(5)	(5)
Sarcoma, poorly differentiated				1 (20%)
Pancreas	(50)	(50)	(50)	(47)
Adenoma		2 (4%)	2 (4%)	
Salivary glands	(16)	(14)	(12)	(10)
Stomach	(50)	(50)	(50)	(49)
Stomach, forestomach	(49)	(49)	(49)	(46)
Stomach, glandular	(50)	(50)	(49)	(48)
Tongue	(45)	(48)	(47)	(44)
Papilloma squamous				1 (2%)
Cardiovascular System				
Heart	(50)	(18)	(18)	(50)
Schwannoma benign	1 (2%)			
Schwannoma malignant			1 (6%)	

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Endocrine System				
Adrenal gland, cortex	(50)	(18)	(21)	(49)
Adrenal gland, medulla	(50)	(18)	(21)	(49)
Pheochromocytoma malignant	1 (2%)		1 (5%)	2 (4%)
Pheochromocytoma benign	8 (16%)	4 (22%)	9 (43%)	9 (18%)
Pheochromocytoma benign, multiple	4 (8%)		1 (5%)	2 (4%)
Islets, pancreatic	(47)	(15)	(13)	(41)
Adenoma		2 (13%)		3 (7%)
Carcinoma			1 (8%)	
Parathyroid gland	(43)	(45)	(43)	(43)
Adenoma	1 (2%)			
Pituitary gland	(46)	(49)	(50)	(48)
Pars distalis, adenoma	14 (30%)	14 (29%)	18 (36%)	11 (23%)
Pars distalis, adenoma, multiple		3 (6%)	1 (2%)	1 (2%)
Pars distalis, pars intermedia, pars nervosa, leukemia mononuclear			1 (2%)	
Thyroid gland	(50)	(17)	(22)	(49)
C-cell, adenoma	4 (8%)	1 (6%)	4 (18%)	1 (2%)
C-cell, carcinoma	1 (2%)	2 (12%)	1 (5%)	
Follicular cell, adenocarcinoma				1 (2%)
Follicular cell, adenoma	1 (2%)			1 (2%)
General Body System				
Tissue NOS		(1)		
Basosquamous tumor benign		1 (100%)		
Genital System				
Epididymis	(50)	(13)	(13)	(49)
Preputial gland	(13)	(22)	(19)	(15)
Adenoma	2 (15%)	5 (23%)	3 (16%)	1 (7%)
Carcinoma	1 (8%)		1 (5%)	3 (20%)
Squamous cell carcinoma		1 (5%)		
Prostate	(49)	(14)	(12)	(48)
Seminal vesicle	(50)	(22)	(23)	(49)
Testes	(50)	(46)	(48)	(50)
Interstitial cell, adenoma	44 (88%)	43 (93%)	45 (94%)	45 (90%)
Hematopoietic System				
Bone marrow	(11)	(12)	(12)	(9)
Lymph node	(49)	(29)	(26)	(50)
Carcinoma, metastatic, thyroid gland			1 (4%)	
Mediastinal, sarcoma, metastatic, uncertain primary site	1 (2%)			
Lymph node, mandibular	(46)	(18)	(15)	(47)
Carcinoma, metastatic, thyroid gland		1 (6%)		
Lymph node, mesenteric	(22)	(14)	(17)	(19)
Spleen	(50)	(25)	(38)	(50)
Hemangioma			1 (3%)	
Hemangiosarcoma			1 (3%)	
Sarcoma			1 (3%)	
Thymus	(14)	(11)	(13)	(5)
Mediastinum, basosquamous tumor NOS	1 (7%)			

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Integumentary System				
Mammary gland	(13)	(10)	(14)	(9)
Fibroadenoma	5 (38%)	1 (10%)	5 (36%)	3 (33%)
Skin	(20)	(18)	(19)	(18)
Basal cell carcinoma	1 (5%)			
Basosquamous tumor benign			1 (5%)	
Keratoacanthoma			1 (5%)	
Papilloma squamous	2 (10%)		3 (16%)	1 (6%)
Subcutaneous tissue, fibroma	2 (10%)	1 (6%)	1 (5%)	3 (17%)
Subcutaneous tissue, fibrosarcoma	1 (5%)			
Subcutaneous tissue, lipoma	1 (5%)			
Subcutaneous tissue, myxoma			1 (5%)	
Subcutaneous tissue, sarcoma		1 (6%)	1 (5%)	1 (6%)
Musculoskeletal System				
Bone	(10)	(12)	(15)	(23)
Osteoma	1 (10%)			
Skeletal muscle	(1)	(2)		
Sarcoma	1 (100%)			
Nervous System				
Brain	(50)	(15)	(12)	(50)
Meningioma benign		1 (7%)		
Choroid plexus, sarcoma, metastatic, uncertain primary site	1 (2%)			
Respiratory System				
Lung	(50)	(28)	(31)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		1 (3%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple			1 (3%)	
Carcinoma, metastatic, thyroid gland	1 (2%)	1 (4%)	1 (3%)	
Cholangiocarcinoma, metastatic, liver			1 (3%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal gland	1 (2%)			1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Squamous cell carcinoma				1 (2%)
Mediastinum, schwannoma malignant, metastatic, heart			1 (3%)	
Nose	(44)	(48)	(49)	(49)
Papilloma squamous				1 (2%)
Glands, carcinoma		1 (2%)		
Trachea	(50)	(12)	(12)	(50)
Special Senses System				
Eye	(2)	(9)	(6)	(3)

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Proximal convoluted renal tubule, adenoma				1 (2%)
Renal tubule, adenocarcinoma				1 (2%)
Renal tubule, adenoma				2 (4%)
Urinary bladder	(50)	(49)	(49)	(48)
Systemic Lesions				
Multiple organs[a]	(50)	(50)	(50)	(50)
Leukemia mononuclear	16 (32%)	18 (36%)	22 (44%)	13 (26%)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant lymphocytic	3 (6%)			
Lymphoma malignant mixed		1 (2%)	1 (2%)	
Lymphoma malignant undifferentiated cell		1 (2%)		
Mesothelioma benign		1 (2%)	1 (2%)	
Mesothelioma malignant	4 (8%)	3 (6%)	2 (4%)	1 (2%)
Tumor Summary				
Total animals with primary neoplasms[b]	50	50	50	48
Total primary neoplasms	125	111	139	113
Total animals with benign neoplasms	49	48	50	48
Total benign neoplasms	95	82	102	88
Total animals with malignant neoplasms	27	27	32	21
Total malignant neoplasms	29	29	37	25
Total animals with metastatic neoplasms	4	1	3	1
Total metastatic neoplasms	8	2	4	1
Total animals with malignant neoplasms of uncertain primary site	1			
Total animals with neoplasms uncertain-benign or malignant	1			
Total uncertain neoplasms	1			

[a] Number of animals with any tissue examined microscopically
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 0 ppm

Number of Days on Study	2 2 6	4 5 8	5 1 9	5 6 2	5 7 3	5 7 5	5 9 0	6 2 0	6 3 6	6 3 6	6 4 0	6 5 4	6 5 4	6 5 6	6 6 4	6 7 4	6 7 4	6 8 9	6 8 2	7 8 9	7 0 4	7 1 7	7 1 7	7 2 0	7 2 1	7 2 4
Carcass ID Number	0 0 1 4	0 0 3 5	0 1 3 5	0 0 2 3	0 0 1 5	0 1 2 4	0 0 6 4	0 1 4 4	0 0 1 2	0 1 2 3	0 1 1 4	0 0 9 5	0 1 3 2	0 1 8 2	0 1 0 4	0 1 0 3	0 1 3 4	0 0 3 3	0 0 5 3	0 1 1 2	0 0 3 3	0 1 6 3	0 1 1 1	0 1 3 4	0 0 5 2	0 0 4 3
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	M
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																										
Sarcoma, metastatic, uncertain primary site																										
Mesentery					+				+	+						+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+		+	+	+	+						+			+						M
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue		+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Cardiovascular System																										
Blood vessel																										+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																					X					
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																						X				
Pheochromocytoma benign						X														X	X			X		X
Pheochromocytoma benign, multiple																							X			
Islets, pancreatic	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+
Adenoma																										
Pituitary gland	A	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X									X				X	X		X						X	

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 4 4	0 0 5 1	0 0 7 3	0 0 9 3	0 0 9 4	0 1 4 3	0 0 5 5	0 0 6 1	0 0 6 2	0 0 7 2	0 1 0 2	0 0 3 2	0 0 1 3	0 0 2 1	0 0 3 1	0 0 4 1	0 0 4 2	0 0 8 1	0 0 9 1	0 0 9 2	0 1 1 2	0 1 2 1	0 1 3 2	0 1 3 1	0 1 3 2	0 1 3 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X								X	X								3
Sarcoma, metastatic, uncertain primary site					X																					1
Mesentery									+						+									+		7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands												+	M	+	+	+										16
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign						X						X												X		8
Pheochromocytoma benign, multiple							X							X					X							4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	47
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Adenoma																X										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Pars distalis, adenoma		X			X	X	X		X		X								X		X					14

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	2 2 6	4 5 8	5 1 9	5 6 2	5 7 3	5 7 5	5 9 0	6 2 0	6 3 6	6 3 6	6 4 0	6 5 4	6 5 4	6 5 6	6 6 4	6 7 4	6 7 9	6 8 2	6 8 9	7 0 4	7 1 7	7 1 7	7 2 0	7 2 1	7 2 4
Carcass ID Number	0 0 1 4	0 0 3 5	0 1 3 5	0 0 2 3	0 1 1 5	0 2 2 4	0 6 4 4	0 4 1 2	0 1 2 3	1 1 1 4	0 1 9 5	1 0 1 3	0 1 8 2	1 0 0 4	1 1 0 3	0 3 4 3	0 5 3 2	1 1 3 3	0 3 6 3	0 4 1 1	1 1 3 1	1 0 5 4	0 1 4 2	0 0 4 3
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X				X					X			
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Coagulating gland		+															+								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	+	+	+	+	+	+	+	+	+	+			+	+										
Adenoma				X										X											
Carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma					X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, sarcoma, metastatic, uncertain primary site																									
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+		+	+	+	+	+	+		+	+	+	+		+	M	+	M	+	+	+		M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+		+		M	+	+	+		+	+			+			+					M
Mediastinum, basosquamous tumor NOS																									
Integumentary System																									
Mammary gland	M	M	+	+	+	M	+	+	M	+	+	+							+						
Fibroadenoma							X												X						
Skin	+	+	+	+	+	+	+	+	+	+	+						+					+			
Basal cell carcinoma																									
Papilloma squamous																									
Subcutaneous tissue, fibroma																						X			
Subcutaneous tissue, fibrosarcoma		X																							
Subcutaneous tissue, lipoma	X																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 0 4	0 0 5 1	0 0 7 3	0 0 9 3	0 0 9 4	0 1 4 3	0 0 5 5	0 0 6 1	0 0 6 2	0 0 7 2	0 1 0 2	0 0 3 2	0 0 1 3	0 0 2 1	0 0 3 1	0 0 4 1	0 0 4 2	0 0 8 1	0 0 9 1	0 0 9 2	0 1 2 1	0 1 2 2	0 1 3 1	0 1 3 2	0 1 3 3	**Total Tissues/ Tumors**
Endocrine System (continued)																											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
C-cell, adenoma																					X						4
C-cell, carcinoma								X																			1
Follicular cell, adenoma																								X			1
General Body System																											
None																											
Genital System																											
Coagulating gland																											2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland											+																13
Adenoma																											2
Carcinoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		44
Hematopoietic System																											
Bone marrow																											11
Lymph node	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Mediastinal, sarcoma, metastatic, uncertain primary site					X																						1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		46
Lymph node, mesenteric												M	+		+		M	+		+							22
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus										+		M	M			M	+										14
Mediastinum, basosquamous tumor NOS										X																	1
Integumentary System																											
Mammary gland							+		+								+							+			13
Fibroadenoma							X										X							X			5
Skin						+	+		+		+						+			+					+		20
Basal cell carcinoma																				X							1
Papilloma squamous									X																X		2
Subcutaneous tissue, fibroma											X																2
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, lipoma																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	2 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 2 5 1 6 7 7 9 2 3 3 4 5 5 5 6 7 7 8 8 0 1 1 2 2 2 6 8 9 2 3 5 0 0 6 6 0 4 4 6 4 4 9 2 9 4 7 7 0 1 4
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 1 0 1 0 1 1 0 1 0 1 1 0 0 1 0 0 1 1 0 0 1 3 3 2 1 2 6 4 1 2 1 9 1 8 0 0 3 5 1 3 6 1 3 5 4 4 5 5 3 5 4 4 4 2 3 4 5 3 2 4 3 4 3 2 3 3 1 4 2 3
Musculoskeletal System	
Bone	+ + + + + + + + + + +
Osteoma	X
Skeletal muscle	
Sarcoma	
Nervous System	
Brain	+ +
Choroid plexus, sarcoma, metastatic, uncertain primary site	
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	
Carcinoma, metastatic, thyroid gland	
Osteosarcoma, metastatic, bone	X
Pheochromocytoma malignant, metastatic, adrenal gland	X
Sarcoma, metastatic, uncertain primary site	
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	I + + I
Harderian gland	+
Urinary System	
Kidney	+ +
Sarcoma, metastatic, uncertain primary site	
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X X X X X X
Lymphoma malignant lymphocytic	X X X
Mesothelioma malignant	X X X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 4 4	0 0 5 1	0 0 7 3	0 0 9 3	0 0 9 4	0 1 4 3	0 0 5 5	0 0 6 1	0 0 6 2	0 0 7 2	0 1 0 2	0 0 3 2	0 0 1 3	0 0 2 1	0 0 3 1	0 0 4 1	0 0 4 1	0 0 4 2	0 0 8 1	0 0 9 1	0 0 9 2	0 1 1 2	0 1 2 1	0 1 3 2	0 1 3 1	0 1 3 2	0 1 3 3	**Total Tissues/ Tumors**
Musculoskeletal System																											
Bone																											10
Osteoma																											1
Skeletal muscle																+											1
Sarcoma																X											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Choroid plexus, sarcoma, metastatic, uncertain primary site					X																						1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X													X							2
Carcinoma, metastatic, thyroid gland								X																			1
Osteosarcoma, metastatic, bone																											1
Pheochromocytoma malignant, metastatic, adrenal gland																											1
Sarcoma, metastatic, uncertain primary site					X																						1
Nose	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	+		+	+	+	+		44
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye													M														2
Harderian gland																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site					X																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X										X	X						X				X					16
Lymphoma malignant lymphocytic																											3
Mesothelioma malignant																X											4

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

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

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

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 6 3	0 2 1 3	0 2 1 4	0 2 6 4	0 2 7 2	0 2 2 1	0 1 6 2	0 1 9 1	0 2 0 4	0 2 1 1	0 2 1 2	0 2 5 2	0 2 7 1	0 2 8 2	0 2 8 3	0 1 6 1	0 1 7 1	0 2 0 1	0 2 0 3	0 2 3 1	0 2 4 1	0 2 4 2	0 2 5 1	0 2 6 3	0 2 8 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										12
Intestine large										+																12
Intestine large, cecum										+																11
Intestine large, colon										+																12
Intestine large, rectum										+																11
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																				X						1
Hepatocellular adenoma																		X								1
Neoplastic nodule						X																				1
Neoplastic nodule, multiple																	X									1
Mesentery								+										+								6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X			X																		2
Salivary glands																										14
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart						+		+	+	+										+						18
Endocrine System																										
Adrenal gland					+	+						+														18
Adrenal gland, cortex					+	+						+														18
Adrenal gland, medulla					+	+						+														18
Pheochromocytoma benign					X							X														4
Islets, pancreatic																		+					+			15
Adenoma																		X								2
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	49
Pars distalis, adenoma	X					X					X						X	X			X	X				14
Pars distalis, adenoma, multiple									X																	3
Thyroid gland				+		+								+					+							17
C-cell, adenoma																			X							1
C-cell, carcinoma				X																						2

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

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

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

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 6 3	0 2 1 3	0 2 1 4	0 2 6 4	0 2 7 2	0 2 2 1	0 1 6 2	0 1 9 1	0 2 0 4	0 2 1 1	0 2 1 2	0 2 5 2	0 2 7 1	0 2 8 2	0 2 8 3	0 2 6 1	0 1 7 1	0 2 0 1	0 2 0 3	0 2 3 1	0 2 4 1	0 2 4 2	0 2 5 1	0 2 6 3	0 2 8 1	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																								+	1
Basosquamous tumor benign																								X	1
Genital System																										
Coagulating gland																									1
Epididymis								+																	13
Preputial gland			+					+	+				+					+		+				22
Adenoma								X																	5
Squamous cell carcinoma																									1
Prostate																		+							14
Seminal vesicle	+	+							+											+				+	22
Testes	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	46
Interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	43
Hematopoietic System																										
Bone marrow																									12
Lymph node		+				+		+	+					+				+	+						29
Lymph node, mandibular		+						+																	18
Carcinoma, metastatic, thyroid gland																									1
Lymph node, mesenteric																									14
Spleen	+			+									+					+							25
Thymus																									11
Integumentary System																										
Mammary gland						+												+							10
Fibroadenoma						X																			1
Skin					+			+											+		+				18
Subcutaneous tissue, fibroma																									1
Subcutaneous tissue, sarcoma																									1
Musculoskeletal System																										
Bone																									12
Skeletal muscle																									2
Nervous System																										
Brain																		+	+						15
Meningioma benign																			X						1

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

Number of Days on Study	4 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 5 0 4 5 6 7 8 9 1 1 2 4 5 7 7 8 9 0 1 2 2 2 2 2 2 8 9 6 6 2 2 4 9 8 8 0 3 4 1 8 5 5 4 6 0 1 3 4 4 7
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2 2 2 1 1 2 2 1 1 1 2 1 1 2 2 1 1 2 2 2 2 2 2 2 1 2 3 2 8 9 5 4 8 8 9 2 7 6 7 7 7 7 2 2 4 3 6 3 1 6 5 5 4 4 3 3 4 4 2 1 2 3 4 4 4 3 3 2 2 4 3 1 2 5 5 1
Respiratory System	
Lung	+ +
Carcinoma, metastatic, thyroid gland	X
Nose	+ +
Glands, carcinoma	X
Trachea	+ + + + + + + + + + + +
Special Senses System	
Eye	+ + + + I +
Urinary System	
Kidney	+ +
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X X X X X X X X X
Lymphoma malignant mixed	X
Lymphoma malignant undifferentiated cell type	X
Mesothelioma benign	
Mesothelioma malignant	X X

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

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 6 3	0 2 1 3	0 2 1 4	0 2 6 4	0 2 7 2	0 2 2 1	0 1 6 2	0 1 9 1	0 2 0 4	0 2 1 1	0 2 1 2	0 2 1 2	0 2 5 2	0 2 7 1	0 2 8 2	0 2 8 3	0 1 6 1	0 1 7 1	0 2 0 1	0 2 0 3	0 2 3 1	0 2 4 1	0 2 4 2	0 2 5 1	0 2 6 3	0 2 8 1	**Total Tissues/ Tumors**
Respiratory System																										
Lung			+			+	+	+	+						+									+	+	28
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	48
Glands, carcinoma																										1
Trachea																										12
Special Senses System																										
Eye			+											+								+				9
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							18
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1
Mesothelioma benign														X												1
Mesothelioma malignant								X																		3

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

Number of Days on Study	4 2 0	4 2 7	5 4 9	5 5 5	5 5 5	5 7 4	5 9 2	6 0 8	6 1 7	6 2 4	6 4 3	6 4 3	6 7 3	6 7 3	6 7 4	6 7 4	6 8 0	6 8 4	6 8 7	6 9 0	6 9 5	6 9 9	7 0 3	7 0 4	7 0 4
Carcass ID Number	0 4 0 5	0 3 9 5	0 4 2 3	0 2 9 3	0 3 0 1	0 3 7 5	0 4 2 2	0 3 6 5	0 4 1 4	0 3 8 4	0 3 6 4	0 4 1 5	0 3 7 2	0 4 2 1	0 3 2 4	0 3 3 4	0 3 1 3	0 3 9 3	0 2 9 2	0 3 6 3	0 4 1 2	0 3 8 3	0 3 7 4	0 3 6 1	0 3 6 2
Alimentary System																									
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+													
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+						+							
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+						+							
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+													
Intestine large, rectum	+	+	M	+	+	+	+	A	+	+	+	+													
Intestine small	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																								X	
Hemangiosarcoma																									
Hepatocellular adenoma, multiple																									
Neoplastic nodule																									
Neoplastic nodule, multiple																									
Mesentery	+						+								+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+													
Schwannoma malignant																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+								+	+				
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+								+	+				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+								+	+				
Pheochromocytoma malignant																									
Pheochromocytoma benign				X		X					X	X									X				
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+										+			
Carcinoma																						X			
Parathyroid gland	M	I	+	M	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X				X		X	X			X	X	X		X			X	
Pars distalis, adenoma, multiple																									

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

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 3 2 2	0 3 2 3	0 3 4 4	0 3 5 3	0 4 1 1	0 2 9 1	0 3 1 2	0 3 5 2	0 3 9 2	0 4 0 4	0 3 1 1	0 3 3 2	0 3 3 5	0 3 4 3	0 4 0 3	0 3 2 1	0 3 4 2	0 3 5 1	0 3 7 1	0 3 7 3	0 3 8 1	0 3 8 2	0 3 9 1	0 4 0 1	0 4 0 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										11
Intestine large														+												13
Intestine large, cecum														+												13
Intestine large, colon																										11
Intestine large, rectum																										10
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+		42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hemangiosarcoma																X										1
Hepatocellular adenoma, multiple																							X			1
Neoplastic nodule															X									X		2
Neoplastic nodule, multiple																						X				1
Mesentery								+						+												5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							2
Salivary glands																										12
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Cardiovascular System																										
Blood vessel																										1
Heart													+	+		+			+			+		+		18
Schwannoma malignant																X										1
Endocrine System																										
Adrenal gland			+					+						+		+	+		+			+				21
Adrenal gland, cortex			+					+						+		+	+		+			+				21
Adrenal gland, medulla			+					+						+		+	+		+			+				21
Pheochromocytoma malignant								X																		1
Pheochromocytoma benign			X													X	X		X							9
Pheochromocytoma benign, multiple														X												1
Islets, pancreatic																										13
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X	X			X							X			X	X		X			X	18
Pars distalis, adenoma, multiple																		X								1

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

Number of Days on Study	4 2 0	4 2 7	5 4 9	5 5 5	5 5 5	5 7 4	5 9 2	6 0 8	6 1 7	6 2 4	6 4 3	6 4 3	6 7 3	6 7 3	6 7 4	6 7 4	6 8 0	6 8 4	6 8 7	6 9 0	6 9 5	6 9 9	7 0 3	7 0 4	7 0 4
Carcass ID Number	0 4 0 5	0 3 9 5	0 4 2 3	0 2 9 3	0 3 0 1	0 3 7 5	0 4 2 2	0 3 6 5	0 4 1 4	0 3 8 4	0 3 6 4	0 4 1 5	0 3 7 2	0 4 2 1	0 3 2 4	0 3 3 4	0 3 1 3	0 3 9 3	0 2 9 2	0 3 6 3	0 4 1 2	0 3 8 3	0 3 7 4	0 3 6 1	0 3 6 2
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+		+			+	+	+	+					+
C-cell, adenoma										X								X							X
C-cell, carcinoma																		X							
General Body System																									
None																									
Genital System																									
Coagulating gland		+												+											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+			+										
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+						+							+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+													
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+				+		+				+			
Testes	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X		X	X	X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+	+					+	
Carcinoma, metastatic, thyroid gland																		X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+													
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+				+			+					+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+	+		+
Hemangioma															X										
Hemangiosarcoma																									
Sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+													
Integumentary System																									
Mammary gland	M	+	M	+	+	+	M	+	+	+	+	+		+								+			
Fibroadenoma														X								X			
Skin	+	M	M	+	+	+	+	+	+	+	+	+			+		+							+	
Basosquamous tumor benign																									
Keratoacanthoma																								X	
Papilloma squamous																									
Subcutaneous tissue, fibroma				X																					
Subcutaneous tissue, myxoma																									
Subcutaneous tissue, sarcoma																	X								

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

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 3 2 2	0 3 2 3	0 3 4 4	0 3 5 3	0 4 1 1	0 2 9 1	0 3 1 2	0 3 5 2	0 3 9 2	0 4 0 4	0 3 1 1	0 3 3 2	0 3 3 5	0 3 4 3	0 4 0 3	0 3 2 1	0 3 4 2	0 3 5 1	0 3 7 1	0 3 7 3	0 3 8 1	0 3 8 2	0 3 9 1	0 4 0 1	0 4 0 2	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Thyroid gland			+									+												+	+	22
C-cell, adenoma												X														4
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Coagulating gland																										2
Epididymis																										13
Preputial gland			+		+						+	+											+			19
Adenoma			X		X																		X			3
Carcinoma											X															1
Prostate																										12
Seminal vesicle	+			+		+	+								+	+							+		+	23
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		45
Hematopoietic System																										
Bone marrow																										12
Lymph node					+	+						+	+	+		+		+		+		+				26
Carcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular					+									+				+								15
Lymph node, mesenteric						+								+												17
Spleen	+	+	+	+		+	+				+	+		+		+	+	+	+	+			+	+		38
Hemangioma																										1
Hemangiosarcoma																	X									1
Sarcoma							X																			1
Thymus														+												13
Integumentary System																										
Mammary gland																					+	+	+			14
Fibroadenoma																					X	X	X			5
Skin			+								+			+				+					+		+	19
Basosquamous tumor benign																							X			1
Keratoacanthoma																										1
Papilloma squamous			X										X												X	3
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, myxoma											X															1
Subcutaneous tissue, sarcoma																										1

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

Number of Days on Study	4 2 0	4 2 0	5 4 9	5 5 5	5 5 5	5 7 4	5 9 2	6 0 8	6 1 7	6 2 4	6 4 3	6 4 3	6 7 3	6 7 3	6 7 4	6 7 4	6 8 0	6 8 4	6 8 7	6 9 0	6 9 5	6 9 9	7 0 3	7 0 4	7 0 4
Carcass ID Number	0 4 0 5	0 3 9 5	0 4 2 3	0 2 9 3	0 3 0 1	0 3 7 5	0 4 2 2	0 3 6 5	0 4 1 4	0 3 8 4	0 3 6 4	0 4 1 5	0 3 7 2	0 4 2 1	0 3 2 4	0 3 3 4	0 1 9 3	0 3 9 3	0 3 9 2	0 2 6 3	0 3 6 2	0 4 1 2	0 3 8 3	0 3 7 4	0 3 6 1	0 3 6 2
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+		+							+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+													
Peripheral nerve													+												
Spinal cord													+								+				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		+	+		+	+	+	+	+
Alveolar/bronchiolar adenoma		X																							
Alveolar/bronchiolar carcinoma, multiple		X																							
Carcinoma, metastatic, thyroid gland																		X							
Cholangiocarcinoma, metastatic, liver																								X	
Mediastinum, schwannoma malignant, metastatic, heart																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+													
Special Senses System																									
Ear													+							+					
Eye			+	+										I				+	+		I				
Harderian gland			+																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X				X	X		X		X	X	X				X			X		X
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed							X																		
Mesothelioma benign							X																		
Mesothelioma malignant	X														X										

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

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 3 2 2	0 3 2 3	0 3 4 4	0 3 5 3	0 4 1 1	0 2 9 1	0 3 1 2	0 3 5 2	0 3 9 2	0 4 0 4	0 3 1 1	0 3 3 2	0 3 3 5	0 3 4 3	0 4 0 3	0 3 2 1	0 3 4 2	0 3 5 1	0 3 7 1	0 3 7 3	0 3 8 1	0 3 8 2	0 3 9 1	0 4 0 1	0 4 0 2	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone									M		+			M												15
Nervous System																										
Brain																										12
Peripheral nerve																										1
Spinal cord																										2
Respiratory System																										
Lung					+	+			+		+			+			+				+	+	+			31
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma, multiple																										1
Carcinoma, metastatic, thyroid gland																										1
Cholangiocarcinoma, metastatic, liver																										1
Mediastinum, schwannoma malignant, metastatic, heart																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea																										12
Special Senses System																										
Ear																										2
Eye							I				+			I				I					+			6
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X			X			X		X		X	X		X			X			X	X			22
Lymphoma malignant histiocytic										X																1
Lymphoma malignant mixed																										1
Mesothelioma benign																										1
Mesothelioma malignant																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 5 1 1	0 5 1 2	0 4 8 3	0 5 3 3	0 5 4 1	0 5 4 5	0 4 3 1	0 4 4 1	0 4 4 2	0 4 5 3	0 5 5 2	0 5 1 2	0 4 6 1	0 4 6 2	0 4 6 3	0 4 8 1	0 5 3 1	0 5 5 1	0 5 5 2	0 5 6 1	0 4 4 2	0 4 5 1	0 4 6 4	0 4 8 2	0 5 5 3	0 5 5 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma											X															1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X																	1
Mesentery	+			+										+												5
Sarcoma, poorly differentiated																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands												+	M													10
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Papilloma squamous																										1
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant		X																								2
Pheochromocytoma benign			X	X														X			X	X				9
Pheochromocytoma benign, multiple														X												2
Islets, pancreatic	+	+	+	+	+	+	+		+	+	+	+	+	+	M	+	+		+	+		+	+	+		+	41
Adenoma																X										3
Parathyroid gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X	X							X				X		X											11
Pars distalis, adenoma, multiple																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	3 1 5	3 2 6	4 2 2	5 5 5	5 7 4	5 8 1	6 1 7	6 2 6	6 2 2	6 6 7	6 7 3	6 7 4	6 7 6	6 7 6	6 8 6	6 9 0	6 9 2	6 9 3	6 9 4	6 9 7	6 9 8	7 0 0	7 0 4	7 1 3	7 1 5
Carcass ID Number	0 4 3 2	0 4 7 4	0 5 3 2	0 5 2 4	0 5 3 5	0 5 0 2	0 4 9 2	0 4 7 2	0 5 3 4	0 4 9 1	0 4 4 3	0 5 2 2	0 4 8 5	0 5 2 1	0 4 5 4	0 4 3 4	0 5 6 4	0 5 1 3	0 5 0 1	0 4 8 4	0 5 4 5	0 4 3 3	0 4 7 1	0 5 4 4	0 5 4 3
Endocrine System (continued)																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X											
Follicular cell, adenocarcinoma														X										
Follicular cell, adenoma								X																
General Body System																								
None																								
Genital System																								
Epididymis		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+		+	+	+			+				+	+		+						
Adenoma																								
Carcinoma								X										X						
Prostate	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma				X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+		+														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+		+			+	+	+		+		+		+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	M	M	+	+	+	+			+														
Integumentary System																								
Mammary gland	M	M	+	+		+	+	+																
Fibroadenoma																								
Skin	+	+	+	+	+	+	+	+			+	+		+										
Papilloma squamous														X										
Subcutaneous tissue, fibroma					X						X													
Subcutaneous tissue, sarcoma				X																				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+				+	+		+		+			+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 5 1 1	0 5 4 2	0 4 8 3	0 5 3 3	0 5 4 1	0 5 5 5	0 4 3 1	0 4 4 1	0 4 5 2	0 4 5 3	0 5 1 2	0 4 6 1	0 4 6 2	0 4 6 3	0 4 8 1	0 5 3 1	0 5 5 1	0 5 5 1	0 5 5 2	0 5 6 1	0 4 4 2	0 4 5 1	0 4 6 4	0 4 8 2	0 5 5 3	0 5 5 4	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																										1
Follicular cell, adenocarcinoma																										1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland			+														+		+						+	15
Adenoma																			X							1
Carcinoma			X																							3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Hematopoietic System																										
Bone marrow																										9
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+																		+		+					19
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus																										5
Integumentary System																										
Mammary gland	+												+						+		+					9
Fibroadenoma													X						X		X					3
Skin	+		+				+					+							+		+				+	18
Papilloma squamous																										1
Subcutaneous tissue, fibroma			X																							3
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone													+		+					+		+		+		23

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	3 1 5	3 2 6	4 2 2	5 5 5	5 7 4	5 8 1	6 1 7	6 2 6	6 2 6	6 6 2	6 6 7	6 7 3	6 7 4	6 7 6	6 7 6	6 8 6	6 9 0	6 9 2	6 9 3	6 9 4	6 9 7	6 9 8	7 0 0	7 0 4	7 1 3	7 1 5
Carcass ID Number	0 4 3 2	0 4 7 4	0 5 3 2	0 5 2 4	0 5 3 5	0 5 0 2	0 4 9 2	0 4 7 2	0 5 3 4	0 4 9 1	0 4 4 3	0 5 2 2	0 4 2 5	0 5 8 1	0 4 2 4	0 5 5 4	0 4 3 4	0 5 6 4	0 5 1 3	0 5 0 1	0 4 8 4	0 5 4 5	0 4 3 3	0 4 7 1	0 5 4 4	0 5 4 3
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																		+								
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Pheochromocytoma malignant, metastatic, adrenal gland									X																	
Squamous cell carcinoma										X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear							+																			
Eye							+							+										+		
Harderian gland							+																			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Proximal convoluted renal tubule, adenoma																										
Renal tubule, adenocarcinoma																										
Renal tubule, adenoma														X												
Urethra			+																							
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X										X	X	X	X		X		
Mesothelioma malignant																								X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	723	723	724	724	724	724	727	727	727	727	727	728	728	728	728	728	728	728	729	729	729	729	729	729	
Carcass ID Number	05114	05412	04813	05333	05541	05155	04311	04741	04512	04553	05251	04161	04462	04663	04811	05311	05511	05212	05611	04421	04511	04641	04821	05534	05514	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Squamous cell carcinoma																										1
Nose	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																				X						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye																										3
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Proximal convoluted renal tubule, adenoma																								X		1
Renal tubule, adenocarcinoma			X																							1
Renal tubule, adenoma																						X				2
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X				X		X	X					X		X		X		13
Mesothelioma malignant																										1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Adrenal Medulla: Pheochromocytoma Benign				
Overall rates[a]	12/50 (24%)	4/18 (22%)[e]	10/21 (48%)[e]	11/49 (22%)
Adjusted rates[b]	37.6%			36.0%
Terminal rates[c]	7/26 (27%)			6/23 (26%)
First incidence (days)	575			662
Life table tests[d]				P=0.568N
Logistic regression tests[d]				P=0.503N
Fisher exact test[d]				P=0.522N
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates	13/50 (26%)	4/18 (22%)[e]	11/21 (52%)[e]	12/49 (24%)
Adjusted rates	39.7%			38.5%
Terminal rates	7/26 (27%)			6/23 (26%)
First incidence (days)	575			662
Life table tests				P=0.574N
Logistic regression tests				P=0.501N
Fisher exact test				P=0.523N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	0.0%	11.1%
Terminal rates	0/26 (0%)	0/28 (0%)	0/25 (0%)	2/23 (9%)
First incidence (days)	-[f]			676
Life table tests	P=0.007	-	-	P=0.114
Logistic regression tests	P=0.009	-	-	P=0.122
Cochran-Armitage test[d]	P=0.008			
Fisher exact test				P=0.121
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rates	1/50 (2%)	2/50 (4%)	7/50 (14%)	8/50 (16%)
Adjusted rates	3.8%	7.1%	22.5%	27.5%
Terminal rates	1/26 (4%)	2/28 (7%)	4/25 (16%)	5/23 (22%)
First incidence (days)	724 (T)	724 (T)	617	667
Life table tests	P=0.008	P=0.526	P=0.032	P=0.016
Logistic regression tests	P=0.012	P=0.526	P=0.032	P=0.018
Cochran-Armitage test	P=0.012			
Fisher exact test		P=0.500	P=0.030	P=0.015
Kidney (Renal Tubule): Adenoma or Adenocarcinoma (Single Sections)				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rates	0.0%	0.0%	0.0%	15.3%
Terminal rates	0/26 (0%)	0/28 (0%)	0/25 (0%)	3/23 (13%)
First incidence (days)				676
Life table tests	P=0.001	-	-	P=0.056
Logistic regression tests	P=0.002	-	-	P=0.064
Cochran-Armitage test	P=0.002			
Fisher exact test		-	-	P=0.059

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Kidney (Renal Tubule): Adenoma or Adenocarcinoma (Single and Step Sections)				
Overall rates	1/50 (2%)	2/50 (4%)	7/50 (14%)	9/50 (18%)
Adjusted rates	3.8%	7.1%	22.5%	31.5%
Terminal rates	1/26 (4%)	2/28 (7%)	4/25 (16%)	6/23 (26%)
First incidence (days)	724 (T)	724 (T)	617	667
Life table tests	P=0.003	P=0.526	P=0.032	P=0.008
Logistic regression tests	P=0.005	P=0.526	P=0.032	P=0.010
Cochran-Armitage test	P=0.005			
Fisher exact test		P=0.500	P=0.030	P=0.008
Liver: Neoplastic Nodule or Hepatocellular Adenoma				
Overall rates	3/50 (6%)	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted rates	11.5%	10.7%	16.0%	0.0%
Terminal rates	3/26 (12%)	3/28 (11%)	4/25 (16%)	0/23 (0%)
First incidence (days)	724 (T)	724 (T)	724 (T)	-
Life table tests	P=0.105N	P=0.631N	P=0.478	P=0.142N
Logistic regression tests	P=0.105N	P=0.631N	P=0.478	P=0.142N
Cochran-Armitage test	P=0.082N			
Fisher exact test		P=0.661N	P=0.500	P=0.121N
Liver: Neoplastic Nodule, Hepatocellular Adenoma, or Hepatocellular Carcinoma				
Overall rates	3/50 (6%)	4/50 (8%)	4/50 (8%)	1/50 (2%)
Adjusted rates	11.5%	14.3%	16.0%	4.3%
Terminal rates	3/26 (12%)	4/28 (14%)	4/25 (16%)	1/23 (4%)
First incidence (days)	724 (T)	724 (T)	724 (T)	724 (T)
Life table tests	P=0.208N	P=0.541	P=0.478	P=0.348N
Logistic regression tests	P=0.208N	P=0.541	P=0.478	P=0.348N
Cochran-Armitage test	P=0.161N			
Fisher exact test		P=0.500	P=0.500	P=0.309N
Mammary Gland: Fibroadenoma				
Overall rates	5/50 (10%)	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted rates	16.3%	3.6%	17.3%	13.0%
Terminal rates	3/26 (12%)	1/28 (4%)	3/25 (12%)	3/23 (13%)
First incidence (days)	590	724 (T)	673	724 (T)
Life table tests	P=0.590	P=0.094N	P=0.612	P=0.401N
Logistic regression tests	P=0.546N	P=0.100N	P=0.624	P=0.350N
Cochran-Armitage test	P=0.551N			
Fisher exact test		P=0.102N	P=0.630N	P=0.357N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	0/47 (0%)	2/15 (13%)[e]	1/13 (8%)[e]	3/41 (7%)
Adjusted rates	0.0%			11.9%
Terminal rates	0/25 (0%)			1/18 (6%)
First incidence (days)	-			694
Life table tests				P=0.101
Logistic regression tests				P=0.100
Fisher exact test				P=0.097

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	14/46 (30%)	17/49 (35%)	19/50 (38%)	12/48 (25%)
Adjusted rates	42.9%	45.4%	54.0%	34.5%
Terminal rates	8/25 (32%)	9/27 (33%)	10/25 (40%)	3/23 (13%)
First incidence (days)	519	546	592	422
Life table tests	P=0.278N	P=0.401	P=0.219	P=0.444N
Logistic regression tests	P=0.191N	P=0.413	P=0.245	P=0.360N
Cochran-Armitage test	P=0.192N			
Fisher exact test		P=0.412	P=0.287	P=0.360N
Skin: Squamous Papilloma				
Overall rates	2/50 (4%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rates	7.7%	0.0%	12.0%	2.6%
Terminal rates	2/26 (8%)	0/28 (0%)	3/25 (12%)	0/23 (0%)
First incidence (days)	724 (T)	-	724 (T)	676
Life table tests	P=0.632N	P=0.221N	P=0.482	P=0.516N
Logistic regression tests	P=0.589N	P=0.221N	P=0.482	P=0.495N
Cochran-Armitage test	P=0.586N			
Fisher exact test		P=0.247N	P=0.500	P=0.500N
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	2/50 (4%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rates	7.1%	3.0%	2.1%	8.8%
Terminal rates	1/26 (4%)	0/28 (0%)	0/25 (0%)	1/23 (4%)
First incidence (days)	717	704	555	574
Life table tests	P=0.241	P=0.480N	P=0.525N	P=0.476
Logistic regression tests	P=0.265	P=0.489N	P=0.502N	P=0.500
Cochran-Armitage test	P=0.263			
Fisher exact test		P=0.500N	P=0.500N	P=0.500
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	3/50 (6%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rates	8.9%	3.0%	2.1%	8.8%
Terminal rates	1/26 (4%)	0/28 (0%)	0/25 (0%)	1/23 (4%)
First incidence (days)	458	704	555	574
Life table tests	P=0.351	P=0.292N	P=0.330N	P=0.635
Logistic regression tests	P=0.392	P=0.320N	P=0.328N	P=0.664N
Cochran-Armitage test	P=0.378			
Fisher exact test		P=0.309N	P=0.309N	P=0.661N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rates	3/50 (6%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rates	8.9%	6.2%	5.0%	10.7%
Terminal rates	1/26 (4%)	0/28 (0%)	0/25 (0%)	1/23 (4%)
First incidence (days)	458	704	555	555
Life table tests	P=0.282	P=0.474N	P=0.519N	P=0.476
Logistic regression tests	P=0.318	P=0.509N	P=0.523N	P=0.501
Cochran-Armitage test	P=0.304			
Fisher exact test		P=0.500N	P=0.500N	P=0.500

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Testes: Adenoma				
Overall rates	44/50 (88%)	43/46 (93%)	45/48 (94%)	45/50 (90%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	26/26 (100%)	26/26 (100%)	24/24 (100%)	23/23 (100%)
First incidence (days)	573	509	420	555
Life table tests	P=0.252	P=0.477N	P=0.341	P=0.335
Logistic regression tests	P=0.617	P=0.226	P=0.218	P=0.521
Cochran-Armitage test	P=0.521N			
Fisher exact test		P=0.287	P=0.264	P=0.500
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	5/50 (10%)	3/17 (18%)[e]	4/22 (18%)[e]	1/49 (2%)
Adjusted rates	15.6%			2.6%
Terminal rates	2/26 (8%)			0/23 (0%)
First incidence (days)	654			676
Life table tests				P=0.116N
Logistic regression tests				P=0.103N
Fisher exact test				P=0.107N
All Organs: Mononuclear Leukemia				
Overall rates	16/50 (32%)	18/50 (36%)	22/50 (44%)	13/50 (26%)
Adjusted rates	42.4%	39.2%	58.8%	42.5%
Terminal rates	6/26 (23%)	2/28 (7%)	11/25 (44%)	7/23 (30%)
First incidence (days)	590	546	549	662
Life table tests	P=0.257N	P=0.470	P=0.168	P=0.393N
Logistic regression tests	P=0.164N	P=0.394	P=0.151	P=0.322N
Cochran-Armitage test	P=0.164N			
Fisher exact test		P=0.417	P=0.151	P=0.330N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	3/50 (6%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Adjusted rates	8.3%	5.5%	6.2%	0.0%
Terminal rates	0/26 (0%)	1/28 (4%)	1/25 (4%)	0/23 (0%)
First incidence (days)	654	458	592	-
Life table tests	P=0.117N	P=0.488N	P=0.514N	P=0.118N
Logistic regression tests	P=0.102N	P=0.533N	P=0.502N	P=0.121N
Cochran-Armitage test	P=0.107N			
Fisher exact test		P=0.500N	P=0.500N	P=0.121N
All Organs: Mesothelioma (Benign or Malignant)				
Overall rates	4/50 (8%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rates	10.8%	11.8%	6.9%	3.6%
Terminal rates	1/26 (4%)	2/28 (7%)	0/25 (0%)	0/23 (0%)
First incidence (days)	573	599	420	704
Life table tests	P=0.133N	P=0.626N	P=0.501N	P=0.192N
Logistic regression tests	P=0.111N	P=0.635	P=0.534N	P=0.179N
Cochran-Armitage test	P=0.120N			
Fisher exact test		P=0.643N	P=0.500N	P=0.181N

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
All Organs: Benign Tumors				
Overall rates	49/50 (98%)	48/50 (96%)	50/50 (100%)	48/50 (96%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	26/26 (100%)	28/28 (100%)	25/25 (100%)	23/23 (100%)
First incidence (days)	226	509	420	422
Life table tests	P=0.340	P=0.359N	P=0.413	P=0.467
Logistic regression tests	P=0.643	P=0.307N	P=0.627	P=0.612N
Cochran-Armitage test	P=0.464N			
Fisher exact test		P=0.500N	P=0.500	P=0.500N
All Organs: Malignant Tumors				
Overall rates	29/50 (58%)	27/50 (54%)	32/50 (64%)	21/50 (42%)
Adjusted rates	64.9%	54.7%	73.5%	57.0%
Terminal rates	11/26 (42%)	6/28 (21%)	14/25 (56%)	9/23 (39%)
First incidence (days)	458	458	420	422
Life table tests	P=0.170N	P=0.392N	P=0.339	P=0.177N
Logistic regression tests	P=0.047N	P=0.438N	P=0.340	P=0.081N
Cochran-Armitage test	P=0.050N			
Fisher exact test		P=0.420N	P=0.341	P=0.081N
All Organs: Benign or Malignant Tumors				
Overall rates	50/50 (100%)	50/50 (100%)	50/50 (100%)	48/50 (96%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	26/26 (100%)	28/28 (100%)	25/25 (100%)	23/23 (100%)
First incidence (days)	226	458	420	422
Life table tests	P=0.427	P=0.419N	P=0.470	P=0.523
Logistic regression tests	P=0.058N	[g]	[g]	P=0.162N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=1.000N	P=1.000N	P=0.247N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.
[f] Not applicable; no tumors in animal group.
[g] Value of statistic cannot be computed.

TABLE A4
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma or Carcinoma	Adenoma, Adenocarcimona or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
4-Hydroxyacetanilide	3/50	0/50	3/50
Pentaerythritol tetranitrate	0/49	0/49	0/49
Total	3/99 (3.0%)		3/99 (3.0%)
Overall Historical Incidence			
Total	4/499 (0.8%)	4/499 (0.8%)	8/499 (1.6%)
Standard deviation	1.9%	1.1%	2.3%
Range	0%–6%	0%–4%	0%–6%

[a] Data as of 17 September 1990

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
6-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	3	7	3	6
Moribund	21	15	22	21
Survivors				
Moribund			1	1
Terminal sacrifice	25	27	22	19
Died last week of study	1	1	2	3
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(11)	(13)	(46)
Parasite metazoan	4 (8%)	1 (9%)		4 (9%)
Intestine large, colon	(49)	(12)	(11)	(47)
Parasite metazoan	9 (18%)	2 (17%)	1 (9%)	3 (6%)
Epithelium, pigmentation				1 (2%)
Intestine large, rectum	(49)	(11)	(10)	(46)
Parasite metazoan	3 (6%)			4 (9%)
Intestine small	(49)	(50)	(49)	(46)
Autolysis			1 (2%)	
Intestine small, duodenum	(48)	(47)	(48)	(46)
Epithelium, pigmentation				3 (7%)
Intestine small, ileum	(47)	(47)	(48)	(45)
Necrosis, coagulative		1 (2%)		
Epithelium, pigmentation		1 (2%)	15 (31%)	28 (62%)
Peyer's patch, hyperplasia			1 (2%)	
Intestine small, jejunum	(48)	(44)	(42)	(44)
Epithelium, pigmentation			2 (5%)	19 (43%)
Liver	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)	2 (4%)	2 (4%)
Basophilic focus	16 (32%)	17 (34%)	18 (36%)	20 (40%)
Clear cell focus	7 (14%)	10 (20%)	5 (10%)	8 (16%)
Congestion	1 (2%)			
Cyst				1 (2%)
Cyst multilocular				1 (2%)
Cytoplasmic alteration	2 (4%)	3 (6%)	1 (2%)	
Degeneration	4 (8%)	2 (4%)	1 (2%)	
Degeneration, cystic	6 (12%)	5 (10%)	9 (18%)	2 (4%)
Eosinophilic focus	9 (18%)	5 (10%)	7 (14%)	3 (6%)
Fatty change	5 (10%)	12 (24%)	5 (10%)	8 (16%)
Fibrosis	2 (4%)			
Hemorrhage	1 (2%)	4 (8%)	3 (6%)	3 (6%)
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)	2 (4%)		
Inflammation, chronic	24 (48%)	30 (60%)	26 (52%)	23 (46%)
Mixed cell focus	3 (6%)	4 (8%)	4 (8%)	3 (6%)
Mixed cell focus, multiple			1 (2%)	
Necrosis, coagulative	7 (14%)	8 (16%)	9 (18%)	7 (14%)
Thrombus		1 (2%)	1 (2%)	1 (2%)
Bile duct, hyperplasia	46 (92%)	48 (96%)	47 (94%)	30 (60%)
Centrilobular, necrosis, coagulative		1 (2%)	1 (2%)	2 (4%)

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Alimentary System (continued)				
Mesentery	(7)	(6)	(5)	(5)
Fibrosis		1 (17%)	1 (20%)	
Inflammation, chronic	2 (29%)			1 (20%)
Inflammation, granulomatous, chronic				2 (40%)
Mineralization			1 (20%)	1 (20%)
Necrosis, coagulative	1 (14%)	2 (33%)	1 (20%)	1 (20%)
Pigmentation	1 (14%)		1 (20%)	
Pancreas	(50)	(50)	(50)	(47)
Atrophy	23 (46%)	26 (52%)	23 (46%)	24 (51%)
Cyst			1 (2%)	1 (2%)
Cytoplasmic alteration		2 (4%)		3 (6%)
Ectopic liver		1 (2%)		1 (2%)
Fibrosis			2 (4%)	
Hyperplasia		3 (6%)	3 (6%)	1 (2%)
Inflammation, chronic	32 (64%)	28 (56%)	30 (60%)	34 (72%)
Necrosis, coagulative			1 (2%)	
Pigmentation	1 (2%)		2 (4%)	
Thrombus			1 (2%)	
Artery, fibrosis		3 (6%)		
Artery, inflammation, necrotizing, chronic active		1 (2%)	2 (4%)	
Artery, mineralization				1 (2%)
Duct, dilatation	1 (2%)	1 (2%)		
Perivascular, inflammation, chronic		3 (6%)		
Serosa, hyperplasia			1 (2%)	
Salivary glands	(16)	(14)	(12)	(10)
Parotid gland, vacuolization cytoplasmic			1 (8%)	
Stomach, forestomach	(49)	(49)	(49)	(46)
Acanthosis		6 (12%)	2 (4%)	5 (11%)
Edema				1 (2%)
Fibrosis				1 (2%)
Hyperkeratosis		3 (6%)	2 (4%)	5 (11%)
Hyperplasia, basal cell	3 (6%)	9 (18%)	8 (16%)	2 (4%)
Hyperplasia, pseudoepitheliomatous				1 (2%)
Inflammation, acute		1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)		3 (7%)
Mineralization			3 (6%)	2 (4%)
Ulcer		1 (2%)	1 (2%)	
Muscularis, pigmentation			1 (2%)	
Stomach, glandular	(50)	(50)	(49)	(48)
Edema				1 (2%)
Hemorrhage			1 (2%)	
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Necrosis, coagulative		1 (2%)	1 (2%)	
Epithelium, pigmentation			3 (6%)	34 (71%)
Mucosa, mineralization			3 (6%)	7 (15%)
Muscularis, mineralization	1 (2%)		1 (2%)	
Submucosa, fibrosis	1 (2%)			
Tongue	(45)	(48)	(47)	(44)
Hemorrhage		1 (2%)		
Inflammation, necrotizing, acute				1 (2%)
Metaplasia, osseous	1 (2%)			
Artery, mineralization			1 (2%)	4 (9%)
Artery, endothelium, hyperplasia				1 (2%)

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Cardiovascular System				
Blood vessel	(1)		(1)	(2)
Aorta, mineralization	1 (100%)		1 (100%)	2 (100%)
Heart	(50)	(18)	(18)	(50)
Cardiomyopathy	48 (96%)	14 (78%)	15 (83%)	49 (98%)
Cytomegaly		1 (6%)		
Edema				1 (2%)
Inflammation, chronic				1 (2%)
Metaplasia, osseous			2 (11%)	1 (2%)
Mineralization				2 (4%)
Thrombus	6 (12%)	1 (6%)	5 (28%)	1 (2%)
Artery, mineralization				3 (6%)
Coronary artery, inflammation, chronic active	1 (2%)			
Endocrine System				
Adrenal gland, cortex	(50)	(18)	(21)	(49)
Angiectasis	6 (12%)	1 (6%)	2 (10%)	8 (16%)
Atrophy	1 (2%)			
Congestion	1 (2%)	3 (17%)		2 (4%)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage			1 (5%)	
Hyperplasia	10 (20%)	2 (11%)	1 (5%)	14 (29%)
Necrosis, coagulative		2 (11%)	1 (5%)	1 (2%)
Vacuolization cytoplasmic	26 (52%)	12 (67%)	8 (38%)	27 (55%)
Adrenal gland, medulla	(50)	(18)	(21)	(49)
Angiectasis	2 (4%)			1 (2%)
Atrophy	1 (2%)			
Congestion				2 (4%)
Hyperplasia	22 (44%)	2 (11%)	3 (14%)	21 (43%)
Necrosis, coagulative	1 (2%)			1 (2%)
Islets, pancreatic	(47)	(15)	(13)	(41)
Hyperplasia	1 (2%)	1 (7%)		1 (2%)
Parathyroid gland	(43)	(45)	(43)	(43)
Hyperplasia	1 (2%)	6 (13%)	6 (14%)	17 (40%)
Pituitary gland	(46)	(49)	(50)	(48)
Autolysis		1 (2%)		3 (6%)
Hemorrhage				1 (2%)
Pars distalis, angiectasis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Pars distalis, autolysis		1 (2%)	2 (4%)	
Pars distalis, congestion			1 (2%)	
Pars distalis, cyst	7 (15%)	6 (12%)	4 (8%)	7 (15%)
Pars distalis, hyperplasia	18 (39%)	24 (49%)	17 (34%)	20 (42%)
Pars distalis, necrosis		1 (2%)		
Pars distalis, pigmentation		5 (10%)	1 (2%)	
Pars intermedia, angiectasis		2 (4%)	3 (6%)	
Pars intermedia, crystals			1 (2%)	
Pars intermedia, cyst	6 (13%)	10 (20%)	14 (28%)	7 (15%)
Pars intermedia, ectopic tissue			1 (2%)	
Pars intermedia, hyperplasia			1 (2%)	
Pars nervosa, cyst				1 (2%)
Pars nervosa, ectopic tissue			1 (2%)	
Pars nervosa, hyperplasia			1 (2%)	
Rathke's cleft, cyst			1 (2%)	

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Endocrine System (continued)				
Thyroid gland	(50)	(17)	(22)	(49)
Congestion		1 (6%)		
Inflammation, acute	1 (2%)			
Ultimobranchial cyst	2 (4%)			
C-cell, hyperplasia	17 (34%)	3 (18%)	6 (27%)	16 (33%)
Follicle, pigmentation	1 (2%)		1 (5%)	6 (12%)
Follicular cell, cyst				3 (6%)
Follicular cell, hyperplasia	2 (4%)		1 (5%)	1 (2%)
General Body System				
None				
Genital System				
Coagulating gland	(2)	(1)	(2)	
Adventitia, inflammation, chronic active	1 (50%)			
Preputial gland	(13)	(22)	(19)	(15)
Abscess		5 (23%)	2 (11%)	
Cyst	1 (8%)			
Hyperplasia				1 (7%)
Inflammation, chronic	12 (92%)	19 (86%)	13 (68%)	13 (87%)
Duct, dilatation		1 (5%)		
Prostate	(49)	(14)	(12)	(48)
Fibrosis				1 (2%)
Hemorrhage		1 (7%)		
Inflammation, acute		1 (7%)		
Inflammation, chronic				1 (2%)
Inflammation, chronic active	25 (51%)	9 (64%)	10 (83%)	30 (63%)
Epithelium, hyperplasia	2 (4%)			2 (4%)
Seminal vesicle	(50)	(22)	(23)	(49)
Atrophy	36 (72%)	9 (41%)	9 (39%)	39 (80%)
Testes	(50)	(46)	(48)	(50)
Infarct		1 (2%)		
Necrosis, coagulative	1 (2%)			1 (2%)
Interstitial cell, hyperplasia	34 (68%)	35 (76%)	41 (85%)	44 (88%)
Seminiferous tubule, atrophy	44 (88%)	44 (96%)	43 (90%)	46 (92%)
Hematopoietic System				
Bone marrow	(11)	(12)	(12)	(9)
Fibrosis				1 (11%)
Lymph node	(49)	(29)	(26)	(50)
Angiectasis		1 (3%)		
Artery, pancreatic, thrombus			1 (4%)	
Inguinal, ectasia		1 (3%)		
Lumbar, ectasia	1 (2%)	3 (10%)		
Lumbar, hemorrhage	1 (2%)	1 (3%)	1 (4%)	
Lumbar, hyperplasia, plasma cell			1 (4%)	
Lumbar, infiltration cellular, histiocyte		1 (3%)		
Lumbar, inflammation, acute		1 (3%)		
Lumbar, pigmentation		1 (3%)		

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Hematopoietic System (continued)				
Lymph node (continued)				
Mediastinal, depletion lymphoid				1 (2%)
Mediastinal, ectasia		2 (7%)	3 (12%)	
Mediastinal, hemorrhage	6 (12%)	4 (14%)	3 (12%)	6 (12%)
Mediastinal, infiltration cellular, histiocyte			1 (4%)	
Mediastinal, pigmentation	1 (2%)	5 (17%)	2 (8%)	1 (2%)
Pancreatic, ectasia	1 (2%)			
Pancreatic, hemorrhage	3 (6%)	2 (7%)	2 (8%)	2 (4%)
Pancreatic, hyperplasia, plasma cell	1 (2%)			
Pancreatic, infiltration cellular, histiocyte	3 (6%)	5 (17%)	2 (8%)	
Pancreatic, pigmentation	3 (6%)	2 (7%)	3 (12%)	
Renal, ectasia	1 (2%)	2 (7%)	2 (8%)	1 (2%)
Renal, fibrosis		1 (3%)		
Renal, hemorrhage	5 (10%)	4 (14%)	5 (19%)	5 (10%)
Renal, hyperplasia, lymphoid			1 (4%)	
Renal, hyperplasia, plasma cell	1 (2%)			1 (2%)
Renal, infiltration cellular, histiocyte		4 (14%)	2 (8%)	2 (4%)
Renal, pigmentation	6 (12%)	6 (21%)	3 (12%)	5 (10%)
Lymph node, mandibular	(46)	(18)	(15)	(47)
Angiectasis	1 (2%)			
Congestion		1 (6%)		1 (2%)
Depletion lymphoid				1 (2%)
Ectasia	3 (7%)	1 (6%)	3 (20%)	10 (21%)
Hemorrhage	12 (26%)	4 (22%)	2 (13%)	12 (26%)
Hyperplasia, plasma cell	3 (7%)			1 (2%)
Infiltration cellular, histiocyte				3 (6%)
Pigmentation				2 (4%)
Lymph node, mesenteric	(22)	(14)	(17)	(19)
Ectasia			1 (6%)	12 (63%)
Hemorrhage	3 (14%)	1 (7%)	4 (24%)	3 (16%)
Hyperplasia, plasma cell	1 (5%)			
Infiltration cellular, histiocyte	11 (50%)	10 (71%)	14 (82%)	9 (47%)
Pigmentation	9 (41%)	9 (64%)	10 (59%)	8 (42%)
Spleen	(50)	(25)	(38)	(50)
Congestion	1 (2%)	2 (8%)	1 (3%)	
Depletion lymphoid	9 (18%)	14 (56%)	13 (34%)	9 (18%)
Fibrosis	6 (12%)	5 (20%)	8 (21%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	2 (8%)	1 (3%)	3 (6%)
Hyperplasia, lymphoid			1 (3%)	
Infarct	2 (4%)			
Necrosis, coagulative	1 (2%)			
Pigmentation	1 (2%)		1 (3%)	
Thrombus			1 (3%)	
Thymus	(14)	(11)	(13)	(5)
Congestion			1 (8%)	
Depletion lymphoid	7 (50%)	5 (45%)	5 (38%)	5 (100%)
Hemorrhage	1 (7%)	1 (9%)	1 (8%)	

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Integumentary System				
Mammary gland	(13)	(10)	(14)	(9)
Abscess		1 (10%)		
Galactocele	1 (8%)	1 (10%)		1 (11%)
Hyperplasia	7 (54%)	9 (90%)	9 (64%)	6 (67%)
Pigmentation		3 (30%)	3 (21%)	1 (11%)
Skin	(20)	(18)	(19)	(18)
Acanthosis	1 (5%)		1 (5%)	3 (17%)
Cyst epithelial inclusion	2 (10%)	3 (17%)		
Fibrosis			1 (5%)	
Hyperkeratosis	1 (5%)	1 (6%)	1 (5%)	3 (17%)
Hyperplasia, basal cell				1 (6%)
Inflammation, necrotizing, acute				1 (6%)
Subcutaneous tissue, abscess	1 (5%)			1 (6%)
Subcutaneous tissue, edema	1 (5%)			
Subcutaneous tissue, inflammation, chronic active			1 (5%)	
Subcutaneous tissue, inflammation, granulomatous	1 (5%)	1 (6%)		1 (6%)
Subcutaneous tissue, necrosis, coagulative				1 (6%)
Musculoskeletal System				
Skeletal muscle	(1)	(2)		
Hindlimb, mineralization		1 (50%)		
Nervous System				
Brain	(50)	(15)	(12)	(50)
Hemorrhage	2 (4%)	2 (13%)		2 (4%)
Cerebellum, infarct	1 (2%)			
Cerebrum, degeneration, focal			1 (8%)	
Respiratory System				
Lung	(50)	(28)	(31)	(50)
Congestion		1 (4%)	1 (3%)	1 (2%)
Edema			2 (6%)	1 (2%)
Hemorrhage	4 (8%)	6 (21%)	5 (16%)	1 (2%)
Infiltration cellular, histiocyte	31 (62%)	18 (64%)	18 (58%)	43 (86%)
Inflammation, chronic active			1 (3%)	
Metaplasia, osseous			1 (3%)	2 (4%)
Necrosis, coagulative	1 (2%)			
Alveolar epithelium, hyperplasia		4 (14%)	2 (6%)	3 (6%)
Artery, mineralization	34 (68%)	13 (46%)	17 (55%)	43 (86%)
Bronchiole, epithelium, hyperplasia			1 (3%)	1 (2%)

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Respiratory System (continued)				
Nose	(44)	(48)	(49)	(49)
Foreign body		1 (2%)		
Metaplasia, squamous		1 (2%)	2 (4%)	1 (2%)
Glands, inflammation, acute	11 (25%)	11 (23%)	4 (8%)	5 (10%)
Lumen, hemorrhage		1 (2%)		
Lumen, inflammation, acute	2 (5%)	3 (6%)	9 (18%)	3 (6%)
Mucosa, congestion			1 (2%)	
Nasopharyngeal duct, inflammation, acute		1 (2%)		
Nasopharyngeal duct, inflammation, chronic	1 (2%)			
Special Senses System				
Eye	(2)	(9)	(6)	(3)
Atrophy				1 (33%)
Synechia				1 (33%)
Artery, mineralization			1 (17%)	
Cornea, fibrosis	1 (50%)	1 (11%)		1 (33%)
Cornea, inflammation, chronic		1 (11%)		
Posterior chamber, inflammation, chronic				1 (33%)
Retina, degeneration	1 (50%)			1 (33%)
Sclera, metaplasia, osseous		1 (11%)		
Harderian gland	(1)		(1)	(1)
Hyperplasia	1 (100%)			
Inflammation, chronic				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Autolysis		2 (4%)		
Congestion	2 (4%)			2 (4%)
Cyst	2 (4%)	6 (12%)	1 (2%)	7 (14%)
Hemorrhage		1 (2%)	1 (2%)	
Hydronephrosis		1 (2%)	1 (2%)	
Nephropathy	48 (96%)	50 (100%)	50 (100%)	49 (98%)
Artery, inflammation, necrotizing, chronic active		1 (2%)		
Collecting tubule, mineralization			1 (2%)	
Interstitial tissue, inflammation, acute				1 (2%)
Interstitial tissue, proximal convoluted renal tubule, inflammation, acute		1 (2%)		
Proximal convoluted renal tubule, mineralization		1 (2%)	2 (4%)	5 (10%)
Proximal convoluted renal tubule, necrosis		1 (2%)		1 (2%)
Proximal convoluted renal tubule, epithelium, pigmentation	5 (10%)	2 (4%)	3 (6%)	
Renal tubule, hyperplasia	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Renal tubule, hyperplasia, cystic		1 (2%)	1 (2%)	
Transitional epithelium, hyperplasia	14 (28%)	9 (18%)	16 (32%)	27 (54%)
Transitional epithelium, mineralization	1 (2%)			

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Urinary System (continued)				
Urethra				(1)
Calculus micro observation only				1 (100%)
Urinary bladder	(50)	(49)	(49)	(48)
Calculus micro observation only	2 (4%)			1 (2%)
Inflammation, chronic		2 (4%)	1 (2%)	
Artery, mineralization			1 (2%)	
Serosa, mineralization				1 (2%)
Submucosa, hemorrhage		1 (2%)		
Subserosa, mineralization		1 (2%)	1 (2%)	
Transitional epithelium, hyperplasia			1 (2%)	
Wall, mucosa, muscularis, inflammation, necrotizing, acute, diffuse				1 (2%)

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

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
6-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Natural deaths	1	4	2	3
Moribund	19	18	13	19
Survivors				
Terminal sacrifice	29	28	35	27
Moribund				1
Died last week of study	1			
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(50)	(11)	(8)	(48)
Intestine large, colon	(50)	(11)	(7)	(48)
Intestine large, rectum	(48)	(11)	(7)	(47)
Polyp adenomatous				1 (2%)
Intestine small, duodenum	(50)	(48)	(50)	(49)
Leiomyoma		1 (2%)		
Intestine small, ileum	(49)	(48)	(49)	(49)
Intestine small, jejunum	(50)	(47)	(49)	(49)
Liver	(50)	(50)	(50)	(50)
Neoplastic nodule		1 (2%)		1 (2%)
Mesentery	(2)	(6)	(2)	(1)
Pancreas	(50)	(49)	(50)	(50)
Adenoma				1 (2%)
Salivary glands	(7)	(12)	(7)	(11)
Stomach, forestomach	(49)	(50)	(50)	(47)
Stomach, glandular	(50)	(49)	(50)	(50)
Tongue	(29)	(43)	(43)	(39)
Squamous cell carcinoma				2 (5%)
Cardiovascular System				
Heart	(50)	(13)	(7)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (8%)		
Fibrosarcoma, metastatic, skin			1 (14%)	
Endocrine System				
Adrenal gland	(50)	(14)	(13)	(50)
Adrenal gland, cortex	(50)	(13)	(13)	(50)
Adenoma			1 (8%)	1 (2%)
Fibrosarcoma, metastatic, skin			1 (8%)	
Adrenal gland, medulla	(50)	(13)	(12)	(50)
Pheochromocytoma malignant	1 (2%)	1 (8%)		
Pheochromocytoma benign	3 (6%)		3 (25%)	1 (2%)
Islets, pancreatic	(44)	(15)	(8)	(49)
Adenoma	2 (5%)	3 (20%)	1 (13%)	

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Endocrine System (continued)				
Parathyroid gland	(40)	(39)	(36)	(43)
Adenoma	1 (3%)			
Pituitary gland	(50)	(49)	(50)	(49)
Pars distalis, adenoma	32 (64%)	27 (55%)	26 (52%)	25 (51%)
Pars distalis, adenoma, multiple	5 (10%)	4 (8%)	9 (18%)	2 (4%)
Pars distalis, carcinoma		1 (2%)		1 (2%)
Pars distalis, pars intermedia, pars nervosa, leukemia mononuclear	1 (2%)			
Thyroid gland	(50)	(43)	(47)	(50)
C-cell, adenoma	6 (12%)	3 (7%)	4 (9%)	2 (4%)
C-cell, carcinoma	2 (4%)	3 (7%)	2 (4%)	1 (2%)
Follicular cell, adenoma				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(14)	(20)	(14)	(12)
Adenoma	4 (29%)	4 (20%)	3 (21%)	4 (33%)
Carcinoma	1 (7%)	1 (5%)	2 (14%)	
Sarcoma			1 (7%)	
Ovary	(50)	(17)	(15)	(48)
Granulosa cell tumor benign	1 (2%)			
Granulosa-theca tumor malignant				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Adenocarcinoma			1 (2%)	
Leiomyoma	1 (2%)			
Polyp stromal	7 (14%)	8 (16%)	16 (32%)	10 (20%)
Polyp stromal, multiple		1 (2%)		1 (2%)
Sarcoma stromal		2 (4%)	1 (2%)	
Hematopoietic System				
Bone marrow	(8)	(11)	(7)	(11)
Lymph node	(48)	(25)	(17)	(49)
Lumbar, fibrosarcoma, metastatic, skin			1 (6%)	
Lymph node, mandibular	(46)	(19)	(10)	(46)
Lymph node, mesenteric	(9)	(14)	(12)	(9)
Spleen	(50)	(23)	(20)	(50)
Hemangioma	1 (2%)			
Thymus	(8)	(10)	(7)	(9)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (10%)		

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Integumentary System				
Mammary gland	(36)	(36)	(24)	(22)
Adenocarcinoma	1 (3%)		3 (13%)	2 (9%)
Fibroadenoma	21 (58%)	17 (47%)	14 (58%)	6 (27%)
Fibroadenoma, multiple	8 (22%)	10 (28%)	2 (8%)	3 (14%)
Skin	(11)	(15)	(8)	(11)
Subcutaneous tissue, carcinosarcoma, poorly differentiated	1 (9%)			
Subcutaneous tissue, fibroma	2 (18%)	3 (20%)	1 (13%)	
Subcutaneous tissue, fibrosarcoma			1 (13%)	
Subcutaneous tissue, sarcoma, poorly differentiated				1 (9%)
Musculoskeletal System				
Skeletal muscle				(3)
Sarcoma				1 (33%)
Nervous System				
Brain	(50)	(15)	(8)	(50)
Carcinoma, extension, metastatic, pituitary gland				1 (2%)
Medulla, carcinoma, metastatic, pituitary gland		1 (7%)		
Spinal cord	(1)	(2)		(2)
Respiratory System				
Lung	(50)	(20)	(20)	(50)
Alveolar/bronchiolar adenoma	5 (10%)		1 (5%)	
Alveolar/bronchiolar carcinoma		1 (5%)		
Carcinosarcoma, metastatic, skin	1 (2%)			
Granulosa-theca tumor malignant, metastatic, ovary				1 (2%)
Hepatocellular carcinoma, metastatic, uncertain primary site				1 (2%)
Pheochromocytoma malignant, metastatic		1 (5%)		
Sarcoma, metastatic, lung		1 (5%)		
Sarcoma, poorly differentiated, metastatic, skin				1 (2%)
Pleura, alveolar/bronchiolar carcinoma, metastatic, lung		1 (5%)		
Nose	(7)	(12)	(7)	(10)
Special Senses System				
Ear	(1)	(2)	(1)	
Fibrosarcoma	1 (100%)			
Zymbal's gland	(2)	(2)		
Adenoma	1 (50%)			
Squamous cell carcinoma	1 (50%)	2 (100%)		

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Urinary System				
Kidney	(49)	(49)	(50)	(50)
Renal tubule, adenoma			1 (2%)	
Urinary bladder	(50)	(49)	(50)	(50)
Papilloma	1 (2%)			
Systemic Lesions				
Multiple organs[a]	(50)	(50)	(50)	(50)
Leukemia monocytic				1 (2%)
Leukemia mononuclear	9 (18%)	10 (20%)	13 (26%)	12 (24%)
Tumor Summary				
Total animals with primary neoplasms[b]	49	48	43	44
Total primary neoplasms	118	103	106	81
Total animals with benign neoplasms	49	44	42	35
Total benign neoplasms	101	82	82	59
Total animals with malignant neoplasms	15	19	19	19
Total malignant neoplasms	17	21	24	22
Total animals with metastatic neoplasms	1	4	1	4
Total metastatic neoplasms	1	6	3	4
Total animals with malignant neoplasms of uncertain primary site				1

[a] Number of animals with any tissue examined microscopically
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 0 ppm

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 5 9 4	0 6 4 1	0 6 5 4	0 6 6 4	0 6 9 1	0 5 8 2	0 6 6 3	0 6 2 1	0 5 9 2	0 6 1 1	0 6 5 2	0 6 6 1	0 6 0 2	0 7 7 1	0 5 9 1	0 5 9 3	0 5 3 1	0 6 6 1	0 6 5 1	0 6 8 1	0 7 0 1	0 5 8 1	0 6 1 2	0 6 2 2	0 6 3 2	0 6 6 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																			+							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands																										7
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+		+		+	+	+		+	+	+	+	+	+	+	+	+	+		+	+		+	29
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant							X																			1
Pheochromocytoma benign							X																			3
Islets, pancreatic	+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	44
Adenoma																X										2
Parathyroid gland	+	M	+	I	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	40
Adenoma															X											1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X			X	X	X	X	X		X	X			X			X	X		X	X	32
Pars distalis, adenoma, multiple																				X						5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X	X	X		X							X										X		6
C-cell, carcinoma																							X			2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	4 2 2	5 9 7	6 0 6	6 1 3	6 1 9	6 2 5	6 3 2	6 4 1	6 6 0	6 6 0	6 7 2	6 7 2	6 8 6	6 8 7	6 8 7	7 0 0	7 0 0	7 1 8	7 1 8	7 1 8	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4
Carcass ID Number	0 6 4 5	0 6 9 5	0 6 0 3	0 5 8 4	0 6 9 4	0 6 4 2	0 6 1 4	0 5 9 5	0 6 5 3	0 6 8 3	0 5 8 5	0 6 3 3	0 6 1 3	0 6 0 2	0 6 7 3	0 6 8 2	0 6 9 3	0 7 7 3	0 5 6 2	0 6 6 2	0 6 0 1	0 6 7 1	0 7 0 3	0 7 0 4	0 5 7 2
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+		+		+	+							+	+	+								
Adenoma																									
Carcinoma																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Polyp stromal		X			X	X																		X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+																	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mandibular	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+							+										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma	X																								
Thymus	+	+	+	+	+	+	M	+																+	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+		+	+	+	+	+	
Adenocarcinoma											X														
Fibroadenoma		X	X	X		X			X	X		X		X		X					X				
Fibroadenoma, multiple					X								X					X		X				X	
Skin	+	+	+	+	+	+	+	+										+			+				
Subcutaneous tissue, carcinosarcoma, poorly differentiated								X																	
Subcutaneous tissue, fibroma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord								+																	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 5 9 4	0 6 4 1	0 6 5 4	0 6 6 4	0 6 9 1	0 5 8 2	0 6 6 3	0 6 2 1	0 5 9 2	0 6 1 1	0 6 5 2	0 6 6 1	0 6 0 2	0 7 7 1	0 5 9 1	0 5 9 3	0 5 9 3	0 6 3 1	0 6 5 1	0 6 8 1	0 7 0 1	0 5 8 1	0 6 1 2	0 6 2 2	0 6 3 2	0 6 6 2	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland		M	+			+		+	+							+										14
Adenoma			X					X	X							X										4
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma				X																						1
Polyp stromal		X												X	X											7
Hematopoietic System																										
Bone marrow																										8
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		46
Lymph node, mesenteric																										9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangioma																										1
Thymus																										8
Integumentary System																										
Mammary gland	+	+						+		+	+	+	+			+	+		+		+	+	+		+	36
Adenocarcinoma																										1
Fibroadenoma		X						X		X	X	X	X			X	X		X				X		X	21
Fibroadenoma, multiple														X						X	X					8
Skin																								+		11
Subcutaneous tissue, carcinosarcoma, poorly differentiated																										1
Subcutaneous tissue, fibroma																								X		2
Musculoskeletal System																										
Bone																										8
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spinal cord																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	4 2 2	5 9 7	6 0 6	6 1 3	6 1 9	6 2 5	6 3 2	6 4 1	6 6 0	6 6 0	6 7 2	6 7 2	6 8 6	6 8 7	6 8 7	7 0 0	7 0 0	7 1 8	7 1 8	7 1 8	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4
Carcass ID Number	0 6 4 5	0 6 9 5	0 6 0 3	0 5 8 4	0 6 9 4	0 6 4 2	0 6 1 4	0 5 9 5	0 6 5 3	0 6 8 3	0 5 8 5	0 6 3 3	0 6 1 3	0 6 0 2	0 6 7 3	0 6 8 2	0 6 9 3	0 5 7 3	0 6 7 2	0 6 9 2	0 6 0 1	0 6 7 1	0 7 0 3	0 7 0 4	0 5 7 2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X			X														
Carcinosarcoma, metastatic, skin								X																	
Nose	+	+		+	+	+	+	+																	
Trachea	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Fibrosarcoma																									
Eye							+												+						+
Zymbal's gland										+															
Adenoma																									
Squamous cell carcinoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X						X				X		X		X					X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 5 9 4	0 6 4 1	0 6 5 4	0 6 6 4	0 6 9 1	0 5 8 2	0 6 6 3	0 6 2 1	0 5 9 2	0 6 1 1	0 6 5 2	0 6 6 1	0 6 7 2	0 5 7 1	0 5 9 1	0 5 9 3	0 6 3 1	0 6 5 1	0 6 8 1	0 7 0 1	0 5 8 1	0 6 1 2	0 6 2 2	0 6 3 2	0 6 6 2	**Total Tissues/ Tumors**
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X														X							X			5
Carcinosarcoma, metastatic, skin																									1
Nose																									7
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Ear													+												1
Fibrosarcoma													X												1
Eye	+			+									+												6
Zymbal's gland													+												2
Adenoma													X												1
Squamous cell carcinoma																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																	X								1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X								X		X							9

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

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

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

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 7 1	0 7 7 2	0 7 9 1	0 7 9 2	0 8 4 1	0 7 8 2	0 7 9 4	0 7 1 3	0 7 4 2	0 7 6 4	0 8 2 4	0 8 3 1	0 8 3 2	0 8 3 3	0 8 4 4	0 8 4 4	0 7 4 1	0 7 1 1	0 7 5 1	0 7 5 2	0 7 7 3	0 7 8 1	0 7 9 3	0 8 1 1	0 8 2 2	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus																									12
Intestine large																									11
Intestine large, cecum																									11
Intestine large, colon																									11
Intestine large, rectum																									11
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma															X										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																						X			1
Mesentery				+			+			+													+		6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands																									12
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Cardiovascular System																									
Heart	+																								13
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Endocrine System																									
Adrenal gland																									14
Adrenal gland, cortex																									13
Adrenal gland, medulla																									13
Pheochromocytoma malignant																									1
Islets, pancreatic							+						+				+							+	15
Adenoma													X				X							X	3
Parathyroid gland	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	M	+	+	M	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X		X		X	X							X	X	X	X	X	X		X	X	X		27
Pars distalis, adenoma, multiple													X	X											X	4
Pars distalis, carcinoma																									1
Thyroid gland	+	+		+	+			+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
C-cell, adenoma	X							X								X										3
C-cell, carcinoma					X														X	X						3

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

Number of Days on Study	1 8 3	4 9 7	5 0 4	5 1 5	5 4 3	5 9 6	5 9 7	6 0 3	6 0 3	6 1 2	6 1 3	6 2 6	6 4 5	6 6 8	6 7 6	6 8 0	6 8 0	6 8 3	6 8 7	6 9 6	7 0 4	7 2 1	7 2 3	7 2 3
Carcass ID Number	0 8 0 3	0 7 6 5	0 8 3 4	0 7 3 5	0 7 8 5	0 8 1 4	0 7 2 5	0 7 2 2	0 7 2 3	0 7 3 4	0 7 1 5	0 7 3 3	0 7 5 4	0 7 1 2	0 8 3 3	0 7 1 4	0 7 3 2	0 7 7 4	0 7 8 4	0 8 2 5	0 7 2 1	0 8 0 2	0 7 3 1	0 7 5 3	0 7 6 2
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+										+			
Adenoma																					X			
Carcinoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+			M			+			+			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X																	X			
Polyp stromal, multiple													X											
Sarcoma stromal					X										X									
Hematopoietic System																								
Blood														+										
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+			+			+	+	+	+			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+					+							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+			+	+			
Thymus	+	+	M	+	+	+	+	+	+	M	M	+					+							
Alveolar/bronchiolar carcinoma, metastatic, lung	X																							
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		+	+		+		+	
Fibroadenoma							X			X		X		X		X		X	X		X		X	
Fibroadenoma, multiple															X									
Skin	+	+	+	+	+	+	+	+	+	+		+					+				+			
Subcutaneous tissue, fibroma																					X			
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+		+										
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+					+							
Medulla, carcinoma, metastatic, pituitary gland										X														
Spinal cord																								

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

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 7 1	0 7 7 2	0 7 9 1	0 7 9 2	0 8 4 1	0 7 8 2	0 7 9 4	0 7 1 3	0 7 4 2	0 7 6 4	0 8 2 4	0 8 3 1	0 8 3 2	0 8 4 3	0 8 4 4	0 8 4 1	0 7 1 1	0 7 5 1	0 7 5 2	0 7 7 3	0 7 8 1	0 7 9 3	0 8 1 1	0 8 2 1	0 8 2 2	**Total Tissues/ Tumors**
General Body System																									
None																									
Genital System																									
Clitoral gland		+				+					+	+	+					+					+	+	20
Adenoma		X									X		X												4
Carcinoma						X																			1
Ovary				+			+				+														17
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X	X						X				X	X						X						8
Polyp stromal, multiple																									1
Sarcoma stromal																									2
Hematopoietic System																									
Blood																									1
Bone marrow																									11
Lymph node	+			+							+										+		+	+	25
Lymph node, mandibular											+												+		19
Lymph node, mesenteric																								+	14
Spleen		+		+		+										+					+				23
Thymus																									10
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Integumentary System																									
Mammary gland	+	+	+	+	+						+	+	+	+	+	+	+		+	+	+	+	+		36
Fibroadenoma		X	X		X						X	X			X					X	X				17
Fibroadenoma, multiple	X			X									X	X		X	X		X	X			X		10
Skin			+						+																15
Subcutaneous tissue, fibroma			X						X																3
Musculoskeletal System																									
Bone																									13
Nervous System																									
Brain																					+		+		15
Medulla, carcinoma, metastatic, pituitary gland																									1
Spinal cord																					+		+		2

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

Number of Days on Study	1 8 3	4 9 7	5 0 4	5 1 5	5 4 3	5 9 6	5 9 7	6 0 3	6 0 3	6 1 2	6 1 3	6 2 6	6 4 5	6 6 8	6 7 6	6 8 0	6 8 0	6 8 3	6 8 7	6 9 6	7 0 4	7 2 1	7 2 3	7 2 3
Carcass ID Number	0 8 0 3	0 7 6 5	0 8 3 4	0 7 3 5	0 7 8 5	0 8 1 4	0 7 2 5	0 7 2 2	0 7 2 3	0 7 3 4	0 7 1 5	0 7 3 3	0 7 5 4	0 7 1 2	0 8 3 3	0 7 1 4	0 7 3 2	0 7 7 4	0 7 8 4	0 8 2 5	0 7 2 1	0 8 0 2	0 7 3 1	0 7 5 3	0 7 6 2
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+	+	+	+			+
Alveolar/bronchiolar carcinoma	X																							
Pheochromocytoma malignant, metastatic		X																						
Sarcoma, metastatic, lung															X									
Pleura, alveolar/bronchiolar carcinoma, metastatic, lung	X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+												
Special Senses System																								
Ear																								
Eye						+					I							+		I	I	I		
Harderian gland						+					+													
Zymbal's gland																		+			+			
Squamous cell carcinoma																		X			X			
Urinary System																								
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X											X		X	X	X			

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

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 7 1	0 7 7 2	0 7 9 1	0 7 9 2	0 8 4 1	0 7 8 2	0 7 9 4	0 7 1 3	0 7 4 2	0 7 6 4	0 8 2 4	0 8 3 1	0 8 3 2	0 8 4 3	0 8 4 4	0 7 4 1	0 7 1 1	0 7 5 1	0 7 5 2	0 7 7 3	0 7 8 1	0 7 9 3	0 8 1 1	0 8 2 1	0 8 2 2	**Total Tissues/ Tumors**
Respiratory System																									
Lung																								+	20
Alveolar/bronchiolar carcinoma																									1
Pheochromocytoma malignant, metastatic																									1
Sarcoma, metastatic, lung																									1
Pleura, alveolar/bronchiolar carcinoma, metastatic, lung																									1
Nose																									12
Trachea																									12
Special Senses System																									
Ear																						+		+	2
Eye								+	I	+								+		+		+	I	+	8
Harderian gland										+								+							4
Zymbal's gland																									2
Squamous cell carcinoma																									2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X															X			X			10

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

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

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

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 9 2	0 8 9 3	0 9 0 3	0 9 0 5	0 9 1 1	0 9 1 2	0 9 2 1	0 9 2 2	0 9 3 1	0 8 6 3	0 9 2 3	0 9 3 3	0 9 4 3	0 9 5 4	0 9 7 2	0 8 6 1	0 8 8 3	0 9 0 2	0 9 1 5	0 9 4 2	0 9 5 3	0 8 5 2	0 9 0 1	0 9 1 4	0 9 1 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										7
Intestine large								+																		8
Intestine large, cecum								+																		8
Intestine large, colon																										7
Intestine large, rectum																										7
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery														+												2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands																										7
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Cardiovascular System																										
Heart																										7
Fibrosarcoma, metastatic, skin																										1
Endocrine System																										
Adrenal gland						+						M					+						+			13
Adrenal gland, cortex						+											+						+			13
Adenoma																										1
Fibrosarcoma, metastatic, skin																										1
Adrenal gland, medulla						+											+						+			12
Pheochromocytoma benign						X											X						X			3
Islets, pancreatic																										8
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	M	M	+	+	+	+	M	M	M	M	+	M	+	+	+	+	M	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X	X				X					X		X	X	X	X	X			X		26
Pars distalis, adenoma, multiple	X	X		X									X			X						X	X			9
Thyroid gland	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+			+	47
C-cell, adenoma						X								X		X										4
C-cell, carcinoma																						X				2

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

Number of Days on Study	3 3 7	4 4 1	5 2 1	5 4 8	5 4 8	6 0 3	6 0 5	6 6 0	6 6 6	6 8 5	6 9 7	6 9 7	7 0 7	7 0 9	7 1 8	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4
Carcass ID Number	0 9 6 5	0 9 8 5	0 8 9 4	0 9 6 4	0 9 7 4	0 9 3 4	0 9 4 4	0 8 8 5	0 8 7 3	0 9 8 2	0 9 6 2	0 9 7 3	0 8 5 5	0 8 8 4	0 8 5 4	0 8 5 4	0 8 7 2	0 8 9 1	0 9 4 1	0 9 5 1	0 9 6 1	0 9 7 1	0 8 5 1	0 8 6 2	0 8 8 1	0 8 8 2
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	+	+	+	+	+				+		+									+		+	
Adenoma													X												
Carcinoma											X														
Sarcoma				X																					
Ovary	+	+	+	+	+	+	+	M	M	M	M	M	+	M	M	M	M	+	M	+	M	+	M	+	M
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp stromal			X						X	X						X	X				X				X
Sarcoma stromal																									
Vagina									+																
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+																		
Lymph node	+	+	+	+	+	+	+				+				+									+	
Lumbar, fibrosarcoma, metastatic, skin		X																							
Lymph node, mandibular	+	+	+	M	+	+	+																	+	
Lymph node, mesenteric	+	+	+	+	+	+	+								+										
Spleen	+	+	+	+	+	+	+	+	+		+			+	+				+					+	
Thymus	+	+	+	+	+	+	+																		
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+		+	+			+			+						
Adenocarcinoma								X																	
Fibroadenoma							X	X	X			X	X			X			X						
Fibroadenoma, multiple										X															
Skin	+	+	+	+	+	+	+		+																
Subcutaneous tissue, fibroma			X																						
Subcutaneous tissue, fibrosarcoma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+																		
Nervous System																									
Brain	+	+	+	+	+	+	+		+																

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

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 9 2	0 8 9 3	0 9 0 3	0 9 0 5	0 9 1 1	0 9 1 2	0 9 2 1	0 9 2 2	0 9 3 1	0 8 6 3	0 9 2 3	0 9 3 3	0 9 4 3	0 9 5 4	0 9 7 2	0 8 6 1	0 8 8 3	0 9 0 2	0 9 1 5	0 9 4 2	0 9 5 3	0 8 5 2	0 9 0 1	0 9 1 4	0 9 3 2	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland						+					+									+			+			14
Adenoma											X												X			3
Carcinoma																				X						2
Sarcoma																										1
Ovary	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	15
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															1
Polyp stromal	X								X	X	X		X		X					X		X			X	16
Sarcoma stromal					X																					1
Vagina																										1
Hematopoietic System																										
Bone marrow																										7
Lymph node	+	+									+			+	+	+	+									17
Lumbar, fibrosarcoma, metastatic, skin																										1
Lymph node, mandibular	+														+		+									10
Lymph node, mesenteric											+			+		+	+									12
Spleen	+		+						+								+	+					+			20
Thymus																										7
Integumentary System																										
Mammary gland	+			+		+					+			+			+			+	+	+	+		+	24
Adenocarcinoma				X													X									3
Fibroadenoma	X			X						X										X	X		X		X	14
Fibroadenoma, multiple													X													2
Skin																										8
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone																										7
Nervous System																										
Brain																										8

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

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

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

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 9 2	0 8 9 3	0 9 0 3	0 9 0 5	0 9 1 1	0 9 1 2	0 9 2 1	0 9 2 2	0 9 3 1	0 9 6 3	0 9 2 3	0 9 3 3	0 9 4 3	0 9 5 4	0 9 7 2	0 8 6 1	0 8 8 3	0 9 0 2	0 9 1 5	0 9 4 2	0 9 5 3	0 8 5 2	0 9 0 1	0 9 1 4	0 9 3 2	0 9 1 3	**Total Tissues/ Tumors**
Respiratory System																												
Lung		+					+		+					+				+		+				+				20
Alveolar/bronchiolar adenoma																		X										1
Nose																												7
Trachea																												7
Special Senses System																												
Ear																												1
Eye														+											+	+		6
Harderian gland														+								+						2
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Renal tubule, adenoma																								X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear											X						X				X					X		13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 0 7 1	1 0 7 2	1 0 8 2	1 0 9 2	1 1 2 1	1 1 2 2	0 9 9 1	1 0 0 3	1 0 2 4	1 0 3 2	1 0 4 2	1 0 4 4	1 0 6 2	1 0 9 3	1 1 4 4	1 2 3 3	1 0 2 2	1 0 2 1	1 0 2 2	1 0 3 1	1 0 3 3	1 0 4 1	1 0 6 1	1 1 0 1	1 1 2 3	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+		+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous																									1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																									1
Mesentery																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X								1
Salivary glands																									11
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+		+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	39
Squamous cell carcinoma																									2
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X							1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X		X		X				X	X							X	X		X	X	X	25
Pars distalis, adenoma, multiple		X				X																			2
Pars distalis, carcinoma										X															1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X														2
C-cell, carcinoma																							X		1
Follicular cell, adenoma																			X						1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	2 8 4	4 5 7	4 9 2	5 4 9	5 5 3	5 6 0	5 9 4	5 9 7	6 2 3	6 3 0	6 3 2	6 3 7	6 6 0	6 6 7	6 6 8	6 8 6	6 8 8	6 8 8	6 8 8	7 1 5	7 1 6	7 1 6	7 2 3	7 2 3	7 2 3
Carcass ID Number	1 0 5 4	1 0 6 5	0 9 9 3	1 1 1 3	1 0 1 2	1 0 1 3	1 0 7 4	1 0 5 2	1 0 8 4	1 0 6 3	1 1 0 4	1 1 1 2	1 1 1 4	1 0 8 3	1 0 2 5	1 1 0 3	1 9 9 2	1 0 9 4	1 1 0 5	1 0 1 5	1 0 9 5	1 9 0 5	1 0 7 3	1 0 1 2	1 0 1 5
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+				+	+	+								+			+		
Adenoma											X									X			X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant										X															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal	X										X														
Polyp stromal, multiple					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+		+													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	M	+		+	A	+	+	+	+			+					+	+							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	M	+	+	+	+		+						M							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+				+				+			+	+	
Adenocarcinoma																X				X					
Fibroadenoma				X																				X	
Fibroadenoma, multiple																							X		
Skin	+	+	+	+	+	+	+	+	+	+		+													
Subcutaneous tissue, sarcoma, poorly differentiated	X																								
Musculoskeletal System																									
Bone	+	+	+	+		+	+	+	+	+		+											+		
Skeletal muscle		+								+				+											
Sarcoma														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, extension, metastatic, pituitary gland																									
Spinal cord												+		+											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 0 7 1	1 0 7 2	1 0 8 2	1 0 9 2	1 1 2 1	1 1 2 2	0 9 9 1	1 0 0 3	1 0 2 4	1 0 3 2	1 0 4 2	1 0 4 4	1 0 6 2	1 0 9 3	1 1 2 4	1 2 0 3	1 0 2 2	1 0 2 1	1 0 2 2	1 0 3 1	1 0 3 3	1 0 4 1	1 0 6 1	1 1 0 1	1 1 2 3	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland												+														12
Adenoma												X														4
Ovary	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa-theca tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X	X			X										X				X	X	X	X		10
Polyp stromal, multiple																										1
Hematopoietic System																										
Bone marrow																										11
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Lymph node, mesenteric																										9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus																										9
Integumentary System																										
Mammary gland			+						+	+		+							+						+	22
Adenocarcinoma																										2
Fibroadenoma			X						X			X													X	6
Fibroadenoma, multiple										X									X							3
Skin																										11
Subcutaneous tissue, sarcoma, poorly differentiated																										1
Musculoskeletal System																										
Bone											+		+				+									14
Skeletal muscle																										3
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, extension, metastatic, pituitary gland												X														1
Spinal cord																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	2 8 4	4 5 7	4 9 2	5 4 9	5 5 3	5 6 0	5 9 4	5 9 7	6 2 3	6 3 0	6 3 2	6 3 7	6 6 0	6 6 7	6 6 8	6 8 6	6 8 8	6 8 8	6 8 8	7 1 5	7 1 6	7 1 6	7 2 3	7 2 3	7 2 3
Carcass ID Number	1 0 5 4	1 0 6 5	0 9 9 3	1 1 1 3	1 0 1 2	1 0 1 3	1 0 7 4	1 0 5 2	1 0 8 4	1 0 6 3	1 1 0 4	1 1 1 2	1 1 1 4	1 0 8 3	1 0 2 5	1 1 0 3	0 9 9 2	1 0 9 4	1 1 0 5	1 0 1 5	0 9 9 5	1 0 9 3	1 0 7 2	1 0 1 1	1 0 1 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary										X															
Hepatocellular carcinoma, metastatic, uncertain primary site						X																			
Sarcoma, poorly differentiated, metastatic, skin	X																								
Nose	+	+	+	+	A	+	+	+	+	+		+													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+		+						+			+		+							
Harderian gland							+	+																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monocytic												X													
Leukemia mononuclear									X	X		X			X		X	X				X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Quercetin: 40,000 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 0 7 1	1 0 7 2	1 0 8 2	1 0 9 2	1 1 2 1	1 1 2 2	0 9 9 1	1 0 0 3	1 0 2 4	1 0 3 2	1 0 4 2	1 0 4 4	1 0 6 2	1 0 9 3	1 1 1 4	1 1 2 3	1 1 0 2	1 0 2 1	1 0 2 2	1 0 3 1	1 0 3 3	1 0 4 1	1 0 6 1	1 1 0 1	1 1 2 3	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Hepatocellular carcinoma, metastatic, uncertain primary site																										1
Sarcoma, poorly differentiated, metastatic, skin																										1
Nose																										10
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										5
Harderian gland																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia monocytic																										1
Leukemia mononuclear											X					X		X			X	X				12

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates[a]	3/50 (6%)	1/13 (8%)[e]	3/12 (25%)[e]	1/50 (2%)
Adjusted rates[b]	7.8%			3.6%
Terminal rates[c]	1/30 (3%)			1/28 (4%)
First incidence (days)	625			723 (T)
Life table tests[d]				P=0.340N
Logistic regression tests[d]				P=0.305N
Fisher exact test[d]				P=0.309N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	5/50 (10%)	1/20 (5%)[e]	1/20 (5%)[e]	0/50 (0%)
Adjusted rates	14.3%			0.0%
Terminal rates	3/30 (10%)			0/28 (0%)
First incidence (days)	641			-[f]
Life table tests				P=0.044N
Logistic regression tests				P=0.036N
Fisher exact test				P=0.028N
Mammary Gland: Fibroadenoma				
Overall rates	29/50 (58%)	27/50 (54%)	16/50 (32%)	9/50 (18%)
Adjusted rates	66.4%	72.3%	38.4%	30.1%
Terminal rates	16/30 (53%)	18/28 (64%)	10/35 (29%)	8/28 (29%)
First incidence (days)	597	597	605	549
Life table tests	P<0.001N	P=0.531	P=0.008N	P<0.001N
Logistic regression tests	P<0.001N	P=0.553N	P=0.008N	P<0.001N
Cochran-Armitage test[d]	P<0.001N			
Fisher exact test		P=0.420N	P=0.008N	P<0.001N
Mammary Gland: Adenocarcinoma				
Overall rates	1/50 (2%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rates	2.5%	0.0%	7.9%	6.0%
Terminal rates	0/30 (0%)	0/28 (0%)	2/35 (6%)	0/28 (0%)
First incidence (days)	672	-	660	686
Life table tests	P=0.299	P=0.521N	P=0.340	P=0.468
Logistic regression tests	P=0.309	P=0.492N	P=0.304	P=0.492
Cochran-Armitage test	P=0.318			
Fisher exact test		P=0.500N	P=0.309	P=0.500
Mammary Gland: Fibroadenoma or Adenocarcinoma				
Overall rates	30/50 (60%)	27/50 (54%)	17/50 (34%)	11/50 (22%)
Adjusted rates	67.2%	72.3%	40.8%	34.3%
Terminal rates	16/30 (53%)	18/28 (64%)	11/35 (31%)	8/28 (29%)
First incidence (days)	597	597	605	549
Life table tests	P<0.001N	P=0.538N	P=0.008N	P=0.002N
Logistic regression tests	P<0.001N	P=0.468N	P=0.009N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.343N	P=0.008N	P<0.001N

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Pancreatic Islets: Adenoma				
Overall rates	2/44 (5%)	3/15 (20%)[e]	1/8 (13%)[e]	0/49 (0%)
Adjusted rates	6.3%			0.0%
Terminal rates	1/27 (4%)			0/28 (0%)
First incidence (days)	687			-
Life table tests				P=0.245N
Logistic regression tests				P=0.225N
Fisher exact test				P=0.221N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	37/50 (74%)	31/49 (63%)	35/50 (70%)	27/49 (55%)
Adjusted rates	80.3%	74.7%	77.5%	68.5%
Terminal rates	21/30 (70%)	18/28 (64%)	25/35 (71%)	16/28 (57%)
First incidence (days)	597	183	441	549
Life table tests	P=0.166N	P=0.380N	P=0.218N	P=0.157N
Logistic regression tests	P=0.064N	P=0.185N	P=0.441N	P=0.062N
Cochran-Armitage test	P=0.056N			
Fisher exact test		P=0.175N	P=0.412N	P=0.039N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	37/50 (74%)	32/49 (65%)	35/50 (70%)	28/49 (57%)
Adjusted rates	80.3%	75.3%	77.5%	71.2%
Terminal rates	21/30 (70%)	18/28 (64%)	25/35 (71%)	17/28 (61%)
First incidence (days)	597	183	441	549
Life table tests	P=0.197N	P=0.446N	P=0.218N	P=0.199N
Logistic regression tests	P=0.083N	P=0.239N	P=0.441N	P=0.094N
Cochran-Armitage test	P=0.073N			
Fisher exact test		P=0.235N	P=0.412N	P=0.060N
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	2/50 (4%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rates	6.3%	10.2%	2.1%	0.0%
Terminal rates	1/30 (3%)	2/28 (7%)	0/35 (0%)	0/28 (0%)
First incidence (days)	718	704	521	-
Life table tests	P=0.114N	P=0.461	P=0.475N	P=0.266N
Logistic regression tests	P=0.108N	P=0.449	P=0.470N	P=0.256N
Cochran-Armitage test	P=0.107N			
Fisher exact test		P=0.500	P=0.500N	P=0.247N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	2/50 (4%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rates	6.3%	10.2%	4.1%	0.0%
Terminal rates	1/30 (3%)	2/28 (7%)	0/35 (0%)	0/28 (0%)
First incidence (days)	718	704	441	-
Life table tests	P=0.120N	P=0.461	P=0.672N	P=0.266N
Logistic regression tests	P=0.105N	P=0.449	P=0.608N	P=0.256N
Cochran-Armitage test	P=0.112N			
Fisher exact test		P=0.500	P=0.691N	P=0.247N

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rates	2/50 (4%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rates	6.3%	10.2%	4.1%	2.0%
Terminal rates	1/30 (3%)	2/28 (7%)	0/35 (0%)	0/28 (0%)
First incidence (days)	718	704	441	284
Life table tests	P=0.313N	P=0.461	P=0.672N	P=0.527N
Logistic regression tests	P=0.262N	P=0.449	P=0.608N	P=0.339N
Cochran-Armitage test	P=0.297N			
Fisher exact test		P=0.500	P=0.691N	P=0.500N
Thyroid Gland (C-cell): Adenoma				
Overall rates	6/50 (12%)	3/43 (7%)	4/47 (9%)	2/50 (4%)
Adjusted rates	20.0%	12.5%	11.8%	6.4%
Terminal rates	6/30 (20%)	3/24 (13%)	3/32 (9%)	1/28 (4%)
First incidence (days)	723 (T)	723 (T)	709	688
Life table tests	P=0.179N	P=0.358N	P=0.325N	P=0.154N
Logistic regression tests	P=0.171N	P=0.358N	P=0.351N	P=0.161N
Cochran-Armitage test	P=0.162N			
Fisher exact test		P=0.324N	P=0.410N	P=0.134N
Thyroid Gland (C-cell): Carcinoma				
Overall rates	2/50 (4%)	3/43 (7%)	2/47 (4%)	1/50 (2%)
Adjusted rates	5.6%	12.5%	5.7%	3.6%
Terminal rates	1/30 (3%)	3/24 (13%)	1/32 (3%)	1/28 (4%)
First incidence (days)	660	723 (T)	707	723 (T)
Life table tests	P=0.294N	P=0.408	P=0.666N	P=0.528N
Logistic regression tests	P=0.282N	P=0.371	P=0.669	P=0.521N
Cochran-Armitage test	P=0.271N			
Fisher exact test		P=0.428	P=0.668	P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	8/50 (16%)	6/43 (14%)	6/47 (13%)	3/50 (6%)
Adjusted rates	25.2%	25.0%	17.1%	9.9%
Terminal rates	7/30 (23%)	6/24 (25%)	4/32 (13%)	2/28 (7%)
First incidence (days)	660	723 (T)	707	688
Life table tests	P=0.095N	P=0.561N	P=0.334N	P=0.123N
Logistic regression tests	P=0.087N	P=0.609	P=0.408N	P=0.127N
Cochran-Armitage test	P=0.082N			
Fisher exact test		P=0.508N	P=0.436N	P=0.100N
Tongue: Squamous Cell Carcinoma				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rates	0.0%	0.0%	0.0%	4.7%
Terminal rates	0/30 (0%)	0/28 (0%)	0/35 (0%)	0/28 (0%
First incidence (days)	-	-	-	492
Life table tests	P=0.039	-	-	P=0.227
Logistic regression tests	P=0.047	-	-	P=0.327
Cochran-Armitage test	P=0.042			
Fisher exact test		-	-	P=0.247

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Uterus: Stromal Polyp				
Overall rates	7/50 (14%)	9/50 (18%)	16/50 (32%)	11/50 (22%)
Adjusted rates	18.8%	27.7%	41.4%	33.2%
Terminal rates	4/30 (13%)	6/28 (21%)	13/35 (37%)	8/28 (29%)
First incidence (days)	597	515	521	284
Life table tests	P=0.262	P=0.333	P=0.059	P=0.178
Logistic regression tests	P=0.308	P=0.387	P=0.028	P=0.265
Cochran-Armitage test	P=0.314			
Fisher exact test		P=0.393	P=0.028	P=0.218
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	7/50 (14%)	11/50 (22%)	17/50 (34%)	11/50 (22%)
Adjusted rates	18.8%	31.2%	44.0%	33.2%
Terminal rates	4/30 (13%)	6/28 (21%)	14/35 (40%)	8/28 (29%)
First incidence (days)	597	515	521	284
Life table tests	P=0.361	P=0.180	P=0.040	P=0.178
Logistic regression tests	P=0.419	P=0.233	P=0.017	P=0.265
Cochran-Armitage test	P=0.420			
Fisher exact test		P=0.218	P=0.017	P=0.218
All Organs: Leukemia (Monocytic or Mononuclear)				
Overall rates	9/50 (18%)	10/50 (20%)	13/50 (26%)	12/50 (24%)
Adjusted rates	22.8%	26.3%	29.6%	32.6%
Terminal rates	3/30 (10%)	3/28 (11%)	5/35 (14%)	5/28 (18%)
First incidence (days)	422	504	548	623
Life table tests	P=0.286	P=0.420	P=0.323	P=0.264
Logistic regression tests	P=0.336	P=0.586	P=0.258	P=0.331
Cochran-Armitage test	P=0.322			
Fisher exact test		P=0.500	P=0.235	P=0.312
All Organs: Benign Tumors				
Overall rates	49/50 (98%)	44/50 (88%)	42/50 (84%)	35/50 (70%)
Adjusted rates	98.0%	93.5%	87.5%	84.9%
Terminal rates	29/30 (97%)	25/28 (89%)	29/35 (83%)	22/28 (79%)
First incidence (days)	422	183	441	284
Life table tests	P=0.052N	P=0.503N	P=0.041N	P=0.060N
Logistic regression tests	P<0.001N	P=0.069N	P=0.021N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.056N	P=0.015N	P<0.001N
All Organs: Malignant Tumors				
Overall rates	15/50 (30%)	19/50 (38%)	19/50 (38%)	20/50 (40%)
Adjusted rates	36.4%	44.0%	42.5%	46.1%
Terminal rates	6/30 (20%)	6/28 (21%)	10/35 (29%)	6/28 (21%)
First incidence (days)	422	183	441	284
Life table tests	P=0.255	P=0.213	P=0.396	P=0.175
Logistic regression tests	P=0.341	P=0.437	P=0.284	P=0.288
Cochran-Armitage test	P=0.283			
Fisher exact test		P=0.263	P=0.263	P=0.201

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
All Organs: Benign or Malignant Tumors				
Overall rates	49/50 (98%)	48/50 (96%)	43/50 (86%)	45/50 (90%)
Adjusted rates	98.0%	96.0%	87.8%	93.7%
Terminal rates	29/30 (97%)	26/28 (93%)	29/35 (83%)	25/28 (89%)
First incidence (days)	422	183	441	284
Life table tests	P=0.492N	P=0.373	P=0.059N	P=0.541N
Logistic regression tests	P=0.140N	P=0.476N	P=0.035N	P=0.107N
Cochran-Armitage test	P=0.138N			
Fisher exact test		P=0.500N	P=0.030N	P=0.102N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.
[f] Not applicable; no tumors in animal group.

TABLE B4a
Historical Incidence of Renal Tubule Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
Historical Incidence at EG&G Mason Research Institute			
4-Hydroxyacetanilide	0/50	0/50	0/50
Pentaerythritol tetranitrate	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/499 (0.2%)	0/499 (0.0%)	1/499 (0.2%)
Standard deviation	0.6%		0.6%
Range	0%–2%		0%–2%

[a] Data as of 17 September 1990

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

Study	Incidence in Controls		
	Oral Mucosa: Papilloma or Squamous Cell Papilloma	Oral Mucosa: Squamous Cell Carcinoma	Oral Mucosa: Papilloma, Squamous Cell Papilloma, or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
4-Hydroxyacetanilide	0/50	0/50	0/50
Pentaerythritol tetranitrate	0/50	0/50	1/50
Total			1/100 (1%)
Overall Historical Incidence			
Total	3/500 (0.6%)	0/500	4/500 (0.8%)
Standard deviation	1.0%		1.0%
Range	0%-2%		0%–2%

[a] Data as of 17 September 1990; includes oral mucosa, tongue, pharynx (palate), tooth (gingiva), and lip

TABLE B4c
Historical Incidence of Mammary Gland Fibroadenomas in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at EG&G Mason Research Institute	
4-Hydroxyacetanilide	19/50
Pentaerythritol tetranitrate	27/50
Total	46/100 (46.0%)
Overall Historical Incidence	
Total	178/500 (35.6%)
Standard deviation	15.0%
Range	8%–56%

[a] Data as of 17 September 1990

TABLE B4d
Historical Incidence of Uterine Stromal Polyps in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at EG&G Mason Research Institute	
4-Hydroxyacetanilide	15/50
Pentaerythritol tetranitrate	8/50
Total	23/100 (23.0%)
Overall Historical Incidence	
Total	94/500 (19.6%)
Standard deviation	5.4%
Range	12%–30%

[a] Data as of 17 September 1990

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Quercetin

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
6-Month interim evaluations	10	10	10	10
15-Month interim evaluations	10	10	10	10
Early deaths				
Natural deaths	1	4	2	3
Moribund	19	18	13	19
Survivors				
Terminal sacrifice	29	28	35	27
Moribund				1
Died last week of study	1			
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(50)	(11)	(8)	(48)
Necrosis, coagulative, acute				1 (2%)
Parasite metazoan	2 (4%)			4 (8%)
Lymphoid tissue, hypoplasia		1 (9%)		
Intestine large, colon	(50)	(11)	(7)	(48)
Parasite metazoan	9 (18%)	1 (9%)	2 (29%)	5 (10%)
Intestine large, rectum	(48)	(11)	(7)	(47)
Parasite metazoan	5 (10%)			2 (4%)
Intestine small, duodenum	(50)	(48)	(50)	(49)
Autolysis			1 (2%)	
Epithelium, pigmentation				1 (2%)
Intestine small, ileum	(49)	(48)	(49)	(49)
Epithelium, pigmentation			19 (39%)	32 (65%)
Serosa, fibrosis		1 (2%)		
Intestine small, jejunum	(50)	(47)	(49)	(49)
Autolysis		1 (2%)	1 (2%)	
Epithelium, pigmentation			3 (6%)	20 (41%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	5 (10%)	1 (2%)	
Basophilic focus	40 (80%)	38 (76%)	41 (82%)	39 (78%)
Clear cell focus	4 (8%)	4 (8%)	4 (8%)	2 (4%)
Cyst				2 (4%)
Cyst multilocular			1 (2%)	
Cytoplasmic alteration		4 (8%)		1 (2%)
Degeneration		1 (2%)	1 (2%)	
Developmental malformation	3 (6%)			2 (4%)
Eosinophilic focus	3 (6%)			3 (6%)
Fatty change	14 (28%)	12 (24%)	12 (24%)	7 (14%)
Fibrosis, focal				1 (2%)
Granuloma			1 (2%)	
Hematopoietic cell proliferation		1 (2%)		
Hemorrhage		1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule		3 (6%)	5 (10%)	

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Alimentary System (continued)				
Liver (continued)				
Infarct				1 (2%)
Inflammation, acute			1 (2%)	
Inflammation, chronic	1 (2%)		3 (6%)	3 (6%)
Inflammation, chronic active	2 (4%)	2 (4%)	2 (4%)	7 (14%)
Inflammation, granulomatous, chronic	12 (24%)	17 (34%)	10 (20%)	8 (16%)
Mixed cell focus	4 (8%)	7 (14%)	4 (8%)	1 (2%)
Necrosis, coagulative	4 (8%)	5 (10%)	5 (10%)	8 (16%)
Pigmentation	1 (2%)	1 (2%)	1 (2%)	
Bile duct, cyst multilocular				1 (2%)
Bile duct, hyperplasia	17 (34%)	14 (28%)	17 (34%)	15 (30%)
Centrilobular, necrosis, coagulative				1 (2%)
Serosa, fibrosis		1 (2%)		
Serosa, hemorrhage		1 (2%)		
Mesentery	(2)	(6)	(2)	(1)
Fibrosis		6 (100%)	1 (50%)	
Inflammation, chronic		3 (50%)		
Inflammation, chronic active		2 (33%)		
Inflammation, granulomatous, chronic	1 (50%)	1 (17%)	1 (50%)	
Mineralization		1 (17%)	1 (50%)	
Necrosis, coagulative	2 (100%)	3 (50%)		
Pigmentation			1 (50%)	
Pancreas	(50)	(49)	(50)	(50)
Atrophy	21 (42%)	21 (43%)	21 (42%)	15 (30%)
Cytoplasmic alteration		2 (4%)	4 (8%)	2 (4%)
Ectopic liver				1 (2%)
Inflammation, chronic	17 (34%)	22 (45%)	22 (44%)	17 (34%)
Pigmentation		1 (2%)		
Artery, hyperplasia			1 (2%)	
Artery, perivascular, inflammation, necrotizing, chronic		1 (2%)		
Duct, dilatation		1 (2%)		
Stomach, forestomach	(49)	(50)	(50)	(47)
Acanthosis	3 (6%)	3 (6%)	3 (6%)	7 (15%)
Edema	1 (2%)	1 (2%)		1 (2%)
Erosion	1 (2%)			
Hyperkeratosis	3 (6%)	2 (4%)	1 (2%)	7 (15%)
Hyperplasia, basal cell	4 (8%)	2 (4%)	3 (6%)	5 (11%)
Inflammation, acute		1 (2%)		
Inflammation, chronic active	3 (6%)	3 (6%)		2 (4%)
Inflammation, necrotizing, chronic active			1 (2%)	
Necrosis, coagulative		1 (2%)		
Ulcer	1 (2%)	1 (2%)		2 (4%)
Artery, mineralization			1 (2%)	
Artery, muscularis, mineralization		1 (2%)		
Muscularis, mineralization		1 (2%)	3 (6%)	
Submucosa, mineralization			1 (2%)	

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Alimentary System (continued)				
Stomach, glandular	(50)	(49)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Edema		1 (2%)		
Inflammation, chronic active	3 (6%)	1 (2%)		1 (2%)
Ulcer	1 (2%)			
Artery, mineralization		3 (6%)	1 (2%)	
Epithelium, pigmentation			8 (16%)	38 (76%)
Mucosa, dilatation	6 (12%)		5 (10%)	4 (8%)
Muscularis, developmental malformation	1 (2%)			
Muscularis, mineralization	1 (2%)	2 (4%)	6 (12%)	4 (8%)
Tongue	(29)	(43)	(43)	(39)
Hemorrhage		2 (5%)	1 (2%)	
Inflammation, chronic	7 (24%)	7 (16%)	12 (28%)	6 (15%)
Arteriole, necrosis, fibrinoid		2 (5%)	1 (2%)	
Cardiovascular System				
Heart	(50)	(13)	(7)	(50)
Cardiomyopathy	47 (94%)	9 (69%)	3 (43%)	47 (94%)
Atrium left, thrombus				1 (2%)
Coronary artery, inflammation, chronic active				1 (2%)
Coronary artery, inflammation, necrotizing, chronic active	1 (2%)			
Coronary artery, necrosis, fibrinoid				1 (2%)
Epicardium, fibrosis				1 (2%)
Endocrine System				
Adrenal gland	(50)	(14)	(13)	(50)
Hyperplasia				1 (2%)
Adrenal gland, cortex	(50)	(13)	(13)	(50)
Angiectasis	28 (56%)	2 (15%)	2 (15%)	26 (52%)
Atrophy		1 (8%)		
Congestion	1 (2%)		1 (8%)	
Degeneration, fatty	1 (2%)			
Hyperplasia	16 (32%)		2 (15%)	14 (28%)
Necrosis, coagulative	1 (2%)			1 (2%)
Pigmentation		1 (8%)		
Thrombus	1 (2%)			
Vacuolization cytoplasmic	28 (56%)	8 (62%)	3 (23%)	24 (48%)
Adrenal gland, medulla	(50)	(13)	(12)	(50)
Angiectasis	5 (10%)		1 (8%)	
Hyperplasia	3 (6%)		1 (8%)	4 (8%)
Necrosis, coagulative	1 (2%)			
Islets, pancreatic	(44)	(15)	(8)	(49)
Ectopic tissue	1 (2%)			
Hyperplasia		1 (7%)		
Parathyroid gland	(40)	(39)	(36)	(43)
Cyst	1 (3%)			
Hyperplasia	1 (3%)		1 (3%)	

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Endocrine System (continued)				
Pituitary gland	(50)	(49)	(50)	(49)
Angiectasis				1 (2%)
Hyperplasia				2 (4%)
Pars distalis, angiectasis	14 (28%)	11 (22%)	12 (24%)	8 (16%)
Pars distalis, cyst	26 (52%)	21 (43%)	23 (46%)	28 (57%)
Pars distalis, cyst, multiple			1 (2%)	1 (2%)
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	18 (36%)	23 (47%)	18 (36%)	13 (27%)
Pars distalis, infiltration cellular, histiocyte			1 (2%)	
Pars distalis, pigmentation	1 (2%)	3 (6%)	3 (6%)	
Pars intermedia, angiectasis	5 (10%)	6 (12%)	4 (8%)	6 (12%)
Pars intermedia, cyst		2 (4%)	7 (14%)	6 (12%)
Pars intermedia, pigmentation			1 (2%)	
Pars nervosa, angiectasis	1 (2%)	1 (2%)		
Pars nervosa, cyst			1 (2%)	
Thyroid gland	(50)	(43)	(47)	(50)
Ultimobranchial cyst	1 (2%)			3 (6%)
C-cell, hyperplasia	38 (76%)	37 (86%)	40 (85%)	37 (74%)
Follicle, cyst	2 (4%)			4 (8%)
Follicular cell, hyperplasia		1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(14)	(20)	(14)	(12)
Abscess	1 (7%)	2 (10%)		1 (8%)
Cyst	3 (21%)	2 (10%)	1 (7%)	
Hyperplasia	2 (14%)	1 (5%)		
Inflammation, acute		1 (5%)	1 (7%)	
Inflammation, chronic	6 (43%)	10 (50%)	4 (29%)	4 (33%)
Inflammation, chronic active	3 (21%)	2 (10%)	3 (21%)	1 (8%)
Ovary	(50)	(17)	(15)	(48)
Congestion			1 (7%)	
Cyst	3 (6%)			2 (4%)
Periovarian tissue, cyst	5 (10%)	3 (18%)	9 (60%)	5 (10%)
Uterus	(50)	(50)	(50)	(50)
Cyst			3 (6%)	
Hydrometra	11 (22%)	9 (18%)	5 (10%)	14 (28%)
Inflammation, acute				1 (2%)
Inflammation, chronic		2 (4%)		
Inflammation, chronic active			1 (2%)	1 (2%)
Metaplasia, squamous				1 (2%)
Pigmentation		1 (2%)		
Cervix, cyst		1 (2%)		
Cervix, inflammation, chronic		1 (2%)		
Endometrium, hyperplasia	6 (12%)	7 (14%)	8 (16%)	7 (14%)
Lumen, exudate	2 (4%)			

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Hematopoietic System				
Lymph node	(48)	(25)	(17)	(49)
Deep cervical, hyperplasia, plasma cell	1 (2%)			
Lumbar, infiltration cellular, histiocyte				1 (2%)
Lumbar, pigmentation				1 (2%)
Mediastinal, depletion lymphoid				1 (2%)
Mediastinal, hemorrhage	8 (17%)	3 (12%)	3 (18%)	7 (14%)
Mediastinal, infiltration cellular, histiocyte				1 (2%)
Mediastinal, necrosis, coagulative				1 (2%)
Mediastinal, pigmentation	2 (4%)	1 (4%)	1 (6%)	2 (4%)
Pancreatic, ectasia			1 (6%)	1 (2%)
Pancreatic, hemorrhage	1 (2%)			2 (4%)
Pancreatic, infiltration cellular, histiocyte			2 (12%)	2 (4%)
Pancreatic, pigmentation			2 (12%)	3 (6%)
Renal, ectasia		2 (8%)		
Renal, hemorrhage	2 (4%)	1 (4%)	2 (12%)	3 (6%)
Renal, infiltration cellular	1 (2%)			
Renal, infiltration cellular, histiocyte	1 (2%)	3 (12%)	2 (12%)	4 (8%)
Renal, pigmentation	1 (2%)	4 (16%)	2 (12%)	3 (6%)
Lymph node, mandibular	(46)	(19)	(10)	(46)
Congestion		1 (5%)		
Ectasia	11 (24%)	5 (26%)		6 (13%)
Hemorrhage	22 (48%)	6 (32%)	3 (30%)	17 (37%)
Hyperplasia, plasma cell	2 (4%)			
Infiltration cellular, histiocyte		2 (11%)	1 (10%)	2 (4%)
Necrosis, coagulative			1 (10%)	
Pigmentation	1 (2%)	2 (11%)		2 (4%)
Lymph node, mesenteric	(9)	(14)	(12)	(9)
Angiectasis			1 (8%)	
Ectasia			1 (8%)	1 (11%)
Hemorrhage	1 (11%)		2 (17%)	
Infiltration cellular, histiocyte	8 (89%)	14 (100%)	10 (83%)	7 (78%)
Necrosis, coagulative				1 (11%)
Pigmentation	8 (89%)	14 (100%)	8 (67%)	7 (78%)
Thrombus			1 (8%)	
Spleen	(50)	(23)	(20)	(50)
Depletion lymphoid	5 (10%)	5 (22%)	4 (20%)	9 (18%)
Fibrosis		1 (4%)		
Hematopoietic cell proliferation		2 (9%)	1 (5%)	1 (2%)
Hyperplasia, lymphoid			3 (15%)	
Inflammation, granulomatous, chronic		2 (9%)	3 (15%)	1 (2%)
Necrosis				1 (2%)
Pigmentation	1 (2%)			
Thrombus	1 (2%)	1 (4%)		
Capsule, hyperplasia	1 (2%)			
Thymus	(8)	(10)	(7)	(9)
Depletion lymphoid	5 (63%)	7 (70%)	1 (14%)	7 (78%)
Hemorrhage		1 (10%)	1 (14%)	
Necrosis, coagulative				1 (11%)

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Integumentary System				
Mammary gland	(36)	(36)	(24)	(22)
Galactocele		1 (3%)	1 (4%)	1 (5%)
Hyperplasia	13 (36%)	20 (56%)	13 (54%)	13 (59%)
Hyperplasia, cystic	1 (3%)			
Skin	(11)	(15)	(8)	(11)
Inflammation, chronic		1 (7%)		
Inflammation, necrotizing, acute			1 (13%)	
Subcutaneous tissue, edema				1 (9%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(15)	(8)	(50)
Hemorrhage				2 (4%)
Hydrocephalus	2 (4%)	1 (7%)	1 (13%)	1 (2%)
Meninges, hemorrhage		2 (13%)		
Spinal cord	(1)	(2)		(2)
Hemorrhage		1 (50%)		1 (50%)
Respiratory System				
Lung	(50)	(20)	(20)	(50)
Crystals	1 (2%)			
Foreign body			1 (5%)	
Hemorrhage	4 (8%)	3 (15%)	2 (10%)	4 (8%)
Infiltration cellular, histiocyte	14 (28%)	5 (25%)	3 (15%)	18 (36%)
Inflammation, acute				1 (2%)
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, chronic active			1 (5%)	1 (2%)
Leukocytosis			1 (5%)	
Metaplasia, osseous	1 (2%)			
Pigmentation				1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	1 (5%)	2 (10%)	1 (2%)
Artery, mineralization	24 (48%)	3 (15%)	6 (30%)	14 (28%)
Nose	(7)	(12)	(7)	(10)
Congestion		1 (8%)		
Capillary, submucosa, thrombus				1 (10%)
Glands, inflammation, acute			1 (14%)	1 (10%)
Lumen, inflammation, acute		1 (8%)		

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

	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Special Senses System				
Eye	(6)	(8)	(6)	(5)
Cataract	5 (83%)	2 (25%)	3 (50%)	1 (20%)
Synechia	1 (17%)	3 (38%)	3 (50%)	
Cornea, fibrosis		2 (25%)		
Retina, degeneration	5 (83%)	6 (75%)	4 (67%)	2 (40%)
Sclera, metaplasia, osseous				1 (20%)
Sclera, mineralization	1 (17%)			
Harderian gland		(4)	(2)	(2)
Hemorrhage		1 (25%)	1 (50%)	
Inflammation, acute		1 (25%)		
Inflammation, chronic		3 (75%)	1 (50%)	1 (50%)
Urinary System				
Kidney	(49)	(49)	(50)	(50)
Autolysis		1 (2%)	1 (2%)	
Congestion		1 (2%)		1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	
Nephropathy	48 (98%)	48 (98%)	50 (100%)	48 (96%)
Artery, fibrosis		1 (2%)		
Artery, thrombus			1 (2%)	
Collecting tubule, mineralization	1 (2%)			
Papilla, necrosis, coagulative			1 (2%)	
Proximal convoluted renal tubule, degeneration, hyaline		1 (2%)		
Proximal convoluted renal tubule, inflammation, acute		4 (8%)		
Proximal convoluted renal tubule, pigmentation		1 (2%)	1 (2%)	
Renal tubule, hyperplasia	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Renal tubule, hyperplasia, cystic			1 (2%)	
Transitional epithelium, hyperplasia	7 (14%)	9 (18%)	5 (10%)	4 (8%)
Urinary bladder	(50)	(49)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, acute				1 (2%)
Inflammation, chronic		4 (8%)		
Subserosa, mineralization	1 (2%)			
Transitional epithelium, hyperplasia				2 (4%)

APPENDIX C
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983) and Zeiger *et al.* (1988). Quercetin was sent to the laboratory as a coded aliquot from Radian Corporation, Austin, TX. It was incubated with the *Salmonella typhimurium* tester strains TA98 and TA100 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of quercetin. The high dose was limited by toxicity. Tests were repeated for all negative assays, and all positive assays were retested under the conditions that elicited the positive response.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987) and is briefly described as follows. Quercetin was sent to the laboratory as a coded aliquot from Radian Corporation, Austin, TX. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of quercetin; the high dose was limited by toxicity.

In the SCE test without S9, CHO cells were incubated for 26 hours with quercetin in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing quercetin was removed and replaced with fresh medium containing BrdU and Colcemid, and quercetin incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with quercetin, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no quercetin, and incubation proceeded for an additional 25 to 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining procedures were the same as for cells treated without S9.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with quercetin for 18 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with quercetin and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for treatment without S9.

Cell cycle delay was anticipated in the Abs test without S9, based on observance of cell cycle progression in the SCE test, and the incubation period prior to cell harvest was therefore extended to allow accumulation of sufficient metaphases for analysis.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 25 to 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose; 100 to 200 first-division metaphase cells were scored at each dose for the Abs test. Exceptions were made in each test when a culture showed high levels of damage which allowed fewer cells to provide a representative sample of the whole culture, or which made it difficult to locate scorable cells. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing ten or more aberrations).

Statistical analyses were conducted on the slopes of the dose-response curves and on the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Abs data are presented as percentage of cells with aberrations. For aberration data, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P \leq 0.05$) difference for one dose point was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

RESULTS

Exposure to quercetin (0.3 to 1,000 μg/plate) produced a strong, dose-related increase in gene mutations in *Salmonella typhimurium* strains TA100 and TA98 in the presence and in the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table C1). In cytogenetic tests with CHO cells, quercetin induced marked increases in both SCE and Abs, with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Tables C2 and C3). In the SCE test without S9, positive responses were observed over a dose range of 0.67 to 20 μg/mL quercetin; with S9, effective doses ranged from 2 to 45 μg/mL. In the Abs test, the trials conducted in the absence of S9 activation employed a delayed harvest protocol to offset quercetin toxicity; positive responses occurred with 10 to 50 μg/mL quercetin. With S9, standard harvest times were employed and strong increases in aberrations were observed with 25 to 75 μg/mL quercetin. At the highest dose (75 μg/mL), 100% of the cells scored contained aberrations.

TABLE C1
Mutagenicity of Quercetin in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+30% hamster S9 Trial 1	+30% hamster S9 Trial 2	+30% rat S9 Trial 1	+30% rat S9 Trial 2
TA100	0	134 ± 15.8	134 ± 3.4	123 ± 15.7	141 ± 8.8	115 ± 7.8	157 ± 6.7
	1			106 ± 4.3	157 ± 14.5	126 ± 7.0	164 ± 14.1
	3	153 ± 9.1	156 ± 4.4	132 ± 7.8	172 ± 10.2	127 ± 11.5	142 ± 5.8
	10			296 ± 17.8	271 ± 6.5	361 ± 8.7	306 ± 29.4
	33	253 ± 13.6	222 ± 13.6	449 ± 7.2	566 ± 38.7	542 ± 20.5	517 ± 19.8
	66				798 ± 31.7		613 ± 32.6
	100		303 ± 8.2	828 ± 22.1		798 ± 32.4	
	333	440 ± 26.7	341 ± 27.0				
	666	467 ± 19.2	426 ± 22.0				
	1,000	512 ± 29.1[d]					
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control[c]		402 ± 23.7	466 ± 13.6	654 ± 45.6	553 ± 54.3	615 ± 41.0	498 ± 9.8
TA98	0.0	17 ± 0.9	19 ± 0.6	27 ± 3.7	29 ± 0.7	29 ± 2.0	30 ± 0.7
	0.3		22 ± 2.7		26 ± 3.1		30 ± 0.6
	1.0		27 ± 0.6	37 ± 1.9	31 ± 4.8	37 ± 4.4	37 ± 1.0
	3.0	78 ± 4.3	53 ± 2.0	77 ± 8.4	51 ± 3.8	68 ± 4.0	50 ± 2.5
	6.0				162 ± 12.3		199 ± 9.0
	10.0		169 ± 18.8	401 ± 24.3	283 ± 24.2	686 ± 46.4	381 ± 33.0
	33.0	404 ± 9.8	223 ± 3.8	796 ± 64.7		1053 ± 5.1	
	100.0			916 ± 63.5		1,116 ± 60.7[d]	
	333.0	549 ± 16.3					
	666.0	576 ± 39.2					
	1,000.0	671 ± 28.2					
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control		495 ± 25.5	452 ± 18.6	367 ± 30.9	436 ± 2.5	168 ± 7.3	160 ± 8.7

[a] Study performed at SRI, International. The detailed protocol is presented in Haworth *et al.* (1983) with modifications as described by Zeiger *et al.* (1988).
[b] Revertants are presented as mean ± standard error from 3 plates.
[c] 2-aminoanthracene was used on both strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, and sodium azide was tested on TA100.
[d] Slight toxicity

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Quercetin[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosomes	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
-S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,050	410	0.39	8.2	25.8	
Mitomycin-C	0.001	50	1,044	663	0.63	13.3	25.8	62.64
	0.010	5	105	181	1.72	36.2	25.8	341.47
Quercetin	0.67	50	1,044	1,041	0.99	20.8	25.8	155.36*
	2.00	50	1,046	563	0.53	11.3	25.8	37.84*
	6.70	5	104	92	0.88	18.4	25.8	126.55*
	20.00	50	1,046	1,087	1.03	21.7	25.8	166.14*
								P<0.001[c]
+S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,043	404	0.38	8.1	25.8	
Cyclophosphamide	0.40	50	1,048	613	0.58	12.3	25.8	51.01
	2.00	5	104	169	1.62	33.8	25.8	319.53
Quercetin	2.0	50	1,048	506	0.48	10.1	25.8	24.65*
	6.7	50	1,043	587	0.56	11.7	25.8	45.30*
	20.0	50	1,041	597	0.57	11.9	25.8	48.06*
								P<0.001
Trial 2								
Summary: Positive								
Dimethylsulfoxide		25	522	180	0.34	7.2	25.3	
Cyclophosphamide	0.40	25	521	323	0.61	12.9	25.3	79.79
	2.00	5	103	230	2.23	46.0	25.3	547.58
Quercetin	20.0	25	524	272	0.51	10.9	25.3	50.54*
	30.0	25	524	308	0.58	12.3	25.3	70.46*
	45.0	25	522	414	0.79	16.6	25.3	130.00*
								P<0.001

* Positive (≥20% increase over solvent control)

[a] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1985, 1987).

[b] Percent increase in SCEs/chromosome of culture exposed to quercetin relative to those of culture exposed to solvent. Values at least 20% above control levels are considered positive.

[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Quercetin[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 – Harvest time: 20.2 hours Summary: Positive					**Trial 1** – Harvest time: 12.0 hours Summary: Positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	2	0.01	1.0		200	5	0.03	2.5
Mitomycin-C					Cyclophosphamide				
0.05	200	95	0.48	26.5	7.5	200	62	0.31	14.5
0.08	25	38	1.52	72.0	37.5	25	42	1.68	56.0
Quercetin					Quercetin				
7.6	200	7	0.04	3.5	25.2	20	58	2.90	45.0*
10.1	200	37	0.19	10.0*	50.3	48	27	0.56	33.3*
25.2	200	102	0.51	21.5*	75.0	25	171	6.84	100.0*
				P<0.001[b]					P<0.001
Trial 2 – Harvest time: 19.7 hours Summary: Positive									
Dimethylsulfoxide									
	100	1	0.01	1.0					
Mitomycin-C									
0.05	100	45	0.45	30.0					
0.08	25	25	1.00	60.0					
Quercetin									
25.0	100	19	0.19	7.0*					
37.5	100	25	0.25	15.0*					
50.0	100	42	0.42	29.0*					
				P<0.001					

* Positive ($P \leq 0.05$)
[a] Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985, 1987).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

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

TABLE D1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 6-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin 144
TABLE D2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin 145

TABLE D1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 6-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin[a]

Organ	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Male				
n	9	9	10	10
Necropsy body wt	416 ± 10	417 ± 7	397 ± 6	401 ± 8
Brain				
Absolute	1.93 ± 0.03	1.96 ± 0.02	1.72 ± 0.11	1.96 ± 0.02
Relative	4.66 ± 0.11	4.69 ± 0.05	4.36 ± 0.30	4.88 ± 0.07
R. Kidney				
Absolute	1.17 ± 0.05	1.22 ± 0.04[b]	1.13 ± 0.04	1.29 ± 0.02*
Relative	2.79 ± 0.08	2.92 ± 0.12[b]	2.83 ± 0.09	3.23 ± 0.09**
Liver				
Absolute	12.87 ± 0.35[b]	12.68 ± 0.45	12.25 ± 0.34	13.66 ± 0.32
Relative	30.9 ± 0.5[b]	30.3 ± 0.8	30.8 ± 0.6	34.1 ± 0.6**
Female				
n	10	10	10	10
Necropsy body wt	243 ± 5	245 ± 6	234 ± 4	214 ± 5**
Brain				
Absolute	1.82 ± 0.03	1.83 ± 0.03	1.84 ± 0.03	1.87 ± 0.02
Relative	7.48 ± 0.10	7.48 ± 0.14	7.90 ± 0.13*	8.74 ± 0.17**
R. Kidney				
Absolute	0.68 ± 0.01	0.69 ± 0.02	0.68 ± 0.01	0.66 ± 0.02
Relative	2.81 ± 0.04	2.84 ± 0.05	2.89 ± 0.03	3.06 ± 0.05**
Liver				
Absolute	7.31 ± 0.25	7.42 ± 0.20	7.50 ± 0.23	6.88 ± 0.20
Relative	30.0 ± 0.7	30.3 ± 0.5	32.0 ± 0.6*	32.1 ± 0.4*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=10

TABLE D2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin[a]

Organ	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Male				
n	10	10	10	9
Necropsy body wt	460 ± 12	466 ± 8	459 ± 14	456 ± 15
Brain				
Absolute	2.07 ± 0.03	2.06 ± 0.02	2.04 ± 0.03	2.05 ± 0.03
Relative	4.53 ± 0.09	4.44 ± 0.08	4.48 ± 0.14	4.53 ± 0.11
R. Kidney				
Absolute	1.44 ± 0.05	1.51 ± 0.06	1.44 ± 0.04	1.59 ± 0.05
Relative	3.15 ± 0.09	3.27 ± 0.17	3.16 ± 0.07	3.49 ± 0.06*
Liver				
Absolute	15.66 ± 0.65	15.12 ± 0.63	15.23 ± 0.48	17.40 ± 0.75
Relative	34.0 ± 1.0	32.4 ± 0.9	33.2 ± 0.5	38.1 ± 1.0**
Female				
n	10	10	10	10
Necropsy body wt	324 ± 9	337 ± 8	307 ± 6	287 ± 6**
Brain				
Absolute	1.90 ± 0.03	1.90 ± 0.02	1.89 ± 0.02	1.90 ± 0.02
Relative	5.88 ± 0.12	5.65 ± 0.13	6.20 ± 0.13	6.65 ± 0.15**
R. Kidney				
Absolute	0.89 ± 0.03	0.93 ± 0.02	0.87 ± 0.02	0.88 ± 0.02
Relative	2.74 ± 0.06	2.77 ± 0.07	2.85 ± 0.04	3.08 ± 0.09**
Liver				
Absolute	9.21 ± 0.21	9.44 ± 0.31	8.90 ± 0.28	9.53 ± 0.34
Relative	28.5 ± 0.6	27.9 ± 0.4	29.1 ± 0.8	33.2 ± 0.8**

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

APPENDIX E
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE E1 Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 6-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin 148
TABLE E2 Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin 150

TABLE E1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 6-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin[a]

Analysis	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Male				
n	10	10	9	10
Hematology				
Erythrocytes ($10^6/\mu L$)	9.50 ± 0.24	9.39 ± 0.25	9.57 ± 0.24	8.78 ± 0.25*
Leukocytes ($10^3/\mu L$)	5.77 ± 0.16	5.32 ± 0.07*	4.87 ± 0.17**	5.11 ± 0.20**
Segmented neutrophils ($10^3/\mu L$)	1.41 ± 0.12	1.34 ± 0.13	1.40 ± 0.13	1.45 ± 0.14
Lymphocytes ($10^3/\mu L$)	4.04 ± 0.13	3.63 ± 0.18	3.20 ± 0.20**	3.33 ± 0.15**
Monocytes ($10^3/\mu L$)	0.28 ± 0.03	0.28 ± 0.04	0.17 ± 0.03*	0.21 ± 0.03*
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.06 ± 0.03	0.10 ± 0.03	0.12 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Clinical chemistry				
BUN (mg/dL)	12.7 ± 0.9[b]	18.6 ± 3.2	11.9 ± 0.5	10.7 ± 0.3
Creatinine (mg/dL)	0.70 ± 0.05	0.77 ± 0.05	0.60 ± 0.03	0.57 ± 0.02*
Sodium (mEq/L)	147 ± 1	147 ± 1	148 ± 1[c]	144 ± 0
Potassium (mEq/L)	3.75 ± 0.08	3.83 ± 0.08	3.79 ± 0.11[c]	3.67 ± 0.07
Chloride (mEq/L)	108 ± 1	109 ± 1	109 ± 1[c]	106 ± 0
ALT (IU/L)	72 ± 7	63 ± 6[b]	67 ± 5	53 ± 4*
AST (IU/L)	122 ± 9	119 ± 10[b]	115 ± 7	82 ± 4**
SDH (IU/L)	567 ± 113[b]	558 ± 81[d]	792 ± 134	647 ± 104
Urinalysis				
Urinary sodium (mEq/L)	46 ± 14	50 ± 10	66 ± 14[c]	60 ± 11
Urinary potassium (mEq/L)	136 ± 21	144 ± 23	166 ± 21[c]	121 ± 17
Urinary chloride (mEq/L)	91 ± 19	105 ± 18	121 ± 19[c]	98 ± 16

TABLE E1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 6-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin (continued)

Analysis	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Female				
n	10	10	10	10
Hematology				
Erythrocytes ($10^6/\mu L$)	8.18 ± 0.22	8.75 ± 0.16	8.73 ± 0.17	8.56 ± 0.19
Leukocytes ($10^3/\mu L$)	3.73 ± 0.22	4.07 ± 0.22	3.80 ± 0.26	3.43 ± 0.15[b]
Segmented neutrophils ($10^3/\mu L$)	0.78 ± 0.10	0.83 ± 0.05	0.95 ± 0.07[b]	0.74 ± 0.07[b]
Lymphocytes ($10^3/\mu L$)	2.80 ± 0.19	2.95 ± 0.19	2.50 ± 0.15	2.60 ± 0.17
Monocytes ($10^3/\mu L$)	0.11 ± 0.02	0.24 ± 0.03**	0.17 ± 0.02	0.13 ± 0.02[b]
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.05 ± 0.01	0.06 ± 0.03	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Clinical chemistry				
BUN (mg/dL)	17.9 ± 1.3	21.7 ± 2.0	19.9 ± 1.1	21.1 ± 1.0
Creatinine (mg/dL)	0.54 ± 0.03	0.54 ± 0.04	0.47 ± 0.03	0.42 ± 0.04**
Sodium (mEq/L)	143 ± 0	144 ± 0	144 ± 0*	144 ± 0
Potassium (mEq/L)	3.04 ± 0.06	3.13 ± 0.10	3.21 ± 0.14	3.23 ± 0.09
Chloride (mEq/L)	107 ± 0	108 ± 1	108 ± 1	108 ± 1
ALT (IU/L)	30 ± 1[b]	33 ± 2	34 ± 4[b]	42 ± 5
AST (IU/L)	65 ± 2[b]	72 ± 3	83 ± 7*[b]	76 ± 5*
SDH (IU/L)	414 ± 23[b]	557 ± 62*[b]	535 ± 85[e]	635 ± 76[b]
Urinalysis				
Urinary sodium (mEq/L)	43 ± 6	26 ± 2*	31 ± 4	38 ± 4[b]
Urinary potassium (mEq/L)	99 ± 16	61 ± 6	110 ± 23	123 ± 22
Urinary chloride (mEq/L)	70 ± 13	45 ± 3	64 ± 10	92 ± 19

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. BUN=blood urea nitrogen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; SDH=sorbitol dehydrogenase.
[b] n=9
[c] n=10
[d] n=7
[e] n=8

TABLE E2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin[a]

Analysis	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Male				
n	10	10	10	10
Hematology				
Erythrocytes ($10^6/\mu L$)	9.44 ± 0.23	9.65 ± 0.21	9.65 ± 0.14	9.43 ± 0.24
Leukocytes ($10^3/\mu L$)	5.08 ± 0.26	5.33 ± 0.30	4.88 ± 0.21	4.99 ± 0.33
Segmented neutrophils ($10^3/\mu L$)	2.03 ± 0.24	1.67 ± 0.11	1.56 ± 0.16	1.89 ± 0.19
Lymphocytes ($10^3/\mu L$)	2.72 ± 0.19	3.38 ± 0.22	3.02 ± 0.17	2.87 ± 0.18
Monocytes ($10^3/\mu L$)	0.24 ± 0.04	0.20 ± 0.03	0.20 ± 0.03	0.19 ± 0.03
Eosinophils ($10^3/\mu L$)	0.10 ± 0.02	0.08 ± 0.03	0.10 ± 0.03	0.05 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.03 ± 0.02	0.04 ± 0.02	0.06 ± 0.02	0.03 ± 0.02
Cinical chemistry				
BUN (mg/dL)	17.8 ± 1.0	32.4 ± 9.4	18.3 ± 1.0	17.8 ± 1.4
Creatinine (mg/dL)	0.49 ± 0.05	0.72 ± 0.16	0.44 ± 0.02	0.58 ± 0.04
Sodium (mEq/L)	146 ± 0	147 ± 1	147 ± 0	147 ± 0
Potassium (mEq/L)	3.61 ± 0.08	3.72 ± 0.11	3.54 ± 0.08	3.78 ± 0.06
Chloride (mEq/L)	110 ± 1	108 ± 1	109 ± 1	107 ± 1*
SDH (IU/L)	816 ± 114[b]	621 ± 70[b]	708 ± 73[b]	345 ± 34**
Urinalysis				
Urinary sodium (mEq/L)	54 ± 8	57 ± 7	63 ± 7[b]	38 ± 7
Urinary potassium (mEq/L)	177 ± 14	190 ± 12	195 ± 13	141 ± 12
Urinary chloride (mEq/L)	120 ± 12	128 ± 9	139 ± 9[b]	90 ± 10

TABLE E2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of Quercetin (continued)

Analysis	0 ppm	1,000 ppm	10,000 ppm	40,000 ppm
Female				
n	10	10	10	10
Hematology				
Erythrocytes ($10^6/\mu L$)	8.62 ± 0.11	8.48 ± 0.12	8.56 ± 0.10	8.15 ± 0.11**
Leukocytes ($10^3/\mu L$)	3.12 ± 0.16	3.01 ± 0.12	3.10 ± 0.17	3.33 ± 0.23
Segmented neutrophils ($10^3/\mu L$)	1.05 ± 0.06	0.89 ± 0.04	0.95 ± 0.07	0.91 ± 0.10
Lymphocytes ($10^3/\mu L$)	1.90 ± 0.11	1.93 ± 0.12	1.98 ± 0.14	2.23 ± 0.15
Monocytes ($10^3/\mu L$)	0.13 ± 0.02	0.16 ± 0.02	0.15 ± 0.02	0.16 ± 0.04
Eosinophils ($10^3/\mu L$)	0.04 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.04 ± 0.01	0.04 ± 0.02	0.05 ± 0.01	0.04 ± 0.01
Clinical chemistry				
BUN (mg/dL)	16.5 ± 1.2	14.0 ± 0.6[b]	15.8 ± 0.9	17.1 ± 1.7
Creatinine (mg/dL)	0.55 ± 0.04	0.62 ± 0.05	0.54 ± 0.02	0.59 ± 0.04
Sodium (mEq/L)	147 ± 0	147 ± 1	146 ± 1	146 ± 0
Potassium (mEq/L)	3.17 ± 0.07	3.32 ± 0.08	3.30 ± 0.08	3.27 ± 0.09
Chloride (mEq/L)	110 ± 0	111 ± 1	111 ± 1	111 ± 1
ALT (IU/L)	29 ± 2	27 ± 2[b]	29 ± 2	33 ± 3
AST (IU/L)	63 ± 4	63 ± 2[b]	67 ± 5	61 ± 3
SDH (IU/L)	205 ± 21	214 ± 24	180 ± 17	248 ± 35
Urinalysis				
Urinary sodium (mEq/L)	50 ± 5[b]	40 ± 6	35 ± 7[b]	29 ± 7*
Urinary potassium (mEq/L)	143 ± 7[b]	113 ± 5*	121 ± 7*	114 ± 13**
Urinary chloride (mEq/L)	110 ± 7[b]	90 ± 6*	87 ± 6*	78 ± 6**[b]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. BUN=blood urea nitrogen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; SDH=sorbitol dehydrogenase.
[b] n=9

APPENDIX F
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Quercetin was obtained in two lots from Freeman Industries (Tuckahoe, NY). Lot no. 969-3790-05 (anhydrous form) was used during the first year of the studies and lot no. 969-0483-18BL (dihydrate form) was used during the second year of the studies. Identity, purity and stability analyses were conducted by the analytical chemistry laboratory Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the quercetin studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a yellow crystalline powder, was identified as quercetin by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of quercetin, as shown in Figures F1 and F2 (*Sadtler Standard Spectra*).

The purity of both lots was determined by elemental analyses, Karl Fischer water analysis, weight loss on drying, NMR, titration, and chromatographic analyses. Titration of two acid groups was performed in dimethylformamide with 0.1 N tetrabutylammonium hydroxide in methanol:2-propanol (1:9) as the titrant. Thin-layer chromatography was performed with two systems: 1) on MN Polyamide-TLC11 plates with methanol:acetylacetone (60:40), and 2) on silica gel plates with toluene:dioxane:acetic acid:methanol (40:25:20:15). After the plates were sprayed with 2,6-dibromoquinonechloroimide, visualization was accomplished with short wave (254 nm) and long wave (366 nm) ultraviolet light. 2,2′,4,4′-Tetrahydroxybenzophenone in absolute ethanol (1 μL of a 10 mg/mL solution) was used as the reference standard. High-performance liquid chromatography (HPLC) was performed with a μBondapak C_{18} column and a mobile phase mixture of two solvents: A) water with pH adjusted to 2.0 with concentrated phosphoric acid and B) methanol with an equal volume of phosphoric acid as added in solvent A. The ratio of solvents used was 52:48 (A:B), at a flow rate of 1 mL/minute. Ultraviolet detection was at 254 nm.

For the anhydrous form, elemental analyses for carbon and hydrogen showed carbon was low and hydrogen was slightly high. Weight loss on drying indicated the presence of 1% to 3% water. NMR quantification indicated the presence of 2.4% water. Titration of two acid groups indicated a purity of 100.8 ± 1.1%. This method would not necessarily distinguish between quercetin and other non-phenolic acid components or quercetin-like compounds. Thin-layer chromatography indicated a major product spot, a minor spot, and a trace by solvent system 1, and a major spot and two traces by solvent system 2. HPLC indicated three impurities with a combined area of 6.6% relative to the major peak. The largest impurity (6.4% by peak area) was identified as ellagic acid by spectroscopy and mass spectrometry. Quantitation against an ellagic acid standard resulted in an estimate of the impurity level of 2.6% (w/w). The overall purity is estimated at approximately 95% as the anhydrous form.

For the dihydrous form, elemental analyses for carbon and hydrogen showed carbon was slightly high, but the value for hydrogen agreed with the theoretical value. Karl Fischer analysis indicated 11.2 ± 0.5% water, which is consistent with the theoretical value for the dihydrous form. Weight loss on drying indicated the presence of 9.1 ± 0.1% water. Titration of acid groups indicated a purity of 112.5 ± 0.4%. Thin-layer chromatography indicated a major product spot and two traces by both solvent systems. HPLC indicated three impurities with areas greater than 0.1% relative to the major peak and a combined relative area of 3.5%. The largest peak (3.1% by peak area) was identified as ellagic acid by spectroscopy and mass spectrometry. Quantitation against an ellagic acid standard

resulted in an estimate of the impurity level of 1.1% (w/w). The overall purity is estimated at approximately 98% as the dihydrate.

Stability studies performed by HPLC with the system described above but with a flow rate of 2.0 mL/minute and with acetanilide added as an internal standard indicated that quercetin, when stored protected from light and under a nitrogen headspace, was stable as a bulk chemical for 2 weeks at temperatures up to 60° C. During the 2-year studies, the stability of the bulk chemical was monitored by the study laboratory using HPLC, with the system described above and with a flow rate of 1.0 mL/minute, and infrared spectral analysis; no degradation of the study material was seen throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared layering a premix, prepared by grinding equal amounts of quercetin and feed with a mortar and pestle, with the remainder of the feed in a blender, (Patterson-Kelley Twin Shell with intensifier bar) and mixing for 15 minutes (Table F1). Studies were conducted by the analytical chemistry laboratory to determine homogeneity and stability of the dosed feed preparations. For homogeneity analyses, the formulations were extracted with methanol:acetic acid (99:1) and the absorbance of the samples was measured versus methanol by ultraviolet spectroscopy at 370 nm. Concentrations were calculated using a standard curve. For the stability studies, a methanol:hydrochloric acid (99.5:0.5) solution was used for extraction and the extract injected into an HPLC system equipped with a μBondapak C_{18} column and a 254 nm detector. The mobile phase was a mixture of two solvents: A) 1.2 mL phosphoric acid and 800 mL water, with pH approximately 2, and B) 1.2 mL phosphoric acid and 800 mL methanol. The ratio of solvents used was 40:60 (A:B) at a flow rate of 2 mL/minute. Visible detection was at 254 nm.

Quercetin at the 10,000 ppm dose level mixed in rodent feed (NIH-07 Rat and Mouse Ration) produced a homogeneous blend and was found to be stable when stored at temperatures up to 25° C. There was a 3% loss of chemical in feed stored 2 weeks at 45° C.

Periodic analyses of the dose formulations of quercetin were conducted at the study laboratory and at the analytical chemistry laboratory using ultraviolet spectroscopy. During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks. All formulations were within the specified 10% of the target concentrations. Results of the dose formulation analyses studies are presented in Table F2. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table F3).

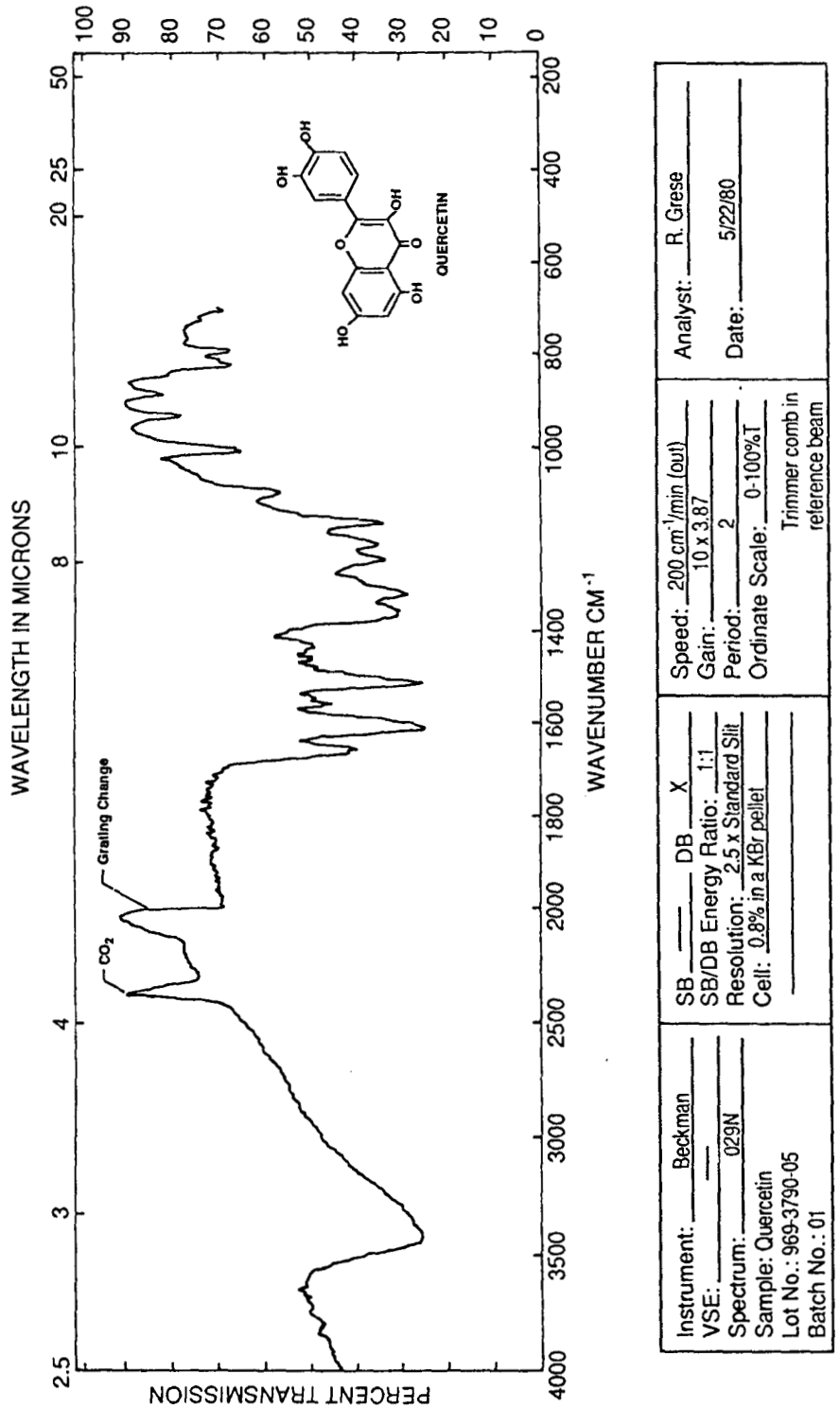

FIGURE F1
Infrared Absorption Spectrum of Quercetin

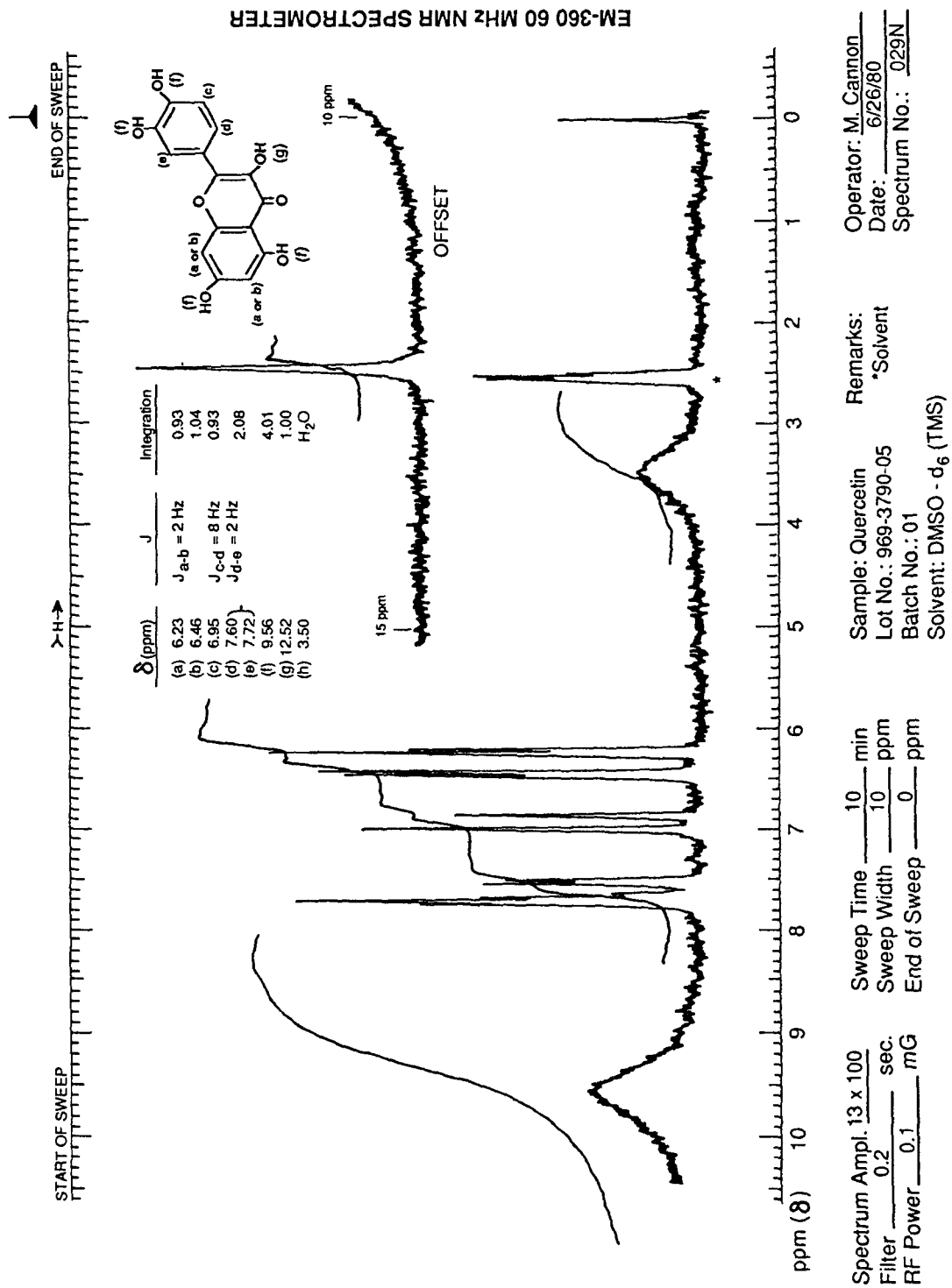

FIGURE F2
Nuclear Magnetic Resonance Spectrum of Quercetin

TABLE F1
Preparation and Storage of Dose Formulations in the Feed Studies of Quercetin

Preparation
Dose formulations prepared weekly. Chemical-feed premix prepared by grinding quercetin and feed with mortar and pestle; premix and remaining feed layered in a blender with intensifier bar and mixed for 15 minutes.

Chemical Lot Number
969-3790-05
969-0483-18BL

Maximum Storage Time
Two weeks

Storage Conditions
Cold room at approximately 4° C, in opaque plastic bags

TABLE F2
Results of Analysis of Dose Formulations in the 2-Year Feed Studies of Quercetin

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
17 June 1982	18 June 1982	1,000	970[b]	-3
17 June 1982	21 June 1982	1,000	952[c]	-5
		1,000	980[d]	-2
		10,000	9,820	-2
		40,000	38,900[b]	-3
		40,000	39,100[c]	-2
		40,000	40,000[d]	0
17 August 1982	18 August 1982	1,000	980	-2
17 August 1982	19 August 1982	10,000	9,970	0
		40,000	39,900	0
9 November 1982	17 November 1982	1,000	980	-2
9 November 1982	18 November 1982	10,000	9,980	0
		40,000	40,200	0
7 December 1982	8 December 1982	1,000	990	-1
7 December 1982	9 December 1982	10,000	10,000	0
		40,000	40,500	+1
1 March 1983	2 March 1983	1,000	990	-1
		10,000	9,900	-1
		40,000	39,800	-1
5 April 1983	7 April 1983	1,000	980	-2
		10,000	10,200	+2
		40,000	39,200	-2
31 May 1983	2 June 1983	1,000	960	-4
		10,000	10,500	+5
		40,000	41,600	+4
19 July 1983	20 July 1983	1,000	1,000	0
19 July 1983	21 July 1983	10,000	9,900	-1
		40,000	40,000	0
2 September 1983	6 September 1983	1,000	970	-3
		10,000	9,950	-1
		40,000	39,800	-1
13 December 1983	14 December 1983	1,000	980	-2
13 December 1983	15 December 1983	10,000	10,100	+1
		40,000	39,400	-2

TABLE F2
Results of Analysis of Dose Formulations in the 2-Year Feed Studies of Quercetin (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
14 February 1984	15 February 1984	1,000	1,000	0
		10,000	10,400	+4
		40,000	39,700	-1
13 March 1984	15 March 1984	1,000	960	-4
		10,000	9,900	-1
		40,000	38,700	-3
15 May 1984	17 May 1984	1,000	970	-3
		10,000	10,050	+1
		40,000	38,900	-3

[a] Results of duplicate analyses
[b] Sample selection from top left zone of PK Blender
[c] Sample selection from top right zone of PK Blender
[d] Sample selection from bottom of PK Blender

TABLE F3
Results of Referee Analysis of Dose Formulations in the 2-Year Feed Studies of Quercetin

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
17 June 1982	1,000	970	1,020
7 December 1982	10,000	10,000	9,980
31 May 1983	40,000	41,600	40,500
13 December 1983	10,000	10,100	9,560

[a] Results of duplicate analysis
[b] Results of triplicate analysis

APPENDIX G
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES

TABLE G1 Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Quercetin 162
TABLE G2 Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Quercetin 163

TABLE G1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Quercetin

Week	0 ppm		1,000 ppm			10,000 ppm			40,000 ppm		
	Feed[a]	Body Weight (g)	Feed	Body Weight (g)	Dose/ Day[b]	Feed	Body Weight (g)	Dose/ Day	Feed	Body Weight (g)	Dose/ Day
1	20.0	162	19.8	160	124	19.8	165	1,198	18.7	167	4,495
2	19.0	195	17.9	196	91	18.0	203	889	16.7	198	3,387
3	17.7	225	18.6	230	81	18.5	233	794	18.0	228	3,145
4	16.6	253	16.8	255	66	17.5	257	680	19.2	252	3,047
5	17.7	271	17.4	272	64	17.6	272	648	18.4	259	2,837
8	19.0	310	18.7	304	62	19.3	312	619	19.6	309	2,529
9	18.8	322	18.3	321	57	18.1	325	559	18.5	320	2,310
12	19.7	340	21.0	337	62	19.1	334	572	19.9	328	2,425
13	18.1	354	18.1	350	52	22.7	343	663	22.8	343	2,656
17	17.6	376	18.0	375	48	19.9	373	535	17.8	364	1,954
21	17.8	399	17.4	399	44	18.7	395	474	17.5	382	1,833
25	20.8	416	24.6	412	60	25.1	409	613	23.7	393	2,408
29	17.7	434	17.3	438	40	17.6	430	410	17.5	413	1,696
30	23.4	445	22.4	438	51	23.1	435	532	22.6	409	2,210
33	18.6	456	18.7	456	41	19.1	448	426	18.1	426	1,701
37	19.1	457	19.1	460	41	20.6	458	450	21.0	432	1,946
41	18.7	464	18.6	466	40	20.0	464	431	21.3	439	1,943
45	21.1	469	18.5	470	39	18.3	464	395	19.7	442	1,784
49	17.7	481	18.6	486	38	19.3	482	400	21.1	453	1,864
53	24.0	484	21.2	487	44	21.1	481	438	22.5	453	1,989
57	24.6	487	24.2	491	49	27.1	488	555	27.2	460	2,369
61	18.2	478	18.5	487	38	19.3	484	399	19.8	457	1,733
65	17.4	485	17.6	491	36	18.2	483	378	18.6	453	1,639
68	19.0	486	18.8	493	38	17.7	490	361	18.7	458	1,631
73	22.4	492	21.0	497	42	21.8	491	444	22.0	458	1,921
81	17.5	492	18.6	492	38	18.3	483	379	20.2	451	1,792
85	21.2	485	20.8	488	43	20.1	480	418	22.6	444	2,037
89	17.2	476	16.7	477	35	17.0	473	359	19.0	436	1,742
93	17.9	473	18.9	482	39	17.0	465	366	19.6	426	1,835
97	18.5	479	19.2	485	40	17.4	450	386	20.6	418	1,972
101	10.9	447	11.8	451	26	10.5	427	247	12.2	402	1,213
104	24.8	464	24.6	451	55	23.1	440	525	24.8	403	2,463
Weeks 1-13:											
Mean	18.5	270	18.5	270	73	19.0	272	736	19.1	267	2,981
Weeks 14-52:											
Mean	19.2	440	19.3	440	44	20.2	436	467	20.0	415	1,934
Weeks 53-104:											
Mean	19.5	479	19.4	483	40	19.1	472	404	20.6	440	1,872

[a] Grams of feed consumed per animal per day
[b] Milligrams of quercetin consumed per day per kilogram of body weight

TABLE G2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Quercetin

Week	0 ppm		1,000 ppm			10,000 ppm			40,000 ppm		
	Feed[a]	Body Weight (g)	Feed	Body Weight (g)	Dose/ Day[b]	Feed	Body Weight (g)	Dose/ Day	Feed	Body Weight (g)	Dose/ Day
1	12.3	138	12.9	141	91	12.3	139	886	11.3	141	3,225
2	11.7	153	12.6	155	81	11.6	152	769	12.1	152	3,171
5	12.6	177	12.6	178	71	12.3	177	692	12.4	176	2,813
6	12.4	187	13.1	186	70	12.2	183	668	12.6	181	2,771
7	12.7	191	13.0	193	67	12.4	189	656	12.1	186	2,599
8	13.6	199	12.9	199	65	12.4	194	642	11.6	190	2,445
12	14.4	215	14.4	214	67	12.5	202	619	12.9	195	2,636
13	14.6	215	14.7	219	67	14.4	207	700	13.8	192	2,885
17	15.0	225	14.7	226	65	13.5	217	621	12.2	203	2,409
21	13.8	233	13.0	233	56	12.8	222	579	11.7	209	2,242
25	13.4	244	13.4	246	55	13.0	232	561	11.5	220	2,092
29	15.5	255	14.3	257	55	13.1	237	554	12.2	220	2,207
33	12.9	257	12.5	263	48	11.8	242	488	11.6	225	2,059
37	14.2	268	15.1	276	55	13.2	252	524	12.2	231	2,113
41	14.0	279	15.3	288	53	13.7	261	526	13.1	239	2,200
45	14.4	292	15.5	299	52	13.7	273	502	13.4	246	2,185
49	14.8	301	14.6	305	48	13.2	279	474	12.5	248	2,027
53	14.6	311	15.3	317	48	13.4	290	460	13.4	256	2,098
57	15.3	319	15.5	329	47	14.1	299	471	14.8	265	2,244
61	14.5	327	16.1	337	48	14.4	310	465	15.7	277	2,274
65	15.4	336	15.2	344	44	14.8	320	463	14.8	285	2,074
69	14.6	343	15.6	349	45	13.7	331	416	15.3	291	2,100
73	14.9	350	14.9	355	42	14.3	335	426	14.2	296	1,928
77	15.3	355	17.0	364	47	15.5	340	455	15.4	303	2,031
81	15.0	362	14.6	368	40	13.9	345	405	14.7	308	1,913
85	15.5	365	15.5	367	42	14.9	348	429	15.4	311	1,983
89	15.5	369	14.8	371	40	15.2	352	431	14.4	314	1,837
93	16.7	369	18.0	376	48	16.1	355	453	17.9	318	2,249
97	10.6	360	9.9	367	27	8.2	340	242	10.1	312	1,295
101	11.4	365	11.5	368	31	12.3	351	350	12.0	317	1,511
104	11.5	357	12.1	360	34	12.5	349	359	12.2	311	1,564
Weeks 1-13:											
Mean	13.1	184	13.3	186	72	12.5	180	704	12.3	177	2,818
Weeks 14-52:											
Mean	14.2	261	14.3	266	54	13.1	246	537	12.3	227	2,170
Weeks 53-104:											
Mean	14.4	349	14.7	355	42	13.8	333	416	14.3	297	1,936

[a] Grams of feed consumed per animal per day
[b] Milligrams of quercetin consumed per day per kilogram of body weight

APPENDIX H
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE H1 Ingredients of NIH-07 Rat and Mouse Ration 166
TABLE H2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 166
TABLE H3 Nutrient Composition of NIH-07 Rat and Mouse Ration 167
TABLE H4 Contaminant Levels in NIH-07 Rat and Mouse Ration 168

TABLE H1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE H2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE H3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.95 ± 1.19	21.2–25.9	26
Crude fat (% by weight)	5.08 ± 0.46	4.2–5.8	26
Crude fiber (% by weight)	3.50 ± 0.60	2.8–4.5	26
Ash (% by weight)	6.66 ± 0.21	6.3–7.1	26
Amino Acids (% of total diet)			
Arginine	1.320 ± 0.072	1.310–1.390	5
Cystine	0.319 ± 0.088	0.218–0.400	5
Glycine	1.146 ± 0.063	1.060–1.210	5
Histidine	0.571 ± 0.026	0.531–0.603	5
Isoleucine	0.914 ± 0.030	0.881–0.944	5
Leucine	1.946 ± 0.056	1.850–1.990	5
Lysine	1.280 ± 0.067	1.200–1.370	5
Methionine	0.436 ± 0.165	0.306–0.699	5
Phenylalanine	0.938 ± 0.158	0.665–1.050	5
Threonine	0.855 ± 0.035	0.824–0.898	5
Tryptophan	0.277 ± 0.221	0.156–0.671	5
Tyrosine	0.618 ± 0.086	0.564–0.769	5
Valine	1.108 ± 0.043	1.050–1.170	5
Essential Fatty Acids (% of total diet)			
Linoleic	2.290 ± 0.313	1.830–2.520	5
Linolenic	0.258 ± 0.040	0.210–0.308	5
Vitamins			
Vitamin A (IU/kg)	11,565 ± 4,265	4,200–22,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α–Tocopherol (ppm)	43.58 ± 6.92	31.1–48.0	5
Thiamine (ppm)	18.46 ± 3.89	12.0–31.0	26
Riboflavin (ppm)	7.6 ± 0.85	6.10–8.20	5
Niacin (ppm)	97.8 ± 31.68	65.0–150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0–34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60–8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80–3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19–0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6–38.0	5
Choline (ppm)	3,122 ± 416.8	2,400–3,430	5
Minerals			
Calcium (%)	1.26 ± 0.10	1.04–1.43	26
Phosphorus (%)	0.96 ± 0.05	0.90–1.10	26
Potassium (%)	0.900 ± 0.098	0.772–0.971	3
Chloride (%)	0.513 ± 0.114	0.380–0.635	5
Sodium (%)	0.323 ± 0.043	0.258–0.371	5
Magnesium (%)	0.167 ± 0.012	0.151–0.181	5
Sulfur (%)	0.304 ± 0.064	0.268–0.420	5
Iron (ppm)	410.3 ± 94.04	262.0–523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70–99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10–58.20	5
Copper (ppm)	10.72 ± 2.76	8.09–15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52–3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44–2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.51 ± 0.14	0.18–0.74	26
Cadmium (ppm)	0.12 ± 0.04	0.10–0.20	26
Lead (ppm)	0.65 ± 0.52	0.27–2.93	26
Mercury (ppm)	<0.05		26
Selenium (ppm)	0.31 ± 0.06	0.21–0.45	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)[b]	9.66 ± 4.49	2.50–19.0	26
Nitrite nitrogen (ppm)[b]	1.43 ± 1.50	0.10–6.10	26
BHA (ppm)[c]	4.04 ± 4.98	2.00–20.0	26
BHT (ppm)[c]	2.92 ± 2.59	1.00–13.0	26
Aerobic plate count (CFU/g)[d]	146,527 ± 143,387	6,200–420,000	26
Coliform (MPN/g)[e]	585 ± 859	<3.0–2400	26
E. coli (MPN/g)[f]	3.83 ± 2.68	<3.00–15.00	25
E. coli (MPN/g)	9.42 ± 28.79	<3.00–150.00	26
Total nitrosoamines (ppb)[g]	5.30 ± 5.98	0.80–30.30	26
N-Nitrosodimethylamine (ppb)[g]	4.47 ± 5.91	0.50–30.00	26
N-Nitrosopyrrolidine (ppb)[g]	0.81 ± 0.65	0.30–2.20	26
Pesticides (ppm)			
α-BHC[h]	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor[i]	<0.05	0.06	26
Dieldrin[i]	<0.01	0.02	26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.1		26
Estimated PCBs	<0.2		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.1		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion[j]	0.15 ± 0.17	0.05–0.81	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony-forming unit
[e] MPN = most probable number
[f] Excludes one high value of 150 MPN/g obtained from the lot milled on 26 August 1982.
[g] All values were corrected for percent recovery.
[h] BHC = hexachlorocyclohexane or benzene hexachloride
[i] Value and date of one observation which was above the detection limit is given under the range. All other values were less than the detection limit.
[j] Fifteen lots contained more than 0.05 ppm.

APPENDIX I
SENTINEL ANIMAL PROGRAM

METHODS 172

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 are untreated, and 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.

Fifteen F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from 10 diet control animals, 5 per sex. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	6, 12, 18, and 24 months
PVM (pneumonia virus of mice)	
Sendai	
KRV (Kilham rat virus)	
H-1 (Toolan's H-1 virus)	
ELISA	6, 12, 18, and 24 months
RCV/SDA (rat corona virus/sialodacryoadenitis virus)	

All test results for sentinel animals were negative.

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
410	Naphthalene
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
415	Polysorbate 80
419	HC Yellow 4

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