NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 427

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TURMERIC OLEORESIN

(CAS NO. 8024-37-1)

(MAJOR COMPONENT 79%-85% CURCUMIN, CAS NO. 458-37-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(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

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P.O. Box 12233
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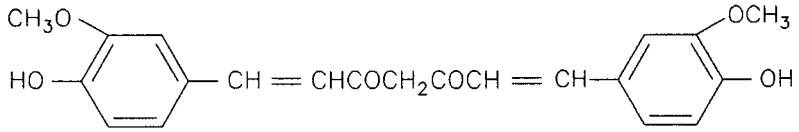
ABSTRACT

TURMERIC OLEORESIN
CAS No. 8024-37-1

Synonyms: curcuma oil; oil of turmeric; turmeric oil; curcuma longa oils; curcuma long oil; Curcumin

Major Component of Turmeric Oleoresin



CURCUMIN
CAS No. 458-37-7

Chemical Formula: $C_{21}H_{20}O_6$ Molecular Weight: 368.37

Synonyms: 1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione; C.I. Natural Yellow 3; C.I. 75300; Curcuma; diferuloylmethane; E 100; Haidr; Halad; Haldar; Halud; HSDB 4334; Indian Saffron; kacha haldi; Kurkumin; merita earth; Souchet; Turmeric Yellow; yellow ginger; yellow root; Yo-kin; Zlut Prirodni 3; NCI-C613253

Turmeric oleoresin is the organic extract of turmeric, a ground powder from the root of the *Curcuma* plant, and is added to food items as a spice and coloring agent. Turmeric oleoresin, turmeric, and curcumin (the major component found in turmeric) were nominated by the National Cancer Institute and the Food and Drug Administration for study because these chemicals are used in food items and curry powders, and there was little information on their toxic or carcinogenic properties. Pure curcumin was not available in sufficient quantities for study, and a turmeric oleoresin with a high curcumin content (79% to 85%) was selected for evaluation. Toxicity and carcinogenicity studies were conducted by administering turmeric oleoresin in feed to groups of male and female F344/N rats and B6C3F$_1$ mice for 13 weeks and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were fed diets containing 0, 1,000, 5,000, 10,000, 25,000, or 50,000 ppm turmeric oleoresin. All rats survived until the end of the study. The final mean body weight of males receiving 50,000 ppm was 5% lower than that of the controls. Feed consumption by exposed male and female rats was similar to that by the controls. Dietary levels of 1,000, 5,000, 10,000, 25,000, or 50,000 ppm turmeric oleoresin were estimated to deliver average daily doses of 50, 250, 480, 1,300, or 2,600 mg/kg body weight to males and 60, 300, 550, 1,450, or 2,800 mg/kg to females. The absolute and relative liver weights of female rats and the relative liver weights of male rats receiving 5,000, 10,000, 25,000, and 50,000 ppm were significantly greater than those of the controls. There were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters. Clinical findings included stained fur, and discolored feces and urine of exposed animals, presumably due to the parent compound or its metabolites. Hyperplasia of the mucosal epithelium was observed in the cecum and colon of male and female rats that received 50,000 ppm.

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were fed diets containing 0, 1,000, 5,000, 10,000, 25,000, or 50,000 ppm turmeric oleoresin. There were no deaths attributed to turmeric oleoresin and the final

mean body weight gains and final mean body weights of all exposed groups of male and female mice were similar to those of the controls. Feed consumption by exposed male and female mice was similar to that by the controls. Dietary levels of 1,000, 5,000, 10,000, 25,000, or 50,000 ppm turmeric oleoresin were estimated to deliver average daily doses of 150, 750, 1,700, 3,850, or 7,700 mg/kg body weight to males and 200, 1,000, 1,800, 4,700 or 9,300 mg/kg to females. Absolute and relative liver weights of male mice that received 5,000 ppm and male and female mice that received 10,000, 25,000 and 50,000 ppm were significantly greater than those of the controls. Clinical findings in mice included stained fur, and discolored feces and urine. There were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters, and there were no chemical-related histopathologic lesions.

2-Year Study in Rats

The exposure level selection for the 2-year study was based on the 13-week study, which showed that rats could tolerate diets containing up to 50,000 ppm. Groups of 60 male and 60 female F344/N rats were fed diets containing 2,000, 10,000, or 50,000 ppm turmeric oleoresin for 104 (males) or 103 (females) weeks, which were estimated to deliver average daily doses of 80, 460, or 2,000 mg/kg to males and 90, 440, or 2,400 mg/kg to females. Nine or 10 rats from each exposure group were evaluated after 15 months.

Survival, Mean Body Weights, Feed Consumption, and Clinical Findings

Survival of exposed male and female rats was similar to that of the controls (male: 0 ppm, 18/50; 2,000 ppm, 17/50; 10,000 ppm, 15/50; 50,000 ppm, 17/50; female: 33/50, 27/50, 28/50, 34/50). The final mean body weights of all exposed male rats and female rats receiving 2,000 and 10,000 ppm were similar to those of the controls. The final mean body weights of male and female rats that received 50,000 ppm were slightly lower (up to 10%) than those of the controls throughout much of the study. Feed consumption by exposed male and female rats was similar to that by controls throughout the study. The absolute and relative liver weights of female rats receiving 10,000 or 50,000 ppm were significantly greater than those of controls at the 15-month interim evaluation. There were no clinical findings related to toxicity.

Hematology and Clinical Chemistry

In male and female rats receiving 50,000 ppm the hematocrit values, hemoglobin concentrations, and erythrocyte counts at the 15-month interim evaluation were significantly lower than those in the controls. In addition, platelet counts in male and female rats that received 50,000 ppm and reticulocyte counts in male rats that received 50,000 ppm were significantly higher than those in the controls. No biologically significant differences were observed in clinical chemistry parameters.

Pathology Findings

Chemical-related nonneoplastic lesions occurred in the gastrointestinal tract of rats that received 50,000 ppm. Males receiving 50,000 ppm had increased incidences of ulcers, hyperplasia, and hyperkeratosis of the forestomach. Male and female rats that received 50,000 ppm had ulcers, chronic active inflammation, and hyperplasia of the cecum. Similar lesions also occurred in the colon of males receiving 50,000 ppm. Male and female rats that received 50,000 ppm and male rats that received 10,000 ppm had significantly increased incidences of sinus ectasia of the mesenteric lymph node.

The incidences of clitoral gland adenoma in all exposed groups of female rats were significantly increased. Clitoral gland carcinomas occurred in one control female and in four 2,000 ppm females, but not in females that received 10,000 or 50,000 ppm. The incidences of clitoral gland adenoma or carcinoma (combined) in all exposed groups of female rats were similar (6/50, 16/48, 15/47, 16/49) and did not increase with exposure level. The incidence of clitoral gland hyperplasia was similar among exposed and control groups of female rats (7/50, 5/48, 4/47, 7/49).

2-Year Study in Mice

The exposure level selection for the 2-year study was based on the 13-week study, which showed that mice could tolerate diets containing up to 50,000 ppm. Groups of 60 male and 60 female B6C3F$_1$ mice were fed diets containing 2,000, 10,000, or 50,000 ppm turmeric oleoresin for 103 weeks, which were estimated to deliver average daily doses of 220, 520, or 6,000 mg/kg to males and 320, 1,620, or 8,400 mg/kg to females. Nine or 10 mice from each exposure group were evaluated after 15 months.

Survival, Mean Body Weights, Feed Consumption, and Clinical Findings

Survival of exposed male and female mice was similar to that of the controls (male: 0 ppm, 43/50; 2,000 ppm, 43/50; 10,000 ppm, 37/50; 50,000 ppm 42/50; female: 39/50, 41/50, 34/50, 42/50). The mean body weight of female mice receiving 50,000 ppm was slightly lower (up to 12%) than that of the controls from about week 25. The final mean body weights of males that received 50,000 ppm and females that received 10,000 and 50,000 ppm were significantly lower than those of controls. The final mean body weights of other exposed groups of male and female mice were similar to those of the controls. Feed consumption by exposed male and female mice was similar to that by the controls throughout the study. The absolute and relative liver weights of male and female mice receiving 10,000 and 50,000 ppm were significantly greater than those of the controls at the 15-month interim evaluation. There were no clinical findings related to toxicity.

Hematology and Clinical Chemistry

No biologically significant differences were observed in hematologic parameters. The alkaline phosphatase values of male and female mice that received 10,000 and 50,000 ppm were significantly higher than those of controls at the 15-month interim evaluation.

Pathology Findings

The incidences of hepatocellular adenoma in male and female mice receiving 10,000 ppm, but not those in mice receiving 2,000 or 50,000 ppm, were significantly increased (male: 25/50, 28/50, 35/50, 30/50; female: 7/50, 8/50, 19/51, 14/50). The number of male and female mice in the 10,000 and 50,000 ppm groups with multiple hepatocellular neoplasms was significantly greater than that in the controls. The incidences of hepatocellular carcinoma were similar among exposed and control groups.

In contrast to rats, there were no chemical-related nonneoplastic lesions of the gastrointestinal tract in mice. Three males that received 2,000 ppm and three males that received 10,000 ppm had carcinomas of the small intestine; neoplasms of the small intestine were not observed in control males or in males that received 50,000 ppm. Female mice receiving 50,000 ppm had a significantly increased incidence of thyroid gland follicular cell hyperplasia.

Genetic Toxicology

Turmeric oleoresin was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 with or without exogenous metabolic activation (S9). It induced small but significant increases in sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. The positive response in the sister chromatid exchange test occurred in the presence of S9, whereas the aberrations response occurred without S9.

Conclusions

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of turmeric oleoresin in male F344/N rats administered 2,000, 10,000, or 50,000 ppm. There was *equivocal evidence of carcinogenic activity* of turmeric oleoresin in female F344/N rats based on increased incidences of clitoral gland adenomas in the exposed groups. There was *equivocal evidence of carcinogenic activity* of turmeric oleoresin in male $B6C3F_1$ mice based on a marginally increased incidence of hepatocellular adenoma at the 10,000 ppm level, and the occurrence of carcinomas of the small intestine in the 2,000 and 10,000 ppm groups. There was *equivocal evidence of carcinogenic activity* of turmeric oleoresin in female $B6C3F_1$ mice based on an increased incidence of hepatocellular adenomas in the 10,000 ppm group.

Turmeric oleoresin ingestion was also associated with increased incidences of ulcers, hyperplasia, and inflammation of the forestomach, cecum, and colon in male rats and of the cecum in female rats. In female mice, ingestion of diets containing turmeric oleoresin was also associated with an increased incidence of thyroid gland follicular cell hyperplasia.

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

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Turmeric Oleoresin

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure Levels	0, 2000, 10,000, or 50,000 ppm in feed (approximately 80, 460, or 2,000 mg/kg)	0, 2,000, 10,000, or 50,000 ppm in feed (approximately 90, 440, or 2,400 mg/kg)	0, 2,000, 10,000, or 50,000 ppm in feed (approximately 220, 520, or 6,000 mg/kg)	0, 2,000, 10,000, or 50,000 ppm in feed (approximately 320, 1,620, or 8,400 mg/kg)
Body weights	50,000 ppm group lower than controls	50,000 ppm group lower than controls	Exposed groups similar to controls	50,000 ppm group lower than controls
2-year survival rates	18/50, 17/50, 15/50, 17/51	33/50, 27/50, 28/50, 34/51	43/50, 43/50, 37/50, 42/50	39/49, 41/50, 34/51, 42/50
Nonneoplastic effects	Forestomach: ulcer (2/49, 3/50, 2/43, 6/51); hyperplasia (7/49, 5/50, 4/43, 18/51); hyperkeratosis (4/49, 5/50, 2/43, 16/51) Cecum: ulcer (0/50, 0/49, 1/50, 26/51); hyperplasia (0/50, 1/49, 0/50, 41/51); inflammation (0/50, 0/49, 0/50, 28/51) Colon: ulcer (0/49, 0/50, 0/49, 6/49); hyperplasia (0/49, 0/50, 0/49, 4/49); inflammation (0/49, 0/50, 0/49, 2/49) Mesenteric lymph node: sinus ectasia (0/49, 1/50, 7/50, 49/51)	Cecum: ulcer (0/50, 0/50, 0/50, 20/51); hyperplasia (0/50, 0/50, 1/50, 48/51); inflammation (0/50, 0/50, 0/50, 36/51) Mesenteric lymph node: sinus ectasia (0/50, 0/50, 1/50, 50/51)	None	Thyroid gland: follicular cell hyperplasia (5/50, 8/50, 7/50, 16/49)
Neoplastic effects	None	None	None	None
Uncertain findings	None	Clitoral gland: adenoma (5/50, 12/48, 15/47, 16/49); adenoma or carcinoma (combined) (6/50, 16/48, 15/47, 16/49)	Liver: hepatocellular adenoma (25/50, 28/50, 35/50, 30/50); hepatocellular adenoma or carcinoma (combined) (30/50, 38/50, 41/50, 37/50) Small intestine: carcinoma (0/50, 3/50, 3/50, 0/50)	Liver: hepatocellular adenoma (7/50, 8/50, 19/51, 14/50); hepatocellular adenoma or carcinoma (combined) (13/50, 12/50, 25/51, 19/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Turmeric Oleoresin (continued)

	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Level of evidence of carcinogenic activity	No evidence	Equivocal evidence	Equivocal evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutation	Negative in strains TA100, TA1535, TA1537, and TA98 with or without S9			
Sister chromatid exchanges				
Chinese hamster ovary cells *in vitro*	Positive with S9			
Chromosomal aberrations				
Chinese hamster ovary cells *in vitro*	Positive 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.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on turmeric oleoresin on June 23, 1992, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

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30 ppm of acetone or chlorinated solvents, and no more than 50 ppm methanol, ethanol, or isopropanol (Govindarajan, 1980). The recommended acceptable daily intake of turmeric, turmeric oleoresin, and/or curcumin is 0.1 to 2.5 mg/kg body weight (FAO/WHO, 1978).

Turmeric oleoresin is used as a food color and imparts a characteristic mild spicy aroma to products such as mustard, pickles, and relishes. Turmeric oleoresin is found in curry powder and is widely used as a spice (Govindarajan, 1980). Curry powders contain 10% to 30% curcumins (Govindarajan, 1980). The dried powder, turmeric, has been reported to be added to gelatins and puddings (0.05 ppm), condiments (760 ppm), soups (30 to 50 ppm), meats (200 ppm), and pickles (690 ppm). Turmeric oleoresin is added to condiments (640 ppm), meats (20 to 100 ppm), and pickles (200 ppm). Curcumin has been reported to be used in the coloring of oils and textiles, and as an alkali indicator, boron detector, and histochemical stain (*Colour Index*, 1971). Turmeric, turmeric oleoresin, and curcumin have been used as dyes to color silk and cotton, as colorings in a variety of different foods, and as a fragrance in soaps, detergents, creams, lotions, and perfumes. Turmeric spice is not produced in the United States. Between 1975 and 1978 the annual amount of imported turmeric was estimated at 1.2×10^9 g to 1.9×10^9 g (U.S. Imports for Consumption and General Imports, 1978).

Curcumin has long been used as a folk medicine in India for the treatment of sprain and inflammation (Chopra *et al.*, 1958; Donatus *et al.*, 1990), although clinical trials to determine efficacy for these uses have not been performed. Kunchandy and Rao (1990), using an *in vitro* assay system, have shown that curcumin can scavenge reactive oxygen radicals. Curcumin has been reported to protect against acetaminophen-induced lipid peroxidation in isolated hepatocytes (Donatus *et al.*, 1990) and smoke-induced DNA damage in human lymphocytes (Shalini and Srinivas, 1990). Other studies report that topical application of curcumin inhibits neoplasm promotion in mouse skin by 12-*O*-tetra-decanoylphorbol-13-acetate (Huang *et al.*, 1988). Curcumin has also been shown to inhibit neoplasm promotion by phorbol esters in mouse fibroblast cells (Huang *et al.*, 1991).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

In male Wistar rats administered an oral bolus dose of 10, 80, or 400 mg [^{3}H]-curcumin, the percentage of curcumin absorbed (60% to 66%) remained constant over the range of doses studied, and curcumin was detected in the blood, liver, and kidney. At doses of 10 and 80 mg, the bulk of the chemical was excreted in the feces (60% to 90%) within 3 days, while at 400 mg excretion in the feces was more prolonged, occurring over a 12-day period. The authors suggest that this prolonged excretion pattern was indicative of enterohepatic circulation (Vijayalakshmi and Chandrasekhara, 1982), which is supported by evidence from other studies where glucuronide conjugates of curcumin were found in the bile (Holder *et al.*, 1978).

In contrast to the findings by Vijayalakshmi and Chandrasekhara (1982), Wahlström and Blennow (1978) reported that in Sprague-Dawley rats receiving 1 g/kg curcumin orally, very low or undetectable amounts of curcumin were found in the blood, urine, and bile. Curcumin in the Wahlström and Blennow (1978) studies was measured by spectrofluorimetric analyses and this method may not have been able to detect conjugates of curcumin occurring in blood and urine. Wahlström and Blennow (1978) also reported that 90% of the curcumin was metabolized by isolated hepatocytes, although studies to identify the metabolites were not conducted.

Holder *et al.* (1978) have reported on studies comparing the oral, intraperitoneal, and intravenous administration of 0.6 mg [^{3}H]-curcumin in male Sprague-Dawley rats. After oral administration, 90% of the label was excreted in the feces and approximately 6% was excreted in the urine, while after intraperitoneal administration 80% was excreted in the feces and 10% was excreted in the urine within 72 hours. The bile from cannulated rats was found to contain 85% of the label after an intravenous dose. The primary metabolites identified in the bile by mass spectrometry were the glucuronides of tetrahydrocurcumin and hexahydrocurcumin.

Humans

No information on the absorption, distribution, metabolism, and excretion of turmeric or related

chemicals in humans has been reported in the literature.

Toxicity

Experimental Animals

The toxicity information for turmeric oleoresin, turmeric, or curcumin is limited, and 14-day and 13-week rodent toxicity studies which include histopathologic analyses of major organ systems have not been reported (FAO/WHO, 1980; RTECS, 1991). The complete chemical composition of the turmeric or curcumin oil used in the studies described below was not reported.

The oral LD_{50} of curcumin oil in rats was reported to be greater than 5 g/kg (Opdyke and Letizia, 1983). The oral LD_{50} of curcumin in mice was reported to be more than 2 g/kg (Srimal and Dhawan, 1973). Undiluted curcuma oil applied to intact or abraded rabbit skin for 24 hours was slightly irritating, whereas curcuma oil applied to the backs of hairless mice was not irritating (Opdyke and Letizia, 1983).

When powdered turmeric (2.5 g/kg body weight) or its alcoholic extract (300 mg alcohol extract/kg body weight) was administered in the diet for one day to rats, guinea pigs, or monkeys, no toxicity was noted one day or three weeks after treatment. There were no treatment-related gross or microscopic lesions in the liver, kidney, or heart. The powdered turmeric used in these studies contained 2.5% curcumin (Shankar *et al.*, 1980).

When turmeric oleoresin with a curcumin content of 17% (the remaining constituents were not specified) was fed to pigs for 102 to 109 days at doses of 60, 296, or 1,551 mg/kg body weight, the liver and thyroid weights were increased at all dose levels. Microscopic evaluations of major organ systems were conducted, and treatment-related findings included pericholangitis, hyperplasia of the thyroid, and an increase in the number of cell layers in the urinary bladder epithelium (Bille *et al.*, 1985).

Rats fed a diet containing 0.04% turmeric for 15 weeks had lower cholesterol levels in plasma and liver than control rats (Bhuvaneswaran *et al.*, 1963). Serum cholesterol levels were reported to be lower in rats fed diets containing 0.1% or 0.5% curcumin for 7 weeks (Rao *et al.*, 1970). An anti-inflammatory effect of turmeric or curcumin has been reported in mice and rats (Chandra and Gupta, 1972; Ghatak and Basu, 1972; Srimal and Dhawan, 1973). In these studies a chemical such as formalin or carrageenan was injected into the paw of the rodent, and the ability of curcumin to inhibit inflammation was measured. Curcumin, at oral doses ranging from 20 to 80 mg/kg, as well as cortisone and phenylbutazone were found to inhibit edema in rats and mice (Srimal and Dhawan, 1973).

Humans

The literature contains no information on the toxicity of turmeric, turmeric oleoresin, or curcumin in humans.

Reproductive and Developmental Toxicity

Experimental Animals

Govindarajan (1980) reported that the Central Drug Research Institute (Lucknow, India), administered curcumin in doses of 600 or 1,600 mg/kg body weight on days 6 through 15 of gestation to rats and rabbits, and no treatment-related effects on total implants, resorption, live and dead embryos, or skeletal or visceral abnormalities were observed. Govindarajan (1980) also summarized studies done at the National Institute of Nutrition, Hyderabad, India, where rats fed diets containing 0.5% turmeric or 0.015% curcuminoids were mated after 12 weeks of treatment without adverse effects on pregnancy rate, mean number of live and dead embryos, or total implants. Further details on these studies were not available in the literature.

Humans

There is no information in the literature on human reproductive and developmental toxicity of turmeric oleoresin, curcumin, or turmeric powder.

Carcinogenicity

Experimental Animals

There have been no carcinogenicity studies in experimental animals reported in the literature for turmeric oleoresin, curcumin, or turmeric powder.

Humans

No information on the potential carcinogenicity of turmeric or related chemicals in humans has been reported in the literature.

GENETIC TOXICITY

Turmeric oleoresin was not mutagenic in most systems in which it was tested. No growth inhibition due to DNA damage was observed in the *Bacillus subtilis* Rec assay (Ungsurungsie *et al.*, 1982), and tests for induction of gene mutation in *Salmonella typhimurium* were negative, with and without S9 (Jensen, 1982; Mortelmans *et al.*, 1986; Nagabhushan and Bhide, 1986; Shah and Netrawali, 1988). No gene conversion was observed in *Saccharomyces cerevisiae* following treatment with turmeric without S9 (Sankaranarayanan and Murthy, 1979). Turmeric did not induce sex-linked recessive lethal mutations in germ cells of *Drosophila melanogaster* (Abraham and Kesavan, 1985).

In contrast to the negative results in gene mutation assays, *in vitro* mammalian cell clastogenicity studies with turmeric gave positive results. Chromosome breakage and mitotic arrest were induced *in vitro* in mouse, hamster, and deer fibroblasts, and in human lymphocytes without S9 (Goodpasture and Arrighi, 1976). However, no induction of micronuclei or chromosomal aberrations in bone marrow cells, or dominant lethal mutations in sperm, were observed in mice fed a diet containing 0.5% turmeric oleoresin for 12 weeks (Vijayalaxmi, 1980; Abraham and Kesavan, 1984). No induction of chromosomal aberrations was observed in bone marrow cells of rats fed a diet of 0.5% turmeric for 12 weeks (Vijayalaxmi, 1980).

Genotoxicity test results with curcumin, a major component of turmeric oleoresin, showed similar patterns of responses. Although growth inhibition due to DNA damage was observed in the *B. subtilis* Rec assay (Kawachi *et al.*, 1980), all tests for induction of gene mutation in *S. typhimurium* were negative, with and without S9 (Bonin and Baker, 1980; Jensen, 1982; Yasui *et al.*, 1982; Ishidate *et al.*, 1984; Mortelmans *et al.*, 1986; Nagabhushan and Bhide, 1986). Curcumin did not induce gene mutations in silkworm larvae (Kawachi *et al.*, 1980). Induction of chromosomal aberrations by curcumin was reported in cultured hamster fibroblasts (Kawachi *et al.*, 1980; Ishidate *et al.*, 1981), and micronuclei were induced in hamster and human fibroblasts *in vitro* (Sasaki *et al.*, 1980). As with turmeric oleoresin, tests for induction of chromosomal aberrations, micronuclei, or dominant lethal mutations in mice fed 0.015% curcumin in the diet for 12 weeks were negative (Vijayalaxmi, 1980).

Genotoxicity data are available on two of the minor components of turmeric oleoresin: cineol and caprylic acid. Cineol was negative in the *B. subtilis* Rec assay (Oda *et al.*, 1978) and the *S. typhimurium* gene mutation test (Haworth *et al.*, 1983). It did not induce chromosomal aberrations, but did increase the frequency of sister chromatid exchanges, in Chinese hamster ovary cells in the absence of S9 (Galloway *et al.*, 1987). Caprylic acid was also nonmutagenic in *S. Typhimurium* (Zeiger *et al.*, 1988).

STUDY RATIONALE

Turmeric (containing a mixture of chemicals, with curcumin being the major component) and curcumin were nominated by the Food and Drug Administration and the National Cancer Institute for testing because of the lack of toxicity and carcinogenicity test data for these chemicals, and because there is widespread exposure to these chemicals in the diet. Pure curcumin was not available, and a turmeric oleoresin (the organic extract of turmeric) with a high curcumin content was selected for testing. The chemical was administered in the feed to rats and mice because this is the route of exposure in humans.

MATERIALS AND METHODS

Procurement and Characterization of Turmeric Oleoresin

Turmeric oleoresin was obtained from Kalsec, Incorporated (Kalamazoo, MI), in four lots (2173-A, 2327-A, 2452-A, and 2558-A). Lots 2173-A and 2327-A were used sequentially throughout the 13-week studies and lots 2452-A and 2558-A were used sequentially throughout the 2-year studies. The material was a purified oleoresin that was produced by extracting turmeric with acetone, followed by concentration and acid precipitation. Identity, characterization, and stability analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and confirmed by the study laboratory (Appendix H).

All lots of the purified extract, a yellow-orange crystalline powder, had infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopic characteristics expected for turmeric oleoresin. The melting point range was 173.5° to 174.5° C. The lots were characterized by elemental analyses, Karl Fischer water analysis, nonaqueous titration, thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography of all lots indicated one major spot with some minor and trace spots. High-performance liquid chromatography of all lots indicated one major peak and several smaller peaks. The major component was identified as curcumin (79% to 85%) with two other components tentatively identified as 1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (11.3% to 16.9%) and 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (1.3% to 3.1%). Stability studies performed at the analytical chemistry laboratory indicated that the percent composition of turmeric oleoresin did not change when heated to 60° C for 2 weeks while being protected from light. The percent composition was monitored periodically at the study laboratory with free-acid titration and high-performance liquid chromatography methods; no change in composition was observed.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared weekly by mixing turmeric oleoresin with feed (Table H1). Homogeneity and stability studies of the 10,000 ppm dose formulation were performed using high-performance liquid chromatography by the analytical chemistry laboratory. Homogeneity was confirmed and the stability of the dose formulations was confirmed for at least 2 weeks at room temperature, when stored in the dark, and at least 1 week under simulated dosing conditions (exposed to light and air). No special handling was required during dosing.

Periodic analyses of the dose formulations of turmeric oleoresin were conducted at the study laboratory and the analytical chemistry laboratory using ultraviolet spectroscopy. During the 13-week studies, the dose formulations were analyzed at the initiation, midpoint, and termination of the studies (Table H2). During the 2-year studies, the dose formulations were analyzed at least every 8 weeks (Table H3). In the 2-year studies, 100% of the dose formulations were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table H4).

13-Week Studies

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to turmeric oleoresin and to determine the appropriate exposure levels to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). Upon receipt, the rats were 6 (male) or 7 (female) weeks old and the mice were 5 (male) or 6 (female) weeks old. The animals were quarantined for up to 18 days before exposure began.

At the end of quarantine, five males and five females of each species were randomly selected and evaluated for evidence of disease. At the end of the studies, serologic analyses were performed on five rats and five mice of each sex using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats and mice received 0, 1,000, 5,000, 10,000, 25,000, or 50,000 ppm turmeric oleoresin in feed 5 days per week for 13 weeks. Animals were housed five per cage. Water and feed were available *ad libitum* and feed consumption was measured once a week. Clinical findings were recorded once daily. The animals were weighed at the beginning of the studies, weekly, and at the end of the studies. Further details of study design and animal maintenance are summarized in Table 1.

At the end of the 13-week studies, blood for hematology was collected from the tail of unanesthetized animals, blood for clinical chemistry was collected from the external jugular vein of anesthetized animals, and urine samples were collected in individual metabolism cages for 18 to 24 hours. The clinical pathology parameters measured are listed in Table 1. A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. Tissues for microscopic examination were embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all control animals, animals killed moribund, and all 50,000 ppm animals. Table 1 lists the tissues and organs examined.

2-Year Studies

Study Design

Groups of 60 male and 60 female rats and mice received 0, 2,000, 10,000, or 50,000 ppm turmeric oleoresin in feed for 104 weeks (male rats) and 103 weeks (female rats and male and female mice). Up to 10 rats and mice per group were designated for interim evaluations after 15 months of chemical exposure.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD) for use in the 2-year studies. Rats were quarantined for 14 (males) or 15 (females) days, and mice were quarantined for 15 (males) or 12 (females) days before the beginning of the studies. Five rats and five mice of each sex were randomly selected and evaluated for evidence of disease. Serology samples were collected for viral screening. Rats and mice were 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Feed and water were available *ad libitum* and feed consumption was recorded once a month (Appendix I). Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded weekly for the first 13 weeks, and monthly thereafter. Animals were weighed at study initiation, weekly for the first 13 weeks, and monthly thereafter. At the 15-month interim evaluations blood for hematology was collected from the tail of unanesthetized animals, and blood for clinical chemistry was collected from the external jugular vein of anesthetized animals. The clinical pathology parameters measured are listed in Table 1. The brain, right kidney, and liver were weighed at the 15-month interim evaluations.

A complete necropsy was performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all tissues with grossly visible lesions. Complete histopathology was performed on all rats and mice. Tissues examined are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and

pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. A quality assessment pathologist reviewed the cecum, forestomach, and mesenteric lymph nodes of male and female rats; the colon and liver of male rats; the clitoral gland of female rats; the liver of male and female mice; and the uterus and thyroid gland of female mice for accuracy and consistency of lesion diagnosis.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the potential target tissues and any other tissues when there was disagreement in diagnosis between the laboratory and quality assessment pathologist. Representative examples of potential chemical-related lesions, including neoplasms of the forestomach, large intestine, mesenteric lymph node, and clitoral gland from rats and the liver, uterus, thyroid gland, and forestomach from mice, and examples of disagreements in diagnosis between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of exposure groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidences

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

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975),

appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in these studies were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluations, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

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

Historical Control Data

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

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of turmeric oleoresin was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and chromosome damage in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of turmeric oleoresin are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure of the chemical and its responses in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of

electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Turmeric Oleoresin

13-Week Studies	2-Year Studies
Study Laboratory	
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)
Strain and Species	
Rats: F344/N	Rats: F344/N
Mice: $B6C3F_1$	Mice: $B6C3F_1$
Animal Source	
Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)
Time Held Before Studies	
Rats: 19 days	Rats: 14 (males) or 15 (females) days
Mice: 20 days	Mice: 15 (males) or 12 (females) days
Average Age When Studies Began	
8 (males) and 9 (females) weeks	6 weeks
Date of First Exposure	
Rats: males – 18 October 1982	Rats: males – 24 July 1984
females – 25 October 1982	females – 8 August 1984
Mice: males – 2 November 1982	Mice: males – 5 September 1984
females – 9 November 1982	females – 17 September 1984
Duration of Exposure	
90 days	Rats: 104 (male) and 103 (female) weeks
	Mice: 103 weeks
Date of Last Exposure	
Rats: males – 19-21 January 1983	Rats: males – 15 July 1986
females – 26-28 January 1983	females – 28 July 1986
Mice: males – 2-4 February 1983	Mice: males – 27 August 1986
females – 9-11 February 1983	females – 8 September 1986
Average Age When Killed	
21 (males) and 22 (females) weeks	110 weeks
Method of Sacrifice	
Carbon dioxide asphyxiation	Same as 13-week studies
Necropsy Dates	
Rats: males – 19-21 January 1983	Rats: males – 22-28 July 1986
females – 26-28 January 1983	females – 4-12 August 1986
Mice: males – 2-4 February 1983	Mice: males – 3-11 September 1986
females – 9-11 February 1983	females – 15-23 September 1986
Size of Study Groups	
10 males and 10 females	60 males and 60 females

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Turmeric Oleoresin (continued)

13-Week Studies	2-Year Studies
Method of Animal Distribution	
Caged by one gram weight classes and then distributed into treatment groups such that within a given sex and species of each group, all cage weights are approximately equal.	Animals distributed using random numbers chart.
Animals per Cage	
5	Rats: 5 Mice: 1
Method of Animal Identification	
Ear punch	Toe clip
Diet	
NIH-07 open formula (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as 13-week studies
Maximum Storage Time for Feed	
120 days from milling date	Same as 13-week studies
Water	
Automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 13-week studies
Cages	
Polycarbonate (Lab Products Inc., Rochelle Park, NJ), changed twice weekly	Same as 13-week studies
Bedding	
Heat-treated hardwood chips (American Excelsior Co., Baltimore, MD), changed twice weekly	BetaChips, hardwood laboratory bedding (Northeastern Products Corp., Warrensburg, NY), changed twice weekly
Cage Filters	
Nonwoven polyester (Snow Filtration, Cincinnati, OH), changed once every 2 weeks	Same as 13-week studies
Cage Racks	
Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed once every 2 weeks	Same as 13-week studies
Animal Room Environment	
Average temperature: 22°-26° C Relative humidity: 12%-59% Fluorescent light: 12 hours/day Room air changes: 12 changes/hour	Average temperature: 21°-23° C Relative humidity: 40%-56% Fluorescent light: 12 hours/day Room air changes: 12 changes/hour
Exposure Levels	
0, 1,000, 5,000, 10,000, 25,000, or 50,000 ppm in feed available *ad libitum*	0, 2,000, 10,000 or 50,000 ppm in feed available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Turmeric Oleoresin (continued)

13-Week Studies	2-Year Studies
Type and Frequency of Observation	
Observed twice daily; animals weighed initially, weekly, and at the end of the studies; clinical findings recorded daily; feed consumption measured once a week.	Observed twice daily; animal weights and clinical findings recorded weekly through week 13, monthly thereafter, and at interim evaluations or at the end of the studies; feed consumption measured once a month.
Necropsy	
Necropsy performed on all animals. Organ weights were recorded for brain, heart, right kidney, liver, lungs, right testis, and thymus.	Necropsy performed on all animals. Organ weights were recorded for the brain, right kidney, and liver of interim evaluation animals.
Clinical Pathology	
Blood and urine were collected from all animals. Blood for hematology was collected from the tail and blood for clinical chemistry was collected from the external jugular vein. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, and total leukocyte counts and differentials. ***Clinical chemistry:*** urea nitrogen, creatinine, sodium potassium, calcium, phosphorus, total protein, albumin, globulin, A/G ratio, total bilirubin, alanine transferase, aspartate transferase, lactate dehydrogenase, ornithine carbamoyltransferase, sorbitol dehydrogenase, bicarbonate, cholinesterase, PH, chlorine. ***Urinalysis:*** specific gravity	Blood was collected from all interim evaluation animals. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, platelets, leukocyte counts and differentials, and nucleated erythrocytes. ***Clinical chemistry:*** urea nitrogen, creatinine, sodium (rats), potassium (rats), chloride (rats), calcium, phosphorus, alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, and cholinesterase (males only).
Histopathology	
Complete histopathology was performed on all animals dying early, all controls, and all animals in the 50,000 ppm group. In addition to gross lesions, the tissues examined included: adrenal gland (rats), brain, cecum (rats), colon (rats), epididymis (mice), forestomach (rats), heart, kidney, liver, lung, mandibular lymph node (rats), mesenteric lymph node (rats), ovary (mice), pancreas (rats), pituitary gland, preputial gland, prostate gland (rats), salivary gland (mice), spleen (mice), testis, thymus (rats), thyroid gland (rats), urinary bladder, and uterus.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland, mandibular lymph node (rats), mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, ileum, jejunum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

13-WEEK STUDY

All male and female rats survived to the end of the study (Table 2). The final mean body weight of male rats receiving 50,000 ppm was 5% lower than that of the controls, but the final mean body weights of all other exposed groups of male and female rats were similar to those of the controls. Feed consumption by exposed male and female rats was similar to that by the controls. Dietary levels of 1,000, 5,000, 10,000, 25,000, or 50,000 ppm turmeric oleoresin were estimated to deliver average daily doses of 50, 250, 480, 1,300, or 2,600 mg/kg body weight to males and 60, 300, 550, 1,450, or 2,800 mg/kg to females. The fur and feces from exposed animals were stained yellow, which was most likely due to the parent compound or its metabolites. Urine samples collected from rats that received 5,000 to 50,000 ppm turmeric oleoresin varied from yellow to dark yellow, whereas the urine from control rats was light yellow. The color difference was most likely due to the parent compound or its metabolites.

In female rats receiving 5,000, 10,000, 25,000, and 50,000 ppm, the hematocrit values were significantly lower than that in controls (Table G1). While this difference may have been related to intestinal toxicity, similar differences in the hematocrit values in male rats were not observed. In the clinical chemistry, urinalysis, and other hematologic parameters no differences were observed that were considered to be biologically significant.

TABLE 2
Survival, Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of Turmeric Oleoresin

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13
Male							
0	10/10	156 ± 3	358 ± 7	203 ± 5		14.9	18.4
1,000	10/10	155 ± 4	353 ± 6	199 ± 5	99	15.3	16.6
5,000	10/10	154 ± 4	353 ± 10	199 ± 7	98	13.5	18.5
10,000	10/10	153 ± 4	354 ± 7	200 ± 5	99	13.9	16.0
25,000	10/10	153 ± 3	347 ± 8	194 ± 7	97	14.5	17.3
50,000	10/10	155 ± 4	339 ± 6	184 ± 4*	95	13.5	18.5
Female							
0	10/10	132 ± 2	195 ± 3	63 ± 2		12.2	13.4
1,000	10/10	132 ± 2	203 ± 2	71 ± 1	104	11.9	15.2
5,000	10/10	132 ± 2	197 ± 3	65 ± 4	101	12.4	15.2
10,000	10/10	133 ± 2	201 ± 3	69 ± 3	103	12.4	12.4
25,000	10/10	132 ± 2	196 ± 3	64 ± 3	101	11.7	12.4
50,000	10/10	132 ± 2	191 ± 2	59 ± 2	98	11.6	11.8

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test.
[a] Number of animals surviving at 13 weeks/number initially in group.
[b] Weights given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

The absolute and relative liver weights of female rats and the relative liver weights of male rats that received 5,000, 10,000, 25,000, and 50,000 ppm were significantly greater than those of the controls (Table F1). These increases may have been due to mild hepatocellular swelling or hypertrophy which is sometimes too subtle to detect histologically.

Chemical-related lesions occurred in the cecum and colon of male and female rats in the 13-week study (Table 3). Male and female rats receiving 50,000 ppm turmeric oleoresin had mild to moderate glandular hyperplasia of the cecum or colon, while hyperplasia was not observed in the controls. Mucosal hyperplasia of the cecum or colon was characterized by a thickened, irregular surface which sometimes had an atypical, almost villar appearance (Plates 1 and 2). Hyperplastic glands were tortuous, hypercellular, and dilated (Plates 3 and 4). Increased numbers of mitotic figures and variable degrees of mucus production were also observed. Chemical-related lesions were not present in the mesenteric lymph nodes.

Dose selection rationale: The highest exposure level selected for the 2-year rat study was 50,000 ppm turmeric oleoresin. At this exposure level, the mean body weights, mean body weight gains, feed consumption, and clinical findings in both males and females were similar to those of the controls in the 13-week study. The lesions in the cecum and colon were not considered to be life threatening in the 13-week study. 2,000 ppm and 10,000 ppm were selected to provide a wide range of exposure concentrations.

TABLE 3
Incidences of Selected Intestinal Nonneoplastic Lesions in Rats in the 13-Week Feed Study of Turmeric Oleoresin

Dose (ppm)	0	1,000	5,000	10,000	25,000	50,000
Male						
Cecum[a]	6	–[c]	–	–	–	10
Hyperplasia[b]	0					9**
Colon	10	–	–	–	–	10
Hyperplasia	0					9**
Female						
Cecum	6	–	–	–	–	5
Hyperplasia	0					5**
Colon	10	–	–	–	–	10
Hyperplasia	0					3

** Significantly different (P≤0.01) from the control group by the Fisher exact test
[a] Number of rats with organ examined microscopically.
[b] Number of rats with lesion.
[c] Organ not examined microscopically

2-Year Study

Survival

Estimates of survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier curves in Figure 1. Survival of all exposed groups of male and female rats was similar to that of the controls.

Body Weights, Feed Consumption, and Clinical Findings

The mean body weights of male and female rats that received 2,000 and 10,000 ppm were similar to those of the controls throughout the study (Figure 2 and Tables 5 and 6). Most mean body weights of male and female rats receiving 50,000 ppm were 5% to 12% lower than those of the controls during the last half of the study. Feed consumption by exposed male and female rats was similar to that by the controls, which was estimated to be between 12 and 16 g per day (Tables I1 and I2), and the estimated turmeric oleoresin consumption was 80, 460 and 2,000 mg/kg for males and 90, 440, and 2,400 mg/kg for females. The fur of all exposed rats was stained yellow, as were the feces of rats that received 50,000 ppm. Male and female rats receiving 50,000 ppm were found to be hyperactive during some of the observation periods.

Table 4
Survival of Rats in the 2-Year Feed Study of Turmeric Oleoresin

Dose (ppm)	0	2,000	10,000	50,000
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	9
Natural deaths	6	4	3	6
Moribund kills	26	29	32	28
Animals surviving to study termination	18	17	15	17
Percent probability of survival at end of study[b]	36	34	30	34
Mean survival (days)[c]	616	640	608	582
Survival analysis[d]	P=0.258	P=0.707N	P=0.778	P=0.440
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	9
Natural deaths	3	1	3	2
Moribund kills	14	22	19	15
Animals surviving to study termination	33[e]	27[e]	28	34
Percent probability of survival at end of study	66	54	56	67
Mean survival (days)	648	646	631	643
Survival analysis	P=0.549N	P=0.391	P=0.366	P=0.866

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or lower mortality in an exposure group is indicated by N.
[e] Includes one animal that died during the last week of the study.

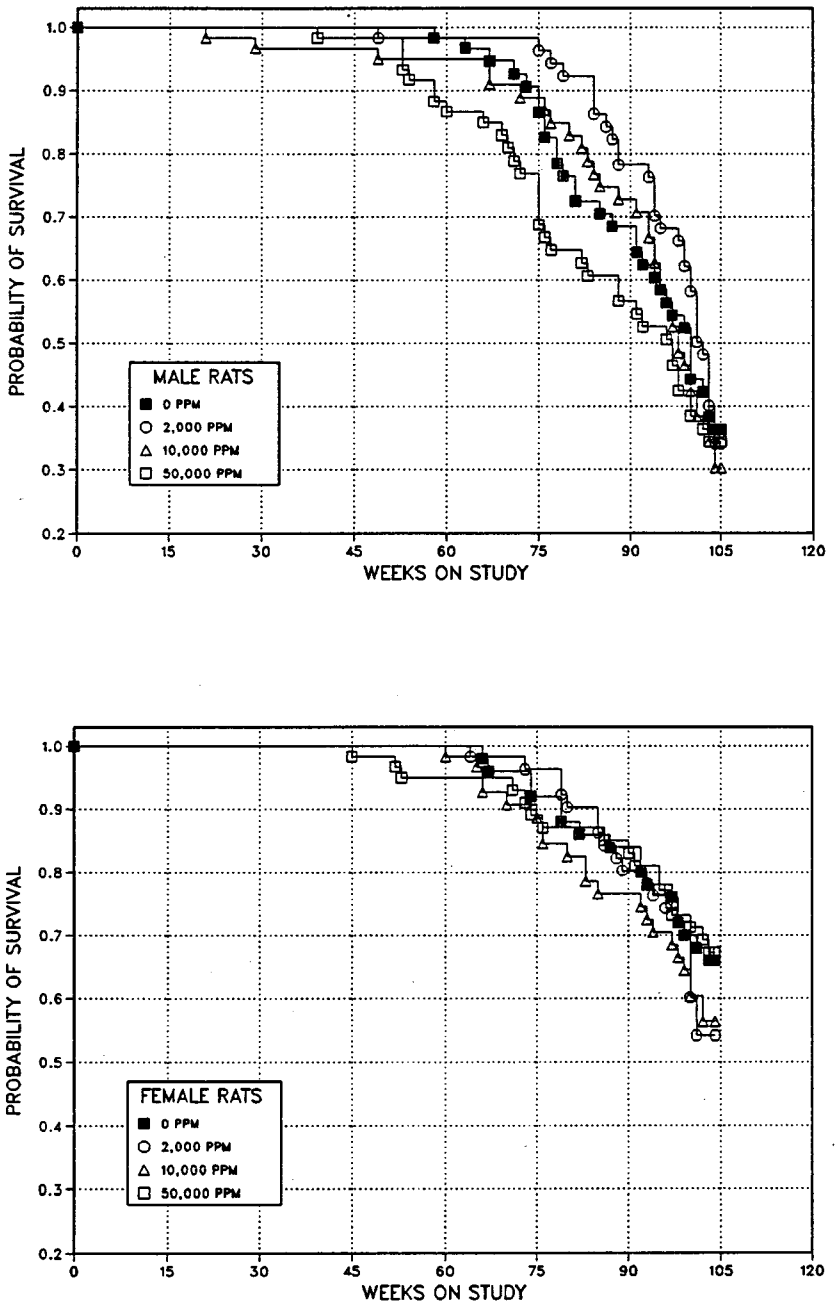
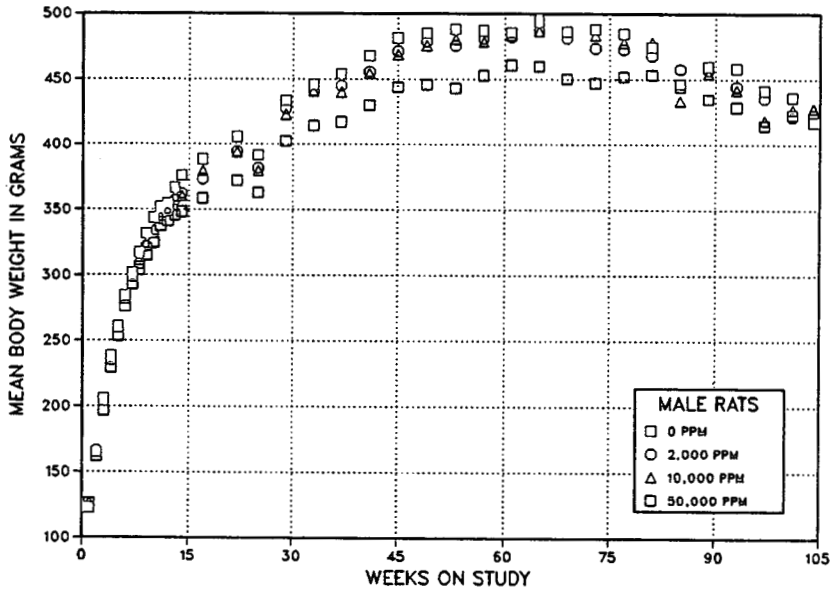


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Turmeric Oleoresin in Feed for 2 Years



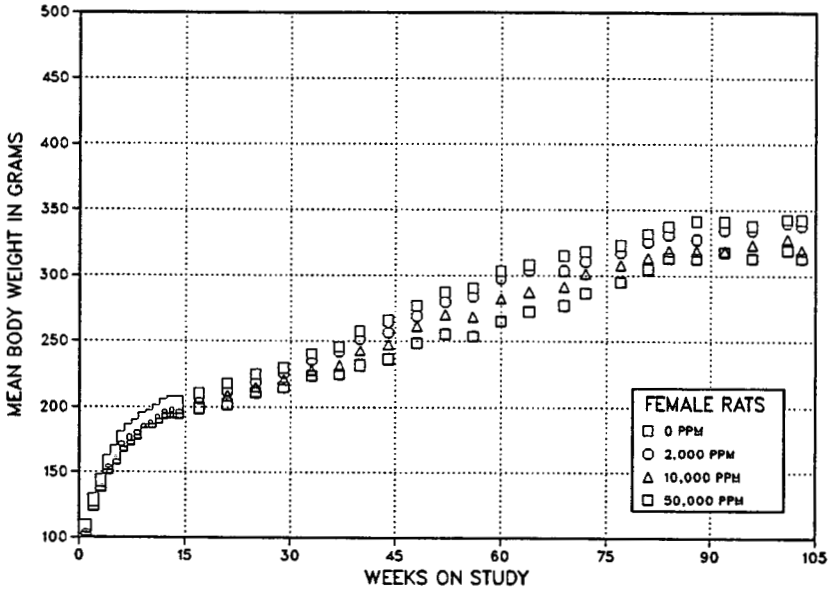


FIGURE 2
Growth Curves for Male and Female Rats Administered Turmeric Oleoresin in Feed for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Turmeric Oleoresin

Weeks on Study	0 ppm		2,000 ppm			10,000 ppm			50,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	123	60	123	100	60	127	103	60	126	103	60
2	165	60	167	101	60	166	101	60	162	98	60
3	206	60	206	100	60	207	101	60	197	96	60
4	238	60	235	99	60	237	100	60	230	96	60
5	261	60	260	100	60	261	100	60	254	97	60
6	285	60	284	100	60	282	99	60	276	97	60
7	302	60	299	99	60	299	99	60	293	97	60
8	317	60	309	97	60	314	99	60	304	96	60
9	332	60	322	97	60	325	98	60	315	95	60
10	344	60	325	94	60	335	97	60	325	95	60
11	352	60	343	97	60	348	99	60	338	96	60
12	355	60	349	98	60	351	99	60	342	96	60
13	367	60	357	97	60	360	98	60	346	94	60
14	376	60	363	96	60	361	96	60	348	93	60
17	389	60	374	96	60	380	98	60	359	92	60
22	406	60	395	97	60	394	97	59	372	92	60
25	392	60	382	98	60	380	97	59	363	93	60
29	434	60	428	99	60	423	98	59	403	93	60
33	446	60	441	99	60	441	99	58	414	93	60
37	454	60	445	98	60	440	97	58	417	92	60
41	468	60	456	97	60	454	97	58	430	92	59
45	481	60	471	98	60	469	97	58	444	92	59
49	485	60	479	99	59	476	98	57	446	92	59
53	488	60	476	97	59	481	99	57	443	91	59
57	487	60	481	99	59	479	98	57	453	93	55
61	486	59	482	99	59	484	100	57	461	95	52
65	494	58	487	99	59	487	99	57	460	93	52
69[a]	486	47	481	99	49	487	100	45	450	93	42
73	488	45	474	97	49	483	99	44	447	92	38
77	485	41	473	98	48	478	99	43	452	93	33
81	474	38	468	99	46	478	101	41	453	96	32
85	447	35	458	103	44	434	97	38	444	100	30
89	460	34	457	99	39	454	99	36	435	95	28
93	458	31	444	97	39	442	96	35	429	94	26
97	442	28	435	99	34	419	95	28	415	94	25
101	436	22	421	97	29	427	98	21	423	97	19
104	417	19	423	101	20	428	103	17	417	100	17
Mean for weeks											
1-13	281		275	98		278	99		270	96	
14-52	433		423	98		422	97		400	92	
53-104	468		461	99		462	99		442	94	

[a] Interim evaluation occurred during week 66.

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Turmeric Oleoresin

Weeks on Study	0 ppm		2,000 ppm			10,000 ppm			50,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	110	60	107	98	60	108	98	60	105	96	60
2	130	60	127	98	60	128	99	60	124	96	60
3	144	60	143	99	60	142	99	60	139	96	60
4	159	60	157	99	60	155	98	60	152	96	60
5	167	60	165	99	60	163	98	60	160	96	60
6	177	60	174	98	60	173	98	60	170	96	60
7	183	60	178	97	60	177	97	60	175	96	60
8	187	60	185	99	60	182	97	60	179	96	60
9	192	60	192	100	60	190	99	60	187	98	60
10	194	60	193	100	60	191	98	60	187	97	60
11	198	60	198	100	60	195	99	60	191	97	60
12	202	60	199	99	60	199	99	60	195	97	60
13	204	60	199	98	60	200	98	60	196	96	60
14	204	60	202	99	60	199	98	60	195	96	60
17	210	60	207	99	60	207	98	60	199	95	60
21	218	60	211	97	60	208	96	60	202	93	60
25	225	60	219	97	60	215	95	60	211	94	60
29	230	60	226	98	60	221	96	60	215	94	60
33	240	60	236	98	60	228	95	60	224	93	60
37	246	60	242	98	60	231	94	60	225	92	60
40	258	60	252	98	60	243	94	60	232	90	60
44	266	60	257	96	60	247	93	60	236	89	60
48	277	60	269	97	60	262	94	60	248	90	59
52	288	60	280	97	60	270	94	60	256	89	58
56	291	60	284	98	60	269	93	60	254	87	57
60	303	60	298	98	60	283	93	59	266	88	57
64	308	60	304	99	59	288	93	59	273	89	57
69[a]	315	48	304	96	49	292	93	46	278	88	48
72	319	48	311	98	49	302	95	45	287	90	47
77	323	46	318	98	48	308	95	42	295	91	44
81	332	44	326	98	45	314	95	41	305	92	44
84	338	43	331	98	45	319	95	39	314	93	44
88	342	42	328	96	41	319	93	38	313	92	43
92	342	40	335	98	40	319	93	37	318	93	41
96	338	39	335	99	37	324	96	35	313	93	39
101	343	35	341	99	30	328	96	30	320	93	36
103	343	33	338	99	27	320	93	28	314	92	35
Mean for weeks											
1-13	173		171	99		169	98		166	96	
14-52	242		236	98		230	95		222	92	
53-103	326		319	98		307	94		296	91	

[a] Interim evaluation occurred during week 65.

Hematology and Clinical Chemistry

At the 15-month interim evaluation, the hematocrit values, hemoglobin concentrations, and erythrocyte counts in male and female rats receiving 50,000 ppm were significantly lower than those in controls (Table G2). In addition, the platelet counts in male and female rats that received 50,000 ppm and the reticulocyte count in male rats that received 50,000 ppm were significantly greater. These findings were consistent with mild to moderate regenerative anemia and were considered chemical related. The hematologic and clinical chemistry findings in the 2,000 and 10,000 ppm groups were similar to those in the controls.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the forestomach, large intestine, and mesenteric lymph nodes of male and female rats, and the clitoral gland of female rats. Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal tumor diagnoses, the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group, and historical control incidences for the biologically significant neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Forestomach: Male rats receiving 50,000 ppm turmeric oleoresin had increased incidences of gastric ulcers, squamous epithelial hyperplasia, and hyperkeratosis (Tables 7 and A5). A chemical-related response was not observed in exposed female rats.

Lesions of the forestomach were characterized by superficial to deep ulcerations of the mucosa (Plates 5 and 6). The underlying submucosa was thickened by edema, mixed inflammatory cell infiltrates, and increased connective tissue. The epithelium adjacent to ulcerated areas was often markedly hyperplastic and characterized by a thickened squamous epithelium, often accompanied by hyperkeratosis and minimal basal cell hyperplasia. The spectrum of lesions consisting of ulcerations, hyperplasia, and hyperkeratosis were most likely sequentially related. Thus, hyperplasia and hyperkeratosis were considered adaptive or reparative responses to the mucosal injury. Focal hyperplasia was also observed without evidence of ulceration (Plates 7 and 8).

A few squamous cell papillomas of the forestomach were observed in control and exposed female rats (0 ppm, 1/50; 2,000 ppm, 1/50; 10,000 ppm, 1/50; 50,000 ppm, 0/51; Table B1). One squamous cell papilloma was seen in a male rat that received 50,000 ppm. Although squamous cell papillomas are very uncommon in F344/N rats (historical incidence in recent NTP feed studies: male, 2/1,002, 0.2%; female, 1/1,000, 0.1%; Tables A4 and B4a), these were not considered to be related to the administration of turmeric oleoresin because no more than one occurred in any exposure group and one was seen in a control animal.

Large intestine: Many male and female rats receiving 50,000 ppm had ulcers, chronic active inflammation, and hyperplasia of the cecum (Tables 7, A5, and B5). Similarly, the majority of 50,000 ppm male and female rats had ulcers, inflammation, and hyperplasia of the cecum at the 15-month interim evaluation. Similar lesions occurred in the colon of 50,000 ppm male rats at the end of the 2-year study, but were less frequent and less severe than the same lesions in the cecum at the 15-month interim evaluation.

The lesions produced by turmeric oleoresin are depicted in Plates 9 through 12. Ulcers in the cecum and colon were either superficial or deep and occasionally involved extensive areas of the mucosa. Ulcers were often associated with chronic active inflammation and hyperplasia. Hyperplasia was also observed without evidence of ulceration. Hyperplasia of the glandular epithelium was characterized by a thickened mucosa; glands were convoluted at the base and the mitotic index was high near areas of ulceration. Well-differentiated glands, occasionally present in the submucosa, were considered to be downgrowths into the gut-associated lymphoid tissue or glands trapped during the healing process. Epithelial neoplasms of the cecum or colon were not observed in exposed male or female rats.

Mesenteric lymph node: Male and female rats that received 50,000 ppm and male rats that received 10,000 ppm had significantly increased incidences of sinus ectasia (Tables 7, A5, and B5). Male rats receiving 50,000 ppm also had a significantly increased incidence of chronic active inflammation of the mesenteric lymph node (Tables 7 and A5).

TABLE 7
Incidences of Nonneoplastic Lesions of the Gastrointestinal Tract in Rats in the 2-Year Feed Study of Turmeric Oleoresin

Dose (ppm)	0	2,000	10,000	50,000
Male				
15-Month Interim Evaluation				
Cecum[a]	10	10	10	9
Ulcer[b]	0	0	0	7**(1.6)[c]
Hyperplasia	0	0	0	8**(2.3)
Inflammation	0	1 (1.0)	0	9**(2.3)
Mesenteric Lymph Node	10	10	10	9
Sinus Ectasia	0	0	2 (1.5)	7**(3.4)
2-Year Study				
Forestomach	49	50	43	51
Ulcer	2 (3.0)	3 (3.3)	2 (3.0)	6 (2.5)
Hyperplasia	7 (2.1)	5 (2.2)	4 (2.0)	18*(2.6)
Hyperkeratosis	4 (1.8)	5 (1.0)	2 (1.0)	16*(2.1)
Cecum	50	49	50	51
Ulcer	0	0	1 (1.0)	26**(2.7)
Hyperplasia	0	1 (4.0)	0	41**(1.9)
Inflammation	1 (2.0)	0	0	29**(2.3)
Colon	49	50	49	49
Ulcer	0	0	0	6*(3.5)
Hyperplasia	0	0	0	4 (1.5)
Inflammation	0	0	0	2 (2.5)
Mesenteric Lymph Node	49	50	50	51
Sinus Ectasia	0	1 (1.0)	7**(2.3)	49**(3.4)
Chronic Active Inflammation	0	0	0	10*(3.1)
Female				
15-Month Interim Evaluation				
Cecum	10	10	10	9
Ulcer	0	0	0	6**(2.5)
Hyperplasia	0	0	0	8**(2.3)
Inflammation	0	0	0	9**(2.2)
Mesenteric Lymph Node	10	10	6	9
Sinus Ectasia	0	0	0	9**(2.6)

(continued)

TABLE 7
Incidences of Nonneoplastic Lesions of the Gastrointestinal Tract in Rats in the 2-Year Feed Study of Turmeric Oleoresin (continued)

Dose (ppm)	0	2,000	10,000	50,000
Female (continued)				
2-Year Study				
Forestomach	50	50	50	51
Ulcer	2 (2.0)	5 (2.4)	2 (3.5)	1 (2.0)
Hyperplasia	3 (2.0)	6 (1.7)	7 (2.3)	4 (1.5)
Hyperkeratosis	2 (2.0)	5 (1.2)	6 (1.5)	3 (1.3)
Cecum	50	50	50	51
Ulcer	0	0	0	20**(2.1)
Hyperplasia	0	0	1 (2.0)	48**(2.2)
Inflammation	0	0	0	36**(2.1)
Colon	50	50	50	50
Hyperplasia	0	0	0	1 (2.0)
Mesenteric Lymph Node	50	50	50	51
Sinus Ectasia	0	0	1 (2.0)	50**(2.9)

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

Sinus ectasia was characterized by variably sized cystic lymph-filled spaces in regional (cecal and colonic) mesenteric lymph nodes (Plates 13 and 14). Sinus ectasia was possibly due to excessive drainage of lymph from the cecum and colon via the lymphatics as a result of the intestinal injury.

Clitoral gland: All exposed groups of female rats had significantly increased incidences of adenoma and adenoma or carcinoma (combined) (Tables 8 and B3). The incidence of clitoral gland adenoma in the exposed groups exceeds the historical rate in control female F344/N rats from recent NTP 2-year feed studies (77/1,000, 7.7%; range 0%-18%; Table B4b). A chemical-related increased incidence of clitoral gland hyperplasia was not observed. Despite the 25-fold increase in the dietary concentration of turmeric oleoresin, the incidence of clitoral gland neoplasms did not increase with exposure level. Since there was no clear dose-related response and no increased incidence of clitoral gland hyperplasia, it was uncertain whether the clitoral gland neoplasms were related to chemical administration. The incidence of preputial gland adenomas was not increased in exposed male rats (5/48, 5/48, 3/49, 4/51; Table A3).

Adenomas were well circumscribed and sometimes compressed the surrounding tissue. The neoplastic cells formed acini and clusters, which were spherical to elongated in shape and varied in size. Many of the neoplastic cells had discrete borders and granular cytoplasm. Foci of cellular debris, necrosis, and cysts were often present. Carcinomas were usually larger and less circumscribed than adenomas and often infiltrated the adjacent normal tissue.

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Clitoral Gland in Female Rats in the 2-Year Feed Study of Turmeric Oleoresin

Dose (ppm)	0	2,000	10,000	50,000
15-Month Interim Evaluation				
Clitoral Gland[a]	10	3	2	9
Hyperplasia[b]	0	0	1	0
Adenoma	2	1	1	1
2-Year Study				
Clitoral Gland	50	48	47	49
Hyperplasia	7	5	4	7
Adenoma[c]				
Overall rate[d]	5/50 (10%)	12/48 (25%)	15/47 (32%)	16/49 (33%)
Adjusted rate[e]	14.7%	39.2%	46.3%	46.8%
Terminal rate[f]	4/33 (12%)	9/26 (35%)	11/28 (39%)	15/33 (45%)
First incidence (days)	717	560	576	661
Logistic regression test[g]	P=0.050	P=0.041	P=0.004	P=0.005
Carcinoma[h]				
Overall rate	1/50 (2%)	4/48 (8%)	0/47 (0%)	0/49 (0%)
Adjusted rate	3.0%	13.8%	0.0%	0.0%
Terminal rate	1/33 (3%)	3/26 (12%)	0/28 (0%)	0/33 (0%)
First incidence (days)	727 (T)	654	–[i]	–
Logistic regression test	P=0.131N	P=0.158	P=0.533N	P=0.500N
Adenoma or Carcinoma (combined)[j]				
Overall rate	6/50 (12%)	16/48 (33%)	15/47 (32%)	16/49 (33%)
Adjusted rate	17.6%	51.2%	46.3%	46.8%
Terminal rate	5/33 (15%)	12/26 (46%)	11/28 (39%)	15/33 (45%)
First incidence (days)	717	560	576	661
Logistic regression test	P=0.152	P=0.009	P=0.008	P=0.011

(T)Terminal sacrifice
[a] Number of rats with clitoral gland examined microscopically
[b] Number of rats with lesion
[c] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 77/1,000 (7.7% ± 4.2%); range 0%-18%
[d] Number of animals with lesion or neoplasm per number of animals with clitoral gland examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression tests regard these lesions as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[h] Historical incidence: 29/1,000 (2.9% ± 3.9%); range 0%-14%
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 105/1,000 (10.5% ± 4.9%); range 4%-20%

MICE

13-Week Study

Although one female mouse receiving 25,000 ppm and one control male mouse were accidentally killed, there were no deaths attributed to chemical toxicity (Table 9). The mean body weight gains and final mean body weights of all exposed groups of male and female mice were similar to those of the controls, and feed consumption by exposed male and female mice was similar to that by the controls. Dietary levels of 1,000, 5,000, 10,000, 25,000, or 50,000 ppm turmeric oleoresin were estimated to deliver average daily doses of 150, 750, 1,700, 3,850, or 7,700 mg/kg body weight to males and 200, 1,000, 1,800, 4,700, or 9,300 mg/kg to females. Clinical findings included stained fur and feces, particularly in the 50,000 ppm groups. In addition, urine collected from mice that received 5,000, 10,000, 25,000, and 50,000 ppm varied from yellow to dark yellow in males, while that from female mice varied in color from light yellow to yellow. The color was most likely due to the parent compound or its metabolites.

There were no biologically significant differences in the hematologic, clinical chemistry, or urinalysis parameters in exposed male and female mice (Table G3). Absolute and relative liver weights of male mice that received 5,000, 10,000, 25,000, and 50,000 ppm were significantly greater than those of the controls (Table F3). Absolute and relative liver weights of female mice that received 10,000, 25,000, and 50,000 ppm were also significantly greater than those of the controls. Increases in absolute and relative liver weights may have been the result of either mild hepatocellular swelling or hypertrophy, which is sometimes too subtle to detect histopathologically.

Table 9
Survival, Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of Turmeric Oleoresin

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13
Male							
0	9/10[d]	24.1 ± 0.5	32.3 ± 0.9	8.1 ± 0.4		4.9	5.4
1,000	10/10	24.0 ± 0.4	33.0 ± 0.8	9.0 ± 0.6	102	5.6	6.1
5,000	10/10	24.2 ± 0.4	32.9 ± 0.6	8.7 ± 0.4	102	5.1	6.1
10,000	10/10	24.1 ± 0.5	32.7 ± 0.9	8.6 ± 0.6	101	5.7	7.1
25,000	10/10	24.4 ± 0.4	32.6 ± 0.5	8.2 ± 0.3	101	5.2	6.4
50,000	10/10	24.7 ± 0.4	33.8 ± 0.6	9.1 ± 0.4	105	5.5	6.1
Female							
0	10/10	19.2 ± 0.4	24.8 ± 0.8	5.6 ± 0.5		4.5	5.6
1,000	10/10	19.2 ± 0.3	26.0 ± 1.1	6.8 ± 0.9	105	4.9	6.7
5,000	10/10	19.2 ± 0.3	26.0 ± 1.1	6.8 ± 0.9	105	4.8	6.6
10,000	10/10	19.3 ± 0.3	26.1 ± 0.9	6.9 ± 0.7	106	4.5	5.8
25,000	9/10[e]	19.3 ± 0.3	25.3 ± 0.7	6.2 ± 0.5	102	4.4	6.1
50,000	10/10	19.2 ± 0.4	25.5 ± 0.7	6.3 ± 0.4	103	4.3	5.6

[a] Number of animals surviving at 13 weeks/number initially in group.
[b] Weights given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group are not significant by Williams' or Dunnett's test.
[c] Feed consumption is expressed as grams per animal per day.
[d] Week of death: 13
[e] Week of death: 4

There were no chemical-related gross or histopathologic lesions in male or female mice receiving turmeric oleoresin for 13 weeks.

Dose selection rationale: The highest exposure level selected for the 2-year mouse study was 50,000 ppm. At this level, final mean body weights, mean body weight gains, feed consumption, clinical chemistry and hematology parameters, and histopathologic findings in both males and females were similar to those of controls. The low exposure levels of 2,000 ppm and 10,000 ppm were selected to provide a broad range of exposure concentrations.

2-Year Study

Survival

Estimates of survival probabilities for male and female mice are shown in Table 10 and in the Kaplan-Meier curves in Figure 3. Survival of all groups of exposed male and female mice was similar to that of the controls.

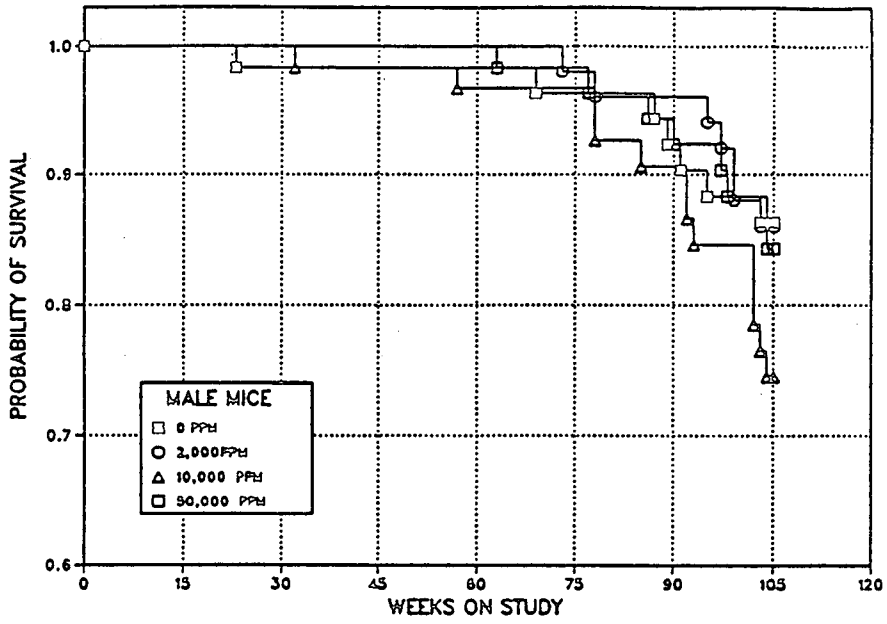
Body Weights, Feed Consumption, and Clinical Findings

The mean body weights of male and female mice receiving 2,000 ppm and male mice receiving 10,000 ppm were similar to those of the controls throughout the study (Figure 4 and Tables 11 and 12). The mean body weight of female mice that received 50,000 ppm was approximately 10% lower than that of the controls after week 25. The final mean body weights of 50,000 ppm males and females and 10,000 ppm females were significantly lower than those of controls. Feed consumption by exposed male and female mice was similar to that by the controls and was estimated to be between 4 and 6 g per day (Tables I3 and I4), with estimated average daily turmeric oleoresin consumption values of 220, 520, or 6,000 mg/kg for males and 320, 1,620, or 8,400 mg/kg for females. In the male and female exposed groups, clinical findings included discolored fur, most likely due to the parent compound or its metabolites.

Table 10
Survival of Mice in the 2-Year Feed Study of Turmeric Oleoresin

Dose (ppm)	0	2,000	10,000	50,000
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Natural deaths	2	1	5	2
Moribund kills	5	6	8	6
Animals surviving to study termination	43	43[b]	37	42
Percent probability of survival at end of study[c]	86	86	75	84
Mean survival (days)[d]	663	673	656	670
Survival analysis[e]	P=1.000N	P=1.000N	P=0.223	P=0.982
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	9	10
Natural deaths	3	2	7	1
Moribund kills	7	7	10	7
Accidental deaths[a]	1	0	0	0
Animals surviving to study termination	39	41	34	42
Percent probability of survival at end of study	80	83	68	85
Mean survival (days)	655	655	627	665
Survival analysis	P=0.505N	P=0.980N	P=0.198	P=0.743N

[a] Censored from survival analyses
[b] Includes one animal that died during the last week of the study
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[e] 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 exposed columns. A negative trend or lower mortality in an exposure group is indicated by N.



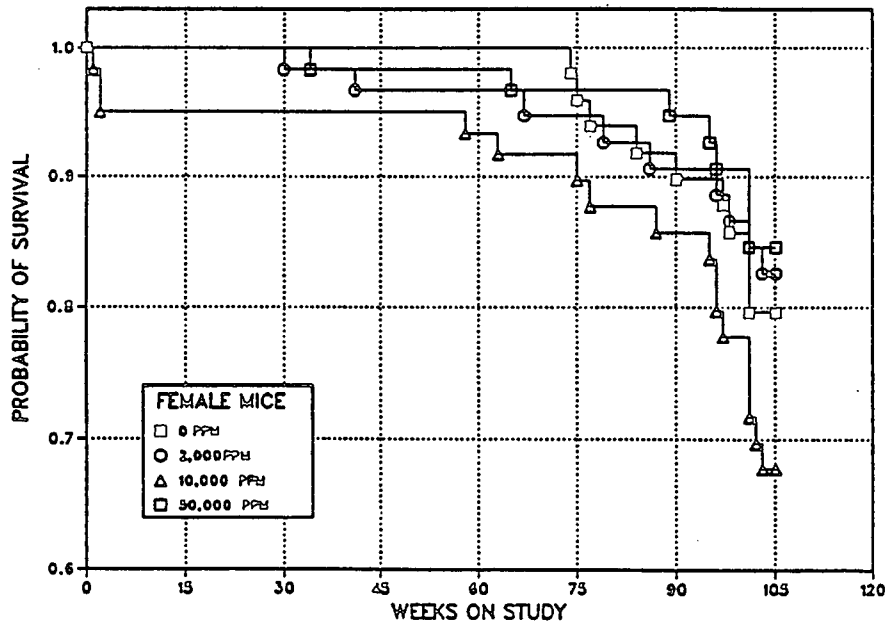


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Turmeric Oleoresin in Feed for 2 Years

TABLE 12
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	2,000 ppm Av. Wt. (g)	2,000 ppm Wt. (% of controls)	2,000 ppm No. of Survivors	10,000 ppm Av. Wt. (g)	10,000 ppm Wt. (% of controls)	10,000 ppm No. of Survivors	50,000 ppm Av. Wt. (g)	50,000 ppm Wt. (% of controls)	50,000 ppm No. of Survivors
1	16.5	60	16.3	99	60	16.0	97	60	16.6	101	60
2	17.2	60	17.3	101	60	16.5	96	59	16.6	97	60
3	18.2	60	18.4	101	60	18.4	101	57	18.6	102	60
4	19.1	60	19.0	100	60	19.2	101	57	19.0	100	60
5	20.1	60	19.8	99	60	19.8	99	57	19.9	99	60
6	20.7	60	21.0	101	60	20.6	100	57	20.9	101	60
7	21.5	60	21.5	100	60	21.5	100	57	21.6	101	60
8	22.1	60	22.0	99	60	21.8	99	57	21.8	99	60
9	22.8	60	22.9	100	60	23.1	101	57	22.9	100	60
10	23.0	60	23.4	102	60	23.2	101	57	23.3	101	60
11	23.9	60	24.0	100	60	24.0	100	57	24.0	100	60
12	23.8	60	24.0	101	60	24.0	101	57	23.9	100	60
13	24.3	59	24.2	100	60	24.7	102	57	23.9	98	60
14	24.8	59	25.0	100	60	25.5	103	57	24.6	99	60
17	26.8	59	27.3	102	60	26.3	98	57	25.8	96	60
21	27.9	59	27.4	98	60	28.4	102	57	27.8	100	60
25	31.7	59	31.0	98	60	30.5	96	57	29.0	91	60
29	33.4	59	32.6	98	60	31.9	96	57	30.3	90	60
33	35.2	59	34.8	99	59	33.9	96	57	31.7	90	60
37	37.9	59	36.5	96	59	35.2	93	57	33.5	88	59
41	39.2	59	38.4	98	59	37.9	97	57	34.9	89	59
45	40.6	59	40.8	100	58	40.5	100	57	37.4	92	59
49	42.5	59	43.1	101	58	43.5	102	57	39.4	93	59
53	44.3	59	43.8	99	58	42.7	96	57	40.4	91	59
57	44.0	59	44.5	101	58	42.9	98	57	40.1	91	59
61	44.3	59	45.0	102	58	43.3	98	56	41.0	93	59
65	45.6	52	46.1	101	54	44.4	97	49	41.6	91	55
69[a]	46.3	49	45.9	99	47	45.2	98	46	41.9	91	48
73	46.7	49	45.5	97	47	43.5	93	46	40.8	87	48
77	45.6	47	45.0	99	47	43.5	95	45	40.6	89	48
81	47.1	46	46.9	100	46	45.3	96	44	42.9	91	48
85	47.4	45	47.1	99	46	45.8	97	44	42.8	90	48
89	47.0	45	45.8	97	45	43.2	92	43	41.6	89	48
93	45.4	44	45.1	99	45	42.6	94	43	41.6	91	47
97	45.0	44	44.5	99	44	41.7	93	40	40.6	90	45
101	45.0	42	44.5	99	43	42.1	94	39	40.8	91	45
103	45.2	39	44.1	98	41	42.3	94	34	40.6	90	42
Mean for weeks											
1-13	21.0		21.1	100		21.0	100		21.0	100	
13-52	34.0		33.7	99		33.4	98		31.4	92	
53-103	45.6		45.3	99		43.5	95		41.2	90	

[a] Interim evaluation occurred during week 65.

Hematology and Clinical Chemistry

Alkaline phosphatase values in male and female mice receiving 10,000 and 50,000 ppm were significantly higher than those in controls (Table G4). Differences in hematologic and other clinical chemistry parameters in exposed male and female mice were not biologically significant.

Pathology and Statistical Analyses of Results

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

Liver: At the 15-month interim evaluation, the absolute and relative liver weights of male and female mice that received 10,000 and 50,000 ppm were significantly greater than those of controls (Table F4). Increases in absolute and relative liver weights may have been due to mild hepatocellular swelling or hypertrophy. At the 15-month interim evaluation, hepatocellular neoplasms occurred in several exposed male and female mice, but not in controls. At the end of the 2-year study, significantly increased incidences of hepatocellular adenoma occurred in male and female mice receiving 10,000 ppm, but not in groups receiving 2,000 or 50,000 ppm (Tables 13, C3, and D3). Although the incidences of hepatocellular carcinoma in exposed groups of male and female mice were similar to controls, the number of mice with multiple neoplasms [multiple adenomas, multiple carcinomas, or adenoma or carcinoma (combined)] in each of the exposed groups was greater than that in the controls (Tables 13, C1, and D1). Hepatoblastomas, a variant of hepatocellular carcinoma, occurred in three males that received 10,000 ppm and one male that received 50,000 ppm.

The incidences of hepatocellular adenoma or carcinoma (combined) in all exposed groups of male mice exceeded the range for these neoplasms in control male B6C3F$_1$ mice from recent NTP 2-year feed studies (range 10%-68%; 363/1,114, 32.6%; Table C4a). In female mice, the incidences of hepatocellular adenoma or carcinoma (combined) in the 10,000 and 50,000 ppm groups exceeded the range for these neoplasms in control female B6C3F$_1$ mice (range 3%-34%; 153/1,113, 13.7%; Table D4a) from recent NTP feed studies.

Although the incidences of hepatocellular neoplasms were significantly increased in male and female mice receiving 10,000 ppm, there were no corresponding increased incidences of hepatic foci (all types) in groups of exposed mice (Tables 13, C5, and D5).

Hepatic foci (basophilic, eosinophilic, clear, or mixed cell types), hepatocellular adenoma, and hepatocellular carcinoma constitute a morphologic continuum. Hepatic foci consist of cells with altered cytoplasmic staining properties usually associated with changes in the amounts of rough or smooth endoplasmic reticulum, ribosomes, glycogen, or lipids. Although the cells and their nuclei were often slightly enlarged, the hepatic plates were generally minimally altered within foci and the lobular architecture was maintained. Hepatocellular adenomas also consisted of cells with altered staining properties, but the adenomas were generally larger than foci, lacked normal lobular architecture, and caused compression of the surrounding tissue. In contrast to the adenomas, the hepatocellular carcinomas generally exhibited heterogeneous growth patterns, with hepatic plates one to many cells thick forming trabeculae or gland-like structures. Neoplastic cells had altered staining properties and showed nuclear pleomorphism and atypia. The hepatoblastomas consisted of cells similar to those in the hepatocellular carcinomas as well as a subpopulation of small basophilic cells with round hyperchromatic nuclei arranged in compact sheets resembling the hepatic blastema.

Forestomach: Four squamous cell papillomas (0 ppm, 0/49; 2,000 ppm, 0/50; 10,000 ppm, 1/51; 50,000 ppm, 3/49) and a squamous cell carcinoma (0/49, 0/50, 1/51, 0/49) were observed in female mice (Table D1). Two control male mice also had squamous cell papillomas (Table C1). No forestomach neoplasms were observed in male or female mice at the 15-month interim evaluation. Since the incidence of squamous cell papilloma in female mice was within the NTP 2-year historical control range of 0% to 14% (25/1,121, 2.2%; Table D4b), these lesions were

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Turmeric Oleoresin

Dose (ppm)	0	2,000	10,000	50,000
Male				
15-Month Interim Evaluation				
Liver	10	9	10	10
Basophilic Focus	1	0	0	0
Hepatocellular Adenoma	0	1	2	0
Hepatocellular Adenoma, Multiple	0	0	0	1
Hepatocellular Carcinoma	0	0	2	0
2-Year Study				
Liver	50	50	50	50
Basophilic Focus	0	2	0	1
Clear Cell Focus	10	5	5	2*
Eosinophilic Focus	6	8	5	7
Mixed Cell Focus	1	2	1	6
Foci (all types)	17	17	11	16
Hepatocellular Adenoma, Single or Multiple[a]				
Overall rate	25/50 (50%)	28/50 (56%)	35/50 (70%)	30/50 (60%)
Adjusted rate	55.5%	63.6%	83.3%	63.7%
Terminal rate	23/43 (53%)	27/43 (63%)	30/37 (81%)	25/42 (60%)
First incidence (days)	634	715	541	537
Logistic regression test	P=0.356	P=0.395	P=0.012	P=0.226
Hepatocellular Adenoma, Multiple				
Overall rate	9/50 (18%)	17/50 (34%)	24/50 (48%)	18/50 (36%)
Hepatocellular Carcinoma, Single or Multiple[b]				
Overall rate	12/50 (24%)	18/50 (36%)	16/50 (32%)	18/50 (36%)
Adjusted rate	25.0%	38.0%	34.9%	37.4%
Terminal rate	7/43 (16%)	14/43 (33%)	8/37 (22%)	12/42 (29%)
First incidence (days)	479	507	541	537
Logistic regression test	P=0.249	P=0.108	P=0.267	P=0.124
Hepatocellular Carcinoma, Multiple				
Overall rate	0/50 (0%)	3/50 (6%)	4/50 (8%)	5/50 (10%)
Hepatoblastoma[c]				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	7.6%	2.4%
Terminal rate	0/43 (0%)	0/43 (0%)	1/37 (3%)	1/42 (2%)
First incidence (days)	–	–	713	729 (T)
Logistic regression test	P=0.522	–	P=0.112	P=0.495
Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma (combined)[d]				
Overall rate	30/50 (60%)	38/50 (76%)	41/50 (82%)	38/50 (76%)
Adjusted rate	62.5%	79.1%	87.2%	77.6%
Terminal rate	25/43 (58%)	33/43 (77%)	31/37 (84%)	31/42 (74%)
First incidence (days)	479	507	541	537
Logistic regression test	P=0.259	P=0.072	P=0.009	P=0.073

(continued)

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

Dose (ppm)	0	2,000	10,000	50,000
Female				
15-Month Interim Evaluation				
Liver	10	2	5	10
Clear Cell Focus	1	0	0	0
Hepatocellular Adenoma	0	0	1	0
Hepatocellular Carcinoma	0	0	0	1
2-Year Study				
Liver	50	50	51	50
Basophilic Focus	0	0	2	0
Clear Cell Focus	4	2	2	2
Eosinophilic Focus	2	2	8	8*
Foci (all types)	6	4	12	10
Hepatocellular Adenoma, Single or Multiple[e]				
Overall rate	7/50 (14%)	8/50 (16%)	19/51 (37%)	14/50 (28%)
Adjusted rate	17.0%	19.5%	50.9%	33.3%
Terminal rate	5/39 (13%)	8/41 (20%)	16/34 (47%)	14/42 (33%)
First incidence (days)	701	729 (T)	667	729 (T)
Logistic regression test	P=0.167	P=0.522	P=0.003	P=0.091
Hepatocellular Adenoma, Multiple				
Overall rate	0/50 (0%)	3/50 (6%)	9/51 (18%)	6/50 (12%)
Hepatocellular Carcinoma, Single or Multiple[f]				
Overall rate	7/50 (14%)	5/50 (10%)	10/51 (20%)	6/50 (12%)
Adjusted rate	16.3%	12.2%	25.2%	13.2%
Terminal rate	4/39 (10%)	5/41 (12%)	5/34 (15%)	3/42 (7%)
First incidence (days)	536	729 (T)	524	662
Logistic regression test	P=0.468N	P=0.379N	P=0.285	P=0.502N
Hepatocellular Carcinoma, Multiple				
Overall rate	0/50 (0%)	0/50 (0%)	2/51 (4%)	2/50 (4%)
Hepatocellular Adenoma or Carcinoma (combined)[g]				
Overall rate	13/50 (26%)	12/50 (24%)	25/51 (49%)	19/50 (38%)
Adjusted rate	30.0%	29.3%	60.7%	42.2%
Terminal rate	9/39 (23%)	12/41 (29%)	18/34 (53%)	16/42 (38%)
First incidence (days)	536	729 (T)	524	662
Logistic regression test	P=0.202	P=0.495N	P=0.007	P=0.159

* Significantly different (P≤0.05) from the control group by the logistic regression test.
[a] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 226/1,114 (20.3% ± 13.2%); range 4%-60%
[b] Historical incidence: 169/1,114 (15.2% ± 7.1%); range 3%-27%
[c] Historical incidence: 0/1,114
[d] Historical incidence: 363/1,114 (32.2% ± 13.6%); range 10%-68%
[e] Historical incidence: 110/1,113 (9.9% ± 7.2%); range 0%-28%
[f] Historical incidence: 54/1,113 (4.9% ± 4.7%); range 0%-20%
[g] Historical incidence: 153/1,113 (13.7% ± 8.6%); range 3%-34%

not considered to be related to chemical administration. A few male and female mice had inflammatory lesions, hyperplasia, and hyperkeratosis of the forestomach (Tables C5 and D5).

Squamous cell papillomas were characterized by finger-like exophytic growths which protruded into the lumen of the forestomach and were supported by narrow fibrovascular stalks. The surface of the papillomas was covered by a prominent keratin layer with an orderly maturation of the epithelium beneath the keratin. Squamous cell carcinomas were broad based with evidence of invasion through the basement membrane. Invasion was associated with a scirrhous response. Neoplastic cells displayed pleomorphism and anaplasia. Variable amounts of keratinization, hemorrhage, and necrosis were present.

Small intestine: Three male mice that received 2,000 ppm and three male mice that received 10,000 ppm had carcinomas of the small intestine (Table C1), while none were observed in the control or 50,000 ppm groups. A control female had a carcinoma, but none were observed in the exposed groups (Table D1). No carcinomas of the small intestine were seen in control male or female mice from recent NTP 2-year feed studies (Table C4b and D4c). Because of the relatively rare appearance of carcinomas in the small intestine, the occurrence in this study was considered unusual. Since there was not a dose-response trend, and the number of neoplasms was low, it was uncertain if these neoplasms were chemical related.

Pituitary gland: Adenomas of the pars distalis occurred more frequently in the exposed groups of female mice than in the controls, and the incidence in females receiving 50,000 ppm was significantly increased (0/46, 2/49, 4/50, 5/50; Table D3). However, the incidence of adenoma in each of the exposed groups was within the range for historical control female B6C3F$_1$ mice (2%-36%; 183/1,065, 17.2%; Table D4d) from recent NTP 2-year feed studies. The absence of pituitary gland adenomas in the control group was unusual. Further, the incidence of hyperplasia was highest in the control and 2,000 ppm groups and lowest in female mice that received 50,000 ppm (8/46, 11/49, 7/50, 2/50; Table D5). Thus, the marginally increased incidence of pituitary gland adenoma was not considered chemical related.

Thyroid gland: Female mice that received 50,000 ppm had a significantly increased incidence of follicular cell hyperplasia (5/50, 8/50, 7/50, 16/49; Table D5). No increased incidence of thyroid gland neoplasms was observed in any group of female mice (1/50, 1/50, 2/50, 0/49; Table D1). The incidence of follicular cell hyperplasia was not increased in exposed male mice (0/50, 1/50, 4/50, 0/50; Table C5).

GENETIC TOXICOLOGY

Turmeric oleoresin (1 to 333 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 when tested in a preincubation protocol with and without S9 (Table E1; Mortelmans *et al.*, 1986). In cytogenetic tests with cultured Chinese hamster ovary cells, turmeric oleoresin induced small but significant increases in sister chromatid exchanges (Table E2) and chromosomal aberrations (Table E3). No evidence of cell cycle delay was noted in either test. In the sister chromatid exchange test, a weakly positive response was observed in the first trial without S9, but this was not repeated in a second trial conducted with the same concentrations of turmeric oleoresin (0.16 to 5.00 μg/mL). With S9, the results of the first trial were questionable due to the absence of a dose response, but the second trial was clearly positive, with significant increases in sister chromatid exchanges seen at the two highest doses (1.60 and 5.00 μg/mL). In the chromosomal aberration test, small increases in the percentage of cells with chromosomal aberrations were noted at the highest dose tested (16.00 μg/mL) in each of two trials conducted without S9. With S9, results of a single trial using a top concentration of 10 μg/mL were negative.

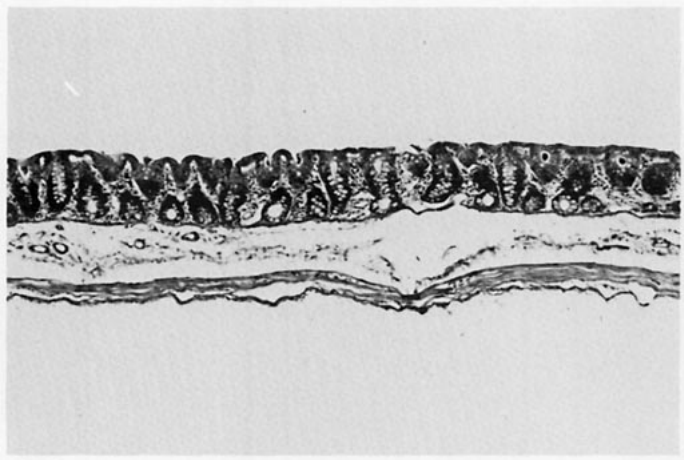


PLATE 1
Normal mucosa of the cecum in a control male F344/N rat in the 13-week feed study of turmeric oleoresin. Note the smooth surface (no villi). H&E, 60X

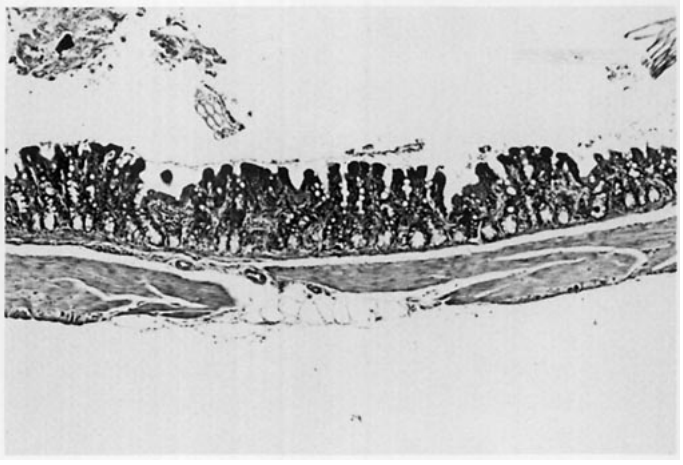


PLATE 2
Hyperplastic (thickened) mucosa of the cecum with an irregular surface which has an atypical, almost villar appearance in a female F344/N rat receiving 50,000 ppm turmeric oleoresin in the 13-week feed study. Compare with Plate 1. H&E, 60X

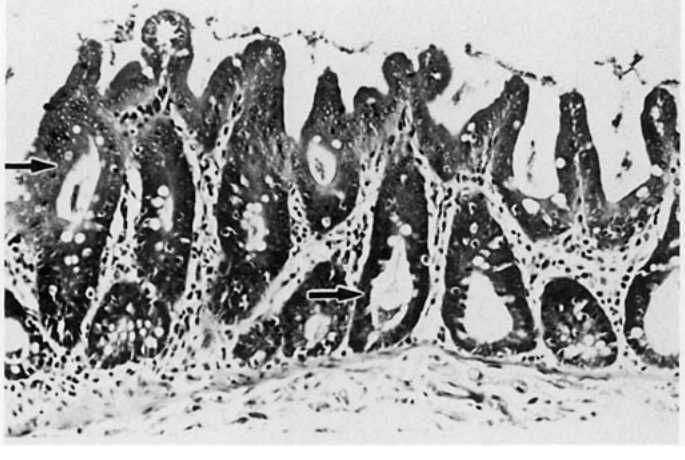


PLATE 3
Hyperplastic mucosa and dilated hyperplastic glands (arrows) of the cecum in a female F344/N rat receiving 50,000 ppm turmeric oleoresin in the 13-week feed study. H&E, 180X

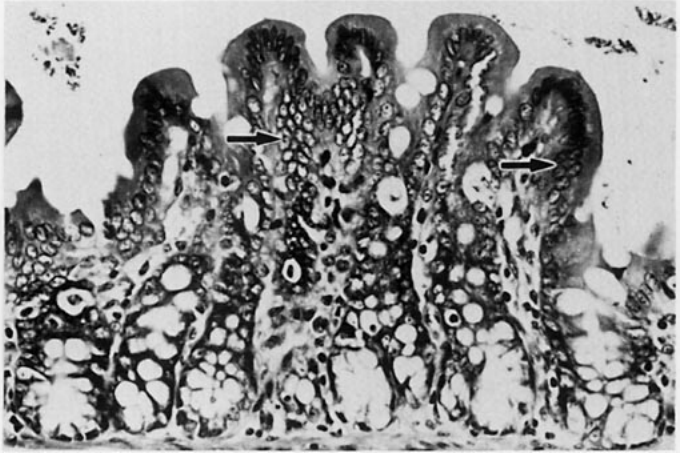


PLATE 4
Higher magnification of hyperplastic mucosa of the cecum in a female F344/N rat receiving 50,000 ppm in the 13-week feed study. H&E, 300X

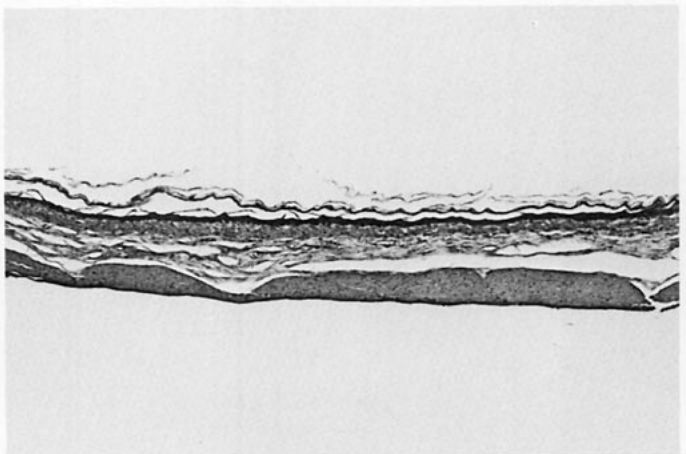


PLATE 5
Normal mucosa of the forestomach in a control male F344/N rat in the 2-year feed study of turmeric oleoresin. H&E, 60X

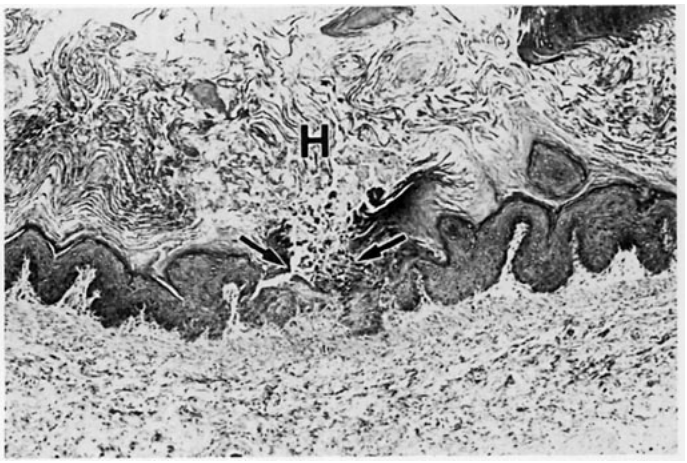


PLATE 6
Superficial ulceration (arrows) of the mucosa in the forestomach of a male F344/N rat receiving 50,000 ppm turmeric oleoresin in the 2-year feed study. The epithelium is irregularly thickened (hyperplastic) and accompanied by marked hyperkeratosis (H). Compare with Plate 5. H&E, 60X

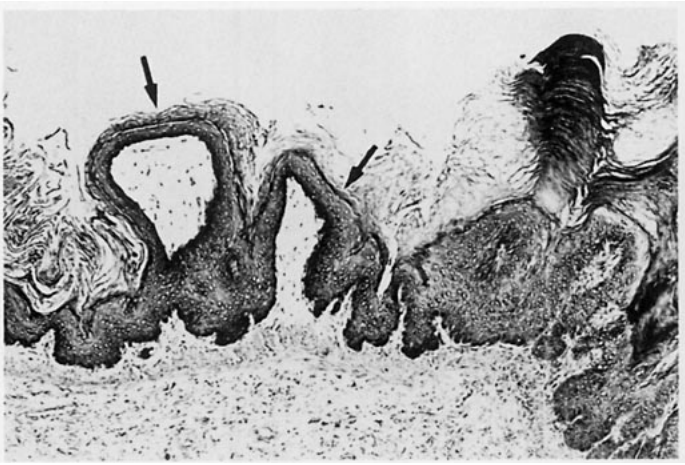


PLATE 7
Squamous hyperplasia of the forestomach in a male F344/N rat receiving 50,000 ppm turmeric oleoresin in the 2-year feed study. Note the prominent outgrowth of the epithelium (arrows) and hyperkeratosis. H&E, 60X

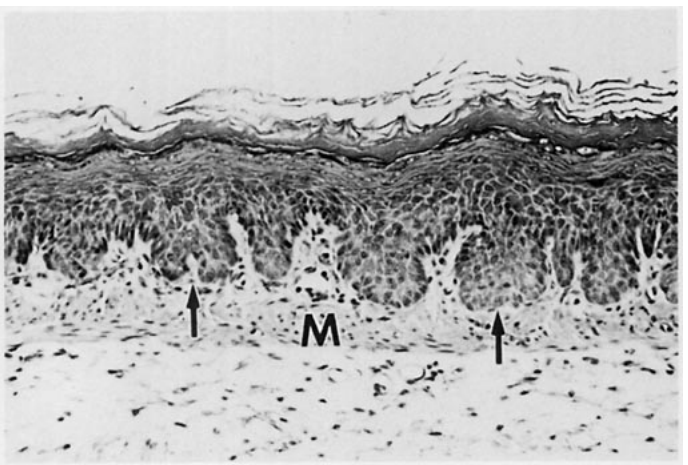


PLATE 8
Squamous hyperplasia of the forestomach in a male F344/N male rat receiving 50,000 ppm turmeric oleoresin in the 2-year feed study. Note the prominent downgrowth of the basal layer (arrows) and intact muscularis mucosa (M). H&E, 150X

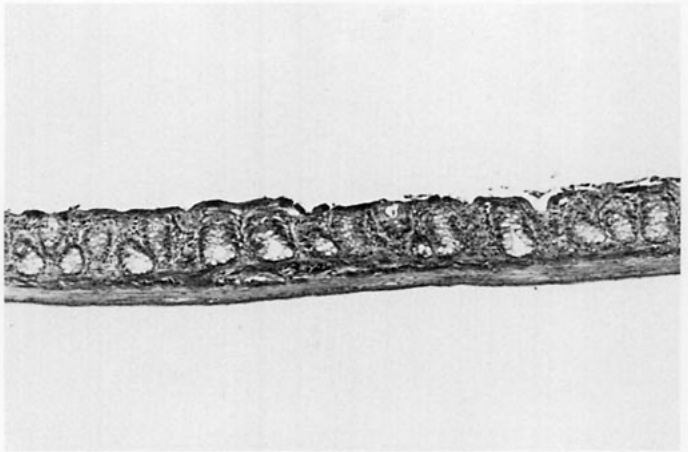


Plate 9
Normal mucosa of the cecum in a control female F344/N rat in the 2-year feed study of tumeric oleoresin. H&E, 60X

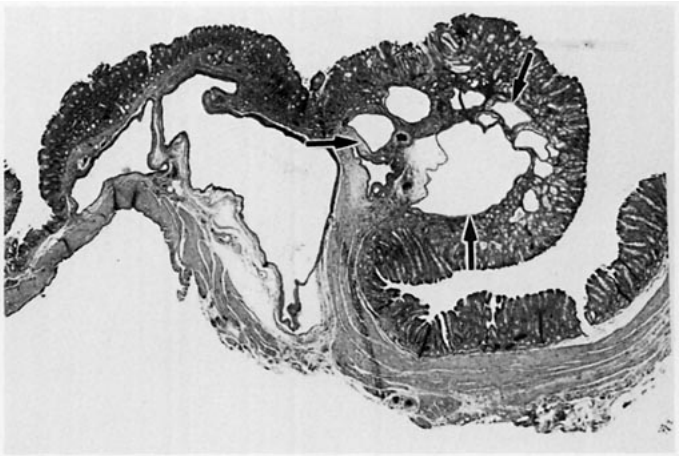


Plate 10
Diffuse hyperplasia of the mucosa in the cecum of a male F344/N rat receiving 50,000 ppm turmeric oleoresin in the 2-year feed study. Note the well-differentiated dilated glands in the submucosa (arrows). Compare with Plate 11. H&E, 12X

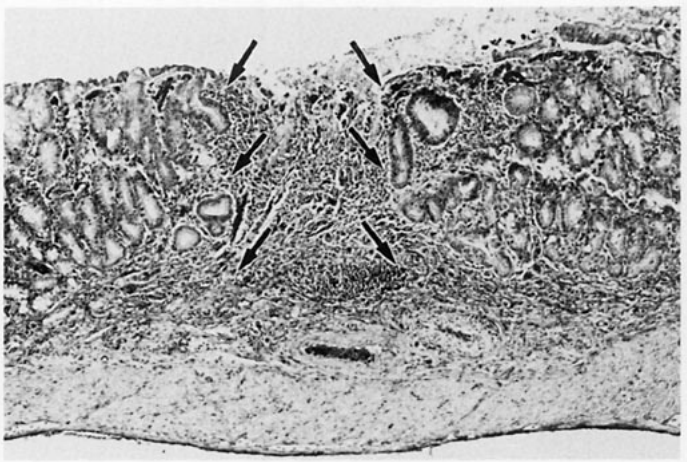


Plate 11
Focal ulceration (arrows) extending through the muscularis mucosa of the cecum in a male F344/N rat receiving 50,000 ppm turmeric oleoresin in the 2-year feed study. Note mixed inflammatory cell infiltrate. H&E, 60X

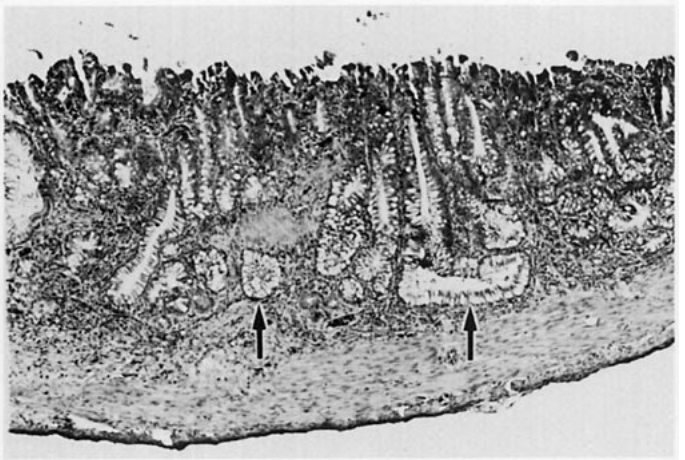


Plate 12
Hyperplasia of the mucosa in the cecum of a male F344/N rat receiving 50,000 ppm turmeric oleoresin in the 2-year feed study. Note the increased numbers of goblet cells (arrows) and thickened mucosa. H&E, 60X

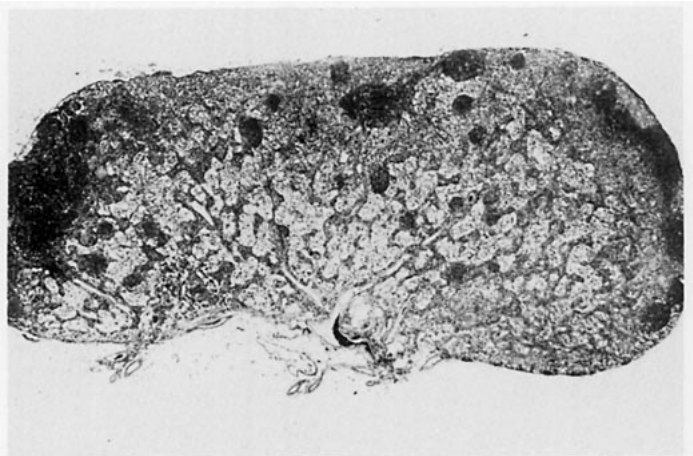


PLATE 13
Normal mesenteric lymph node in a control female F344/N rat in the 2-year feed study of turmeric oleoresin. H&E, 15X

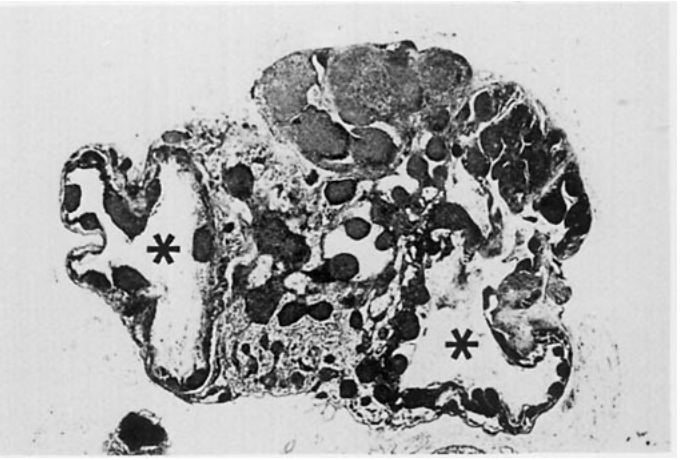


PLATE 14
Sinus ectasia of the mesenteric lymph node in a male F344/N rat receiving 50,000 ppm turmeric oleoresin in the 2-year feed study. Note the cystic lymph-filled spaces (asterisks). Compare with Plate 13. H&E, 15X

DISCUSSION AND CONCLUSIONS

Turmeric, turmeric oleoresin, and curcumin are commonly used as coloring agents and spices in foods (Govindarajan, 1980). Turmeric is the ground powder from the rhizome of *Curcuma longa* and contains approximately 1% to 5% curcumin. Turmeric oleoresin, an organic extract from turmeric, contains 15% to 40% curcumin along with volatile oils and other plant constituents (Krishnamurthy *et al.*, 1976). The World Health Organization recommended that the daily intake of turmeric, turmeric oleoresin, or curcumin should not exceed 0.1 to 2.5 mg/kg of body weight.

Turmeric oleoresin was nominated for study by the Food and Drug Administration and the National Cancer Institute because of widespread human exposure and the lack of information on its toxicity or carcinogenicity in rodents. No epidemiologic studies or case reports examining the relationship between exposure to turmeric or curcumin and human cancer were found in the literature. Turmeric oleoresin containing approximately 79% to 85% curcumin was selected for the NTP studies because sufficient quantities of pure curcumin were not available. Because human exposure to turmeric oleoresin would most likely occur from low-level exposure in foods, the oral route of administration was chosen for the 13-week and 2-year studies in F344/N rats and $B6C3F_1$ mice.

During the NTP 13-week and 2-year studies, survival and feed consumption were similar in exposed and control rats and mice. These results are similar to previous studies where turmeric (2.5 g/kg body weight) did not cause mortality in rats, guinea pigs, or monkeys (Shankar *et al.*, 1980). In the NTP studies, slight body weight differences were observed in rats and mice receiving 50,000 ppm. The primary site of toxicity was the gastrointestinal tract in 50,000 ppm rats but not mice. In contrast, no significant differences in body weights and no gastrointestinal lesions were observed in the study by Shankar *et al.* (1980). Variations in response to treatment between the two studies may be due to differences in the compounds studied (turmeric, turmeric oleoresin), percentage curcumin, doses administered, or observational criteria.

In the NTP studies, chemical-related intestinal lesions consisting of hyperplasia were observed primarily in the cecum, and to a lesser extent in the colon, of male and female rats receiving 50,000 ppm at 13 weeks. Similarly, ulcers, inflammation, and hyperplasia of the cecum, and to a minor degree of the colon, were present in 50,000 ppm male and female rats at the 15-month interim evaluation and at the end of the 2-year study. Although ulcers were not seen at 13 weeks, the mucosal hyperplasia suggests that necrosis, or an increased rate of cellular senescence, occurred early or at a level not observed by light microscopy. The epithelial hyperplasia was characterized by increased thickness of the surface mucosa with outgrowths or downgrowths of cecal epithelium which formed glands deep within the submucosa. Although the glands extended into the submucosa, there was normal cell differentiation and cellular atypia was not present. None of the hyperplastic lesions progressed to neoplasms of the cecum or of the colon in the 2-year study.

In the 2-year rat study, the incidences of ulceration, hyperplasia, and hyperkeratosis of the forestomach were also increased in male rats. The hyperplastic lesions of the forestomach were most likely regenerative rather than part of a neoplastic process. Since there were no squamous cell papillomas, there was no evidence of progression from hyperplasia to squamous cell papillomas and squamous cell carcinomas. Furthermore, minimal basal cell hyperplasia was observed in the forestomach, adding evidence that the lesions were most likely regenerative in nature. Prominent basal cell hyperplasia and dysplasia are frequently associated with chemicals that result in neoplasms of the forestomach mucosa in F344 rats (Brown and Hardisty, 1990).

The mechanisms of turmeric oleoresin-induced ulcerative lesions in the forestomach, cecum, and colon are unknown, but they may be due to direct cytotoxicity or to mechanisms similar to ulcerative

lesions induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in the gastrointestinal tract. A possible mechanism of cytotoxicity is that turmeric oleoresin caused cell injury and death (necrosis) of the superficial mucosal cells, formation of erosions and ulcers, and compensatory regeneration and hyperplasia.

A common feature of NSAIDs is that they induce ulcers of the gastrointestinal tract (Shriver *et al.*, 1975; Whittle *et al.*, 1985). Nonsteroidal agents such as curcumin, aspirin, and phenylbutazone inhibit cyclooxygenase in the arachidonic acid pathway; a pathway important in the generation of prostaglandins (Tønnesen *et al.*, 1989a,b; Simmons *et al.*, 1990). Prostaglandins have important roles in the gastrointestinal tract in maintaining vascular and mucosal perfusion and integrity, and exerting cytoprotective effects (Robert *et al.*, 1971; Miller *et al.*, 1983). They also modulate motility, acid and mucus secretion, and electrolyte and water absorption, prevent ulcer formation, and accelerate ulcer healing (Robert *et al.*, 1971, 1976, 1977). A proposed mechanism of toxicity (ulceration) by NSAIDs is suppression of prostaglandin production via NSAID effects on the enzyme cyclooxygenase. Development of gastrointestinal ulceration by NSAIDs is thought to result from decreased prostaglandin synthesis and resultant decreases in mucus formation, diminishing the cytoprotective effect. Subsequently, decreased biological activity causes vasoconstriction of the gastrointestinal blood supply, resulting in ischemic necrosis (Meschter *et al.*, 1990).

Evidence that turmeric oleoresin may be acting by a NSAID mechanism is supported by the following data: (1) the nonsteroidal anti-inflammatory activity of curcumin has been reported to be as potent as the NSAID phenylbutazone in an acute model of inflammation and half as potent in a chronic model of inflammation (Srimal and Dhawan, 1973; Mukhopadhyay *et al.*, 1982); (2) NSAIDs generally induce ulcerative lesions in the gastrointestinal tract of other species (Karcher *et al.*, 1990; Simmons *et al.*, 1990); and (3) since the turmeric oleoresin used in these NTP studies contained approximately 79% to 85% curcumin, ulceration in rats may have been due to the curcumin. Curcumin was shown to have a lower ulcerogenic index than phenylbutazone (Srimal and Dhawan, 1973). Whether mechanisms of ulceration in the gastrointestinal tract (forestomach, cecum, and colon) of rats is due to inhibition of cyclooxygenase or direct cytotoxic effects of turmeric oleoresin needs to be further evaluated.

The distribution of lesions in the gastrointestinal tract was consistent with absorption and distribution studies in rats which showed that 24 hours after oral administration of 400 mg curcumin, the concentration of the chemical remaining in the lower part of the gut was confined primarily to the cecum and large intestine and amounted to 38% of the quantity administered (Vijayalakshmi and Chandrasekhara, 1980, 1982). When rats were administered an oral dose of 1 g/kg, 75% of the curcumin was excreted in the feces (Wahlström and Blennow, 1978). Studies by Holder *et al.* (1978) using [^{3}H]-curcumin found that 70% to 80% of an intraperitoneal or intravenous dose of 0.6 mg curcumin was excreted in the bile within 6 to 8 hours after dosing, suggesting that the enterohepatic circulation of curcumin may also play a role in the localization of the chemical in the cecum and the colon. Since relatively poor absorption of curcumin occurs in the gastrointestinal tract, and a significant amount is localized in the cecum and colon, continued exposure of gastrointestinal epithelial cells to turmeric oleoresin most likely resulted in toxicity (ulceration, hyperplasia, and inflammation).

While turmeric oleoresin caused gastrointestinal toxicity in the forestomach, NSAIDs usually cause toxicity within the glandular stomach of rodents (Hingson and Ito, 1971; Shriver *et al.*, 1975). The location of toxic lesions in the gastrointestinal tract may be due in part to the experimental conditions used. NSAIDs, including aspirin and phenylbutazone, administered orally to fasted rats caused ulcers of the glandular stomach, but when administered to nonfasted rats, lesions were not observed in the glandular stomach (Shriver *et al.*, 1975). In the NTP 2-year rat study, phenylbutazone caused ulcers and hyperplasia in the forestomach similar to those induced by turmeric oleoresin, which supports the observations that feeding decreases the susceptibility of the glandular stomach to toxicity from NSAIDs. An additional factor which may be responsible for the localization of the lesions in the forestomach may be the increased transit time within the forestomach compared to the glandular stomach.

Unlike male and female rats, ulcerative, inflammatory, or hyperplastic lesions were not present in the cecum or colon of mice. Thus, the rat appears to be

more sensitive to the toxic effects of turmeric oleoresin. Differences in absorption, metabolism, and excretion rates of turmeric oleoresin may have played a role in the lack of gastrointestinal lesions in mice. Metabolism and distribution studies for turmeric oleoresin have not been reported for mice. Species differences between rats and mice were also seen with the NSAID phenylbutazone (NTP, 1990). Phenylbutazone caused forestomach toxicity in the rat but not in the mouse. Whether there is a difference in the local production of prostaglandins in rats versus mice is not known. Ahlquist *et al.* (1982) showed that there are regional and species differences in prostaglandin production in the gastrointestinal tract of humans, pigs, dogs, and guinea pigs. Information on differences in local prostaglandin production and effects in rats and mice is not available.

In the NTP 2-year study of turmeric oleoresin, there were significantly increased incidences of clitoral gland adenoma in all exposed groups of female rats. The incidence in each of the exposure groups also exceeded the range for this neoplasm in historical control female rats from recent NTP feed studies (range: 4%-20%; 105/1,000, 11%). However, despite the 25-fold increase in dietary concentration of turmeric oleoresin, the incidence of clitoral gland adenoma did not increase with exposure level. While the kinetics of absorption, metabolism, and excretion have not been thoroughly characterized, particularly following repeated dose administration, in single dose studies using Wistar rats the amount of curcumin absorbed was similar (60% to 66%) over a wide range of doses from 10 to 400 mg (Vijayalakshmi and Chandrasekhara, 1982). Therefore, it is unlikely that the lack of dose response in the present study is related to saturation of absorption at the 10,000 and 50,000 ppm levels. Because of the lack of a dose response, no corresponding increased incidence of clitoral gland hyperplasia, and no corresponding increased incidence of preputial gland neoplasms in male rats, it was uncertain whether the increased incidence of clitoral gland adenoma in exposed groups of females was chemical related. Furthermore, chemicals known to induce clitoral gland neoplasms generally are mutagens in the *Salmonella* assay and also induce neoplasms at other sites, particularly Zymbal's gland, skin, mammary gland, preputial gland, or a combination of these (Copeland-Haines and Eustis, 1990). Turmeric oleoresin is not mutagenic in *Salmonella*. Based on all these considerations, the increased incidence of clitoral gland adenoma in exposed groups of females was considered to be "equivocal" rather than "some" evidence of carcinogenic activity.

The incidences of hepatocellular neoplasms, primarily adenomas, in male and female mice receiving 10,000 ppm were significantly increased. The number of male and female mice with multiple hepatocellular neoplasms (multiple adenomas, multiple carcinomas, or multiple adenomas or carcinomas) was greater in each of the exposure groups than in the controls. In contrast, the incidences of hepatocellular carcinomas in males and females that received 50,000 ppm were not significantly greater than those in controls. Further, there was no corresponding increased incidence of altered hepatocellular foci (the putative precursor of hepatocellular neoplasms) in exposed groups of male and female mice. Thus, the increased incidences of hepatocellular neoplasms in the 10,000 ppm groups were considered to be "equivocal evidence of carcinogenic activity."

In the small intestine of male mice three carcinomas occurred in the 2,000 ppm group and three carcinomas occurred in the 10,000 ppm group. This response may have been chemical related because carcinomas have not been previously reported in control male or female mice in the NTP historical database. The evidence was not considered to be strong enough to place these neoplasms in the "some evidence" category because (1) the incidence of the carcinomas in the 2,000 and 10,000 ppm groups were not statistically significant, (2) there were no carcinomas of the small intestine in 50,000 ppm male mice, and (3) there were no neoplasms in the small intestine of exposed female mice.

There was a marginally increased incidence of thyroid gland follicular cell hyperplasia in female mice. This finding is similar to studies in pigs receiving turmeric oleoresin at dietary levels of 296 and 1,551 mg/kg body weight per day (Bille *et al.*, 1985). Although there was no striking dose-related response, the findings of Bille *et al.* (1985) suggest that the hyperplasia in mice was related to chemical administration. It is unknown whether or not turmeric oleoresin induces thyroid gland follicular cell hyperplasia by mechanisms such as inhibition of iodine uptake by follicular epithelial cells, or if the chemical functions as a "goitrogen" or "antithyroid" compound.

The NTP studies were considered adequate for assessing the carcinogenicity of turmeric oleoresin. In the 13-week studies, gastrointestinal lesions were observed in rats receiving 50,000 ppm. In the 2-year studies, minor body weight differences were also observed in rats and mice that received less than 50,000 ppm. The mean body weights of male and female rats and of female mice receiving 50,000 ppm were 5% to 10% lower than those of controls during most of the last half of the studies, and the mean body weights of male mice receiving 50,000 ppm were 4% to 5% lower than those of the controls during the last 4 months of the study. For the 2-year studies, the high exposure level of 50,000 ppm was selected because substitution of more than 5% of the diet with a test compound for 2 years may compromise nutritional adequacy.

Previous genotoxic studies of turmeric oleoresin and curcumin, at doses of 1.28, 6.4, 32, or 160 μg/plate, did not show mutagenic responses in strains TA1535, TA100, and TA98 in *Salmonella*/microsome assay (Jensen, 1982). In addition, significant genotoxic effects were not seen in the micronucleus test of turmeric and curcumin in mice, the bone marrow chromosome analysis test in mice and rats, or the dominant-lethal test in mice (Vijayalaxmi, 1980). Furthermore, an aqueous turmeric component protected cellular DNA in lymphocytes up to 90% against smoke condensate from twigs and dry leaves, and 65% against 12-*O*-tetradecanoylphorbol-13-acetate. Conversely, Goodpasture and Arrighi (1976) found that turmeric caused a dose- and time-dependent induction of chromosome aberrations in several mammalian cell lines.

In these NTP studies, turmeric oleoresin was not mutagenic in any of four strains of *Salmonella typhimurium* tested, with or without exogenous metabolic activation (S9). It induced a small, but significant, increase in sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. The positive response in the sister chromatid exchange test occurred with S9, whereas the aberrations response occurred without S9. Collectively, the genotoxicity studies of turmeric oleoresin are consistent with the results of the studies in rats and mice where there was no clear evidence of carcinogenicity.

Recently, the effectiveness of four of the most commonly used *in vitro* short-term genetic toxicity tests for prediction of chemical carcinogenicity was evaluated using 114 chemicals studied by the NTP. The tests used were induction of gene mutations in *S. typhimurium* and mouse lymphoma L5178Y cells, and induction of sister chromatid exchanges and chromosome abberations in cultured Chinese hamster ovary cells (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). The *S. typhimurium* assay was shown to have the lowest sensitivity (proportion of carcinogens positive in *S. typhimurium*), the highest specificity (proportion of noncarcinogens negative in *S. typhimurium*), and the highest positive predictivity for carcinogenic activity in rodents. The other tests had lower predictivities for carcinogens, and no combination of the four tests was more predictive for carcinogenic activity than the *S. typhimurium* assay alone.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of turmeric oleoresin in male F344/N rats administered 2,000, 10,000, or 50,000 ppm. There was *equivocal evidence of carcinogenic activity* of turmeric oleoresin in female F344/N rats based on increased incidences of clitoral gland adenoma in all exposed groups. There was *equivocal evidence of carcinogenic activity* of turmeric oleoresin in male $B6C3F_1$ mice based on a marginally increased incidence of hepatocellular adenoma at the 10,000 ppm level, and the occurrence of carcinomas of the small intestine in the 2,000 and 10,000 ppm groups. There was *equivocal evidence of carcinogenic activity* of turmeric oleoresin in female $B6C3F_1$ mice based on an increased incidence of hepatocellular adenomas in the 10,000 ppm group.

Turmeric oleoresin ingestion was also associated with increased incidence of ulcers, hyperplasia, and inflammation of the forestomach, cecum, and colon in male rats and of the cecum in female rats. In female mice ingestion of diets containing turmeric oleoresin was also associated with an increased incidence of thyroid gland follicular cell hyperplasia.

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

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

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	26	29	32	28
Natural deaths	6	4	3	6
Survivors				
Terminal sacrifice	18	17	15	17
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(7)	(6)	(9)
Hepatocellular adenoma			1 (17%)	1 (11%)
Leukemia mononuclear		1 (14%)		
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(1)	(1)	(9)
Pars distalis, adenoma	3 (30%)	1 (100%)	1 (100%)	1 (11%)
Thyroid gland	(9)		(1)	(9)
C-cell, adenoma	2 (22%)			
General Body System				
None				
Genital System				
Preputial gland	(9)	(3)	(1)	(9)
Adenocarcinoma		1 (33%)		
Adenoma		1 (33%)		
Testes	(10)	(3)	(4)	(9)
Bilateral, interstitial cell, adenoma	1 (10%)	2 (67%)	2 (50%)	2 (22%)
Interstitial cell, adenoma	2 (20%)	1 (33%)	2 (50%)	1 (11%)
Hematopoietic System				
Spleen	(10)	(2)		(9)
Leukemia mononuclear		1 (50%)		

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Integumentary System				
Skin	(10)	(2)	(3)	(9)
Fibrosarcoma		1 (50%)		
Sebaceous gland, adenoma			1 (33%)	
Subcutaneous tissue, hemangioma				1 (11%)
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(7)	(7)	(9)
Alveolar/bronchiolar adenoma			1 (14%)	
Leukemia mononuclear		1 (14%)		
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(9)
Leukemia mononuclear		1 (10%)		
2-Year Study				
Alimentary System				
Esophagus	(49)	(49)	(49)	(49)
Intestine large, cecum	(50)	(49)	(50)	(51)
Intestine large, colon	(49)	(50)	(49)	(49)
Adenocarcinoma	1 (2%)			
Intestine small, duodenum	(50)	(50)	(49)	(51)
Intestine small, ileum	(49)	(50)	(49)	(51)
Intestine small, jejunum	(50)	(50)	(49)	(49)
Sarcoma			1 (2%)	
Liver	(50)	(50)	(50)	(51)
Hepatocellular carcinoma	1 (2%)		1 (2%)	1 (2%)
Hepatocellular adenoma		1 (2%)	2 (4%)	1 (2%)
Hepatocellular adenoma, multiple			1 (2%)	1 (2%)
Histiocytic sarcoma			1 (2%)	

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(9)	(3)	(8)	(5)
Liposarcoma			1 (13%)	
Pancreas	(48)	(50)	(50)	(50)
Mixed tumor benign		1 (2%)		
Salivary glands	(49)	(49)	(50)	(50)
Stomach, forestomach	(49)	(50)	(43)	(51)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(49)
Tongue		(1)	(1)	(2)
Squamous cell papilloma				1 (50%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Schwannoma benign		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(49)	(51)
Adenoma	1 (2%)		1 (2%)	
Adrenal gland, medulla	(47)	(50)	(50)	(50)
Pheochromocytoma malignant		1 (2%)	2 (4%)	1 (2%)
Pheochromocytoma benign	9 (19%)	15 (30%)	13 (26%)	6 (12%)
Pheochromocytoma benign, multiple	5 (11%)	5 (10%)	5 (10%)	3 (6%)
Islets, pancreatic	(47)	(50)	(48)	(49)
Adenoma	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Carcinoma			1 (2%)	
Parathyroid gland	(47)	(47)	(49)	(46)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Pituitary gland	(50)	(50)	(49)	(49)
Pars distalis, adenoma	22 (44%)	15 (30%)	14 (29%)	11 (22%)
Pars distalis, adenoma, multiple	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Pars intermedia, adenoma				1 (2%)
Pars nervosa, adenoma	1 (2%)			
Pars nervosa, craniopharyngioma		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(51)
Carcinoma			1 (2%)	
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	2 (4%)	7 (14%)	5 (10%)	6 (12%)
C-cell, carcinoma	2 (4%)			
Follicular cell, adenocarcinoma		1 (2%)		
Follicular cell, adenoma	1 (2%)	2 (4%)		1 (2%)
General Body System				
Tissue NOS			(1)	

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Genital System				
Coagulating gland	(10)	(2)	(2)	(9)
Epididymis	(49)	(50)	(50)	(50)
Preputial gland	(48)	(48)	(49)	(51)
Adenocarcinoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Adenoma	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Bilateral, adenoma	1 (2%)			
Prostate	(50)	(50)	(50)	(51)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(51)
Bilateral, interstitial cell, adenoma	30 (60%)	37 (74%)	32 (64%)	32 (63%)
Interstitial cell, adenoma	7 (14%)	7 (14%)	8 (16%)	8 (16%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(51)
Sternal, histiocytic sarcoma			1 (2%)	
Lymph node	(49)	(50)	(50)	(51)
Lymph node, mandibular	(22)	(12)	(20)	(15)
Squamous cell carcinoma, metastatic	1 (5%)			
Lymph node, mesenteric	(49)	(50)	(50)	(51)
Spleen	(50)	(50)	(50)	(50)
Thymus	(41)	(47)	(45)	(43)
Thymoma benign		1 (2%)		
Integumentary System				
Mammary gland	(38)	(39)	(40)	(41)
Adenocarcinoma			1 (3%)	
Adenoma, multiple	1 (3%)			
Fibroadenoma			1 (3%)	1 (2%)
Skin	(50)	(49)	(50)	(51)
Basal cell adenoma				1 (2%)
Fibroma		1 (2%)		
Keratoacanthoma			3 (6%)	
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma	3 (6%)		2 (4%)	1 (2%)
Squamous cell papilloma, multiple	1 (2%)			
Subcutaneous tissue, fibroma	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Subcutaneous tissue, fibroma, multiple	1 (2%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Subcutaneous tissue, lipoma		1 (2%)	1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)		1 (2%)
Subcutaneous tissue, schwannoma malignant	1 (2%)		1 (2%)	
Musculoskeletal System				
Skeletal muscle			(1)	(1)
Rhabdomyosarcoma			1 (100%)	

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(51)
Astrocytoma malignant		1 (2%)	1 (2%)	
Glioma malignant		1 (2%)		
Meninges, granular cell tumor benign			1 (2%)	
Respiratory System				
Lung	(49)	(50)	(50)	(51)
Adenocarcinoma, metastatic, thyroid gland		1 (2%)		
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	4 (8%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, skin	1 (2%)			
Squamous cell carcinoma				1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Nose	(50)	(50)	(49)	(50)
Chondroma	1 (2%)			
Squamous cell carcinoma	1 (2%)			
Respiratory epithelium, adenoma			1 (2%)	
Trachea	(50)	(50)	(50)	(51)
Adenocarcinoma, metastatic, thyroid gland		1 (2%)		
Special Senses System				
Ear		(1)		(3)
Pinna, schwannoma malignant				1 (33%)
Eye	(15)	(4)	(7)	(9)
Lids, fibroma			1 (14%)	
Zymbal's gland			(1)	(1)
Adenocarcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(51)
Renal tubule, adenoma			1 (2%)	
Urinary bladder	(49)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(51)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	27 (54%)	28 (56%)	35 (70%)	23 (45%)
Mesothelioma benign		1 (2%)		
Mesothelioma malignant		2 (4%)	1 (2%)	1 (2%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	7	5	7	5
2-Year study	49	50	48	44
Total primary neoplasms				
15-Month interim evaluation	8	8	8	6
2-Year study	135	145	152	119
Total animals with benign neoplasms				
15-Month interim evaluation	7	4	7	5
2-Year study	47	49	46	43
Total benign neoplasms				
15-Month interim evaluation	8	5	8	6
2-Year study	96	108	103	88
Total animals with malignant neoplasms				
15-Month interim evaluation		3		
2-Year study	34	33	40	26
Total malignant neoplasms				
15-Month interim evaluation		3		
2 Year study	39	37	49	31
Total animals with metastatic neoplasms				
2-Year study	2	2	1	
Total metastatic neoplasms				
2-Year study	2	3	1	

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

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

Number of Days on Study	404	435	465	494	505	521	522	529	531	543	543	553	563	567	589	609	633	634	644	655	662	671	676	687	695
Carcass ID Number	0055	0045	0013	0091	0094	0053	0093	0075	0103	0024	0064	0044	0115	0074	0084	0073	0071	0063	0061	0081	0083	0012	0072	0013	0052
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Adenocarcinoma																				X					
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Mesentery					+			+								+	+	+	+						
Pancreas	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Adrenal gland, medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Pheochromocytoma benign																X		X			X	X	X		
Pheochromocytoma benign, multiple																				X					
Islets, pancreatic	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																						X			
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X	X	X	X		X		X				X		X	X	X	X		X	X	
Pars distalis, adenoma, multiple																						X			
Pars nervosa, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																	X								
Follicular cell, adenoma												X													
General Body System																									
None																									

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

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

Number of Days on Study	695	696	696	711	715	718	722	732	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	0112	0062	0124	0034	0061	0011	0033	0022	0023	0043	0081	0082	0092	0101	0112	0121	0021	0031	0032	0041	0042	0051	0121	0122	0123	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma								X																		1
Mesentery																	+			+		+				9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign											X								X	X				X		9
Pheochromocytoma benign, multiple	X	X													X										X	5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																									X	2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X			X											X	X					X		X	X	22
Pars distalis, adenoma, multiple																										1
Pars nervosa, adenoma																	X									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X																	X	2
C-cell, carcinoma																X										2
Follicular cell, adenoma																										1
General Body System																										
None																										

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

Number of Days on Study	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6
	0	3	6	9	0	2	2	2	3	4	4	5	6	6	8	0	3	3	4	5	6	7	7	8	9
	4	5	5	4	5	1	1	9	1	3	3	3	3	7	9	9	3	4	4	5	2	1	6	7	5
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	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0
	5	4	1	9	9	5	9	7	0	2	6	4	1	7	8	7	7	6	1	8	3	1	7	1	5
	5	5	3	1	4	3	3	5	3	4	4	4	5	4	4	3	1	3	4	3	5	2	2	3	2
Genital System																										
Coagulating gland																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																					+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma								X																		
Adenoma																										
Bilateral, adenoma																						X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X		X		X	X		X	X			X				X	X	
Interstitial cell, adenoma						X									X			X			X					
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular		+	+		+				+	+					+	+				+	+					+
Squamous cell carcinoma, metastatic															X											
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	I	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																										
Mammary gland	M	M	+	M	+	M	+	+	M	+	+	M	M	+	M	M	M	+	+	M	+	+	+	+	+	+
Adenoma, multiple																							X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma															X											
Squamous cell papilloma																X										
Squamous cell papilloma, multiple																										
Subcutaneous tissue, fibroma																										
Subcutaneous tissue, fibroma, multiple																							X			
Subcutaneous tissue, fibrosarcoma																										
Subcutaneous tissue, sarcoma													X													
Subcutaneous tissue, schwannoma malignant											X															
Musculoskeletal System																										
Bone		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	695	696	696	711	715	718	722	732	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	
Carcass ID Number	0012	0062	0124	0034	0061	0111	0073	0022	0023	0043	0081	0082	0092	0101	0112	0121	0121	0123	0132	0141	0142	0151	0112	0122	0123	Total Tissues/ Tumors
Genital System																										
Coagulating gland	+	+		+			+					+	+						+	+	+		+			10
Epididymis	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																										1
Preputial gland	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	48
Adenocarcinoma											X															2
Adenoma										X					X											2
Bilateral, adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X		X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	30
Interstitial cell, adenoma				X				X									X									7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular				+		+	+				+			+	+		+	+	+		+		+	+		22
Squamous cell carcinoma, metastatic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+	M	M	+	+	+	41
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Adenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Squamous cell papilloma	X											X														3
Squamous cell papilloma, multiple													X													1
Subcutaneous tissue, fibroma		X														X										2
Subcutaneous tissue, fibroma, multiple																										1
Subcutaneous tissue, fibrosarcoma					X																					1
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
	0	3	6	9	0	2	2	2	3	4	4	5	6	6	8	0	3	3	4	5	6	7	7	8	9
	4	5	5	4	5	1	1	9	1	3	3	3	3	7	9	9	3	4	4	5	2	1	6	7	5
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	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0
	5	4	1	9	9	5	9	7	0	2	6	4	1	7	8	7	7	6	1	8	3	1	7	1	5
	5	5	3	1	4	3	3	5	3	4	4	4	5	4	4	3	1	3	4	3	5	2	2	3	2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar carcinoma																									
Sarcoma, metastatic, skin													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																								X	
Squamous cell carcinoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+			+					+		+	+			+	+		+		+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X				X			X				X	X		X	X	X	X		X	

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

Number of Days on Study	695	696	696	711	715	718	722	732	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	0112	0062	0124	0034	0061	0011	0033	0022	0023	0043	0081	0082	0092	0101	0112	0111	0121	0031	0032	0041	0042	0051	0112	0122	0123	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma								X																		2
Alveolar/bronchiolar carcinoma										X																1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondroma																										1
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+	+	+		+	+														+					15
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	X	X	X	X			27

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

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

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

Number of Days on Study	710	715	718	718	721	722	722	723	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	
Carcass ID Number	0241	0135	0163	0171	0220	0221	0222	0134	0162	0263	0131	0131	0133	0141	0142	0151	0152	0161	0181	0182	0192	0201	0221	0221	0191	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery																				+						3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor benign																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																						+				1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign	X																									1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																	X									1
Pheochromocytoma benign				X	X		X	X					X	X									X		X	15
Pheochromocytoma benign, multiple	X	X																		X	X					5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X				X	X				X	X	X	X				X					15
Pars distalis, adenoma, multiple							X																			2
Pars nervosa, craniopharyngioma																		X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma															X											1
C-cell, adenoma		X																								7
Follicular cell, adenocarcinoma																										1
Follicular cell, adenoma																X						X				2

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

Number of Days on Study	3	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7
	3	1	3	4	8	8	8	0	0	1	1	4	5	5	5	6	8	9	9	9	9	0	0	0	0
	7	9	4	9	2	3	8	2	6	1	2	8	2	8	8	0	3	0	0	6	6	3	3	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	1	2	2	1	1	1	1	1	2	2	2	1	2	1	1	2	2	1	1
	1	0	1	5	5	4	9	3	3	8	6	7	8	9	0	4	3	5	2	6	7	1	2	9	8
	5	4	4	5	4	3	5	4	3	5	5	3	4	4	3	2	2	3	4	4	2	3	3	3	3
General Body System																									
None																									
Genital System																									
Coagulating gland										+															
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									X
Adenoma									X			X			X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X			X	X	X			X		X		X	X	X	X	X			X
Interstitial cell, adenoma			X				X					X	X		X		X						X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular		+				+							+		+	+			+		+				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	M	M	M	+	M	M	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X										
Subcutaneous tissue, fibroma										X															
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, sarcoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Glioma malignant							X																		
Spinal cord																								+	

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

Number of Days on Study	710	715	718	718	721	722	722	723	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	
Carcass ID Number	0241	0135	0163	0171	0220	0221	0222	0123	0162	0213	0133	0112	0133	0141	0142	0151	0152	0161	0181	0182	0192	0201	0211	0221	0191	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Coagulating gland																									+	2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Adenoma													X													4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		37
Interstitial cell, adenoma																										7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular		+	+		+						+	+														12
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma benign												X														1
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	39
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	49
Fibroma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, lipoma											X															1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Glioma malignant																										1
Spinal cord																										1

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

Number of Days on Study	3	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7
	3	1	3	4	8	8	8	0	0	1	1	4	5	5	5	6	8	9	9	9	9	0	0	0	0
	7	9	4	9	2	3	8	2	6	1	2	8	2	8	8	0	3	0	0	6	6	3	3	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	1	2	2	1	1	1	1	1	2	2	2	1	2	1	1	2	2	1	1
	1	0	1	5	5	4	9	3	3	8	6	7	8	9	0	4	3	5	2	6	7	1	2	9	8
	5	4	4	5	4	3	5	4	3	5	5	3	4	4	3	2	2	3	4	4	2	3	3	3	3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, thyroid gland					X																				
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, thyroid gland					X																				
Special Senses System																									
Ear															+										
Eye				+								+			+		+								
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
Mesothelioma benign																									
Mesothelioma malignant											X														

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

Number of Days on Study	710	715	718	718	721	722	722	723	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	
Carcass ID Number	0241	0135	0163	0171	0202	0212	0222	0134	0162	0213	0231	0231	0233	0241	0242	0251	0252	0261	0281	0282	0291	0201	0221	0221	0291	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, thyroid gland																										1
Alveolar/bronchiolar adenoma	X																									2
Alveolar/bronchiolar carcinoma											X															1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung											X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, thyroid gland																										1
Special Senses System																										
Ear																										1
Eye																										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X		X					X			X	X			X		X		X		X	28
Mesothelioma benign							X																			1
Mesothelioma malignant							X																			2

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

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

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

Number of Days on Study	682	687	695	697	703	707	715	715	722	722	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	034	035	023	022	025	026	032	035	054	062	025	052	053	071	072	081	011	011	012	033	033	041	042	043	061	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																						X				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X																							1
Hepatocellular adenoma		X			X																					2
Hepatocellular adenoma, multiple										X																1
Histiocytic sarcoma																										1
Mesothelioma malignant, metastatic			X																							1
Mesentery			+	+		+						+				+										8
Liposarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+		I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X																				1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant							X					X														2
Pheochromocytoma benign	X						X				X						X	X	X	X						13
Pheochromocytoma benign, multiple			X	X						X						X										5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma										X																1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X					X					X		X	X					X			X	14
Pars distalis, adenoma, multiple																		X								2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma				X																						1
C-cell, adenoma	X							X															X			5

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

Number of Days on Study	1	1	3	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6
	4	9	3	6	6	9	3	3	5	6	7	8	9	1	3	4	4	5	5	6	6	6	7	7	8
	1	9	7	4	7	9	2	9	6	8	9	5	4	2	4	5	8	3	4	1	2	7	4	6	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	3	2	3	3	3	3	3	3	2	3	2	3	3	3	2	3	3	2	3	2	2	2	2	2
	1	3	9	3	3	0	5	6	1	8	0	9	2	6	1	6	0	5	6	0	7	7	8	9	9
	5	5	5	4	1	5	4	4	4	3	4	3	4	3	3	3	3	3	2	2	4	3	2	2	1
General Body System																									
Tissue NOS																									
Genital System																									
Coagulating gland	+	+																							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma					X																				
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma											X	X	X	X			X	X	X		X	X	X		X
Interstitial cell, adenoma								X	X	X						X								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Sternal, histiocytic sarcoma																									X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+					+	+		+		+				+		+	+	+			+	+		+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	M	M	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	M
Adenocarcinoma			X																						
Fibroadenoma																					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma															X			X							
Squamous cell papilloma																							X		
Subcutaneous tissue, fibroma																								X	
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Skeletal muscle										+															
Rhabdomyosarcoma										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Meninges, granular cell tumor benign																									

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

Number of Days on Study	682	687	695	697	703	707	715	715	722	722	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	0344	0352	0323	0322	0225	0261	0321	0315	0254	0362	0321	0322	0323	0271	0272	0281	0301	0311	0312	0323	0333	0341	0342	0343	0361	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS			+																							1
Genital System																										
Coagulating gland																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Adenoma																		X					X			2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	32
Interstitial cell, adenoma	X		X	X																						8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sternal, histiocytic sarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+			+	+		+		+						+	+									20
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	40
Adenocarcinoma																										1
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma							X																			3
Squamous cell papilloma																								X		2
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, lipoma																						X				1
Subcutaneous tissue, schwannoma malignant																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																						X				1
Meninges, granular cell tumor benign																							X			1

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

Number of Days on Study	141	199	337	464	467	499	532	539	556	568	579	585	594	612	634	645	648	653	654	661	662	667	674	676	682
Carcass ID Number	0315	0325	0329	0334	0331	0335	0335	0336	0341	0232	0330	0239	0324	0363	0331	0236	0303	0353	0256	0302	0322	0277	0282	0292	0291
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X		X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+			+			+	+						I					
Lids, fibroma																									
Harderian gland																									
Lacrimal gland																				+					
Zymbal's gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Leukemia mononuclear				X		X	X	X	X		X		X		X	X	X	X	X		X	X	X	X	X
Mesothelioma malignant																									

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

Number of Days on Study	682	687	695	697	703	707	715	715	722	722	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	034	035	032	032	025	026	021	035	025	026	025	025	025	027	027	028	030	031	031	032	033	034	044	043	036	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X						X		4
Nose	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory epithelium, adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+		+	+													7
Lids, fibroma													X													1
Harderian gland					+																					1
Lacrimal gland																										1
Zymbal's gland					+																					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma			X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear	X	X	X	X	X	X	X	X	X	X		X			X		X	X		X		X	X	X		35
Mesothelioma malignant			X																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm

Number of Days on Study	270	367	368	371	374	400	404	414	456	479	487	492	504	521	521	522	522	528	538	569	680	610	615	633	640	669
Carcass ID Number	0425	0385	0442	0475	0445	0483	0423	0435	0444	0465	0382	0414	0441	0375	0445	0448	0484	0473	0464	0393	0443	0413	0373	0373	0442	0393
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, rectum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																										
Hepatocellular adenoma					X																					
Hepatocellular adenoma, multiple																										
Mesentery			+				M								+			+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Salivary glands	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+
Tongue																										
Squamous cell papilloma																										
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																										
Pheochromocytoma benign																							X			
Pheochromocytoma benign, multiple																										X
Islets, pancreatic	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																	X				X					X
Parathyroid gland	+	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X								X			X		X
Pars distalis, adenoma, multiple																	X									
Pars intermedia, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X			X	X			
Follicular cell, adenoma																										
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	673	676	682	682	695	695	711	716	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	
Carcass ID Number	0372	0441	0403	0445	0402	0442	0412	0443	0373	0338	0339	0401	0443	0443	0445	0445	0445	0445	0461	0462	0447	0447	0448	0441	0443	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma											X															1
Hepatocellular adenoma																										1
Hepatocellular adenoma, multiple												X														1
Mesentery					+				+																	5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma													X													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue			+																	+						2
Squamous cell papilloma																				X						1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant														X												1
Pheochromocytoma benign			X										X	X		X				X						6
Pheochromocytoma benign, multiple					X										X											3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X		X		X					X	X				X	X							11
Pars distalis, adenoma, multiple																				X						2
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma	X												X			X										6
Follicular cell, adenoma																		X								1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm
(continued)

Number of Days on Study	270	367	368	371	374	400	404	414	446	469	487	492	504	521	521	522	522	528	538	569	580	601	615	633	640	669
Carcass ID Number	0425	0385	0424	0475	0445	0383	0423	0443	0444	0445	0382	0441	0421	0375	0445	0443	0444	0473	0464	0393	0434	0413	0433	0433	0442	0392
Genital System																										
Coagulating gland																		+		+						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Adenoma					X															X						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X	X						X	X		X	X	X	X		X	X
Interstitial cell, adenoma									X			X			X	X								X		
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular										+					+	+		+	+		+	+		+		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+
Integumentary System																										
Mammary gland	+	+	M	M	M	+	+	M	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	M	M	+
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																										
Squamous cell papilloma																								X		
Subcutaneous tissue, fibroma																				X						
Subcutaneous tissue, sarcoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+																						
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Squamous cell carcinoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	673	676	682	682	695	695	711	716	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	
Carcass ID Number	0372	0441	0403	0445	0402	0442	0412	0463	0371	0381	0391	0401	0443	0443	0451	0452	0453	0454	0461	0462	0471	0472	0481	0411	0443	Total Tissues/ Tumors
Genital System																										
Coagulating gland		+			+		+					+		+	+						+					9
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma														X												1
Adenoma																					X					3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	32
Interstitial cell, adenoma							X	X		X																8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular			+	+	+								+					+	+	+						15
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Fibroadenoma																				X						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell adenoma										X																1
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																		X						X		3
Subcutaneous tissue, sarcoma															X											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																									+	1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord																										4
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																X							X			2
Squamous cell carcinoma		X																								1
Nose	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm
(continued)

Number of Days on Study	270	367	368	371	374	400	404	441	456	469	478	492	504	521	521	522	522	528	538	569	680	601	615	633	640	669
Carcass ID Number	0425	0385	0424	0475	0445	0384	0423	0445	0444	0465	0382	0444	0441	0375	0485	0483	0484	0473	0463	0393	0443	0413	0437	0433	0442	0393
Special Senses System																										
Ear						+									+											
Pinna, schwannoma malignant															X											
Eye						+	+		+				M					+			+			+		
Lacrimal gland						+	+																			
Zymbal's gland																										
Adenocarcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X	X		X	X		X	X	X	X	X	X
Mesothelioma malignant																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	673	676	682	682	695	695	711	716	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	
Carcass ID Number	0372	0441	0403	0445	0402	0448	0412	0463	0371	0381	0391	0401	0443	0433	0451	0452	0453	0454	0461	0462	0471	0472	0481	0411	0413	Total Tissues/ Tumors
Special Senses System																										
Ear																		+								3
Pinna, schwannoma malignant																										1
Eye							+	+									+	M								9
Lacrimal gland																										2
Zymbal's gland						+																				1
Adenocarcinoma						X																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear	X		X	X	X	X		X		X		X			X			X	X		X					23
Mesothelioma malignant												X														1

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	14/47 (30%)	20/50 (40%)	18/50 (36%)	9/50 (18%)
Adjusted rate[b]	49.6%	61.9%	62.9%	41.9%
Terminal rate[c]	6/18 (33%)	6/17 (35%)	6/15 (40%)	5/16 (31%)
First incidence (days)	609	588	634	615
Life table test[d]	P=0.112N	P=0.259	P=0.210	P=0.299N
Logistic regression test[d]	P=0.107N	P=0.324	P=0.308	P=0.270N
Cochran-Armitage test[d]	P=0.020N			
Fisher exact test[d]		P=0.200	P=0.332	P=0.130N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	14/47 (30%)	21/50 (42%)	19/50 (38%)	9/50 (18%)
Adjusted rate	49.6%	65.3%	67.1%	41.9%
Terminal rate	6/18 (33%)	7/17 (41%)	7/15 (47%)	5/16 (31%)
First incidence (days)	609	588	634	615
Life table test	P=0.091N	P=0.203	P=0.157	P=0.299N
Logistic regression test	P=0.088N	P=0.259	P=0.235	P=0.270N
Cochran-Armitage test	P=0.015N			
Fisher exact test		P=0.149	P=0.262	P=0.130N
Liver: Hepatocellular Adenoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	2/51 (4%)
Adjusted rate	0.0%	2.9%	14.1%	7.9%
Terminal rate	0/18 (0%)	0/17 (0%)	0/15 (0%)	1/17 (6%)
First incidence (days)	–[e]	660	687	374
Life table test	P=0.288	P=0.531	P=0.108	P=0.227
Logistic regression test	P=0.346	P=0.498	P=0.117	P=0.299
Cochran-Armitage test	P=0.357			
Fisher exact test		P=0.500	P=0.121	P=0.252
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	3/51 (6%)
Adjusted rate	5.6%	2.9%	17.8%	13.6%
Terminal rate	1/18 (6%)	0/17 (0%)	0/15 (0%)	2/17 (12%)
First incidence (days)	729 (T)	660	687	374
Life table test	P=0.235	P=0.750N	P=0.152	P=0.284
Logistic regression test	P=0.242	P=0.737N	P=0.172	P=0.293
Cochran-Armitage test	P=0.302			
Fisher exact test		P=0.753N	P=0.181	P=0.316
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/49 (4%)	2/50 (4%)	4/50 (8%)	2/51 (4%)
Adjusted rate	8.2%	6.3%	17.1%	11.8%
Terminal rate	1/17 (6%)	0/17 (0%)	2/15 (13%)	2/17 (12%)
First incidence (days)	543	611	467	729 (T)
Life table test	P=0.612N	P=0.651N	P=0.316	P=0.673
Logistic regression test	P=0.565N	P=0.687	P=0.355	P=0.660
Cochran-Armitage test	P=0.541N			
Fisher exact test		P=0.684N	P=0.349	P=0.676N

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/49 (6%)	3/50 (6%)	4/50 (8%)	2/51 (4%)
Adjusted rate	13.9%	11.9%	17.1%	11.8%
Terminal rate	2/17 (12%)	1/17 (6%)	2/15 (13%)	2/17 (12%)
First incidence (days)	543	611	467	729 (T)
Life table test	P=0.430N	P=0.626N	P=0.467	P=0.523N
Logistic regression test	P=0.421N	P=0.630N	P=0.513	P=0.552N
Cochran-Armitage test	P=0.368N			
Fisher exact test		P=0.651N	P=0.511	P=0.481N
Pancreatic Islets: Adenoma				
Overall rate	2/47 (4%)	1/50 (2%)	1/48 (2%)	3/49 (6%)
Adjusted rate	9.0%	3.2%	2.4%	9.5%
Terminal rate	1/17 (6%)	0/17 (0%)	0/15 (0%)	0/17 (0%)
First incidence (days)	662	696	568	522
Life table test	P=0.190	P=0.456N	P=0.499N	P=0.448
Logistic regression test	P=0.295	P=0.444N	P=0.493N	P=0.519
Cochran-Armitage test	P=0.268			
Fisher exact test		P=0.477N	P=0.492N	P=0.520
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	2/47 (4%)	1/50 (2%)	2/48 (4%)	3/49 (6%)
Adjusted rate	9.0%	3.2%	8.9%	9.5%
Terminal rate	1/17 (6%)	0/17 (0%)	1/15 (7%)	0/17 (0%)
First incidence (days)	662	696	568	522
Life table test	P=0.238	P=0.456N	P=0.682	P=0.448
Logistic regression test	P=0.320	P=0.444N	P=0.689N	P=0.519
Cochran-Armitage test	P=0.315			
Fisher exact test		P=0.477N	P=0.684N	P=0.520
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	23/50 (46%)	17/50 (34%)	16/49 (33%)	13/49 (27%)
Adjusted rate	58.8%	58.6%	60.4%	48.4%
Terminal rate	5/18 (28%)	7/17 (41%)	6/14 (43%)	5/17 (29%)
First incidence (days)	435	519	499	504
Life table test	P=0.220N	P=0.131N	P=0.228N	P=0.134N
Logistic regression test	P=0.139N	P=0.159N	P=0.130N	P=0.052N
Cochran-Armitage test	P=0.075N			
Fisher exact test		P=0.154N	P=0.124N	P=0.035N
Preputial Gland: Adenoma				
Overall rate	3/48 (6%)	4/48 (8%)	2/49 (4%)	3/51 (6%)
Adjusted rate	14.8%	12.9%	13.3%	10.8%
Terminal rate	2/17 (12%)	1/17 (6%)	2/15 (13%)	1/17 (6%)
First incidence (days)	671	606	729 (T)	374
Life table test	P=0.610	P=0.559	P=0.550N	P=0.636
Logistic regression test	P=0.580N	P=0.548	P=0.489N	P=0.650N
Cochran-Armitage test	P=0.535N			
Fisher exact test		P=0.500	P=0.490N	P=0.632N

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rate	5/48 (10%)	5/48 (10%)	3/49 (6%)	4/51 (8%)
Adjusted rate	22.3%	16.2%	15.2%	16.3%
Terminal rate	3/17 (18%)	1/17 (6%)	2/15 (13%)	2/17 (12%)
First incidence (days)	529	606	467	374
Life table test	P=0.553N	P=0.561N	P=0.402N	P=0.541N
Logistic regression test	P=0.469N	P=0.598N	P=0.343N	P=0.496N
Cochran-Armitage test	P=0.441N			
Fisher exact test		P=0.630N	P=0.346N	P=0.461N
Skin: Keratoacanthoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/51 (0%)
Adjusted rate	0.0%	0.0%	10.7%	0.0%
Terminal rate	0/18 (0%)	0/17 (0%)	0/15 (0%)	0/17 (0%)
First incidence (days)	–	–	634	–
Life table test	P=0.613N	–	P=0.127	–
Logistic regression test	P=0.568N	–	P=0.119	–
Cochran-Armitage test	P=0.534N			
Fisher exact test		–	P=0.121	–
Skin: Squamous Cell Papilloma				
Overall rate	4/50 (8%)	0/50 (0%)	2/50 (4%)	1/51 (2%)
Adjusted rate	17.0%	0.0%	10.0%	3.6%
Terminal rate	2/18 (11%)	0/17 (0%)	1/15 (7%)	0/17 (0%)
First incidence (days)	609	–	674	633
Life table test	P=0.422N	P=0.058N	P=0.386N	P=0.227N
Logistic regression test	P=0.429N	P=0.049N	P=0.338N	P=0.216N
Cochran-Armitage test	P=0.355N			
Fisher exact test		P=0.059N	P=0.339N	P=0.175N
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	2/50 (4%)	1/51 (2%)
Adjusted rate	19.3%	0.0%	10.0%	3.6%
Terminal rate	2/18 (11%)	0/17 (0%)	1/15 (7%)	0/17 (0%)
First incidence (days)	589	–	674	633
Life table test	P=0.334N	P=0.029N	P=0.254N	P=0.145N
Logistic regression test	P=0.314N	P=0.029N	P=0.219N	P=0.122N
Cochran-Armitage test	P=0.265N			
Fisher exact test		P=0.028N	P=0.218N	P=0.098N
Skin: Basal Cell Adenoma, Keratoacanthoma, Squamous Cell Papilloma, or Squamous Cell Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	5/50 (10%)	2/51 (4%)
Adjusted rate	19.3%	0.0%	19.6%	9.2%
Terminal rate	2/18 (11%)	0/17 (0%)	1/15 (7%)	1/17 (6%)
First incidence (days)	589	–	634	633
Life table test	P=0.503N	P=0.029N	P=0.594	P=0.277N
Logistic regression test	P=0.481N	P=0.029N	P=0.626	P=0.261N
Cochran-Armitage test	P=0.396N			
Fisher exact test		P=0.028N	P=0.630N	P=0.210N

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	3/51 (6%)
Adjusted rate	12.7%	2.4%	3.7%	14.5%
Terminal rate	1/18 (6%)	0/17 (0%)	0/15 (0%)	2/17 (12%)
First incidence (days)	676	611	676	569
Life table test	P=0.302	P=0.259N	P=0.338N	P=0.608
Logistic regression test	P=0.310	P=0.282N	P=0.306N	P=0.600
Cochran-Armitage test	P=0.384			
Fisher exact test		P=0.309N	P=0.309N	P=0.652N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	5/50 (10%)	2/50 (4%)	1/50 (2%)	4/51 (8%)
Adjusted rate	19.1%	5.6%	3.7%	20.2%
Terminal rate	1/18 (6%)	0/17 (0%)	0/15 (0%)	3/17 (18%)
First incidence (days)	563	611	676	569
Life table test	P=0.354	P=0.163N	P=0.124N	P=0.572N
Logistic regression test	P=0.374	P=0.203N	P=0.104N	P=0.580N
Cochran-Armitage test	P=0.465			
Fisher exact test		P=0.218N	P=0.102N	P=0.487N
Testes: Adenoma				
Overall rate	37/50 (74%)	44/50 (88%)	40/50 (80%)	40/51 (78%)
Adjusted rate	100.0%	95.6%	100.0%	100.0%
Terminal rate	18/18 (100%)	15/17 (88%)	15/15 (100%)	17/17 (100%)
First incidence (days)	521	534	539	456
Life table test	P=0.200	P=0.342	P=0.217	P=0.154
Logistic regression test	P=0.013	P=0.269	P=0.325	P=0.010
Cochran-Armitage test	P=0.448N			
Fisher exact test		P=0.062	P=0.318	P=0.386
Thyroid Gland (C-cell): Adenoma				
Overall rate	2/50 (4%)	8/50 (16%)	5/50 (10%)	6/51 (12%)
Adjusted rate	11.1%	24.9%	19.0%	23.3%
Terminal rate	2/18 (11%)	1/17 (6%)	1/15 (7%)	2/17 (12%)
First incidence (days)	729 (T)	602	467	538
Life table test	P=0.287	P=0.082	P=0.187	P=0.108
Logistic regression test	P=0.337	P=0.066	P=0.213	P=0.102
Cochran-Armitage test	P=0.424			
Fisher exact test		P=0.046	P=0.218	P=0.141
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	8/50 (16%)	5/50 (10%)	6/51 (12%)
Adjusted rate	19.1%	24.9%	19.0%	23.3%
Terminal rate	3/18 (17%)	1/17 (6%)	1/15 (7%)	2/17 (12%)
First incidence (days)	633	602	467	538
Life table test	P=0.411	P=0.249	P=0.449	P=0.307
Logistic regression test	P=0.467	P=0.229	P=0.494	P=0.302
Cochran-Armitage test	P=0.562			
Fisher exact test		P=0.178	P=0.500	P=0.383

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	1/51 (2%)
Adjusted rate	2.6%	13.7%	0.0%	5.9%
Terminal rate	0/18 (0%)	2/17 (12%)	0/15 (0%)	1/17 (6%)
First incidence (days)	553	582	-	729 (T)
Life table test	P=0.530N	P=0.333	P=0.485N	P=0.732
Logistic regression test	P=0.517N	P=0.284	P=0.463N	P=0.759
Cochran-Armitage test	P=0.479N			
Fisher exact test		P=0.309	P=0.500N	P=0.748N
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/50 (54%)	28/50 (56%)	35/50 (70%)	23/51 (45%)
Adjusted rate	76.8%	70.5%	83.0%	65.9%
Terminal rate	11/18 (61%)	7/17 (41%)	8/15 (53%)	6/17 (35%)
First incidence (days)	465	519	464	400
Life table test	P=0.465N	P=0.466N	P=0.103	P=0.524N
Logistic regression test	P=0.225N	P=0.576	P=0.059	P=0.396N
Cochran-Armitage test	P=0.087N			
Fisher exact test		P=0.500	P=0.074	P=0.243N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	47/50 (94%)	46/51 (90%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	18/18 (100%)	17/17 (100%)	15/15 (100%)	17/17 (100%)
First incidence (days)	404	519	337	371
Life table test	P=0.288	P=0.352N	P=0.487	P=0.397
Logistic regression test	P=0.600N	P=0.881N	P=0.776N	P=0.668N
Cochran-Armitage test	P=0.047N			
Fisher exact test		P=0.753N	P=0.309N	P=0.107N
All Organs: Malignant Neoplasms				
Overall rate	34/50 (68%)	34/50 (68%)	41/50 (82%)	26/51 (51%)
Adjusted rate	85.8%	80.6%	90.9%	73.3%
Terminal rate	13/18 (72%)	10/17 (59%)	11/15 (73%)	8/17 (47%)
First incidence (days)	465	337	337	400
Life table test	P=0.284N	P=0.389N	P=0.134	P=0.335N
Logistic regression test	P=0.034N	P=0.582	P=0.066	P=0.148N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.585N	P=0.083	P=0.062N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	48/50 (96%)	47/51 (92%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	18/18 (100%)	17/17 (100%)	15/15 (100%)	17/17 (100%)
First incidence (days)	404	337	377	371
Life table test	P=0.287	P=0.354N	P=0.485	P=0.394
Logistic regression test	P=0.109N	-[f]	-	P=0.417N
Cochran-Armitage test	P=0.015N			
Fisher exact test		P=1.000N	P=0.247N	P=0.061N

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

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

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

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	1/50	0/50	1/50
Pentaerythritol Tetranitrate	0/50	0/50	0/50
Quercetin	0/50	0/50	0/50
Overall Historical Incidence			
Total	2/1,002 (0.2%)	1/1,002 (0.1%)	3/1,002 (0.3%)
Standard deviation	0.6%	0.5%	0.7%
Range	0%-2%	0%-2%	0%-2%

[a] Data as of 17 December 1991

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	26	29	32	28
Natural deaths	6	4	3	6
Survivors				
Terminal sacrifice	18	17	15	17
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)	(10)	(10)	(9)
Erosion				1 (11%)
Hyperplasia, glandular				8 (89%)
Parasite metazoan	7 (70%)	4 (40%)	3 (30%)	
Ulcer				7 (78%)
Epithelium, pigmentation		1 (10%)	1 (10%)	1 (11%)
Lamina propria, inflammation, chronic				1 (11%)
Submucosa, inflammation, chronic active		1 (10%)		
Submucosa, lamina propria, inflammation, chronic active				8 (89%)
Intestine large, colon	(10)	(10)	(10)	(9)
Parasite metazoan	1 (10%)	4 (40%)	3 (30%)	
Intestine large, rectum	(10)	(10)	(10)	(9)
Parasite metazoan	5 (50%)	2 (20%)	1 (10%)	
Epithelium, pigmentation				1 (11%)
Intestine small, ileum	(10)	(10)	(10)	(9)
Epithelium, pigmentation		1 (10%)	4 (40%)	5 (56%)
Peyer's patch, hyperplasia			1 (10%)	
Submucosa, inflammation, acute			1 (10%)	
Intestine small, jejunum	(10)	(10)	(10)	(9)
Epithelium, pigmentation				1 (11%)
Liver	(10)	(7)	(6)	(9)
Basophilic focus	1 (10%)	1 (14%)	1 (17%)	4 (44%)
Clear cell focus				1 (11%)
Degeneration			1 (17%)	
Fatty change		2 (29%)		
Hepatodiaphragmatic nodule			1 (17%)	1 (11%)
Inflammation, chronic active	7 (70%)	5 (71%)	4 (67%)	7 (78%)
Bile duct, hyperplasia	5 (50%)	4 (57%)	1 (17%)	5 (56%)
Mesentery				(2)
Fibrosis				1 (50%)
Inflammation, chronic active				1 (50%)
Necrosis				1 (50%)
Artery, hyperplasia				1 (50%)
Perivascular, inflammation, chronic				1 (50%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Pancreas	(10)			(9)
Atrophy	3 (30%)			3 (33%)
Inflammation, chronic	5 (50%)			5 (56%)
Inflammation, chronic active	1 (10%)			
Pigmentation				1 (11%)
Acinus, atrophy	1 (10%)			
Salivary glands	(10)			(9)
Duct, submandibular gland, dilatation				1 (11%)
Duct, submandibular gland, metaplasia, squamous	1 (10%)			1 (11%)
Submandibular gland, inflammation, chronic	6 (60%)			3 (33%)
Submandibular gland, inflammation, chronic active	1 (10%)			
Stomach, glandular	(10)	(10)	(10)	(9)
Inflammation, chronic			1 (10%)	
Metaplasia, squamous				1 (11%)
Epithelium, pigmentation		1 (10%)	2 (20%)	3 (33%)
Muscularis, developmental malformation				1 (11%)
Cardiovascular System				
Heart	(10)			(9)
Cardiomyopathy	10 (100%)			9 (100%)
Endocrine System				
Adrenal gland, cortex	(10)		(1)	(9)
Hyperplasia	2 (20%)			1 (11%)
Vacuolization cytoplasmic	1 (10%)			
Adrenal gland, medulla	(10)		(1)	(9)
Inflammation, chronic active	1 (10%)			
Pituitary gland	(10)	(1)	(1)	(9)
Pars distalis, cyst	1 (10%)			2 (22%)
Pars distalis, hyperplasia	4 (40%)			4 (44%)
Thyroid gland	(9)		(1)	(9)
C-cell, hyperplasia	2 (22%)			1 (11%)
Follicle, pigmentation				1 (11%)
General Body System				
None				
Genital System				
Epididymis	(10)			(9)
Inflammation, chronic				1 (11%)
Preputial gland	(9)	(3)	(1)	(9)
Inflammation, chronic	3 (33%)	1 (33%)	1 (100%)	3 (33%)
Inflammation, chronic active	4 (44%)			3 (33%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Genital System (continued)				
Prostate	(10)			(9)
Inflammation, acute	1 (10%)			2 (22%)
Inflammation, chronic	1 (10%)			
Inflammation, chronic active	2 (20%)			4 (44%)
Testes	(10)	(3)	(4)	(9)
Interstitial cell, hyperplasia	8 (80%)	3 (100%)	4 (100%)	9 (100%)
Seminiferous tubule, atrophy	1 (10%)	1 (33%)	2 (50%)	
Seminiferous tubule, mineralization		1 (33%)	1 (25%)	
Hematopoietic System				
Lymph node	(10)	(10)	(10)	(9)
Mediastinal, hemorrhage			1 (10%)	1 (11%)
Mediastinal, infiltration cellular, histiocyte			1 (10%)	
Mediastinal, pigmentation			1 (10%)	
Pancreatic, hemorrhage	2 (20%)			1 (11%)
Pancreatic, infiltration cellular, histiocyte	4 (40%)			
Pancreatic, pigmentation	4 (40%)			
Pancreatic, sinus, ectasia	1 (10%)			
Sinus, ectasia				1 (11%)
Lymph node, mandibular		(3)	(2)	(2)
Hemorrhage		3 (100%)	2 (100%)	2 (100%)
Lymph node, mesenteric	(10)	(10)	(10)	(9)
Hemorrhage			1 (10%)	
Hyperplasia, lymphoid		1 (10%)	1 (10%)	
Infiltration cellular, histiocyte	10 (100%)	10 (100%)	9 (90%)	6 (67%)
Pigmentation	9 (90%)	10 (100%)	9 (90%)	5 (56%)
Sinus, ectasia			2 (20%)	7 (78%)
Sinus, ectasia, multiple				1 (11%)
Spleen	(10)	(2)		(9)
Congestion		1 (50%)		
Thymus	(9)	(1)		(9)
Depletion lymphoid	1 (11%)			2 (22%)
Integumentary System				
Mammary gland	(9)			(9)
Hyperplasia	9 (100%)			8 (89%)
Skin	(10)	(2)	(3)	(9)
Inflammation, necrotizing, acute		1 (50%)		
Subcutaneous tissue, hemorrhage				1 (11%)
Musculoskeletal System				
None				
Nervous System				
None				

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(7)	(7)	(9)
Congestion	1 (10%)	1 (14%)		
Hemorrhage			1 (14%)	
Infiltration cellular, histiocyte	1 (10%)	1 (14%)		1 (11%)
Alveolar epithelium, hyperplasia				1 (11%)
Artery, mineralization	7 (70%)	5 (71%)	5 (71%)	7 (78%)
Nose	(10)		(1)	(9)
Metaplasia, squamous	2 (20%)			1 (11%)
Glands, hyperplasia			1 (100%)	
Lumen, inflammation, acute	3 (30%)		1 (100%)	
Mucosa, submucosa, inflammation, chronic active	2 (20%)			1 (11%)
Mucosa, submucosa, lumen, inflammation, chronic active	1 (10%)			
Nasopharyngeal duct, inflammation, acute				1 (11%)
Respiratory epithelium, metaplasia, squamous			1 (100%)	
Special Senses System				
None				
Urinary System				
Kidney	(10)	(2)		(9)
Congestion	1 (10%)			
Cyst				1 (11%)
Nephropathy	10 (100%)	2 (100%)		9 (100%)
Renal tubule, inflammation, acute	1 (10%)			
Urinary bladder	(10)			(9)
Calculus microscopic observation only				1 (11%)
Inflammation, chronic				1 (11%)
2-Year Study				
Alimentary System				
Esophagus	(49)	(49)	(49)	(49)
Autolysis	1 (2%)			
Hyperkeratosis				3 (6%)
Ulcer	1 (2%)			
Intestine large, cecum	(50)	(49)	(50)	(51)
Autolysis	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, glandular		1 (2%)		41 (80%)
Inflammation, chronic active				1 (2%)
Metaplasia, osseous				1 (2%)
Parasite metazoan	10 (20%)	7 (14%)	13 (26%)	2 (4%)
Polyarteritis			1 (2%)	

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Intestine large, cecum (continued)	(50)	(49)	(50)	(51)
Ulcer			1 (2%)	25 (49%)
Ulcer, multiple				1 (2%)
Mucosa, ulcer				1 (2%)
Perivascular, inflammation, chronic active	1 (2%)			
Submucosa, proliferation				1 (2%)
Submucosa, lamina propria, inflammation, chronic active				28 (55%)
Intestine large, colon	(49)	(50)	(49)	(49)
Autolysis	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, glandular				4 (8%)
Inflammation, chronic active				2 (4%)
Parasite metazoan	12 (24%)	10 (20%)	11 (22%)	2 (4%)
Polyarteritis	1 (2%)			
Ulcer				6 (12%)
Submucosa, epithelium, proliferation				1 (2%)
Intestine large, rectum	(48)	(49)	(48)	(49)
Autolysis	2 (4%)	2 (4%)	2 (4%)	4 (8%)
Parasite metazoan	9 (19%)	3 (6%)	6 (13%)	
Epithelium, pigmentation				3 (6%)
Intestine small, duodenum	(50)	(50)	(49)	(51)
Autolysis	3 (6%)	3 (6%)	2 (4%)	4 (8%)
Intestine small, ileum	(49)	(50)	(49)	(51)
Autolysis	4 (8%)	4 (8%)	2 (4%)	3 (6%)
Fibrosis			2 (4%)	
Hyperplasia, glandular			1 (2%)	
Hyperplasia, lymphoid	1 (2%)	5 (10%)		1 (2%)
Inflammation, chronic active			1 (2%)	1 (2%)
Ulcer, multiple			1 (2%)	
Epithelium, pigmentation				2 (4%)
Intestine small, jejunum	(50)	(50)	(49)	(49)
Autolysis	5 (10%)	3 (6%)	2 (4%)	6 (12%)
Inflammation, chronic		1 (2%)	1 (2%)	
Muscularis, hyperplasia		1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)	(51)
Angiectasis	5 (10%)	3 (6%)	5 (10%)	
Autolysis	1 (2%)		1 (2%)	
Basophilic focus	8 (16%)	6 (12%)	9 (18%)	18 (35%)
Clear cell focus	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Degeneration	7 (14%)	6 (12%)	16 (32%)	3 (6%)
Eosinophilic focus	4 (8%)	6 (12%)	7 (14%)	3 (6%)
Fatty change	9 (18%)	6 (12%)	6 (12%)	7 (14%)
Hepatodiaphragmatic nodule	7 (14%)	6 (12%)	4 (8%)	10 (20%)
Hyperplasia	1 (2%)	4 (8%)	3 (6%)	3 (6%)
Inflammation, acute				1 (2%)
Inflammation, chronic active	9 (18%)	8 (16%)	5 (10%)	12 (24%)
Mixed cell focus	1 (2%)	1 (2%)	5 (10%)	1 (2%)
Necrosis, coagulative			1 (2%)	2 (4%)
Pigmentation	2 (4%)	2 (4%)	2 (4%)	
Bile duct, hyperplasia	47 (94%)	44 (88%)	44 (88%)	38 (75%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(9)	(3)	(8)	(5)
Fibrosis	7 (78%)	1 (33%)	6 (75%)	2 (40%)
Hemorrhage	1 (11%)			
Inflammation, chronic active	3 (33%)	1 (33%)	5 (63%)	3 (60%)
Necrosis, liquefactive	5 (56%)	1 (33%)	6 (75%)	2 (40%)
Artery, inflammation, chronic	2 (22%)			
Pancreas	(48)	(50)	(50)	(50)
Autolysis		2 (4%)	2 (4%)	1 (2%)
Cytoplasmic alteration	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	15 (31%)	19 (38%)	10 (20%)	16 (32%)
Polyarteritis		2 (4%)	4 (8%)	
Vacuolization cytoplasmic	10 (21%)	7 (14%)	6 (12%)	6 (12%)
Acinus, atrophy	21 (44%)	22 (44%)	24 (48%)	20 (40%)
Acinus, hyperplasia	5 (10%)			2 (4%)
Salivary glands	(49)	(49)	(50)	(50)
Duct, submandibular gland, hyperplasia	7 (14%)	8 (16%)	3 (6%)	3 (6%)
Duct, submandibular gland, inflammation, chronic active	3 (6%)	1 (2%)	1 (2%)	
Duct, submandibular gland, metaplasia, squamous	10 (20%)	13 (27%)	5 (10%)	5 (10%)
Sublingual gland, inflammation, chronic active	4 (8%)			1 (2%)
Submandibular gland, atrophy	1 (2%)			2 (4%)
Submandibular gland, fibrosis		1 (2%)		
Submandibular gland, inflammation, chronic active	17 (35%)	12 (24%)	11 (22%)	11 (22%)
Submandibular gland, necrosis, coagulative			1 (2%)	
Stomach	(50)	(50)	(50)	(51)
Lamina propria, inflammation, chronic active			1 (2%)	
Stomach, forestomach	(49)	(50)	(43)	(51)
Acanthosis	1 (2%)			
Autolysis	1 (2%)		1 (2%)	
Erosion				1 (2%)
Hyperkeratosis	4 (8%)	5 (10%)	2 (5%)	16 (31%)
Hyperplasia, squamous	7 (14%)	5 (10%)	4 (9%)	18 (35%)
Inflammation, chronic active	4 (8%)		1 (2%)	6 (12%)
Ulcer	2 (4%)	3 (6%)	2 (5%)	5 (10%)
Ulcer, multiple				1 (2%)
Muscularis, mineralization	1 (2%)			
Submucosa, inflammation, chronic active				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(49)
Autolysis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Fibrosis	1 (2%)	1 (2%)	1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, chronic active	4 (8%)		1 (2%)	
Metaplasia, squamous	1 (2%)			
Necrosis, coagulative		3 (6%)	2 (4%)	2 (4%)
Ulcer, acute	1 (2%)			

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, glandular (continued)	(50)	(50)	(50)	(49)
Epithelium, pigmentation			1 (2%)	2 (4%)
Mucosa, dilatation	40 (80%)	45 (90%)	38 (76%)	36 (73%)
Muscularis, submucosa, inflammation, chronic active				1 (2%)
Submucosa, inflammation, chronic active				1 (2%)
Tongue		(1)	(1)	(2)
Hemorrhage		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Abscess	1 (2%)			1 (2%)
Autolysis	1 (2%)			
Cardiomyopathy	48 (96%)	48 (96%)	48 (96%)	48 (94%)
Congestion				1 (2%)
Mineralization	1 (2%)			
Atrium, thrombosis	2 (4%)		1 (2%)	
Endocrine System				
Adrenal gland	(50)	(50)	(50)	(51)
Capsule, thrombosis			1 (2%)	
Adrenal gland, cortex	(50)	(50)	(49)	(51)
Angiectasis	8 (16%)	6 (12%)	4 (8%)	9 (18%)
Autolysis	1 (2%)		1 (2%)	
Hematopoietic cell proliferation		1 (2%)	1 (2%)	1 (2%)
Hyperplasia	6 (12%)	3 (6%)	3 (6%)	2 (4%)
Necrosis, coagulative				1 (2%)
Necrosis, coagulative, focal				1 (2%)
Vacuolization cytoplasmic	21 (42%)	16 (32%)	16 (33%)	22 (43%)
Adrenal gland, medulla	(47)	(50)	(50)	(50)
Angiectasis				1 (2%)
Autolysis	1 (2%)		1 (2%)	
Hematopoietic cell proliferation			1 (2%)	
Hyperplasia	13 (28%)	8 (16%)	13 (26%)	15 (30%)
Inflammation, chronic active		1 (2%)		
Necrosis, coagulative		1 (2%)		1 (2%)
Islets, pancreatic	(47)	(50)	(48)	(49)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	
Parathyroid gland	(47)	(47)	(49)	(46)
Hyperplasia	2 (4%)	5 (11%)	4 (8%)	
Pituitary gland	(50)	(50)	(49)	(49)
Autolysis			1 (2%)	
Pars distalis, angiectasis			2 (4%)	1 (2%)
Pars distalis, autolysis	1 (2%)	1 (2%)		1 (2%)
Pars distalis, cyst	3 (6%)	4 (8%)	2 (4%)	6 (12%)
Pars distalis, hyperplasia	21 (42%)	18 (36%)	17 (35%)	22 (45%)
Pars intermedia, angiectasis	1 (2%)	1 (2%)	1 (2%)	
Pars intermedia, cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(51)
Autolysis	1 (2%)		1 (2%)	2 (4%)
Inflammation, chronic active	1 (2%)			1 (2%)
Pigmentation	3 (6%)	2 (4%)	1 (2%)	2 (4%)
C-cell, hyperplasia	16 (32%)	20 (40%)	18 (36%)	12 (24%)
Follicular cell, cyst		1 (2%)	2 (4%)	
Follicular cell, hyperplasia		1 (2%)	4 (8%)	
General Body System				
None				
Genital System				
Coagulating gland	(10)	(2)	(2)	(9)
Atrophy	5 (50%)			8 (89%)
Epididymis	(49)	(50)	(50)	(50)
Autolysis	1 (2%)			
Inflammation, chronic active	3 (6%)	3 (6%)		
Penis	(1)			
Inflammation, acute	1 (100%)			
Preputial gland	(48)	(48)	(49)	(51)
Autolysis	1 (2%)			
Hyperplasia	1 (2%)			
Inflammation, chronic				1 (2%)
Inflammation, chronic active	42 (88%)	46 (96%)	45 (92%)	41 (80%)
Duct, dilatation		4 (8%)	2 (4%)	1 (2%)
Prostate	(50)	(50)	(50)	(51)
Autolysis	1 (2%)		1 (2%)	1 (2%)
Dilatation	1 (2%)			
Fibrosis				1 (2%)
Inflammation, acute				1 (2%)
Inflammation, chronic active	37 (74%)	26 (52%)	24 (48%)	37 (73%)
Epithelium, hyperplasia	1 (2%)	3 (6%)	2 (4%)	
Seminal vesicle	(50)	(50)	(50)	(50)
Atrophy	33 (66%)	34 (68%)	32 (64%)	30 (60%)
Autolysis	1 (2%)			1 (2%)
Cyst				1 (2%)
Inflammation, chronic active	2 (4%)			
Epithelium, hyperplasia	1 (2%)			1 (2%)
Testes	(50)	(50)	(50)	(51)
Autolysis	1 (2%)		1 (2%)	1 (2%)
Hemorrhage	1 (2%)		1 (2%)	
Polyarteritis		1 (2%)		
Interstitial cell, hyperplasia	29 (58%)	24 (48%)	25 (50%)	30 (59%)
Seminiferous tubule, atrophy	32 (64%)	40 (80%)	36 (72%)	35 (69%)
Seminiferous tubule, mineralization	22 (44%)	19 (38%)	22 (44%)	18 (35%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(51)
Calvarium, myelofibrosis	1 (2%)			
Sternal, autolysis	1 (2%)	1 (2%)		
Sternal, hypocellularity	1 (2%)			2 (4%)
Sternal, myelofibrosis	1 (2%)	5 (10%)	1 (2%)	
Lymph node	(49)	(50)	(50)	(51)
Bronchial, hyperplasia, lymphoid			1 (2%)	
Mediastinal, hyperplasia, lymphoid		1 (2%)		1 (2%)
Pancreatic, hyperplasia, lymphoid		1 (2%)		
Pancreatic, infiltration cellular, histiocyte	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pancreatic, sinus, ectasia			1 (2%)	
Lymph node, mandibular	(22)	(12)	(20)	(15)
Autolysis			1 (5%)	
Hyperplasia, lymphoid	2 (9%)	3 (25%)	1 (5%)	4 (27%)
Hyperplasia, plasma cell	4 (18%)	2 (17%)	2 (10%)	2 (13%)
Infiltration cellular, histiocyte	1 (5%)			
Sinus, ectasia	6 (27%)	4 (33%)	2 (10%)	
Lymph node, mesenteric	(49)	(50)	(50)	(51)
Abscess				1 (2%)
Autolysis			1 (2%)	
Hyperplasia, lymphoid		2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, histiocyte	46 (94%)	48 (96%)	47 (94%)	37 (73%)
Inflammation, chronic active				10 (20%)
Sinus, ectasia		1 (2%)	7 (14%)	49 (96%)
Spleen	(50)	(50)	(50)	(50)
Abscess				1 (2%)
Autolysis	1 (2%)	1 (2%)	1 (2%)	
Bacterium				1 (2%)
Depletion lymphoid	19 (38%)	17 (34%)	26 (52%)	13 (26%)
Fibrosis	8 (16%)	10 (20%)	12 (24%)	7 (14%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)		1 (2%)	
Necrosis, coagulative	1 (2%)			
Capsule, inflammation, chronic	1 (2%)			
Thymus	(41)	(47)	(45)	(43)
Angiectasis	1 (2%)			
Autolysis			1 (2%)	1 (2%)
Congestion				1 (2%)
Cyst			2 (4%)	1 (2%)
Depletion lymphoid			1 (2%)	4 (9%)
Ectopic parathyroid gland		1 (2%)	1 (2%)	
Integumentary System				
Mammary gland	(38)	(39)	(40)	(41)
Galactocele	3 (8%)	3 (8%)	1 (3%)	1 (2%)
Hyperplasia	34 (89%)	36 (92%)	36 (90%)	38 (93%)
Inflammation, chronic		1 (3%)		
Pigmentation				1 (2%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Skin	(50)	(49)	(50)	(51)
Abscess			1 (2%)	
Acanthosis		1 (2%)	1 (2%)	
Hyperkeratosis		1 (2%)	1 (2%)	
Hyperplasia, basal cell		1 (2%)		
Foot, acanthosis		1 (2%)		
Foot, hyperkeratosis		1 (2%)		
Lip, inflammation, necrotizing, acute	1 (2%)			
Subcutaneous tissue, inflammation, chronic	1 (2%)			
Subcutaneous tissue, necrosis, liquifactive			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(49)	(51)
Cranium, hyperostosis		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(51)
Abscess	1 (2%)			
Autolysis	1 (2%)		1 (2%)	1 (2%)
Gliosis		1 (2%)		
Infarct		4 (8%)	2 (4%)	3 (6%)
Thrombosis			1 (2%)	
Cerebellum, infarct	2 (4%)			
Cerebrum, infarct	1 (2%)		1 (2%)	
Pons, infarct	1 (2%)			
Respiratory System				
Lung	(49)	(50)	(50)	(51)
Autolysis	1 (2%)		1 (2%)	1 (2%)
Bronchiectasis				1 (2%)
Fibrosis			1 (2%)	
Foreign body	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, histiocyte	8 (16%)	7 (14%)	8 (16%)	11 (22%)
Inflammation, chronic active	5 (10%)	2 (4%)	1 (2%)	1 (2%)
Metaplasia, osseous				1 (2%)
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)		5 (10%)	2 (4%)
Artery, mineralization	20 (41%)	19 (38%)	17 (34%)	20 (39%)
Bronchiole, epithelium, hyperplasia			1 (2%)	
Perivascular, inflammation, chronic active				1 (2%)
Nose	(50)	(50)	(49)	(50)
Inflammation, chronic active	36 (72%)	31 (62%)	39 (80%)	31 (62%)
Metaplasia, squamous	11 (22%)	10 (20%)	9 (18%)	8 (16%)
Lumen, foreign body	3 (6%)	4 (8%)	2 (4%)	2 (4%)
Mucosa, inflammation, chronic active				1 (2%)
Mucosa, ulcer		4 (8%)	4 (8%)	3 (6%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Respiratory System (continued)				
Nose (continued)	(50)	(50)	(49)	(50)
Nasolacrimal duct, inflammation, chronic active	2 (4%)			4 (8%)
Nasolacrimal duct, metaplasia, squamous				4 (8%)
Trachea	(50)	(50)	(50)	(51)
Autolysis	1 (2%)		1 (2%)	1 (2%)
Special Senses System				
Eye	(15)	(4)	(7)	(9)
Cataract	2 (13%)		1 (14%)	1 (11%)
Phthisis bulbi	1 (7%)			
Anterior chamber, hemorrhage	1 (7%)			
Cornea, neovascularization				1 (11%)
Retina, degeneration	2 (13%)		1 (14%)	
Sclera, metaplasia, osseous	1 (7%)			
Lacrimal gland			(1)	(2)
Inflammation, chronic				1 (50%)
Zymbal's gland			(1)	(1)
Cyst			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(51)
Abscess	1 (2%)		1 (2%)	1 (2%)
Autolysis	2 (4%)	1 (2%)	2 (4%)	5 (10%)
Cyst	3 (6%)	4 (8%)	2 (4%)	
Glomerulosclerosis	1 (2%)			
Inflammation, chronic				1 (2%)
Mineralization				1 (2%)
Nephropathy	48 (96%)	50 (100%)	48 (96%)	48 (94%)
Adventitia, inflammation, chronic active				1 (2%)
Artery, mineralization	1 (2%)			
Proximal convoluted renal tubule, inflammation, acute	10 (20%)	5 (10%)	8 (16%)	6 (12%)
Proximal convoluted renal tubule, pigmentation				1 (2%)
Renal tubule, hyperplasia			1 (2%)	
Renal tubule, mineralization	1 (2%)			
Transitional epithelium, hyperplasia	19 (38%)	16 (32%)	14 (28%)	5 (10%)
Urinary bladder	(49)	(50)	(50)	(50)
Autolysis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Calculus gross observation			1 (2%)	1 (2%)
Calculus microscopic observation only	3 (6%)		2 (4%)	2 (4%)
Cyst			1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, chronic active	3 (6%)		2 (4%)	1 (2%)
Polyarteritis	1 (2%)	1 (2%)		
Artery, necrosis, fibrinoid	1 (2%)			
Subserosa, mineralization				1 (2%)

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

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

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	14	22	19	15
Natural deaths	3	1	3	2
Survivors				
Died last week of study	1	1		
Terminal sacrifice	32	26	28	34
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(1)	(2)	(9)
Pars distalis, adenoma	2 (20%)	1 (100%)	1 (50%)	1 (11%)
General Body System				
None				
Genital System				
Clitoral gland	(10)	(3)	(2)	(9)
Adenoma	2 (20%)	1 (33%)	1 (50%)	1 (11%)
Uterus	(10)			(9)
Polyp stromal	1 (10%)			1 (11%)
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Intestine large, cecum	(50)	(50)	(50)	(51)
Intestine large, colon	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(51)
Intestine small, ileum	(50)	(50)	(50)	(51)
Intestine small, jejunum	(50)	(49)	(50)	(51)
Liver	(50)	(50)	(50)	(51)
Hepatocellular adenoma	1 (2%)			
Mesentery	(4)	(4)	(4)	(2)
Leiomyoma			1 (25%)	
Sarcoma		1 (25%)		
Pancreas	(50)	(50)	(50)	(50)
Pharynx	(1)			(1)
Palate, squamous cell carcinoma	1 (100%)			1 (100%)
Salivary glands	(50)	(50)	(50)	(51)
Parotid gland, schwannoma malignant		1 (2%)		
Submandibular gland, schwannoma malignant		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(51)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(51)
Tongue		(1)		(1)
Squamous cell papilloma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(51)
Adenoma			3 (6%)	1 (2%)
Adrenal gland, medulla	(50)	(49)	(50)	(51)
Pheochromocytoma benign	3 (6%)		2 (4%)	2 (4%)
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma	2 (4%)			1 (2%)
Carcinoma	1 (2%)			1 (2%)
Parathyroid gland	(46)	(47)	(49)	(47)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(50)	(48)	(50)	(51)
Pars distalis, adenoma	23 (46%)	24 (50%)	23 (46%)	23 (45%)
Pars distalis, adenoma, multiple	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Pars distalis, carcinoma	2 (4%)		1 (2%)	
Thyroid gland	(50)	(50)	(50)	(51)
C-cell, adenoma	6 (12%)	2 (4%)	3 (6%)	3 (6%)
C-cell, carcinoma	2 (4%)		1 (2%)	
Follicular cell, adenocarcinoma		1 (2%)		
Follicular cell, adenoma			1 (2%)	
General Body System				
Tissue NOS	(1)		(1)	(2)
Genital System				
Clitoral gland	(50)	(48)	(47)	(49)
Adenocarcinoma	1 (2%)	4 (8%)		
Adenoma	5 (10%)	12 (25%)	14 (30%)	16 (33%)
Adenoma, multiple			1 (2%)	
Ovary	(50)	(50)	(50)	(51)
Granulosa cell neoplasm malignant			1 (2%)	
Granulosa cell neoplasm benign	2 (4%)			
Uterus	(50)	(50)	(50)	(51)
Leiomyosarcoma	1 (2%)			
Polyp stromal	9 (18%)	10 (20%)	11 (22%)	8 (16%)
Hematopoietic System				
Blood	(1)			
Bone marrow	(50)	(50)	(50)	(51)
Lymph node	(50)	(50)	(50)	(51)
Lymph node, mandibular	(3)	(9)	(4)	(7)
Lymph node, mesenteric	(50)	(50)	(50)	(51)
Spleen	(50)	(50)	(50)	(51)
Thymus	(41)	(48)	(45)	(41)
Integumentary System				
Mammary gland	(50)	(49)	(49)	(51)
Adenocarcinoma	2 (4%)	1 (2%)	2 (4%)	
Adenoma	1 (2%)			
Fibroadenoma	7 (14%)	18 (37%)	17 (35%)	14 (27%)
Fibroadenoma, multiple	6 (12%)	4 (8%)	2 (4%)	2 (4%)
Skin	(48)	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)			
Subcutaneous tissue, schwannoma malignant		2 (4%)		1 (2%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(51)
Astrocytoma malignant			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Alveolar/bronchiolar adenoma	1 (2%)		2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		
Carcinoma, metastatic, pituitary gland	1 (2%)			
Sarcoma, metastatic, mesentery		1 (2%)		
Squamous cell carcinoma, metastatic, uncertain primary site			1 (2%)	
Nose	(49)	(47)	(50)	(51)
Squamous cell carcinoma			1 (2%)	
Special Senses System				
Eye	(9)	(9)	(5)	(11)
Zymbal's gland	(2)		(1)	
Adenocarcinoma	1 (50%)			
Carcinoma	1 (50%)		1 (100%)	
Urinary System				
Kidney	(50)	(50)	(49)	(51)
Urinary bladder	(50)	(48)	(49)	(51)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(51)
Leukemia mononuclear	15 (30%)	19 (38%)	18 (36%)	21 (41%)
Lymphoma malignant mixed	1 (2%)			
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	5	2	2	3
2-Year study	48	48	47	46
Total primary neoplasms				
15-Month interim evaluation	5	2	2	3
2-Year study	100	104	108	97
Total animals with benign neoplasms				
15-Month interim evaluation	5	2	2	3
2-Year study	41	45	42	41
Total benign neoplasms				
15-Month interim evaluation	5	2	2	3
2-Year study	71	73	82	73

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Neoplasm Summary (continued)				
Total animals with malignant neoplasms				
2-Year study	25	25	24	24
Total malignant neoplasms				
2-Year study	29	31	26	24
Total animals with metastatic neoplasms				
2-Year study	1	1	1	
Total metastatic neoplasms				
2-Year study	1	1	1	
Total animals with malignant neoplasms of uncertain primary site				
2-Year study			1	

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

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

Number of Days on Study	461	468	517	517	550	553	574	603	643	643	646	767	680	681	692	707	717	730	734	734	734	734	734	734	734
Carcass ID Number	056	064	061	065	061	054	062	061	059	065	062	059	060	062	063	065	065	054	054	054	055	055	055	056	057
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery					+										+		+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx				+																					
Palate, squamous cell carcinoma				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma																									
Parathyroid gland	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X				X		X	X		X				X	X	X	X		X	X			X	X
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma												X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X						
C-cell, carcinoma																X									
General Body System																									
Tissue NOS					+																				

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

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

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	0572	0581	0582	0583	0584	0601	0602	0611	0621	0641	0642	0644	0543	0561	0562	0564	0573	0591	0622	0631	0632	0633	0634	0643	0651	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																								X		1
Mesentery													+													4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Palate, squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign										X		X		X												3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X														2
Carcinoma																					X					1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X	X			X					X		X	X	X	X				X				23
Pars distalis, adenoma, multiple							X				X													X		3
Pars distalis, carcinoma												X														2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X		X			X							X								X					6
C-cell, carcinoma																		X								2
General Body System																										
Tissue NOS																										1

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

Number of Days on Study	461	468	517	517	550	553	574	603	433	433	466	466	480	481	492	507	517	530	534	534	534	534	534	534	534
Carcass ID Number	0565	0645	0664	0665	0661	0655	0662	0661	0659	0664	0662	0659	0660	0662	0663	0665	0662	0654	0544	0545	0551	0552	0553	0563	0571
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																	X	X	X					X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign															X					X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma							X																		
Polyp stromal	X		X				X										X	X							
Vagina	+																								
Hematopoietic System																									
Blood																				+					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular																			+	+					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	M	+	+	+	+	+	+	M	+	M	+	I	M	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																								X	
Fibroadenoma			X											X				X				X		X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Subcutaneous tissue, sarcoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, pituitary gland												X													
Nose	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	0057 2	0058 1	0058 2	0058 3	0058 4	0060 1	0060 2	0061 1	0062 1	0064 1	0064 2	0064 4	0065 3	0065 1	0065 2	0065 4	0065 3	0065 9	0066 2	0066 1	0066 2	0066 3	0066 4	0066 3	0066 5	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															1
Adenoma			X																							5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal	X									X									X						X	9
Vagina																										1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular																				+						3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma													X						X							2
Adenoma																										1
Fibroadenoma						X																	X			7
Fibroadenoma, multiple				X							X	X					X		X						X	6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				1
Carcinoma, metastatic, pituitary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	461	468	517	517	550	553	574	603	643	643	646	676	680	681	692	707	717	730	734	734	734	734	734	734	734
Carcass ID Number	0565	0664	0661	0665	0661	0654	0662	0661	0659	0664	0662	0659	0660	0662	0663	0665	0665	0654	0654	0655	0655	0655	0656	0655	0657
Special Senses System																									
Ear																			+						
Eye			+	+		+	+	+			+						+								
Zymbal's gland							+												+						
Adenocarcinoma																			X						
Carcinoma							X																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X				X	X		X				X	X		X				X	
Lymphoma malignant mixed					X																				

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

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	0572	0581	0582	0583	0584	0601	0602	0611	0621	0641	0642	0644	0653	0661	0662	0664	0671	0691	0622	0631	0632	0633	0634	0643	0651	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Eye												+		+												9
Zymbal's gland																										2
Adenocarcinoma																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X									X	X								X	X			X	X		15
Lymphoma malignant mixed																										1

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

Number of Days on Study	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	4	0	5	5	6	9	9	9	1	2	4	5	6	8	9	0	0	0	0	0	0	0	0	3	3
	4	6	2	2	0	1	5	8	5	2	7	4	7	5	4	0	0	0	0	0	2	2	2	1	1
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	7	7	7	7	7	7	7	7	7	7	6	7	7	6	6	6	7	7	7	7	7	7	6	6
	7	7	2	3	0	1	0	6	2	0	5	8	0	7	9	6	8	3	5	6	2	2	7	6	6
	5	5	3	5	5	4	4	5	4	3	4	3	2	4	3	5	2	4	3	4	1	2	3	1	2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+			+																			
Sarcoma			X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parotid gland, schwannoma malignant										X															
Submandibular gland, schwannoma malignant										X															
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue												+													
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma	X	X		X	X				X		X			X	X		X	X					X	X	
Pars distalis, adenoma, multiple												X	X												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X									
Follicular cell, adenocarcinoma																		X							
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X													X
Adenoma					X	X										X								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X								X					X									
Vagina																					+				

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

Number of Days on Study	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	734	734	
Carcass ID Number	0663	0664	0681	0691	0692	0713	0673	0711	0712	0713	0732	0733	0741	0742	0743	0752	0772	0671	0672	0701	0751	0763	0771	0761	0762	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+						+													4
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parotid gland, schwannoma malignant																										1
Submandibular gland, schwannoma malignant																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X				X	X	X		X			X	X		X	X						X		X	X	24
Pars distalis, adenoma, multiple																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X																					2
Follicular cell, adenocarcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma			X		X																					4
Adenoma		X		X		X					X		X		X								X		X	12
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X								X			X	X				X					X		X		10
Vagina	+																									2

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

Number of Days on Study	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	4	0	5	5	6	9	9	9	1	2	4	5	6	8	9	0	0	0	0	0	0	0	0	3	3
	4	6	2	2	0	1	5	8	5	2	7	4	7	5	4	0	0	0	0	0	2	2	2	1	1
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	7	7	7	7	7	7	7	7	7	7	6	7	7	6	6	6	7	7	7	7	7	7	6	6
	7	7	2	3	0	1	0	6	2	0	5	8	0	7	9	6	8	3	5	6	2	2	7	6	6
	5	5	3	5	5	4	4	5	4	3	4	3	2	4	3	5	2	4	3	4	1	2	3	1	2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular					+	+		+								+	+			+	+				+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenocarcinoma																									
Fibroadenoma				X			X				X		X						X			X	X		X
Fibroadenoma, multiple														X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, schwannoma malignant										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Sarcoma, metastatic, mesentery			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+		+		+				+			+									+			+	
Harderian gland																								+	
Lacrimal gland																								+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X	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 Turmeric Oleoresin: 2,000 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	734	734	
Carcass ID Number	0663	0664	0681	0691	0692	0713	0673	0711	0712	0731	0732	0733	0741	0742	0743	0752	0772	0771	0762	0772	0701	0751	0763	0771	0762	0762	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+																										9
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma					X																						1
Fibroadenoma	X		X					X	X			X	X	X							X	X				X	18
Fibroadenoma, multiple										X					X					X							4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, schwannoma malignant										X																	2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																									X		1
Sarcoma, metastatic, mesentery																											1
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye												+												+			9
Harderian gland																											1
Lacrimal gland																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X		X									X						X		X		X		19

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

Number of Days on Study	414	455	456	462	489	519	526	528	556	576	577	591	643	647	655	677	680	688	700	700	708	708	729	729	729
Carcass ID Number	0795	0895	0883	0874	0844	0785	0882	0873	0833	0813	0805	0872	0825	0832	0874	0773	0804	0803	0802	0864	0843	0894	0791	0792	0793
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery						+																			
Leiomyoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X							X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X	X				X		X			X		X		X	X	X	X	X	X		X
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma												X													
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+		+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Adenoma										X						X					X	X		X	X
Adenoma, multiple																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X			X		X														X	X	

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	
Carcass ID Number	0794	0801	0811	0812	0823	0824	0891	0892	0893	0781	0782	0821	0822	0841	0842	0851	0852	0853	0854	0863	0871	0881	0831	0861	0862	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery														+				+					+			4
Leiomyoma																		X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X																							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																								X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X				X	X			X	X			X	X					X					23
Pars distalis, adenoma, multiple																	X									1
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X														X	X	3
C-cell, carcinoma																										1
Follicular cell, adenoma															X											1
General Body System																										
Tissue NOS					+																					1
Genital System																										
Clitoral gland	+	+	+	+	+						+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma			X								X						X			X		X	X		X	14
Adenoma, multiple													X													1
Ovary	+	+	+	+	+	+					+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																										1
Uterus	+	+	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X						X	X	X			X										X		11

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

Number of Days on Study	4	4	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7
	1	5	5	6	8	1	2	2	5	7	7	9	4	4	5	7	8	8	0	0	0	0	2	2	2
	4	5	6	2	9	9	6	8	6	6	7	1	3	7	5	7	0	8	0	0	8	8	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	8	8	8	8	7	8	8	8	8	8	8	8	8	7	7	8	8	8	8	8	8	7	7	7
	9	9	8	7	4	8	8	7	3	1	0	7	2	3	8	8	0	0	0	6	4	9	9	9	9
	5	5	3	4	4	5	2	3	3	3	5	2	5	2	4	3	4	3	2	4	3	4	1	2	3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+				+										+										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X			
Fibroadenoma					X				X									X	X	X	X			X	
Fibroadenoma, multiple														X								X			
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Squamous cell carcinoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																					+				
Eye					I											+					+			+	
Zymbal's gland										+															
Carcinoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X		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 Turmeric Oleoresin: 10,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	
Carcass ID Number	0794	0801	0811	0812	0823	0824	0891	0892	0893	0781	0782	0821	0822	0841	0842	0851	0852	0853	0854	0863	0871	0881	0831	0861	0862	**Total Tissues/ Tumors**
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular											+															4
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma							X																			2
Fibroadenoma	X		X		X				X				X			X	X		X		X			X		17
Fibroadenoma, multiple																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																					X					1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			2
Squamous cell carcinoma, metastatic, uncertain primary site												X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye				+																				+		5
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X			X				X	X	X		X	X		18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm

Number of Days on Study	311	359	367	493	510	518	528	598	624	632	659	661	673	673	700	708	721	727	727	727	727	727	727	727	727	727
Carcass ID Number	1005	1004	0925	1013	0935	0965	0934	0944	0945	1003	0993	1012	0905	0973	0964	0904	0984	0921	0922	0923	0924	0932	0933	0971	0972	0981
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+				+																		
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx													+													
Palate, squamous cell carcinoma													X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue												+														
Squamous cell papilloma												X														
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																										
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Carcinoma																			X							
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X		X	X			X	X		X	X		X			X		
Pars distalis, adenoma, multiple																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																										
General Body System																										
Tissue NOS													+													
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X							X	X			X		X	X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X					X							X										
Vagina				+																						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	727	727	727	727	727	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	0982	0983	0991	0992	1011	0913	0961	0962	0963	1010	1002	0901	0902	0903	0911	0912	0913	0914	0941	0942	0943	0951	0952	0953	0954	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Palate, squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma								X																		1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign																			X	X						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma			X		X	X		X	X	X		X	X				X	X	X		X	X				23
Pars distalis, adenoma, multiple																							X			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma						X	X													X						3
General Body System																										
Tissue NOS					+																					2
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X	X	X		X			X			X		X	X					X	X			16
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp stromal	X															X				X				X	X	8
Vagina																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	727	727	727	727	727	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	098	098	099	099	101	093	096	096	096	100	100	099	099	099	099	091	091	091	094	094	094	095	095	095	098	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular							+							+												7
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibroadenoma	X					X	X		X			X				X								X		14
Fibroadenoma, multiple															X											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye										+																11
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear	X					X	X				X			X		X			X				X			21

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/51 (2%)
Adjusted rate[b]	0.0%	0.0%	9.0%	2.9%
Terminal rate[c]	0/33 (0%)	0/27 (0%)	1/28 (4%)	1/34 (3%)
First incidence (days)	–[e]	–	591	727 (T)
Life table test[d]	P=0.549	–	P=0.104	P=0.506
Logistic regression test[d]	P=0.525	–	P=0.121	P=0.506
Cochran-Armitage test[d]	P=0.527			
Fisher exact test[d]		–	P=0.121	P=0.505
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	3/50 (6%)	0/49 (0%)	2/50 (4%)	2/51 (4%)
Adjusted rate	9.1%	0.0%	6.4%	5.9%
Terminal rate	3/33 (9%)	0/26 (0%)	1/28 (4%)	2/34 (6%)
First incidence (days)	727 (T)	–	680	727 (T)
Life table test	P=0.617	P=0.165N	P=0.570N	P=0.486N
Logistic regression test	P=0.599	P=0.165N	P=0.551N	P=0.486N
Cochran-Armitage test	P=0.576			
Fisher exact test		P=0.125N	P=0.500N	P=0.491N
Clitoral Gland: Adenoma				
Overall rate	5/50 (10%)	12/48 (25%)	15/47 (32%)	16/49 (33%)
Adjusted rate	14.7%	39.2%	46.3%	46.8%
Terminal rate	4/33 (12%)	9/26 (35%)	11/28 (39%)	15/33 (45%)
First incidence (days)	717	560	576	661
Life table test	P=0.093	P=0.022	P=0.005	P=0.006
Logistic regression test	P=0.050	P=0.041	P=0.004	P=0.005
Cochran-Armitage test	P=0.045			
Fisher exact test		P=0.044	P=0.007	P=0.005
Clitoral Gland: Carcinoma				
Overall rate	1/50 (2%)	4/48 (8%)	0/47 (0%)	0/49 (0%)
Adjusted rate	3.0%	13.8%	0.0%	0.0%
Terminal rate	1/33 (3%)	3/26 (12%)	0/28 (0%)	0/33 (0%)
First incidence (days)	727 (T)	654	–	–
Life table test	P=0.121N	P=0.128	P=0.533N	P=0.500N
Logistic regression test	P=0.131N	P=0.158	P=0.533N	P=0.500N
Cochran-Armitage test	P=0.134N			
Fisher exact test		P=0.168	P=0.515N	P=0.505N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	16/48 (33%)	15/47 (32%)	16/49 (33%)
Adjusted rate	17.6%	51.2%	46.3%	46.8%
Terminal rate	5/33 (15%)	12/26 (46%)	11/28 (39%)	15/33 (45%)
First incidence (days)	717	560	576	661
Life table test	P=0.240	P=0.004	P=0.010	P=0.013
Logistic regression test	P=0.152	P=0.009	P=0.008	P=0.011
Cochran-Armitage test	P=0.137			
Fisher exact test		P=0.011	P=0.016	P=0.012

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	0/51 (0%)
Adjusted rate	9.1%	3.7%	6.8%	0.0%
Terminal rate	3/33 (9%)	1/27 (4%)	1/28 (4%)	0/34 (0%)
First incidence (days)	727 (T)	727 (T)	708	-
Life table test	P=0.126N	P=0.378N	P=0.571N	P=0.115N
Logistic regression test	P=0.131N	P=0.378N	P=0.560N	P=0.115N
Cochran-Armitage test	P=0.145N			
Fisher exact test		P=0.309N	P=0.500N	P=0.118N
Mammary Gland: Fibroadenoma				
Overall rate	13/50 (26%)	22/50 (44%)	19/50 (38%)	16/51 (31%)
Adjusted rate	36.5%	61.4%	52.1%	42.8%
Terminal rate	11/33 (33%)	14/27 (52%)	11/28 (39%)	13/34 (38%)
First incidence (days)	517	552	489	598
Life table test	P=0.252N	P=0.016	P=0.071	P=0.361
Logistic regression test	P=0.377N	P=0.039	P=0.094	P=0.331
Cochran-Armitage test	P=0.377N			
Fisher exact test		P=0.046	P=0.142	P=0.353
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	14/50 (28%)	23/50 (46%)	20/50 (40%)	16/51 (31%)
Adjusted rate	39.4%	64.4%	54.9%	42.8%
Terminal rate	12/33 (36%)	15/27 (56%)	12/28 (43%)	13/34 (38%)
First incidence (days)	517	552	489	598
Life table test	P=0.179N	P=0.015	P=0.068	P=0.448
Logistic regression test	P=0.283N	P=0.039	P=0.091	P=0.418
Cochran-Armitage test	P=0.287N			
Fisher exact test		P=0.048	P=0.146	P=0.439
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/49 (6%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	9.1%	0.0%	0.0%	5.9%
Terminal rate	3/33 (9%)	0/27 (0%)	0/28 (0%)	2/34 (6%)
First incidence (days)	727 (T)	-	-	727 (T)
Life table test	P=0.529	P=0.158N	P=0.151N	P=0.486N
Logistic regression test	P=0.529	P=0.158N	P=0.151N	P=0.486N
Cochran-Armitage test	P=0.481			
Fisher exact test		P=0.117N	P=0.117N	P=0.490N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	26/50 (52%)	26/48 (54%)	24/50 (48%)	24/51 (47%)
Adjusted rate	62.9%	64.3%	59.1%	59.5%
Terminal rate	18/33 (55%)	13/26 (50%)	12/28 (43%)	18/34 (53%)
First incidence (days)	468	444	455	367
Life table test	P=0.222N	P=0.310	P=0.477	P=0.383N
Logistic regression test	P=0.329N	P=0.493	P=0.464N	P=0.418N
Cochran-Armitage test	P=0.316N			
Fisher exact test		P=0.495	P=0.421N	P=0.383N

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	28/50 (56%)	26/48 (54%)	25/50 (50%)	24/51 (47%)
Adjusted rate	66.3%	64.3%	60.0%	59.5%
Terminal rate	19/33 (58%)	13/26 (50%)	12/28 (43%)	18/34 (53%)
First incidence (days)	468	444	455	367
Life table test	P=0.166N	P=0.428	P=0.532	P=0.259N
Logistic regression test	P=0.239N	P=0.511N	P=0.374N	P=0.270N
Cochran-Armitage test	P=0.230N			
Fisher exact test		P=0.508N	P=0.344N	P=0.242N
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	2/50 (4%)	3/50 (6%)	3/51 (6%)
Adjusted rate	18.2%	6.5%	10.7%	8.8%
Terminal rate	6/33 (18%)	1/27 (4%)	3/28 (11%)	3/34 (9%)
First incidence (days)	727 (T)	700	727 (T)	727 (T)
Life table test	P=0.350N	P=0.196N	P=0.325N	P=0.224N
Logistic regression test	P=0.361N	P=0.170N	P=0.325N	P=0.224N
Cochran-Armitage test	P=0.417N			
Fisher exact test		P=0.134N	P=0.243N	P=0.234N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	2/50 (4%)	4/50 (8%)	3/51 (6%)
Adjusted rate	23.5%	6.5%	13.0%	8.8%
Terminal rate	7/33 (21%)	1/27 (4%)	3/28 (11%)	3/34 (9%)
First incidence (days)	707	700	591	727 (T)
Life table test	P=0.205N	P=0.087N	P=0.262N	P=0.090N
Logistic regression test	P=0.239N	P=0.062N	P=0.226N	P=0.087N
Cochran-Armitage test	P=0.257N			
Fisher exact test		P=0.046N	P=0.178N	P=0.094N
Uterus: Stromal Polyp				
Overall rate	9/50 (18%)	10/50 (20%)	11/50 (22%)	8/51 (16%)
Adjusted rate	22.8%	31.3%	33.3%	20.7%
Terminal rate	5/33 (15%)	7/27 (26%)	8/28 (29%)	5/34 (15%)
First incidence (days)	461	552	462	493
Life table test	P=0.276N	P=0.378	P=0.288	P=0.484N
Logistic regression test	P=0.342N	P=0.502	P=0.437	P=0.465N
Cochran-Armitage test	P=0.344N			
Fisher exact test		P=0.500	P=0.402	P=0.482N
All Organs: Mononuclear Cell Leukemia				
Overall rate	15/50 (30%)	19/50 (38%)	18/50 (36%)	21/51 (41%)
Adjusted rate	38.7%	47.3%	44.6%	49.2%
Terminal rate	10/33 (30%)	8/27 (30%)	8/28 (29%)	13/34 (38%)
First incidence (days)	553	444	414	367
Life table test	P=0.350	P=0.178	P=0.219	P=0.193
Logistic regression test	P=0.234	P=0.263	P=0.362	P=0.158
Cochran-Armitage test	P=0.227			
Fisher exact test		P=0.263	P=0.335	P=0.167

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	45/50 (90%)	42/50 (84%)	41/51 (80%)
Adjusted rate	93.2%	97.8%	95.4%	97.6%
Terminal rate	30/33 (91%)	26/27 (96%)	26/28 (93%)	33/34 (97%)
First incidence (days)	461	444	455	367
Life table test	P=0.099N	P=0.090	P=0.201	P=0.417N
Logistic regression test	P=0.284N	P=0.274	P=0.463	P=0.530N
Cochran-Armitage test	P=0.210N			
Fisher exact test		P=0.277	P=0.607N	P=0.416N
All Organs: Malignant Neoplasms				
Overall rate	25/50 (50%)	25/50 (50%)	24/50 (48%)	24/51 (47%)
Adjusted rate	56.2%	59.0%	55.3%	54.0%
Terminal rate	14/33 (42%)	11/27 (41%)	10/28 (36%)	14/34 (41%)
First incidence (days)	517	444	414	367
Life table test	P=0.332N	P=0.390	P=0.435	P=0.472N
Logistic regression test	P=0.413N	P=0.573N	P=0.431N	P=0.462N
Cochran-Armitage test	P=0.429N			
Fisher exact test		P=0.579N	P=0.500N	P=0.462N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	48/50 (96%)	47/50 (94%)	46/51 (90%)
Adjusted rate	98.0%	98.0%	95.9%	97.9%
Terminal rate	32/33 (97%)	26/27 (96%)	26/28 (93%)	33/34 (97%)
First incidence (days)	461	444	414	367
Life table test	P=0.115N	P=0.255	P=0.302	P=0.299N
Logistic regression test	P=0.138N	P=0.500N	P=0.303N	P=0.204N
Cochran-Armitage test	P=0.081N			
Fisher exact test		P=0.500N	P=0.309N	P=0.107N

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

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

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	0/50	0/50	0/50
Pentaerythritol tetranitrate	0/50	0/50	0/50
Quercetin	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/1,000 (0.1%)	0/1,000 (0.0%)	1/1,000 (0.1%)
Standard deviation	0.5%		0.5%
Range	0%-2%		0%-2%

[a] Data as of 17 December 1991

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

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	5/50	4/50	9/50
HC Yellow 4	7/50	0/50	7/50
Pentaerythritol tetranitrate	5/50	0/50	5/50
Quercetin	4/50	1/50	5/50
Overall Historical Incidence			
Total	77/1,000 (8.0%)	29/1,000 (3.0%)	105/1,000 (11.0%)
Standard deviation	4.1%	4.3%	4.9%
Range	2%-18%	0%-14%	4%-20%

[a] Data as of 17 December 1991

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	14	22	19	15
Natural deaths	3	1	3	2
Survivors				
Died last week of study	1	1		
Terminal sacrifice	32	26	28	34
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)	(10)	(10)	(9)
Hyperplasia, glandular				8 (89%)
Parasite metazoan	2 (20%)	1 (10%)	1 (10%)	
Ulcer				6 (67%)
Submucosa, lamina propria, inflammation, chronic active				9 (100%)
Intestine large, colon	(10)	(10)	(10)	(9)
Parasite metazoan	1 (10%)	1 (10%)	2 (20%)	
Epithelium, pigmentation				8 (89%)
Intestine large, rectum	(10)	(10)	(9)	(9)
Parasite metazoan	1 (10%)			
Epithelium, pigmentation				2 (22%)
Intestine small, ileum	(10)	(10)	(9)	(9)
Epithelium, pigmentation				9 (100%)
Liver	(10)	(2)	(4)	(9)
Basophilic focus	2 (20%)	1 (50%)	4 (100%)	3 (33%)
Clear cell focus		1 (50%)		
Hepatodiaphragmatic nodule	2 (20%)		1 (25%)	
Inflammation			1 (25%)	
Inflammation, chronic	4 (40%)	1 (50%)		4 (44%)
Inflammation, chronic active	2 (20%)		1 (25%)	1 (11%)
Inflammation, granulomatous		1 (50%)		
Necrosis, coagulative	1 (10%)			
Bile duct, hyperplasia	3 (30%)			3 (33%)
Mesentery	(1)			
Fibrosis	1 (100%)			
Inflammation, chronic	1 (100%)			
Pancreas	(10)			(9)
Atrophy				1 (11%)
Inflammation, chronic	3 (30%)			3 (33%)
Inflammation, chronic active	1 (10%)			
Acinus, atrophy	1 (10%)			
Salivary glands	(10)			(9)
Sublingual gland, inflammation, chronic	1 (10%)			
Sublingual gland, metaplasia, squamous	1 (10%)			
Submandibular gland, inflammation, chronic	3 (30%)			1 (11%)
Submandibular gland, inflammation, chronic active	1 (10%)			

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Stomach, forestomach	(10)	(10)	(9)	(9)
Muscularis, mineralization		1 (10%)		
Stomach, glandular	(10)	(10)	(9)	(9)
Muscularis, mineralization		1 (10%)		
Cardiovascular System				
Heart	(10)			(9)
Cardiomyopathy	10 (100%)			9 (100%)
Endocrine System				
Adrenal gland, cortex	(10)		(1)	(8)
Angiectasis	9 (90%)		1 (100%)	6 (75%)
Pituitary gland	(10)	(1)	(2)	(9)
Pars distalis, angiectasis			1 (50%)	
Pars distalis, cyst	7 (70%)			4 (44%)
Pars distalis, hyperplasia	1 (10%)			3 (33%)
Pars distalis, pigmentation	1 (10%)			
Pars intermedia, cyst	1 (10%)			
Rathke's cleft, crystals			1 (50%)	
Thyroid gland	(10)	(1)	(2)	(9)
C-cell, hyperplasia	4 (40%)			1 (11%)
General Body System				
None				
Genital System				
Clitoral gland	(10)	(3)	(2)	(9)
Hyperplasia			1 (50%)	
Inflammation, chronic	4 (40%)	3 (100%)		6 (67%)
Inflammation, chronic active	1 (10%)			
Ovary	(10)	(1)	(1)	(9)
Inflammation, chronic				1 (11%)
Periovarian tissue, cyst		1 (100%)		
Uterus	(10)			(9)
Hydrometra	1 (10%)			4 (44%)
Endometrium, cyst	1 (10%)			
Endometrium, hyperplasia				1 (11%)
Hematopoietic System				
Lymph node	(10)	(10)	(6)	(9)
Mediastinal, hemorrhage	5 (50%)			1 (11%)
Mediastinal, infiltration cellular, histiocyte	1 (10%)			
Mediastinal, pigmentation	1 (10%)			

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System (continued)				
Lymph node (continued)	(10)	(10)	(6)	(9)
Pancreatic, infiltration cellular, histiocyte	1 (10%)			1 (11%)
Pancreatic, pigmentation	1 (10%)			1 (11%)
Lymph node, mandibular	(1)		(2)	
Hemorrhage	1 (100%)		1 (50%)	
Hyperplasia, plasma cell			1 (50%)	
Lymph node, mesenteric	(10)	(10)	(6)	(9)
Infiltration cellular, histiocyte	10 (100%)	10 (100%)	6 (100%)	8 (89%)
Pigmentation	7 (70%)	10 (100%)	6 (100%)	8 (89%)
Sinus, ectasia				9 (100%)
Integumentary System				
Mammary gland	(10)			(8)
Hyperplasia	7 (70%)			3 (38%)
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(2)	(2)	(9)
Hemorrhage				1 (11%)
Infiltration cellular, histiocyte	3 (30%)		1 (50%)	2 (22%)
Mineralization			1 (50%)	
Alveolar epithelium, hyperplasia				1 (11%)
Alveolus, mineralization				1 (11%)
Artery, mineralization	3 (30%)			2 (22%)
Artery, muscularis, hyperplasia	1 (10%)			
Nose	(10)	(9)	(2)	(9)
Metaplasia, squamous	1 (10%)			
Lumen, inflammation, acute	1 (10%)			
Mucosa, submucosa, inflammation, chronic active	1 (10%)			1 (11%)
Nasolacrimal duct, inflammation, acute				1 (11%)
Nasopharyngeal duct, inflammation, acute	1 (10%)			1 (11%)
Submucosa, glands, inflammation, acute	1 (10%)			
Special Senses System				
Eye		(1)	(2)	(2)
Lens, cataract				1 (50%)
Retina, degeneration				1 (50%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(1)		(9)
Nephropathy	9 (90%)	1 (100%)		9 (100%)
Renal tubule, mineralization	2 (20%)			5 (56%)
2-Year Study				
Alimentary System				
Intestine large, cecum	(50)	(50)	(50)	(51)
Autolysis	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Hyperplasia, glandular			1 (2%)	48 (94%)
Parasite metazoan	20 (40%)	10 (20%)	10 (20%)	4 (8%)
Ulcer				20 (39%)
Submucosa, lamina propria, inflammation, chronic active				36 (71%)
Intestine large, colon	(50)	(50)	(50)	(50)
Autolysis	2 (4%)	2 (4%)	2 (4%)	
Edema				1 (2%)
Hyperplasia, glandular				1 (2%)
Parasite metazoan	9 (18%)	8 (16%)	9 (18%)	1 (2%)
Intestine large, rectum	(50)	(49)	(50)	(51)
Autolysis	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Edema				1 (2%)
Parasite metazoan	7 (14%)	8 (16%)	3 (6%)	4 (8%)
Intestine small, duodenum	(50)	(50)	(50)	(51)
Autolysis	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Intestine small, ileum	(50)	(50)	(50)	(51)
Autolysis	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Hyperplasia, lymphoid			1 (2%)	
Intestine small, jejunum	(50)	(49)	(50)	(51)
Autolysis	2 (4%)	3 (6%)	2 (4%)	3 (6%)
Liver	(50)	(50)	(50)	(51)
Angiectasis	1 (2%)	1 (2%)		3 (6%)
Autolysis	1 (2%)			
Basophilic focus	30 (60%)	32 (64%)	26 (52%)	32 (63%)
Clear cell focus	8 (16%)	6 (12%)	5 (10%)	6 (12%)
Congestion			1 (2%)	
Cytoplasmic alteration		2 (4%)		2 (4%)
Degeneration		1 (2%)	1 (2%)	2 (4%)
Eosinophilic focus	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Fatty change	9 (18%)	12 (24%)	6 (12%)	4 (8%)
Fibrosis		1 (2%)		
Hematopoietic cell proliferation			1 (2%)	
Hepatodiaphragmatic nodule	8 (16%)	6 (12%)	9 (18%)	9 (18%)
Hyperplasia		1 (2%)		
Hyperplasia, lymphoid		1 (2%)		
Inflammation, chronic			1 (2%)	
Inflammation, chronic active	21 (42%)	26 (52%)	18 (36%)	25 (49%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver (continued)	(50)	(50)	(50)	(51)
Mixed cell focus	5 (10%)	7 (14%)	1 (2%)	
Necrosis, coagulative	6 (12%)	2 (4%)	4 (8%)	1 (2%)
Pigmentation		1 (2%)		
Bile duct, hyperplasia	13 (26%)	19 (38%)	11 (22%)	11 (22%)
Mesentery	(4)	(4)	(4)	(2)
Fibrosis	3 (75%)	2 (50%)	2 (50%)	1 (50%)
Inflammation, chronic active	3 (75%)	2 (50%)	1 (25%)	2 (100%)
Mineralization			2 (50%)	
Necrosis, liquifactive	1 (25%)	1 (25%)	3 (75%)	1 (50%)
Pancreas	(50)	(50)	(50)	(50)
Cytoplasmic alteration		2 (4%)		
Ectopic liver		1 (2%)	1 (2%)	
Inflammation, chronic active	23 (46%)	22 (44%)	23 (46%)	17 (34%)
Pigmentation		1 (2%)		
Vacuolization cytoplasmic	4 (8%)	6 (12%)	4 (8%)	2 (4%)
Acinus, atrophy	23 (46%)	18 (36%)	25 (50%)	18 (36%)
Acinus, hyperplasia	1 (2%)			
Salivary glands	(50)	(50)	(50)	(51)
Inflammation, chronic active		1 (2%)		
Duct, sublingual gland, hyperplasia		1 (2%)		
Duct, sublingual gland, metaplasia, squamous		2 (4%)		
Duct, submandibular gland, hyperplasia	6 (12%)	5 (10%)	5 (10%)	6 (12%)
Duct, submandibular gland, inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Duct, submandibular gland, metaplasia, squamous	12 (24%)	19 (38%)	8 (16%)	10 (20%)
Parotid gland, atrophy	1 (2%)	1 (2%)		2 (4%)
Parotid gland, inflammation, chronic active				1 (2%)
Parotid gland, submandibular gland, inflammation, chronic active	1 (2%)			
Sublingual gland, inflammation, chronic		1 (2%)		
Sublingual gland, inflammation, chronic active	2 (4%)	1 (2%)	3 (6%)	
Submandibular gland, inflammation, chronic active	15 (30%)	15 (30%)	11 (22%)	12 (24%)
Stomach, forestomach	(50)	(50)	(50)	(51)
Acanthosis			1 (2%)	
Foreign body				1 (2%)
Hyperkeratosis	2 (4%)	5 (10%)	6 (12%)	3 (6%)
Hyperplasia, squamous	3 (6%)	6 (12%)	7 (14%)	4 (8%)
Inflammation, chronic active		2 (4%)	1 (2%)	1 (2%)
Ulcer	2 (4%)	5 (10%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(51)
Autolysis	1 (2%)	1 (2%)	1 (2%)	
Fibrosis		1 (2%)		
Hyperplasia		1 (2%)		
Inflammation, chronic active			2 (4%)	
Metaplasia, squamous	1 (2%)			
Necrosis, coagulative		1 (2%)	3 (6%)	
Mucosa, dilatation	44 (88%)	48 (96%)	45 (90%)	44 (86%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Tongue		(1)		(1)
Hyperplasia, squamous		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Cardiomyopathy	48 (96%)	48 (96%)	47 (94%)	49 (96%)
Atrium, thrombosis		2 (4%)		
Endocrine System				
Adrenal gland	(50)	(50)	(50)	(51)
Capsule, fibrosis		1 (2%)		
Adrenal gland, cortex	(50)	(50)	(50)	(51)
Angiectasis	35 (70%)	36 (72%)	36 (72%)	32 (63%)
Autolysis		1 (2%)		
Congestion		2 (4%)		
Degeneration			1 (2%)	
Hematopoietic cell proliferation	2 (4%)	1 (2%)		
Hemorrhage				1 (2%)
Hyperplasia	12 (24%)	10 (20%)	11 (22%)	9 (18%)
Necrosis, coagulative			1 (2%)	
Vacuolization cytoplasmic	22 (44%)	14 (28%)	15 (30%)	11 (22%)
Adrenal gland, medulla	(50)	(49)	(50)	(51)
Autolysis		1 (2%)		
Hyperplasia	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Necrosis, coagulative				1 (2%)
Islets, pancreatic	(49)	(50)	(50)	(50)
Hyperplasia	1 (2%)			
Parathyroid gland	(46)	(47)	(49)	(47)
Hyperplasia			1 (2%)	
Pituitary gland	(50)	(48)	(50)	(51)
Pars distalis, angiectasis	6 (12%)	5 (10%)	5 (10%)	5 (10%)
Pars distalis, cyst	23 (46%)	19 (40%)	21 (42%)	37 (73%)
Pars distalis, hyperplasia	18 (36%)	21 (44%)	14 (28%)	16 (31%)
Pars intermedia, angiectasis	1 (2%)	1 (2%)		1 (2%)
Pars intermedia, cyst			1 (2%)	1 (2%)
Pars intermedia, pigmentation			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(51)
Inflammation, chronic active	1 (2%)			
Ultimobranchial cyst				1 (2%)
C-cell, hyperplasia	29 (58%)	29 (58%)	24 (48%)	28 (55%)
Follicular cell, cyst		1 (2%)	3 (6%)	1 (2%)
Follicular cell, hyperplasia		2 (4%)		
General Body System				
Tissue NOS	(1)		(1)	(2)
Necrosis				1 (50%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Genital System				
Clitoral gland	(50)	(48)	(47)	(49)
Hyperplasia	7 (14%)	5 (10%)	4 (9%)	7 (14%)
Inflammation, chronic active	31 (62%)	23 (48%)	26 (55%)	26 (53%)
Duct, dilatation	4 (8%)	4 (8%)	2 (4%)	3 (6%)
Ovary	(50)	(50)	(50)	(51)
Cyst	2 (4%)	1 (2%)	6 (12%)	2 (4%)
Hemorrhage	1 (2%)			
Uterus	(50)	(50)	(50)	(51)
Angiectasis		1 (2%)		
Hydrometra	7 (14%)	5 (10%)	6 (12%)	3 (6%)
Inflammation, acute	1 (2%)	3 (6%)	4 (8%)	
Necrosis, coagulative			1 (2%)	
Pigmentation	1 (2%)			
Cervix, cyst	1 (2%)	2 (4%)	6 (12%)	
Endometrium, hyperplasia	7 (14%)	5 (10%)	7 (14%)	8 (16%)
Vagina	(1)	(2)		(1)
Exudate		2 (100%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(51)
Sternal, autolysis			1 (2%)	1 (2%)
Sternal, myelofibrosis		1 (2%)		
Lymph node	(50)	(50)	(50)	(51)
Bronchial, fibrosis		1 (2%)		
Bronchial, hyperplasia, lymphoid		1 (2%)		
Mediastinal, hemorrhage		4 (8%)		
Mediastinal, hyperplasia, lymphoid		2 (4%)		
Mediastinal, hyperplasia, plasma cell		1 (2%)		
Pancreatic, infiltration cellular, histiocyte		1 (2%)		1 (2%)
Lymph node, mandibular	(3)	(9)	(4)	(7)
Hyperplasia, lymphoid		2 (22%)		
Hyperplasia, plasma cell			1 (25%)	
Sinus, ectasia	1 (33%)	1 (11%)	1 (25%)	1 (14%)
Lymph node, mesenteric	(50)	(50)	(50)	(51)
Infiltration cellular, histiocyte	50 (100%)	47 (94%)	49 (98%)	47 (92%)
Sinus, ectasia			1 (2%)	50 (98%)
Spleen	(50)	(50)	(50)	(51)
Angiectasis	1 (2%)			
Autolysis	1 (2%)			
Cyst				1 (2%)
Depletion lymphoid	11 (22%)	14 (28%)	8 (16%)	11 (22%)
Fibrosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)		1 (2%)	1 (2%)
Thymus	(41)	(48)	(45)	(41)
Cyst	3 (7%)	1 (2%)	4 (9%)	3 (7%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(49)	(49)	(51)
Galactocele	3 (6%)	1 (2%)	1 (2%)	
Hyperplasia	50 (100%)	47 (96%)	47 (96%)	51 (100%)
Skin	(48)	(50)	(49)	(50)
Abscess	1 (2%)			
Acanthosis		1 (2%)		
Hyperkeratosis		1 (2%)		
Hyperplasia, basal cell		1 (2%)		
Foot, acanthosis	2 (4%)			
Foot, hyperkeratosis	2 (4%)			
Foot, inflammation, chronic active	1 (2%)			
Subcutaneous tissue, cyst epithelial inclusion		2 (4%)	1 (2%)	
Subcutaneous tissue, inflammation, chronic	2 (4%)	1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(51)
Cranium, hyperostosis	1 (2%)	1 (2%)		1 (2%)
Cranium, osteopetrosis	1 (2%)	2 (4%)		1 (2%)
Sternum, osteopetrosis		2 (4%)	1 (2%)	4 (8%)
Nervous System				
Brain	(50)	(50)	(50)	(51)
Gliosis	1 (2%)			
Hydrocephalus	3 (6%)	3 (6%)	2 (4%)	
Infarct		1 (2%)	1 (2%)	
Necrosis, coagulative			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Abscess	1 (2%)			
Fibrosis				1 (2%)
Infiltration cellular, histiocyte	16 (32%)	10 (20%)	11 (22%)	18 (35%)
Inflammation, chronic active		3 (6%)		
Metaplasia, osseous	1 (2%)			
Alveolar epithelium, hyperplasia	4 (8%)	2 (4%)	1 (2%)	3 (6%)
Artery, mineralization	25 (50%)	19 (38%)	32 (64%)	30 (59%)
Nose	(49)	(47)	(50)	(51)
Inflammation, chronic active	28 (57%)	23 (49%)	23 (46%)	35 (69%)
Metaplasia, squamous	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Lumen, foreign body		1 (2%)	2 (4%)	
Mucosa, ulcer	1 (2%)	1 (2%)		
Nasolacrimal duct, inflammation, chronic active				2 (4%)

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

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Special Senses System				
Eye	(9)	(9)	(5)	(11)
Cataract	1 (11%)	2 (22%)	3 (60%)	2 (18%)
Phthisis bulbi	2 (22%)		1 (20%)	1 (9%)
Cornea, inflammation, chronic active	1 (11%)	1 (11%)		
Cornea, neovascularization	2 (22%)	1 (11%)		
Retina, degeneration		3 (33%)	4 (80%)	2 (18%)
Lacrimal gland		(1)		
Inflammation, chronic		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(49)	(51)
Autolysis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Cyst			1 (2%)	1 (2%)
Hydronephrosis	1 (2%)	1 (2%)		
Nephropathy	49 (98%)	48 (96%)	47 (96%)	46 (90%)
Pelvis, inflammation, acute			1 (2%)	
Proximal convoluted renal tubule, inflammation, acute		1 (2%)		1 (2%)
Renal tubule, mineralization	3 (6%)		6 (12%)	9 (18%)
Transitional epithelium, hyperplasia	7 (14%)	8 (16%)	6 (12%)	10 (20%)
Transitional epithelium, mineralization		1 (2%)	2 (4%)	2 (4%)
Urinary bladder	(50)	(48)	(49)	(51)
Autolysis		1 (2%)	1 (2%)	
Inflammation, chronic active	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Subserosa, mineralization	1 (2%)			

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

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF TURMERIC OLEORESIN

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TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	5	6	8	6
Natural deaths	2	1	5	2
Survivors				
Died last week of study		1		
Terminal sacrifice	43	42	37	42
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(9)	(10)	(10)
Hepatocellular carcinoma			2 (20%)	
Hepatocellular adenoma		1 (11%)	2 (20%)	
Hepatocellular adenoma, multiple				1 (10%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
None				
Hematopoietic System				
Lymph node, mesenteric	(10)	(2)	(1)	(9)
Lymphoma malignant mixed				1 (11%)
Spleen	(10)		(2)	(10)
Lymphoma malignant mixed				1 (10%)
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
Lung	(10)			(10)
Alveolar/bronchiolar adenoma				1 (10%)
Special Senses System				
Ear	(1)			
Fibrosarcoma	1 (100%)			
Urinary System				
Kidney	(10)	(3)		(10)
Renal tubule, adenoma	1 (10%)			
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Lymphoma malignant mixed				1 (10%)
2-Year Study				
Alimentary System				
Gallbladder	(43)	(47)	(47)	(46)
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(49)	(50)	(50)
Adenocarcinoma			1 (2%)	
Intestine small, ileum	(50)	(50)	(50)	(50)
Adenocarcinoma		1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)
Adenocarcinoma		2 (4%)	2 (4%)	
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Hepatoblastoma			3 (6%)	1 (2%)
Hepatocellular carcinoma	12 (24%)	15 (30%)	12 (24%)	13 (26%)
Hepatocellular carcinoma, multiple		3 (6%)	4 (8%)	5 (10%)
Hepatocellular adenoma	16 (32%)	11 (22%)	11 (22%)	12 (24%)
Hepatocellular adenoma, multiple	9 (18%)	17 (34%)	24 (48%)	18 (36%)
Pancreas	(50)	(50)	(50)	(49)
Stomach, forestomach	(50)	(50)	(50)	(50)
Papilloma squamous	2 (4%)			
Tongue	(1)	(1)		
Squamous cell carcinoma		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(49)	(49)
Adenoma	1 (2%)			1 (2%)
Adrenal gland, medulla	(50)	(42)	(42)	(49)
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	1 (2%)		1 (2%)	
Pituitary gland	(50)	(49)	(50)	(50)
Thyroid gland	(50)	(49)	(49)	(50)
Adenocarcinoma			1 (2%)	
Follicular cell, adenoma	1 (2%)	1 (2%)		2 (4%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(21)	(20)	(23)	(24)
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(49)
Testes	(50)	(50)	(50)	(50)
Sertoli cell, adenoma			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Lymph node	(47)	(49)	(45)	(47)
Lymph node, mesenteric	(46)	(48)	(45)	(47)
Spleen	(50)	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	1 (2%)	1 (2%)
Thymus	(39)	(47)	(42)	(37)
Integumentary System				
Skin	(48)	(47)	(50)	(50)
Papilloma squamous				1 (2%)
Subcutaneous tissue, hemangioma			2 (4%)	
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle			(1)	
Sarcoma			1 (100%)	
Nervous System				
Brain	(50)	(50)	(49)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, harderian gland		1 (2%)		
Alveolar/bronchiolar adenoma	7 (14%)	8 (16%)	6 (12%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	4 (8%)	6 (12%)		4 (8%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	2 (4%)	2 (4%)	5 (10%)	3 (6%)
Squamous cell carcinoma		1 (2%)		
Mediastinum, hemangioma		1 (2%)		
Nose	(50)	(49)	(50)	(50)
Adenocarcinoma, metastatic, harderian gland		1 (2%)		
Special Senses System				
Harderian gland	(4)	(4)	(1)	(6)
Adenocarcinoma		1 (25%)		
Adenoma	4 (100%)	3 (75%)	1 (100%)	5 (83%)
Bilateral, adenoma				1 (17%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant mixed		3 (6%)	2 (4%)	6 (12%)
Lymphoma malignant undifferentiated cell			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2	1	4	3
2-Year study	38	42	47	42
Total primary neoplasms				
15-Month interim evaluation	2	1	4	3
2-Year study	65	81	77	83
Total animals with benign neoplasms				
15-Month interim evaluation	1	1	2	2
2-Year study	33	32	40	35
Total benign neoplasms				
15-Month interim evaluation	1	1	2	2
2-Year study	45	43	47	50
Total animals with malignant neoplasms				
15-Month interim evaluation	1		2	1
2-Year study	17	28	25	29
Total malignant neoplasms				
15-Month interim evaluation	1		2	1
2-Year study	20	38	30	33
Total animals with metastatic neoplasms				
2-Year study	2	4	5	3
Total metastatic neoplasms				
2-Year study	2	5	5	3

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm

Number of Days on Study	159	479	609	618	634	664	717	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	037	051	013	010	026	020	022	020	003	004	005	006	008	011	012	014	015	016	017	021	022	023	025	027	028
	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Alimentary System																									
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	M	+	M	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Hepatocellular carcinoma		X		X	X	X	X	X	X			X					X								
Hepatocellular adenoma					X			X	X			X				X	X			X			X		
Hepatocellular adenoma, multiple							X						X	X	X			X				X			
Mesentery									+																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous							X																		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue						+																			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	029 1	033 1	034 1	048 1	050 1	052 1	053 1	054 1	055 1	056 1	057 1	058 1	060 1	030 1	031 1	035 1	036 1	039 1	040 1	041 1	042 1	043 1	044 1	047 1	049 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma		X																		X		X				12
Hepatocellular adenoma	X					X				X							X	X	X		X		X			16
Hepatocellular adenoma, multiple		X		X												X										9
Mesentery																+				+						3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																		X								2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Parathyroid gland	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	M	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																X										1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm
(continued)

Number of Days on Study	159	479	609	618	634	664	717	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	037 1	051 1	013 1	010 1	026 1	022 1	024 1	020 1	003 1	004 1	005 1	006 1	008 1	011 1	012 1	014 1	015 1	016 1	017 1	021 1	022 1	023 1	025 1	027 1	028 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland						+	+		+	+	+						+				+	+		+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+		+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	M	M	M	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X		X		X								X							
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma			X									X													X
Hepatocellular carcinoma, metastatic, liver				X					X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear	+																								
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	029 1	033 1	034 1	048 1	050 1	052 1	053 1	054 1	055 1	056 1	057 1	058 1	060 1	030 1	031 1	035 1	036 1	039 1	040 1	041 1	042 1	043 1	044 1	047 1	049 1	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+				+	+	+	+	+			+	+	+	+							+			21
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	I	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	39
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, hemangiosarcoma											X															1
Subcutaneous tissue, sarcoma																X										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X				X			X															7
Alveolar/bronchiolar adenoma, multiple	X														X	X					X					4
Alveolar/bronchiolar carcinoma																X										4
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear																										1
Eye			+							+							+								+	4
Harderian gland			+							+							+								+	4
Adenoma			X							X							X								X	4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																			X							1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm

Number of Days on Study	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	4	6	7	9	9	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	7	2	1	9	1	3	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Carcass ID Number	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	9	2	1	8	7	1	6	6	6	7	6	6	6	6	6	7	7	7	7	8	8	8	8	8
	3	3	0	6	1	5	7	7	8	9	7	1	3	4	5	6	0	2	3	6	0	2	3	5	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Hepatocellular carcinoma	X	X	X			X							X		X	X	X						X	X	
Hepatocellular carcinoma, multiple											X									X		X			
Hepatocellular adenoma								X					X	X			X						X		X
Hepatocellular adenoma, multiple							X			X					X				X			X		X	
Mesentery																	+						+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																					+				
Squamous cell carcinoma																					X				
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	I	M	+	+	M	+	+	+	+	+
Pheochromocytoma benign											X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	+	M	M	+	M	+	M	+	+	+	+	+	M	M	+	M	M	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma							X																		
General Body System																									
Tissue NOS																			+						
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+			+	+			+				+		+				+		+	+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm
(continued)

Number of Days on Study	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	087	088	089	090	091	092	095	096	097	098	099	100	101	102	104	105	107	108	109	111	112	114	115	118	119	Total Tissues/ Tumors
Alimentary System																										
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	44
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma									X																	1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma										X																2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X				X										3
Hepatocellular carcinoma	X						X		X	X														X		15
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma			X								X					X	X			X						11
Hepatocellular adenoma, multiple		X			X	X	X			X		X		X	X			X	X		X					17
Mesentery						+					+		+				+	+	+		+			+		10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	+	M	M	+	+	M	+	+	+	+	M	M	+	+	+	+	M	M	M	+	+	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland		M		+		M	+	+	+		+	+	+			+		+	+			+				20
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm
(continued)

Number of Days on Study	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	4	6	7	9	9	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	7	2	1	9	1	3	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Carcass ID Number	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	9	2	1	8	7	1	6	6	6	7	6	6	6	6	6	7	7	7	7	8	8	8	8	8
	3	3	0	6	1	5	7	7	8	9	7	1	3	4	5	6	0	2	3	6	0	2	3	5	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Thymus	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland							X																		
Alveolar/bronchiolar adenoma										X			X		X										
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma					X			X																	
Alveolar/bronchiolar carcinoma, multiple											X														
Hepatocellular carcinoma, metastatic, liver		X				X																			
Squamous cell carcinoma										X															
Mediastinum, hemangioma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye			+				M									+		+					+		
Harderian gland							+	+								+		+							
Adenocarcinoma							X																		
Adenoma								X								X		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver											X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm (continued)

Number of Days on Study	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	0871	0881	0891	0901	0991	0921	0951	0961	0971	0981	0991	1001	1011	1021	1041	1051	1071	1081	1091	1101	1121	1141	1151	1181	1191	Total Tissues/ Tumors
Hematopoietic System																										
Blood											+															1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																										1
Alveolar/bronchiolar adenoma						X	X							X						X				X		8
Alveolar/bronchiolar adenoma, multiple											X															1
Alveolar/bronchiolar carcinoma	X	X							X										X							6
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																										2
Squamous cell carcinoma																										1
Mediastinum, hemangioma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Special Senses System																										
Ear			+																							1
Eye																										4
Harderian gland																										4
Adenocarcinoma																										1
Adenoma																										3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm
(continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm (continued)

Number of Days on Study	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	081	081	081	091	091	091	095	096	097	098	099	100	101	102	104	105	107	108	109	111	112	114	115	118	119	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed													X													3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm

Number of Days on Study	224	299	541	541	595	639	640	647	708	713	713	716	725	734	734	734	734	734	734	734	734	734	734	734	734
Carcass ID Number	1631	1561	1241	1421	1671	1661	1531	1441	1791	1231	1351	1491	1621	1121	1261	1271	1281	1321	1331	1341	1371	1381	1391	1431	1501
Alimentary System																									
Esophagus	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																	X								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatoblastoma										X			X								X				
Hepatocellular carcinoma							X	X	X	X		X			X	X			X						
Hepatocellular carcinoma, multiple			X	X	X																				
Hepatocellular adenoma									X	X	X			X									X		X
Hepatocellular adenoma, multiple				X									X		X	X		X			X			X	
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																							
Parathyroid gland	+	M	M	+	+	+	M	M	M	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma					X																				
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+					+		+			+						+	+	+	+		+	+	+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sertoli cell, adenoma																			X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm (continued)

Number of Days on Study	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	
Carcass ID Number	1511	1571	1221	1291	1301	1401	1441	1471	1521	1541	1551	1581	1591	1601	1611	1641	1651	1691	1701	1731	1761	1771	1781	1741	1801	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X											X				2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Hepatoblastoma																										3
Hepatocellular carcinoma		X	X						X								X									12
Hepatocellular carcinoma, multiple							X																			4
Hepatocellular adenoma			X										X										X	X	X	11
Hepatocellular adenoma, multiple	X	X		X	X	X	X	X	X	X	X			X	X	X	X		X		X	X				24
Mesentery						+			+								+					+				4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	42
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	M	M	+	+	M	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+		+		+		+	+	+	+	+		+					+			+			+		23
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sertoli cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm
(continued)

Number of Days on Study	2	3	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	9	4	4	9	3	4	4	0	1	1	1	2	3	3	3	3	3	3	3	3	3	3	3	3
	4	9	1	1	5	9	0	7	8	3	3	6	5	4	4	4	4	4	4	4	4	4	4	4	4
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	6	5	2	4	6	6	5	4	7	2	3	4	6	2	2	2	2	3	3	3	3	3	3	4	5
	3	6	4	2	7	6	3	4	9	3	5	9	2	1	6	7	8	2	3	4	7	8	9	3	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System																									
Bone marrow	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Thymus	+	+	M	M	M	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	A	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											
Sarcoma														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X			X											X	X				X		
Alveolar/bronchiolar adenoma, multiple																									
Hepatocellular carcinoma, metastatic, liver			X	X				X		X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+												
Harderian gland													+												
Adenoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed	X						X																		
Lymphoma malignant undifferentiated cell type	X																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm (continued)

Number of Days on Study	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	
Carcass ID Number	151	151	172	229	301	401	441	471	521	541	551	581	591	601	661	664	651	691	701	731	761	771	781	741	801	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	I	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	I	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma											X	X														2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						6
Alveolar/bronchiolar adenoma, multiple																		X								1
Hepatocellular carcinoma, metastatic, liver		X																								5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye																										1
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm

Number of Days on Study	437	537	598	627	678	680	724	724	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	2011	2001	1871	2231	1866	1891	1819	1961	1992	1944	1977	1998	1991	2051	2061	1821	1844	1855	1881	1901	1931	1951	2071	2091	2011
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Hepatoblastoma																									
Hepatocellular carcinoma		X	X				X	X				X								X					
Hepatocellular carcinoma, multiple					X	X											X							X	
Hepatocellular adenoma		X					X												X						X
Hepatocellular adenoma, multiple			X	X		X				X		X	X		X	X	X					X	X	X	
Mesentery			+										+					+							
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+	M	+	+	M	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma					X														X						
General Body System																										
Tissue NOS																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+		+							+		+	+	+	+		+		+					+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	2121	2131	2141	2151	2161	2171	2181	2191	2121	2221	2201	2281	2201	2231	2251	2261	2271	2291	2301	2311	2341	2351	2361	2381	2401	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma																					X					1
Hepatocellular carcinoma	X					X	X						X			X		X						X		13
Hepatocellular carcinoma, multiple																									X	5
Hepatocellular adenoma		X			X				X				X	X				X		X				X		12
Hepatocellular adenoma, multiple								X		X	X	X				X							X			18
Mesentery	+									+				+				+								7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																X										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	M	+	+	I	+	+	I	+	+	M	+	M	+	+	M	M	+	+	+	+	+	+	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
General Body System																										
Tissue NOS									+																	1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+		+	+		+	+	+	+			+			+			+	+	+	+		+			24
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm
(continued)

Number of Days on Study	437	337	598	627	678	680	724	724	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	2011	2011	1871	2321	1861	1911	1891	1961	1921	1941	1971	1981	1991	2051	2061	1821	1841	1851	1881	1901	1931	1951	2071	2091	2011
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Thymus	I	M	+	M	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	I	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X	X										X				X	X		X
Alveolar/bronchiolar adenoma, multiple																	X								
Alveolar/bronchiolar carcinoma																			X						
Hepatocellular carcinoma, metastatic, liver					X	X														X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear								+																	
Eye		+						+					+	+							+				
Harderian gland		+						+					+	+							+				
Adenoma		X						X						X							X				
Bilateral, adenoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																				X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																X					X	X			X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	2121	2131	2141	2151	2161	2171	2181	2191	2121	2221	2201	2281	2301	2321	2221	2261	2271	2291	2301	2331	2341	2351	2361	2381	2401	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	37
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X			X																X		9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma		X																					X	X		4
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye													+													6
Harderian gland													+													6
Adenoma													X													5
Bilateral, adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed				X					X																	6

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	3/50 (6%)	1/50 (2%)	6/50 (12%)
Adjusted rate[b]	9.3%	7.0%	2.6%	13.4%
Terminal rate[c]	4/43 (9%)	3/43 (7%)	0/37 (0%)	4/42 (10%)
First incidence (days)	729 (T)	729 (T)	725	537
Life table test[d]	P=0.146	P=0.500N	P=0.228N	P=0.363
Logistic regression test[d]	P=0.142	P=0.500N	P=0.205N	P=0.370
Cochran-Armitage test[d]	P=0.140			
Fisher exact test[d]		P=0.500N	P=0.181N	P=0.370
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	1/50 (2%)	6/50 (12%)
Adjusted rate	9.3%	9.1%	2.6%	13.4%
Terminal rate	4/43 (9%)	3/43 (7%)	0/37 (0%)	4/42 (10%)
First incidence (days)	729 (T)	715	725	537
Life table test	P=0.201	P=0.642	P=0.228N	P=0.363
Logistic regression test	P=0.196	P=0.632N	P=0.205N	P=0.370
Cochran-Armitage test	P=0.193			
Fisher exact test		P=0.643N	P=0.181N	P=0.370
Intestine Small: Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	7.0%	8.1%	0.0%
Terminal rate	0/43 (0%)	3/43 (7%)	3/37 (8%)	0/42 (0%)
First incidence (days)	-[e]	729 (T)	729 (T)	-
Life table test	P=0.227N	P=0.121	P=0.096	-
Logistic regression test	P=0.227N	P=0.121	P=0.096	-
Cochran-Armitage test	P=0.225N			
Fisher exact test		P=0.121	P=0.121	-
Liver: Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	2.2%	7.0%	2.7%	2.1%
Terminal rate	0/43 (0%)	3/43 (7%)	1/37 (3%)	0/42 (0%)
First incidence (days)	634	729 (T)	729 (T)	627
Life table test	P=0.445N	P=0.311	P=0.741	P=0.758N
Logistic regression test	P=0.448N	P=0.299	P=0.759N	P=0.728
Cochran-Armitage test	P=0.443N			
Fisher exact test		P=0.309	P=0.753N	P=0.753N
Liver: Hepatoblastoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	7.6%	2.4%
Terminal rate	0/43 (0%)	0/43 (0%)	1/37 (3%)	1/42 (2%)
First incidence (days)	-	-	713	729 (T)
Life table test	P=0.520	-	P=0.105	P=0.495
Logistic regression test	P=0.522	-	P=0.112	P=0.495
Cochran-Armitage test	P=0.520			
Fisher exact test		-	P=0.121	P=0.500

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Liver: Hepatocellular Adenoma				
Overall rate	25/50 (50%)	28/50 (56%)	35/50 (70%)	30/50 (60%)
Adjusted rate	55.5%	63.6%	83.3%	63.7%
Terminal rate	23/43 (53%)	27/43 (63%)	30/37 (81%)	25/42 (60%)
First incidence (days)	634	715	541	537
Life table test	P=0.350	P=0.343	P=0.004	P=0.197
Logistic regression test	P=0.356	P=0.395	P=0.012	P=0.226
Cochran-Armitage test	P=0.343			
Fisher exact test		P=0.344	P=0.033	P=0.211
Liver: Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	18/50 (36%)	16/50 (32%)	18/50 (36%)
Adjusted rate	25.0%	38.0%	34.9%	37.4%
Terminal rate	7/43 (16%)	14/43 (33%)	8/37 (22%)	12/42 (29%)
First incidence (days)	479	507	541	537
Life table test	P=0.292	P=0.165	P=0.188	P=0.156
Logistic regression test	P=0.249	P=0.108	P=0.267	P=0.124
Cochran-Armitage test	P=0.265			
Fisher exact test		P=0.138	P=0.252	P=0.138
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	18/50 (36%)	18/50 (36%)	19/50 (38%)
Adjusted rate	25.0%	38.0%	38.8%	39.5%
Terminal rate	7/43 (16%)	14/43 (33%)	9/37 (24%)	13/42 (31%)
First incidence (days)	479	507	541	537
Life table test	P=0.244	P=0.165	P=0.102	P=0.116
Logistic regression test	P=0.200	P=0.108	P=0.146	P=0.087
Cochran-Armitage test	P=0.213			
Fisher exact test		P=0.138	P=0.138	P=0.097
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	30/50 (60%)	38/50 (76%)	41/50 (82%)	37/50 (74%)
Adjusted rate	62.5%	79.1%	87.2%	75.5%
Terminal rate	25/43 (58%)	33/43 (77%)	31/37 (84%)	30/42 (71%)
First incidence (days)	479	507	541	537
Life table test	P=0.372	P=0.101	P=0.005	P=0.122
Logistic regression test	P=0.356	P=0.072	P=0.009	P=0.109
Cochran-Armitage test	P=0.339			
Fisher exact test		P=0.066	P=0.013	P=0.101
Liver: Hepatoblastoma, Hepatocellular Adenoma, or Carcinoma				
Overall rate	30/50 (60%)	38/50 (76%)	41/50 (82%)	38/50 (76%)
Adjusted rate	62.5%	79.1%	87.2%	77.6%
Terminal rate	25/43 (58%)	33/43 (77%)	31/37 (84%)	31/42 (74%)
First incidence (days)	479	507	541	537
Life table test	P=0.293	P=0.101	P=0.005	P=0.088
Logistic regression test	P=0.259	P=0.072	P=0.009	P=0.073
Cochran-Armitage test	P=0.245			
Fisher exact test		P=0.066	P=0.013	P=0.066

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	11/50 (22%)	9/50 (18%)	7/50 (14%)	10/50 (20%)
Adjusted rate	25.0%	20.9%	17.2%	22.7%
Terminal rate	10/43 (23%)	9/43 (21%)	5/37 (14%)	8/42 (19%)
First incidence (days)	664	729 (T)	541	724
Life table test	P=0.521	P=0.399N	P=0.320N	P=0.517N
Logistic regression test	P=0.528	P=0.376N	P=0.226N	P=0.490N
Cochran-Armitage test	P=0.520			
Fisher exact test		P=0.402N	P=0.218N	P=0.500N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	7/50 (14%)	0/50 (0%)	4/50 (8%)
Adjusted rate	8.9%	15.8%	0.0%	9.5%
Terminal rate	3/43 (7%)	6/43 (14%)	0/37 (0%)	4/42 (10%)
First incidence (days)	609	691	-	729 (T)
Life table test	P=0.509N	P=0.267	P=0.083N	P=0.630
Logistic regression test	P=0.503N	P=0.266	P=0.063N	P=0.640N
Cochran-Armitage test	P=0.508N			
Fisher exact test		P=0.262	P=0.059N	P=0.643N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	14/50 (28%)	16/50 (32%)	7/50 (14%)	13/50 (26%)
Adjusted rate	31.0%	36.3%	17.2%	29.5%
Terminal rate	12/43 (28%)	15/43 (35%)	5/37 (14%)	11/42 (26%)
First incidence (days)	609	691	541	724
Life table test	P=0.490N	P=0.419	P=0.133N	P=0.522N
Logistic regression test	P=0.481N	P=0.442	P=0.073N	P=0.487N
Cochran-Armitage test	P=0.490N			
Fisher exact test		P=0.414	P=0.070N	P=0.500N
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	4.4%	9.3%	4.9%	2.1%
Terminal rate	1/43 (2%)	4/43 (9%)	1/37 (3%)	0/42 (0%)
First incidence (days)	634	729 (T)	639	627
Life table test	P=0.248N	P=0.342	P=0.663	P=0.500N
Logistic regression test	P=0.246N	P=0.339	P=0.690N	P=0.536N
Cochran-Armitage test	P=0.242N			
Fisher exact test		P=0.339	P=0.691N	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.4%	11.6%	7.5%	2.1%
Terminal rate	1/43 (2%)	5/43 (12%)	2/37 (5%)	0/42 (0%)
First incidence (days)	634	729 (T)	639	627
Life table test	P=0.183N	P=0.221	P=0.458	P=0.500N
Logistic regression test	P=0.178N	P=0.221	P=0.504	P=0.536N
Cochran-Armitage test	P=0.177N			
Fisher exact test		P=0.218	P=0.500	P=0.500N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
All Organs: Malignant Lymphoma (Histiocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	6/50 (12%)
Adjusted rate	2.3%	6.7%	4.2%	14.3%
Terminal rate	1/43 (2%)	2/43 (5%)	0/37 (0%)	6/42 (14%)
First incidence (days)	729 (T)	691	224	729 (T)
Life table test	P=0.042	P=0.311	P=0.482	P=0.055
Logistic regression test	P=0.032	P=0.312	P=0.511	P=0.055
Cochran-Armitage test	P=0.039			
Fisher exact test		P=0.309	P=0.500	P=0.056
All Organs: Benign Neoplasms				
Overall rate	33/50 (66%)	32/50 (64%)	40/50 (80%)	35/50 (70%)
Adjusted rate	71.7%	72.7%	90.8%	71.4%
Terminal rate	30/43 (70%)	31/43 (72%)	33/37 (89%)	28/42 (67%)
First incidence (days)	634	715	399	537
Life table test	P=0.437	P=0.497N	P=0.011	P=0.383
Logistic regression test	P=0.450	P=0.415N	P=0.048	P=0.447
Cochran-Armitage test	P=0.428			
Fisher exact test		P=0.500N	P=0.088	P=0.415
All Organs: Malignant Neoplasms				
Overall rate	18/50 (36%)	28/50 (56%)	27/50 (54%)	29/50 (58%)
Adjusted rate	36.7%	57.1%	56.0%	59.2%
Terminal rate	12/43 (28%)	22/43 (51%)	16/37 (43%)	22/42 (52%)
First incidence (days)	479	507	224	537
Life table test	P=0.156	P=0.061	P=0.038	P=0.038
Logistic regression test	P=0.103	P=0.028	P=0.062	P=0.021
Cochran-Armitage test	P=0.111			
Fisher exact test		P=0.035	P=0.054	P=0.022
All Organs: Benign or Malignant Neoplasms				
Overall rate	38/50 (76%)	42/50 (84%)	48/50 (96%)	42/50 (84%)
Adjusted rate	77.6%	85.7%	96.0%	85.7%
Terminal rate	32/43 (74%)	36/43 (84%)	35/37 (95%)	35/42 (83%)
First incidence (days)	479	507	224	537
Life table test	P=0.479	P=0.289	P=0.004	P=0.239
Logistic regression test	P=0.473	P=0.250	P=0.004	P=0.252
Cochran-Armitage test	P=0.465			
Fisher exact test		P=0.227	P=0.004	P=0.227

(T)Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls			
	Hepatoblastoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute				
Acetaminophen	0/50	11/50	7/50	16/50
HC Yellow 4	0/49	8/49	5/49	13/49
Pentaerythritol tetranitrate	0/48	9/48	3/48	11/48
Overall Historical Incidence				
Total	0/1,114 (0.0%)	226/1,114 (20.3%)	169/1,114 (15.2%)	363/1,114 (32.6%)
Standard deviation		13.2%	7.1%	13.6%
Range		4%-60%	3%-27%	10%-68%

[a] Data as of 17 December 1991

TABLE C4b
Historical Incidence of Small Intestine Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	0/50	1/50[b]	1/50
HC Yellow 4	0/50	0/50	0/50
Pentaerythritol tetranitrate	0/49	0/49	0/49
Overall Historical Incidence			
Total	6/1,122 (0.5%)	0/1,122 (0.0%)	6/1,122 (0.5%)
Standard deviation	1.1%		1.1%
Range	0%-4%		0%-4%

[a] Data as of 17 December 1991
[b] The single neoplasm incidence shown for the acetaminophen study was originally coded as a duodenal adenocarcinoma. However, current NTP historical neoplasm pooling convention recodes adenocarcinoma to carcinoma.

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	5	6	8	6
Natural deaths	2	1	5	2
Survivors				
Died last week of study		1		
Terminal sacrifice	43	42	37	42
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Gallbladder	(10)		(1)	(9)
Inflammation, acute	1 (10%)			
Inflammation, chronic				1 (11%)
Intestine large, cecum	(10)	(10)	(10)	(10)
Epithelium, hyperplasia				1 (10%)
Epithelium, pigmentation				8 (80%)
Submucosa, epithelium, proliferation				1 (10%)
Intestine large, colon	(10)	(10)	(10)	(10)
Epithelium, pigmentation				5 (50%)
Intestine small, ileum	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)		
Epithelium, pigmentation				7 (70%)
Intestine small, jejunum	(10)	(10)	(10)	(10)
Epithelium, pigmentation				5 (50%)
Liver	(10)	(9)	(10)	(10)
Basophilic focus	1 (10%)			
Fatty change	8 (80%)	9 (100%)	10 (100%)	10 (100%)
Inflammation, acute	2 (20%)			
Inflammation, chronic active		1 (11%)	1 (10%)	
Necrosis, coagulative	2 (20%)	2 (22%)	1 (10%)	
Mesentery	(2)			(1)
Fibrosis	2 (100%)			1 (100%)
Inflammation, chronic	2 (100%)			1 (100%)
Necrosis	1 (50%)			
Necrosis, coagulative				1 (100%)
Pancreas	(10)			(10)
Cytoplasmic alteration	1 (10%)			
Inflammation, chronic				2 (20%)
Duct, concretion				1 (10%)
Duct, dilatation				1 (10%)
Salivary glands	(10)	(2)		(10)
Parotid gland, inflammation, chronic		1 (50%)		
Submandibular gland, inflammation	1 (10%)			
Submandibular gland, inflammation, chronic	2 (20%)	1 (50%)		6 (60%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Stomach, forestomach	(10)	(9)	(10)	(10)
Acanthosis				1 (10%)
Hyperkeratosis				1 (10%)
Hyperplasia	2 (20%)			
Inflammation, acute				1 (10%)
Inflammation, chronic	1 (10%)			
Inflammation, chronic active			1 (10%)	
Mineralization		1 (11%)		
Epithelium, hyperplasia		1 (11%)		1 (10%)
Stomach, glandular	(10)	(10)	(10)	(10)
Inflammation, chronic	1 (10%)		1 (10%)	1 (10%)
Inflammation, chronic active		2 (20%)	1 (10%)	
Mineralization			2 (20%)	
Epithelium, pigmentation				6 (60%)
Mucosa, mineralization		1 (10%)		
Cardiovascular System				
None				
Endocrine System				
Adrenal gland, cortex	(10)		(1)	(10)
Hyperplasia	1 (10%)			3 (30%)
Thyroid gland	(10)			(10)
Follicle, cyst	1 (10%)			
Follicle, cyst, multiple	1 (10%)			
General Body System				
None				
Genital System				
Epididymis	(10)			(10)
Inflammation, chronic	3 (30%)			6 (60%)
Preputial gland	(4)	(4)	(6)	(7)
Cyst	1 (25%)			
Cyst, multiple	3 (75%)	4 (100%)	6 (100%)	7 (100%)
Inflammation, chronic	2 (50%)		5 (83%)	2 (29%)
Inflammation, chronic active			1 (17%)	
Pigmentation		1 (25%)		
Prostate	(10)			(10)
Inflammation, chronic	6 (60%)			4 (40%)
Seminal vesicle		(1)		
Inflammation, chronic		1 (100%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mesenteric	(10)	(2)	(1)	(9)
Hyperplasia, lymphoid			1 (100%)	
Hyperplasia, plasma cell		1 (50%)		
Infiltration cellular, histiocyte	7 (70%)		1 (100%)	6 (67%)
Pigmentation	7 (70%)		1 (100%)	5 (56%)
Spleen	(10)		(2)	(10)
Depletion lymphoid				1 (10%)
Thymus	(9)			(9)
Cyst	2 (22%)			
Integumentary System				
Skin	(10)		(1)	(10)
Epidermis, inflammation, acute				1 (10%)
Subcutaneous tissue, inflammation, chronic active				1 (10%)
Musculoskeletal System				
None				
Nervous System				
Brain	(10)			(10)
Thalamus, mineralization	9 (90%)			9 (90%)
Respiratory System				
Lung	(10)			(10)
Metaplasia, osseous				1 (10%)
Alveolar epithelium, hyperplasia	1 (10%)			
Nose	(8)			(10)
Glands, inflammation, acute	1 (13%)			
Special Senses System				
None				
Urinary System				
Kidney	(10)	(3)		(10)
Inflammation, chronic	9 (90%)	2 (67%)		8 (80%)
Metaplasia, osseous	1 (10%)			
Renal tubule, mineralization	6 (60%)			3 (30%)
Urinary bladder	(10)			(10)
Calculus gross observation				1 (10%)
Inflammation, chronic	3 (30%)			1 (10%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin
(continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study				
Alimentary System				
Gallbladder	(43)	(47)	(47)	(46)
Autolysis		1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)			
Intestine large, cecum	(50)	(50)	(50)	(50)
Autolysis	1 (2%)	2 (4%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Ulcer			1 (2%)	
Intestine large, colon	(50)	(50)	(49)	(50)
Autolysis	1 (2%)	1 (2%)		1 (2%)
Intestine large, rectum	(50)	(50)	(49)	(50)
Autolysis	1 (2%)			1 (2%)
Intestine small, duodenum	(50)	(49)	(50)	(50)
Autolysis	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)			1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(50)
Autolysis	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic active		1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)
Autolysis	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Inflammation, chronic active				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Autolysis		1 (2%)		2 (4%)
Basophilic focus		2 (4%)		1 (2%)
Clear cell focus	10 (20%)	5 (10%)	5 (10%)	2 (4%)
Cyst multilocular	1 (2%)			
Eosinophilic focus	6 (12%)	8 (16%)	5 (10%)	7 (14%)
Fatty change	25 (50%)	14 (28%)	22 (44%)	24 (48%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Inflammation, chronic active	2 (4%)	4 (8%)	2 (4%)	
Mixed cell focus	1 (2%)	2 (4%)	1 (2%)	6 (12%)
Necrosis	3 (6%)	6 (12%)	3 (6%)	2 (4%)
Mesentery	(3)	(10)	(4)	(7)
Angiectasis		1 (10%)		
Fibrosis		1 (10%)	3 (75%)	7 (100%)
Hemorrhage	3 (100%)	8 (80%)	2 (50%)	1 (14%)
Inflammation, chronic active		1 (10%)	3 (75%)	4 (57%)
Necrosis		1 (10%)		3 (43%)
Pancreas	(50)	(50)	(50)	(49)
Autolysis			1 (2%)	
Cytoplasmic alteration		1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic active		2 (4%)	1 (2%)	
Acinus, atrophy			2 (4%)	
Salivary glands	(50)	(47)	(50)	(50)
Parotid gland, inflammation, chronic			4 (8%)	
Sublingual gland, inflammation, chronic	2 (4%)		1 (2%)	
Submandibular gland, inflammation, chronic	41 (82%)	33 (70%)	32 (64%)	36 (72%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Acanthosis		1 (2%)	2 (4%)	1 (2%)
Autolysis				1 (2%)
Hyperkeratosis		1 (2%)	2 (4%)	1 (2%)
Hyperplasia, basal cell			2 (4%)	1 (2%)
Inflammation, chronic active			3 (6%)	2 (4%)
Mineralization		1 (2%)		
Ulcer			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Autolysis				1 (2%)
Erosion		1 (2%)		
Inflammation, chronic active		2 (4%)		
Mineralization	1 (2%)	1 (2%)		
Tongue	(1)	(1)		
Hemorrhage	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic active	3 (6%)	3 (6%)		
Mineralization		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(49)	(49)
Hyperplasia	5 (10%)	5 (10%)	5 (10%)	2 (4%)
Adrenal gland, medulla	(50)	(42)	(42)	(49)
Hyperplasia		2 (5%)		
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia	2 (4%)	2 (4%)		
Parathyroid gland	(38)	(27)	(36)	(33)
Cyst	1 (3%)			
Pituitary gland	(50)	(49)	(50)	(50)
Pars distalis, cyst	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Thyroid gland	(50)	(49)	(49)	(50)
Autolysis				1 (2%)
Cyst		1 (2%)		
Cyst multilocular			1 (2%)	
Inflammation, chronic active	1 (2%)			1 (2%)
Follicular cell, hyperplasia	2 (4%)	1 (2%)	1 (2%)	3 (6%)
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm				1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Preputial gland	(21)	(20)	(23)	(24)
Inflammation, chronic active	13 (62%)	13 (65%)	7 (30%)	15 (63%)
Duct, dilatation	19 (90%)	18 (90%)	21 (91%)	19 (79%)
Prostate	(50)	(50)	(50)	(50)
Inflammation, chronic active	3 (6%)	1 (2%)	1 (2%)	
Epithelium, hyperplasia				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(49)
Fibrosis	2 (4%)			
Inflammation, chronic active		1 (2%)	1 (2%)	
Testes	(50)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		
Seminiferous tubule, atrophy			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Autolysis				1 (2%)
Myeloid cell, sternal, hyperplasia			1 (2%)	
Sternal, myelofibrosis				1 (2%)
Lymph node	(47)	(49)	(45)	(47)
Lumbar, hyperplasia, lymphoid		1 (2%)		
Mandibular, hyperplasia, lymphoid		1 (2%)	1 (2%)	
Mandibular, hyperplasia, plasma cell		1 (2%)		
Mediastinal, angiectasis	2 (4%)			
Mediastinal, hyperplasia, lymphoid				1 (2%)
Pancreatic, hyperplasia, lymphoid	1 (2%)			
Pancreatic, hyperplasia, plasma cell	1 (2%)			
Lymph node, mesenteric	(46)	(48)	(45)	(47)
Angiectasis	6 (13%)	3 (6%)		4 (9%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	2 (4%)	
Hyperplasia, plasma cell		1 (2%)		
Inflammation, granulomatous			1 (2%)	
Polyarteritis	1 (2%)			
Sinus, ectasia			1 (2%)	
Spleen	(50)	(50)	(50)	(49)
Angiectasis			1 (2%)	1 (2%)
Autolysis				1 (2%)
Depletion lymphoid	3 (6%)		4 (8%)	
Hematopoietic cell proliferation		3 (6%)	6 (12%)	3 (6%)
Hyperplasia, lymphoid		2 (4%)	1 (2%)	
Inflammation, granulomatous			1 (2%)	
Thymus	(39)	(47)	(42)	(37)
Cyst			3 (7%)	
Hyperplasia, lymphoid		1 (2%)		
Inflammation, chronic active			1 (2%)	
Necrosis				1 (3%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Integumentary System				
Skin	(48)	(47)	(50)	(50)
Autolysis				1 (2%)
Cyst epithelial inclusion	1 (2%)			
Parakeratosis			1 (2%)	
Ulcer			1 (2%)	
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(49)	(50)
Infarct				1 (2%)
Inflammation, chronic active		1 (2%)		
Thalamus, mineralization	39 (78%)	30 (60%)	31 (63%)	46 (92%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Infiltration cellular, histiocyte	2 (4%)	3 (6%)		1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)	
Leukocytosis			1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	2 (4%)		3 (6%)
Nose	(50)	(49)	(50)	(50)
Inflammation, acute	4 (8%)	7 (14%)	5 (10%)	4 (8%)
Trachea	(49)	(49)	(48)	(50)
Autolysis				1 (2%)
Special Senses System				
Eye	(4)	(4)	(1)	(6)
Cornea, inflammation, chronic active		1 (25%)	1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Autolysis				1 (2%)
Cyst			1 (2%)	1 (2%)
Glomerulosclerosis			1 (2%)	1 (2%)
Inflammation, chronic	47 (94%)	45 (90%)	48 (96%)	37 (74%)
Medulla, foreign body		1 (2%)		
Renal tubule, atrophy		3 (6%)		
Renal tubule, degeneration, hyaline		1 (2%)		
Renal tubule, pigmentation			1 (2%)	
Renal tubule, regeneration	1 (2%)	4 (8%)	2 (4%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Urinary System (continued)				
Urinary bladder	(50)	(50)	(50)	(50)
Autolysis	1 (2%)			1 (2%)
Calculus gross observation	2 (4%)		1 (2%)	2 (4%)
Calculus microscopic observation only		1 (2%)		3 (6%)
Fibrosis	1 (2%)			
Inflammation, chronic active	1 (2%)	1 (2%)		
Ulcer	1 (2%)			
Transitional epithelium, hyperplasia	1 (2%)			

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

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF TURMERIC OLEORESIN

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TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	10
Early deaths				
Accidental deaths	1			
Moribund	7	7	10	7
Natural deaths	3	2	7	1
Survivors				
Died last week of study	2	1		1
Terminal sacrifice	37	40	34	41
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(2)	(5)	(10)
Hepatocellular carcinoma				1 (10%)
Hepatocellular adenoma			1 (20%)	
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Uterus	(10)	(4)	(3)	(10)
Sarcoma stromal	1 (10%)			
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
Lung	(10)		(1)	(10)
Alveolar/bronchiolar adenoma			1 (100%)	
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Gallbladder	(45)	(48)	(46)	(47)
Histiocytic sarcoma, metastatic		1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(50)
Leiomyoma				1 (2%)
Intestine small, duodenum	(50)	(50)	(48)	(50)
Adenocarcinoma	1 (2%)			
Polyp adenomatous	1 (2%)			
Intestine small, ileum	(50)	(50)	(49)	(50)
Intestine small, jejunum	(50)	(50)	(48)	(50)
Liver	(50)	(50)	(51)	(50)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Hepatocellular carcinoma	7 (14%)	5 (10%)	8 (16%)	4 (8%)
Hepatocellular carcinoma, multiple			2 (4%)	2 (4%)
Hepatocellular adenoma	7 (14%)	5 (10%)	10 (20%)	8 (16%)
Hepatocellular adenoma, multiple		3 (6%)	9 (18%)	6 (12%)
Histiocytic sarcoma, metastatic		2 (4%)		1 (2%)
Pancreas	(50)	(50)	(49)	(50)
Salivary glands	(50)	(50)	(51)	(50)
Stomach, forestomach	(49)	(50)	(51)	(49)
Papilloma squamous			1 (2%)	3 (6%)
Squamous cell carcinoma			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(49)
Cardiovascular System				
Heart	(50)	(50)	(51)	(50)
Histiocytic sarcoma, metastatic		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(51)	(49)
Adenoma		1 (2%)		
Adrenal gland, medulla	(50)	(44)	(40)	(45)
Pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(50)	(50)	(49)	(47)
Adenoma				1 (2%)
Parathyroid gland	(33)	(39)	(32)	(25)
Pituitary gland	(46)	(49)	(50)	(50)
Pars distalis, adenoma		2 (4%)	4 (8%)	5 (10%)
Thyroid gland	(50)	(50)	(50)	(49)
Follicular cell, adenoma	1 (2%)	1 (2%)	2 (4%)	
General Body System				
None				
Genital System				
Ovary	(50)	(48)	(50)	(48)
Cystadenoma	1 (2%)	2 (4%)	1 (2%)	
Granulosa cell tumor benign	1 (2%)			
Hemangioma		1 (2%)		
Histiocytic sarcoma, metastatic		1 (2%)		
Luteoma				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)	2 (4%)	3 (6%)
Polyp stromal	1 (2%)	1 (2%)		
Cervix, basosquamous tumor malignant			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Sternal, histiocytic sarcoma, metastatic		2 (4%)		
Lymph node	(47)	(47)	(48)	(50)
Lumbar, histiocytic sarcoma, metastatic				1 (2%)
Mediastinal, histiocytic sarcoma, metastatic		1 (2%)		
Renal, histiocytic sarcoma, metastatic				1 (2%)
Lymph node, mesenteric	(48)	(46)	(47)	(50)
Histiocytic sarcoma, metastatic		1 (2%)		
Spleen	(49)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Thymus	(44)	(43)	(45)	(48)
Integumentary System				
Mammary gland	(45)	(48)	(49)	(48)
Adenocarcinoma		1 (2%)		
Hemangiosarcoma		1 (2%)		
Skin	(50)	(50)	(51)	(49)
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(50)	(50)	(51)	(50)
Chordoma		1 (2%)		
Skeletal muscle	(1)		(1)	(2)
Sarcoma			1 (100%)	
Back, adenocarcinoma, metastatic, uncertain primary site	1 (100%)			
Nervous System				
Brain	(50)	(50)	(51)	(50)
Meninges, sarcoma	1 (2%)			1 (2%)
Meninges, schwannoma malignant, metastatic				1 (2%)
Peripheral nerve				(1)
Schwannoma malignant				1 (100%)
Respiratory System				
Lung	(50)	(50)	(51)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	3 (6%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Histiocytic sarcoma, metastatic		2 (4%)		
Sarcoma, metastatic, skeletal muscle			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic		1 (2%)		
Trachea	(50)	(50)	(51)	(49)
Special Senses System				
Harderian gland		(2)		(1)
Adenoma		2 (100%)		1 (100%)
Urinary System				
Kidney	(50)	(50)	(51)	(50)
Histiocytic sarcoma, metastatic		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(51)	(50)
Histiocytic sarcoma		2 (4%)	2 (4%)	3 (6%)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)		
Lymphoma malignant mixed	9 (18%)	13 (26%)	12 (24%)	7 (14%)
Lymphoma malignant undifferentiated cell		2 (4%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1		2	1
2-Year study	30	33	35	33
Total primary neoplasms				
15-Month interim evaluation	1		2	1
2-Year study	37	48	62	46
Total animals with benign neoplasms				
15-Month interim evaluation			2	
2-Year study	14	18	22	21
Total benign neoplasms				
15-Month interim evaluation			2	
2-Year study	16	21	30	27
Total animals with malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	20	25	23	16
Total malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	21	27	32	19
Total animals with metastatic neoplasms				
2-Year study	3	3	4	4
Total metastatic neoplasms				
2-Year study	3	14	4	7
Total animals with malignant neoplasms of uncertain primary site				
2-Year study	1			

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm

Number of Days on Study	084	515	522	536	586	628	673	681	701	703	703	730	730	731	731	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	3121	3041	2591	3131	2641	2671	3101	2981	2668	2721	2851	2621	2661	2561	2581	2661	2663	2665	2667	2669	2670	2671	2673	2674	2671
Alimentary System																									
Esophagus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																					X				
Polyp adenomatous																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X				X	X						X	X		X	X						
Hepatocellular adenoma									X	X				X											
Mesentery																				+				+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	M	M	M	M	+	+	+	+
Pituitary gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm
(continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	278 1	279 1	281 1	284 1	286 1	305 1	306 1	307 1	311 1	315 1	283 1	288 1	289 1	290 1	291 1	292 1	293 1	294 1	295 1	296 1	297 1	299 1	302 1	303 1	308 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Polyp adenomatous							X																			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										7
Hepatocellular adenoma		X	X												X				X							7
Mesentery															+		+			+		+				7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	+	M	M	+	+	M	+	M	+	M	+	+	+	+	+	+	M	+	M	+	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma													X													1
General Body System																										
Tissue NOS																			+							1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm
(continued)

Number of Days on Study	0	5	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	8	1	2	3	8	2	7	8	0	0	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	5	2	6	6	8	3	1	1	3	3	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	3	3	2	3	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	0	5	1	6	7	1	9	6	7	8	6	6	5	5	6	6	6	6	6	7	7	7	7	7
	2	4	9	3	4	6	0	8	8	2	5	2	6	6	8	1	3	5	7	9	0	1	3	4	7
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign								X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Thymus	+	+	M	+	M	+	+	M	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Back, adenocarcinoma, metastatic, uncertain primary site							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, sarcoma													X												
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma												X													
Hepatocellular carcinoma, metastatic, liver								X	X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X					X									X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 0 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	271	279	281	284	286	305	306	307	311	315	283	288	289	290	291	292	293	294	295	296	297	299	302	303	308	Total Tissues/ Tumors
Genital System																										
Clitoral gland														+												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma					X																					1
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal														X												1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Back, adenocarcinoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, sarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X					X	X												4
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed							X		X	X											X		X		X	9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm

Number of Days on Study	206	281	467	552	599	666	681	701	718	733	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	3591	3181	3581	3551	3271	3621	3661	3401	3441	3311	3281	3291	3341	3361	3371	3391	3411	3451	3471	3481	3491	3501	3521	3541	3551
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Histiocytic sarcoma, metastatic					X																				
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									X
Hepatocellular adenoma											X														
Hepatocellular adenoma, multiple																								X	
Histiocytic sarcoma, metastatic					X	X																			
Mesentery														+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic						X																			
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	M	+	+	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																		X							
General Body System																									
Tissue NOS												+													

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm (continued)

Number of Days on Study	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	3561	3611	3613	3611	3119	3201	3221	3222	3223	3221	3225	3330	3332	3331	3341	3357	3364	3366	3367	3368	3369	3370	3371	3372	3374	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma, metastatic																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma				X																	X	X			X	5
Hepatocellular adenoma		X								X										X			X			5
Hepatocellular adenoma, multiple									X																X	3
Histiocytic sarcoma, metastatic																										2
Mesentery			+		+	+									+									+	+	7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	M	M	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma														X							X					2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
Tissue NOS																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm
(continued)

Number of Days on Study	206	281	467	552	599	666	681	701	718	733	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	3591	3181	3581	3551	3227	3362	3660	3440	3442	3331	3228	3229	3341	3361	3373	3379	3341	3445	3447	3448	3449	3550	3552	3554	3555
Genital System																									
Clitoral gland																									+
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Cystadenoma																									
Hemangioma							X																		
Histiocytic sarcoma, metastatic					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X	X																			
Polyp stromal																					X				
Hematopoietic System																									
Blood																					+				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sternal, histiocytic sarcoma, metastatic					X	X																			
Lymph node	M	+	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma, metastatic					X																				
Lymph node, mesenteric	M	M	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	M	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X									
Hemangiosarcoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																			X						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X										X			X
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma, metastatic					X	X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic					X																				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm (continued)

Number of Days on Study	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	3561	3611	3613	3611	3611	3612	3621	3622	3623	3624	3625	3630	3632	3633	3641	3657	3664	3666	3667	3681	3691	3701	3711	3721	3741	Total Tissues/ Tumors
Genital System																										
Clitoral gland							+																			2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma							X					X														2
Hemangioma																										1
Histiocytic sarcoma, metastatic																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Polyp stromal																										1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sternal, histiocytic sarcoma, metastatic																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mediastinal, histiocytic sarcoma, metastatic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma, metastatic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	48
Adenocarcinoma																										1
Hemangiosarcoma														X												1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										3
Hepatocellular carcinoma, metastatic, liver																					X					1
Histiocytic sarcoma, metastatic																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm
(continued)

Number of Days on Study	206	281	467	552	599	666	681	701	718	733	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	3591	3181	3581	3551	3271	3661	3601	3401	3421	3311	3281	3291	3341	3361	3371	3391	3411	3441	3471	3481	3491	3501	3521	3541	3551
Special Senses System																										
Eye																					+					
Harderian gland																					+					
Adenoma																					X					
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic					X																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X	X																				
Lymphoma malignant lymphocytic																			X							
Lymphoma malignant mixed				X			X		X			X	X		X	X									X	
Lymphoma malignant undifferentiated cell type			X							X																

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 2,000 ppm (continued)

Number of Days on Study	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	3561	3611	3631	3661	3911	3201	3221	3221	3231	3241	3251	3301	3331	3331	3441	3571	3641	3661	3671	3681	3691	3701	3711	3721	3741	**Total Tissues/ Tumors**
Special Senses System																										
Eye										+																2
Harderian gland										+																2
Adenoma										X																2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed		X						X					X										X	X		13
Lymphoma malignant undifferentiated cell type																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	736	
Carcass ID Number	4001	4011	4013	4016	4019	4101	4113	4115	4119	4201	4211	4221	4231	4239	4301	4315	4379	4380	4404	4425	4426	4428	4431	4432	4433	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma		X																		X	X					8
Hepatocellular carcinoma, multiple															X								X			2
Hepatocellular adenoma		X	X			X						X									X	X				10
Hepatocellular adenoma, multiple					X			X									X			X				X		9
Mesentery			+																							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Papilloma squamous																										1
Squamous cell carcinoma																								X		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	M	+	+	+	M	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	40
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	+	M	+	M	+	+	+	M	M	M	M	+	+	M	M	+	M	+	M	M	32
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma									X																X	4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma			X																							2
General Body System																										
None																										
Genital System																										
Clitoral gland																+	+		+							8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma	X																									2
Cervix, basosquamous tumor malignant																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm
(continued)

Number of Days on Study	0	0	0	4	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	1	0	3	2	3	0	6	6	6	7	0	0	0	1	2	3	3	3	3	3	3	3	3	3
	6	9	3	0	7	4	4	9	2	7	7	7	3	4	5	4	1	3	3	3	3	3	3	3	3	3
Carcass ID Number	3	3	3	3	3	3	4	3	4	3	4	3	4	4	3	4	4	3	3	3	3	3	3	3	3	3
	7	9	8	8	8	9	0	8	1	7	0	9	1	2	9	1	1	7	8	8	8	8	8	9	9	9
	8	2	5	4	2	9	2	9	6	7	8	6	1	7	3	7	2	6	1	3	6	7	8	1	4	7
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System																										
Blood																										
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X						X						
Thymus	M	+	+	+	+	M	+	+	+	+	+	+	I	M	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																										
Subcutaneous tissue, hemangiosarcoma														X												
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+															
Sarcoma											X															
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord				+																						
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										X
Hepatocellular carcinoma, metastatic, liver						X							X				X									
Sarcoma, metastatic, skeletal muscle											X															
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																	
Lymphoma malignant histiocytic								X																		
Lymphoma malignant mixed					X			X						X					X		X			X		X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 10,000 ppm
(continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	736		
Carcass ID Number	4001	4011	4031	4061	4091	4101	4131	4151	4191	4201	4221	4221	4231	4291	4301	4351	3791	3801	4241	4251	4261	4281	4311	4321	4331	Total Tissues/ Tumors
Hematopoietic System																										
Blood												+														1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, fibrosarcoma															X											1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma								X																	X	3
Hepatocellular carcinoma, metastatic, liver																										3
Sarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye					+																					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma	X																									2
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed		X						X							X				X					X		12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm

Number of Days on Study	233	449	621	662	667	701	703	703	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730
Carcass ID Number	4601	4541	4771	4451	4661	4581	4431	4621	4361	4371	4381	4391	4411	4421	4441	4461	4491	4501	4521	4531	4871	4471	4481	4551	4571
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Hepatocellular carcinoma							X								X										
Hepatocellular carcinoma, multiple				X				X																	
Hepatocellular adenoma										X				X			X								
Hepatocellular adenoma, multiple																		X			X			X	
Histiocytic sarcoma, metastatic															X										
Mesentery		+									+													+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																					X				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	M	+	+	+	+	M	+	+	+	M	M	+	+	+	+	M	M	+	I	M	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X														X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland																									
Ovary	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X	X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	732	732	732	732	732	732	732	
Carcass ID Number	463 1	465 1	467 1	470 1	471 1	473 1	474 1	475 1	482 1	483 1	484 1	486 1	489 1	490 1	492 1	493 1	494 1	495 1	496 1	561 1	461 1	468 1	469 1	472 1	478 1	480 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma			X																								1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen		X																									1
Hepatocellular carcinoma																				X				X			4
Hepatocellular carcinoma, multiple																											2
Hepatocellular adenoma		X			X													X				X		X			8
Hepatocellular adenoma, multiple							X					X		X													6
Histiocytic sarcoma, metastatic																											1
Mesentery											+																4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																									X	X	3
Stomach, glandular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Adenoma					X																						1
Parathyroid gland	+	M	+	+	+	+	M	+	+	M	+	M	M	M	M	+	M	M	M	+	+	+	M	M	M		25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma														X	X				X								5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
General Body System																											
Tissue NOS							+																				1
Genital System																											
Clitoral gland				+			+			+			+				+										5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Luteoma															X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																		3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm
(continued)

Number of Days on Study	233	449	621	662	667	701	703	703	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730
Carcass ID Number	4601	4541	4771	4451	4661	4581	4431	4621	4361	4371	4381	4391	4411	4421	4441	4461	4491	4501	4521	4531	4871	4471	4481	4551	4571	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lumbar, histiocytic sarcoma, metastatic															X											
Renal, histiocytic sarcoma, metastatic															X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle					+	+																				
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Meninges, sarcoma	X																									
Meninges, schwannoma malignant, metastatic		X																								
Peripheral nerve		+																								
Schwannoma malignant		X																								
Spinal cord					+																					
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																										
Hepatocellular carcinoma, metastatic, liver				X											X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																										
Harderian gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma														X	X											
Lymphoma malignant mixed				X	X	X								X							X	X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Turmeric Oleoresin: 50,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	732	732	732	732	732	732	732	
Carcass ID Number	463 1	465 1	467 1	470 1	471 1	473 1	474 1	475 1	482 1	483 1	484 1	486 1	489 1	490 1	492 1	493 1	494 1	495 1	561 1	561 1	568 1	569 1	572 1	578 1	580 1	**Total Tissues/ Tumors**
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lumbar, histiocytic sarcoma, metastatic																										1
Renal, histiocytic sarcoma, metastatic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, sarcoma																										1
Meninges, schwannoma malignant, metastatic																										1
Peripheral nerve																										1
Schwannoma malignant																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Special Senses System																										
Eye																+										1
Harderian gland																+										1
Adenoma																X										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	3
Lymphoma malignant mixed						X																				7

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Liver: Hepatocellular Adenoma				
Overall rate[a]	7/50 (14%)	8/50 (16%)	19/51 (37%)	14/50 (28%)
Adjusted rate[b]	17.0%	19.5%	50.9%	33.3%
Terminal rate[c]	5/39 (13%)	8/41 (20%)	16/34 (47%)	14/42 (33%)
First incidence (days)	701	729 (T)	667	729 (T)
Life table test[d]	P=0.189	P=0.539	P=0.003	P=0.100
Logistic regression test[d]	P=0.167	P=0.522	P=0.003	P=0.091
Cochran-Armitage test[d]	P=0.120			
Fisher exact test[d]		P=0.500	P=0.007	P=0.070
Liver: Hepatocellular Carcinoma				
Overall rate	7/50 (14%)	5/50 (10%)	10/51 (20%)	6/50 (12%)
Adjusted rate	16.3%	12.2%	25.2%	13.2%
Terminal rate	4/39 (10%)	5/41 (12%)	5/34 (15%)	3/42 (7%)
First incidence (days)	536	729 (T)	524	662
Life table test	P=0.422N	P=0.354N	P=0.237	P=0.451N
Logistic regression test	P=0.468N	P=0.379N	P=0.285	P=0.502N
Cochran-Armitage test	P=0.487N			
Fisher exact test		P=0.380N	P=0.314	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	13/50 (26%)	12/50 (24%)	25/51 (49%)	19/50 (38%)
Adjusted rate	30.0%	29.3%	60.7%	42.2%
Terminal rate	9/39 (23%)	12/41 (29%)	18/34 (53%)	16/42 (38%)
First incidence (days)	536	729 (T)	524	662
Life table test	P=0.268	P=0.450N	P=0.006	P=0.217
Logistic regression test	P=0.202	P=0.495N	P=0.007	P=0.159
Cochran-Armitage test	P=0.158			
Fisher exact test		P=0.500N	P=0.014	P=0.142
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	3/50 (6%)	3/51 (6%)	1/50 (2%)
Adjusted rate	10.3%	7.3%	8.8%	2.4%
Terminal rate	4/39 (10%)	3/41 (7%)	3/34 (9%)	1/42 (2%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table test	P=0.141N	P=0.473N	P=0.575N	P=0.158N
Logistic regression test	P=0.141N	P=0.473N	P=0.575N	P=0.158N
Cochran-Armitage test	P=0.162N			
Fisher exact test		P=0.500N	P=0.489N	P=0.181N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	3/51 (6%)	1/50 (2%)
Adjusted rate	12.8%	7.3%	8.8%	2.4%
Terminal rate	5/39 (13%)	3/41 (7%)	3/34 (9%)	1/42 (2%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table test	P=0.103N	P=0.328N	P=0.433N	P=0.087N
Logistic regression test	P=0.103N	P=0.328N	P=0.433N	P=0.087N
Cochran-Armitage test	P=0.120N			
Fisher exact test		P=0.357N	P=0.346N	P=0.102N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	0/46 (0%)	2/49 (4%)	4/50 (8%)	5/50 (10%)
Adjusted rate	0.0%	5.0%	11.8%	11.4%
Terminal rate	0/37 (0%)	2/40 (5%)	4/34 (12%)	4/42 (10%)
First incidence (days)	-[e]	729 (T)	729 (T)	621
Life table test	P=0.084	P=0.256	P=0.053	P=0.045
Logistic regression test	P=0.073	P=0.256	P=0.053	P=0.041
Cochran-Armitage test	P=0.065			
Fisher exact test		P=0.263	P=0.069	P=0.035
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/50 (0%)	1/51 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	2.9%	7.1%
Terminal rate	0/39 (0%)	0/41 (0%)	1/34 (3%)	3/42 (7%)
First incidence (days)	-	-	729 (T)	729 (T)
Life table test	P=0.034	-	P=0.473	P=0.135
Logistic regression test	P=0.034	-	P=0.473	P=0.135
Cochran-Armitage test	P=0.026			
Fisher exact test		-	P=0.505	P=0.121
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	2/51 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	5.9%	7.1%
Terminal rate	0/39 (0%)	0/41 (0%)	2/34 (6%)	3/42 (7%)
First incidence (days)	-	-	729 (T)	729 (T)
Life table test	P=0.066	-	P=0.209	P=0.135
Logistic regression test	P=0.066	-	P=0.209	P=0.135
Cochran-Armitage test	P=0.052			
Fisher exact test		-	P=0.252	P=0.121
All Organs: Histiocytic Sarcoma				
Overall rate	0/50 (0%)	2/50 (4%)	2/51 (4%)	3/50 (6%)
Adjusted rate	0.0%	4.3%	5.2%	7.1%
Terminal rate	0/39 (0%)	0/41 (0%)	1/34 (3%)	3/42 (7%)
First incidence (days)	-	599	662	729 (T)
Life table test	P=0.224	P=0.245	P=0.222	P=0.135
Logistic regression test	P=0.194	P=0.236	P=0.234	P=0.135
Cochran-Armitage test	P=0.192			
Fisher exact test		P=0.247	P=0.252	P=0.121
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	9/50 (18%)	16/50 (32%)	12/51 (24%)	7/50 (14%)
Adjusted rate	21.7%	35.3%	31.5%	15.3%
Terminal rate	7/39 (18%)	12/41 (29%)	9/34 (26%)	4/42 (10%)
First incidence (days)	628	467	437	622
Life table test	P=0.072N	P=0.115	P=0.224	P=0.342N
Logistic regression test	P=0.083N	P=0.083	P=0.288	P=0.380N
Cochran-Armitage test	P=0.090N			
Fisher exact test		P=0.083	P=0.331	P=0.393N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rate	9/50 (18%)	18/50 (36%)	14/51 (27%)	9/50 (18%)
Adjusted rate	21.7%	38.1%	35.8%	19.8%
Terminal rate	7/39 (18%)	12/41 (29%)	10/34 (29%)	6/42 (14%)
First incidence (days)	628	467	437	662
Life table test	P=0.120N	P=0.059	P=0.114	P=0.537N
Logistic regression test	P=0.141N	P=0.036	P=0.153	P=0.586N
Cochran-Armitage test	P=0.152N			
Fisher exact test		P=0.035	P=0.186	P=0.602N
All Organs: Benign Neoplasms				
Overall rate	14/50 (28%)	18/50 (36%)	23/51 (45%)	21/50 (42%)
Adjusted rate	33.2%	42.8%	60.0%	48.7%
Terminal rate	11/39 (28%)	17/41 (41%)	19/34 (56%)	20/42 (48%)
First incidence (days)	681	681	524	521
Life table test	P=0.315	P=0.317	P=0.020	P=0.164
Logistic regression test	P=0.261	P=0.278	P=0.029	P=0.134
Cochran-Armitage test	P=0.194			
Fisher exact test		P=0.260	P=0.057	P=0.104
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	25/50 (50%)	23/51 (45%)	17/50 (34%)
Adjusted rate	47.6%	53.1%	52.9%	34.6%
Terminal rate	15/39 (38%)	19/41 (46%)	14/34 (41%)	10/42 (24%)
First incidence (days)	522	467	437	233
Life table test	P=0.069N	P=0.427	P=0.338	P=0.175N
Logistic regression test	P=0.080N	P=0.344	P=0.474	P=0.227N
Cochran-Armitage test	P=0.084N			
Fisher exact test		P=0.344	P=0.536	P=0.206N
All Organs: Benign or Malignant Neoplasms				
Overall rate	32/50 (64%)	33/50 (66%)	35/51 (69%)	34/50 (68%)
Adjusted rate	68.1%	70.1%	79.3%	68.0%
Terminal rate	24/39 (62%)	27/41 (66%)	25/34 (74%)	26/42 (62%)
First incidence (days)	522	467	437	233
Life table test	P=0.446N	P=0.543N	P=0.159	P=0.552N
Logistic regression test	P=0.494	P=0.497	P=0.252	P=0.420
Cochran-Armitage test	P=0.433			
Fisher exact test		P=0.500	P=0.389	P=0.417

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

TABLE D4a
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	3/49	0/49	3/49
HC Yellow 4	5/50	1/50	6/50
Pentaerythritol tetranitrate	5/49	1/49	6/49
Overall Historical Incidence			
Total	110/1,113 (9.9%)	54/1,113 (4.9%)	153/1,113 (13.7%)
Standard deviation	7.2%	4.7%	8.6%
Range	0%-28%	0%-20%	3%-34%

[a] Data as of 17 December 1991

TABLE D4b
Historical Incidence of Forestomach Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	0/50	0/50	0/50
HC Yellow 4	3/50	0/50	3/50
Pentaerythritol tetranitrate	1/50	0/50	1/50
Overall Historical Incidence			
Total	25/1,121 (2.2%)	2/1,121 (0.2%)	27/1,121 (2.4%)
Standard deviation	3.2%	0.6%	3.4%
Range	0%-14%	0%-2%	0%-14%

[a] Data as of 17 December 1991

TABLE D4c
Historical Incidence of Small Intestine Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	0/50	1/50[b]	1/50
HC Yellow 4	0/50	0/50	0/50
Pentaerythritol tetranitrate	0/50	0/50	0/50
Overall Historical Incidence			
Total	8/1,121 (0.7%)	0/1,121 (0.0%)	8/1,121 (0.7%)
Standard deviation	1.4%		1.4%
Range	0%-6%		0%-6%

[a] Data as of 17 December 1991
[b] The single neoplasm incidence shown for the acetaminophen study was originally coded as a jejunal adenocarcinoma. However, current NTP historical neoplasm pooling convention recodes adenocarcinoma to carcinoma.

TABLE D4d
Historical Incidence of Pituitary Gland Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Acetaminophen	14/46	1/46	15/46
HC Yellow 4	5/42	0/42	5/42
Pentaerythritol tetranitrate	8/45	1/45	9/45
Overall Historical Incidence			
Total	183/1,065 (17.2%)	7/1,065 (0.7%)	190/1,065 (17.8%)
Standard deviation	9.9%	1.1%	10.4%
Range	2%-36%	0%-4%	2%-36%

[a] Data as of 17 December 1991

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	10
Early deaths				
Accidental deaths	1			
Moribund	7	7	10	7
Natural deaths	3	2	7	1
Survivors				
Died last week of study	2	1		1
Terminal sacrifice	37	40	34	41
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Gallbladder	(10)			(10)
Inflammation, chronic	1 (10%)			3 (30%)
Intestine large, cecum	(9)	(10)	(9)	(10)
Epithelium, pigmentation				10 (100%)
Intestine large, colon	(10)	(10)	(9)	(10)
Epithelium, pigmentation				6 (60%)
Intestine small, ileum	(10)	(10)	(9)	(9)
Epithelium, pigmentation				9 (100%)
Peyer's patch, hyperplasia	1 (10%)			
Intestine small, jejunum	(10)	(10)	(9)	(10)
Epithelium, pigmentation				2 (20%)
Liver	(10)	(2)	(5)	(10)
Clear cell focus	1 (10%)		1 (20%)	
Fatty change			2 (40%)	
Inflammation, acute	1 (10%)			1 (10%)
Inflammation, chronic				3 (30%)
Inflammation, chronic active	1 (10%)	1 (50%)	1 (20%)	
Necrosis		1 (50%)	1 (20%)	
Necrosis, coagulative	2 (20%)		2 (40%)	2 (20%)
Mesentery		(1)	(2)	
Fibrosis		1 (100%)	2 (100%)	
Hemorrhage			1 (50%)	
Inflammation, chronic		1 (100%)	2 (100%)	
Necrosis, coagulative		1 (100%)	2 (100%)	
Pancreas	(10)			(10)
Inflammation, chronic	5 (50%)			4 (40%)
Salivary glands	(10)			(10)
Submandibular gland, inflammation, chronic	9 (90%)			8 (80%)
Stomach, forestomach	(10)	(10)	(8)	(10)
Acanthosis				1 (10%)
Hyperkeratosis				1 (10%)
Hyperplasia, basal cell				1 (10%)
Inflammation, chronic active	1 (10%)			
Ulcer, acute				1 (10%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Alimentary System (continued)				
Stomach, glandular	(10)	(10)	(9)	(10)
Inflammation			1 (11%)	
Inflammation, chronic	1 (10%)	1 (10%)	3 (33%)	
Inflammation, chronic active	2 (20%)	1 (10%)		
Epithelium, hyperplasia				1 (10%)
Epithelium, pigmentation				9 (90%)
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy				1 (10%)
Endocrine System				
Adrenal gland, cortex	(10)	(1)		(10)
Hyperplasia		1 (100%)		
Pigmentation		1 (100%)		
Pituitary gland	(10)			(9)
Pars distalis, hyperplasia	2 (20%)			
Thyroid gland	(10)			(10)
C-cell, hyperplasia	1 (10%)			
General Body System				
None				
Genital System				
Clitoral gland		(5)	(1)	(2)
Cyst		1 (20%)	1 (100%)	
Cyst, multiple		4 (80%)		2 (100%)
Inflammation, acute		1 (20%)		
Inflammation, chronic		1 (20%)	1 (100%)	
Inflammation, chronic active		2 (40%)		
Pigmentation		1 (20%)	1 (100%)	
Ovary	(10)	(3)		(10)
Cyst	4 (40%)	2 (67%)		4 (40%)
Cyst, multiple	1 (10%)			
Hemorrhage	1 (10%)			
Periovarian tissue, cyst		1 (33%)		
Uterus	(10)	(4)	(3)	(10)
Hydrometra		2 (50%)	1 (33%)	2 (20%)
Endometrium, hyperplasia	10 (100%)	1 (25%)	2 (67%)	10 (100%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Bone marrow	(10)			(10)
Sternal, myelofibrosis				3 (30%)
Lymph node, mesenteric	(10)			(9)
Depletion lymphoid	1 (10%)			
Hyperplasia, lymphoid	1 (10%)			
Infiltration cellular, histiocyte	8 (80%)			5 (56%)
Pigmentation	8 (80%)			5 (56%)
Spleen	(10)	(1)		(10)
Hyperplasia, lymphoid	1 (10%)			
Integumentary System				
Skin	(10)	(2)	(4)	(10)
Epidermis, inflammation, acute			1 (25%)	
Subcutaneous tissue, inflammation, acute		1 (50%)		
Musculoskeletal System				
None				
Nervous System				
Brain	(10)			(10)
Thalamus, mineralization	9 (90%)			8 (80%)
Respiratory System				
Lung	(10)		(1)	(10)
Infiltration cellular, histiocyte			1 (100%)	
Nose	(10)			(10)
Glands, inflammation, acute	5 (50%)			1 (10%)
Nasolacrimal duct, inflammation, acute	1 (10%)			
Special Senses System				
None				
Urinary System				
Kidney	(10)			(10)
Inflammation, chronic	9 (90%)			10 (100%)
Urinary bladder	(10)			(10)
Inflammation, chronic	7 (70%)			7 (70%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study				
Alimentary System				
Gallbladder	(45)	(48)	(46)	(47)
Autolysis	2 (4%)	1 (2%)	3 (7%)	1 (2%)
Inflammation, chronic		1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(50)
Autolysis	4 (8%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Inflammation, chronic active		1 (2%)		
Intestine large, colon	(50)	(50)	(49)	(50)
Autolysis	3 (6%)	1 (2%)		
Inflammation, chronic active		1 (2%)		
Intestine large, rectum	(50)	(50)	(49)	(50)
Autolysis	3 (6%)	1 (2%)		
Inflammation, chronic active		1 (2%)		
Intestine small, duodenum	(50)	(50)	(48)	(50)
Autolysis	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid				1 (2%)
Inflammation, chronic			1 (2%)	
Intestine small, ileum	(50)	(50)	(49)	(50)
Autolysis	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Epithelium, hyperplasia			1 (2%)	
Intestine small, jejunum	(50)	(50)	(48)	(50)
Autolysis	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)			
Liver	(50)	(50)	(51)	(50)
Angiectasis	1 (2%)		1 (2%)	
Autolysis	1 (2%)			
Basophilic focus			2 (4%)	
Clear cell focus	4 (8%)	2 (4%)	2 (4%)	2 (4%)
Eosinophilic focus	2 (4%)	2 (4%)	8 (16%)	8 (16%)
Fatty change	1 (2%)	2 (4%)		
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	1 (2%)	1 (2%)		
Infarct			1 (2%)	
Inflammation, chronic		2 (4%)		
Inflammation, chronic active	25 (50%)	28 (56%)	26 (51%)	37 (74%)
Mixed cell focus	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Necrosis	2 (4%)	11 (22%)	2 (4%)	
Oval cell, hyperplasia	1 (2%)			
Mesentery	(7)	(7)	(3)	(4)
Fibrosis	6 (86%)	7 (100%)	3 (100%)	3 (75%)
Hemorrhage				1 (25%)
Inflammation, chronic		4 (57%)		
Inflammation, chronic active			2 (67%)	3 (75%)
Necrosis	5 (71%)	6 (86%)	3 (100%)	3 (75%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(50)	(49)	(50)
Autolysis	1 (2%)			
Cyst		2 (4%)	1 (2%)	
Cytoplasmic alteration		3 (6%)	2 (4%)	
Fibrosis	1 (2%)		1 (2%)	
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)	
Acinus, atrophy	2 (4%)		1 (2%)	
Salivary glands	(50)	(50)	(51)	(50)
Parotid gland, atrophy				1 (2%)
Parotid gland, inflammation, chronic	3 (6%)			3 (6%)
Sublingual gland, inflammation, chronic	7 (14%)		2 (4%)	4 (8%)
Submandibular gland, atrophy		2 (4%)		
Submandibular gland, inflammation, chronic	42 (84%)	34 (68%)	31 (61%)	42 (84%)
Stomach, forestomach	(49)	(50)	(51)	(49)
Acanthosis	1 (2%)		2 (4%)	3 (6%)
Hyperkeratosis	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Inflammation, chronic active	1 (2%)			3 (6%)
Stomach, glandular	(50)	(50)	(50)	(49)
Autolysis	1 (2%)	1 (2%)		
Inflammation, chronic active		1 (2%)		1 (2%)
Mineralization		3 (6%)		2 (4%)
Necrosis	1 (2%)		1 (2%)	
Epithelium, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(51)	(50)
Cardiomyopathy			1 (2%)	
Fibrosis			1 (2%)	
Inflammation, chronic active	7 (14%)	4 (8%)	3 (6%)	1 (2%)
Mineralization		1 (2%)		
Endothelium, hyperplasia				1 (2%)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(51)	(49)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		
Adrenal gland, medulla	(50)	(44)	(40)	(45)
Hyperplasia		3 (7%)		
Islets, pancreatic	(50)	(50)	(49)	(47)
Autolysis	1 (2%)			
Hyperplasia	1 (2%)			1 (2%)
Parathyroid gland	(33)	(39)	(32)	(25)
Inflammation, chronic		1 (3%)		1 (4%)
Pituitary gland	(46)	(49)	(50)	(50)
Pars distalis, angiectasis	3 (7%)	4 (8%)		3 (6%)
Pars distalis, cyst		1 (2%)		1 (2%)
Pars distalis, hyperplasia	8 (17%)	11 (22%)	7 (14%)	2 (4%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(49)
Cyst		2 (4%)		
Cyst multilocular			1 (2%)	
Inflammation, chronic active	4 (8%)	3 (6%)	2 (4%)	9 (18%)
Polyarteritis			1 (2%)	
Ultimobranchial cyst			1 (2%)	2 (4%)
C-cell, hyperplasia		1 (2%)		2 (4%)
Follicular cell, hyperplasia	5 (10%)	8 (16%)	7 (14%)	16 (33%)
General Body System				
Tissue NOS	(1)	(1)		(1)
Hemorrhage				1 (100%)
Genital System				
Clitoral gland	(1)	(2)	(8)	(5)
Pigmentation	1 (100%)	2 (100%)	6 (75%)	4 (80%)
Duct, dilatation		1 (50%)	2 (25%)	4 (80%)
Ovary	(50)	(48)	(50)	(48)
Abscess	1 (2%)			
Angiectasis			1 (2%)	
Cyst	21 (42%)	18 (38%)	18 (36%)	18 (38%)
Hemorrhage	11 (22%)	2 (4%)	4 (8%)	3 (6%)
Periovarian tissue, inflammation, chronic		1 (2%)		
Periovarian tissue, necrosis	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Angiectasis	3 (6%)		2 (4%)	1 (2%)
Hydrometra	12 (24%)	11 (22%)	13 (26%)	22 (44%)
Infarct		1 (2%)		
Metaplasia, osseous		1 (2%)		
Thrombus	1 (2%)			1 (2%)
Cervix, inflammation, acute	1 (2%)			
Endometrium, hyperplasia	45 (90%)	45 (90%)	38 (76%)	40 (80%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myeloid cell, sternal, hyperplasia		1 (2%)		
Sternal, myelofibrosis	36 (72%)	32 (64%)	36 (72%)	34 (68%)
Lymph node	(47)	(47)	(48)	(50)
Mandibular, hyperplasia, lymphoid	1 (2%)	1 (2%)		2 (4%)
Mandibular, inflammation, chronic active	2 (4%)			
Mandibular, pigmentation		1 (2%)		
Mediastinal, fibrosis	1 (2%)			
Mediastinal, hyperplasia, lymphoid	2 (4%)			
Mediastinal, inflammation, chronic active	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node (continued)	(47)	(47)	(48)	(50)
Pancreatic, fibrosis	1 (2%)			
Pancreatic, hyperplasia, lymphoid			1 (2%)	
Pancreatic, inflammation, chronic active	1 (2%)			
Renal, angiectasis	1 (2%)			
Lymph node, mesenteric	(48)	(46)	(47)	(50)
Angiectasis	1 (2%)		1 (2%)	1 (2%)
Autolysis	1 (2%)			
Depletion lymphoid			1 (2%)	1 (2%)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	3 (7%)	2 (4%)	
Inflammation, chronic active	1 (2%)			
Thrombus			1 (2%)	
Spleen	(49)	(50)	(50)	(50)
Depletion lymphoid	1 (2%)	2 (4%)	1 (2%)	
Fibrosis	1 (2%)		1 (2%)	
Hematopoietic cell proliferation	7 (14%)	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	2 (4%)	4 (8%)	1 (2%)	5 (10%)
Inflammation, granulomatous			1 (2%)	
Endothelium, hyperplasia				1 (2%)
Thymus	(44)	(43)	(45)	(48)
Autolysis	1 (2%)			
Depletion lymphoid	1 (2%)		1 (2%)	
Hyperplasia, lymphoid			1 (2%)	
Inflammation, chronic active	1 (2%)			
Necrosis			1 (2%)	
Integumentary System				
Mammary gland	(45)	(48)	(49)	(48)
Hyperplasia	2 (4%)		1 (2%)	1 (2%)
Skin	(50)	(50)	(51)	(49)
Cyst epithelial inclusion			1 (2%)	
Sebaceous gland, hyperplasia				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(51)	(50)
Joint, tarsal, hyperostosis			1 (2%)	
Nervous System				
Brain	(50)	(50)	(51)	(50)
Autolysis	1 (2%)			
Thalamus, mineralization	41 (82%)	25 (50%)	29 (57%)	42 (84%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Turmeric Oleoresin (continued)

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(51)	(50)
Infiltration cellular, histiocyte	1 (2%)		2 (4%)	
Inflammation, chronic active		2 (4%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)	
Alveolar epithelium, hyperplasia				1 (2%)
Nose	(50)	(50)	(50)	(50)
Inflammation, acute	9 (18%)	15 (30%)	16 (32%)	11 (22%)
Vomeronasal organ, inflammation, acute			1 (2%)	
Special Senses System				
Eye	(1)	(2)	(1)	(1)
Cornea, inflammation, chronic active		1 (50%)		
Lens, cataract			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(51)	(50)
Autolysis	1 (2%)			
Glomerulosclerosis		1 (2%)		
Hemorrhage				1 (2%)
Inflammation, chronic	47 (94%)	40 (80%)	45 (88%)	47 (94%)
Metaplasia, osseous		2 (4%)		1 (2%)
Papilla, necrosis			1 (2%)	
Renal tubule, atrophy			1 (2%)	
Renal tubule, degeneration, hyaline		3 (6%)		
Renal tubule, regeneration	2 (4%)	3 (6%)	4 (8%)	1 (2%)
Transitional epithelium, hyperplasia			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Autolysis	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active		1 (2%)		
Polyarteritis	1 (2%)			

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

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Turmeric oleoresin was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of turmeric oleoresin. 333 μg/plate was selected as the high dose; higher doses were toxic. All trials were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS TEST PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Turmeric oleoresin was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of turmeric oleoresin; the high dose was 16 μg/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with turmeric oleoresin in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing turmeric oleoresin was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with turmeric oleoresin, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no turmeric oleoresin, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at

two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P \leq 0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with turmeric oleoresin for 10 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 turmeric oleoresin and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

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

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose-response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) are considered weak evidence for a positive response; significant differences for two or more doses indicate the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose results in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

RESULTS

Turmeric oleoresin (1 to 333 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 when tested in a preincubation protocol with and without S9 (Table E1; Mortelmans *et al.,* 1986). In cytogenetic tests with cultured Chinese hamster ovary cells, turmeric oleoresin induced small but significant increases in SCEs (Table E2) and chromosomal Abs (Table E3). No evidence of cell cycle delay was noted in either test. In the SCE test, a weakly positive response was observed in the first trial without S9, but this was not repeated in a second trial conducted with the same concentrations of test chemical (0.16 to 5.00 μg/mL). With S9, the results of the first trial were questionable due to the absence of a dose-response, but the second trial was clearly positive, with significant increases in SCEs seen at the two highest doses (1.60 and 5.00 μg/mL). In the Abs test, small increases in the percent cells with Abs were noted at the highest dose tested (16.00 μg/mL) in each of two trials conducted in the absence of S9. With S9, results of a single trial using a top concentration of 10 μg/mL were negative.

TABLE E1
Mutagenicity of Turmeric Oleoresin in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	118 ± 12.3	78 ± 3.4	111 ± 1.8	95 ± 5.3	105 ± 8.5	99 ± 0.3
	1	105 ± 5.7	99 ± 5.5				
	3	105 ± 1.5	110 ± 6.2	100 ± 9.0	126 ± 6.7	108 ± 2.9	103 ± 6.7
	10	104 ± 11.3	93 ± 2.0	86 ± 3.2	102 ± 1.7	107 ± 4.7	108 ± 2.9
	33	110 ± 12.7	106 ± 10.4	103 ± 6.1	121 ± 6.4	116 ± 14.5	101 ± 1.5
	100	99 ± 6.2	95 ± 6.7	97 ± 6.7	106 ± 4.4	87 ± 3.5	128 ± 4.3
	333			90 ± 3.4	99 ± 3.6	72 ± 3.4	133 ± 7.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		383 ± 14.9	208 ± 16.4	1,784 ± 26.1	1,024 ± 61.8	922 ± 112.2	438 ± 5.6
TA1535	0	36 ± 1.9	20 ± 3.2	11 ± 2.1	7 ± 0.6	13 ± 3.5	7 ± 0.7
	1	38 ± 0.9	25 ± 4.8				
	3	34 ± 3.9	26 ± 7.5	9 ± 1.3	11 ± 1.9	9 ± 2.7	9 ± 2.3
	10	35 ± 1.0	26 ± 0.6	9 ± 2.2	6 ± 0.9	8 ± 0.9	6 ± 1.2
	33	29 ± 4.7	25 ± 1.3	11 ± 2.9	5 ± 1.8	8 ± 0.3	7 ± 0.7
	100	33 ± 3.3	22 ± 3.0	9 ± 3.0	5 ± 0.9	10 ± 2.2	10 ± 2.8
	333			8 ± 2.5	7 ± 0.9	6 ± 1.8	10 ± 3.4
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		395± 21.7	250 ± 13.5	492 ± 17.2	351 ± 10.4	211 ± 18.1	158 ± 11.5
TA1537	0	4 ± 0.9	5 ± 0.0	9 ± 0.9	5 ± 1.0	7 ± 0.3	4 ± 0.9
	1	5 ± 1.5	7 ± 1.2				
	3	6 ± 1.2	4 ± 0.7	7 ± 1.8	5 ± 0.6	5 ± 0.6	5 ± 1.2
	10	6 ± 1.0	5 ± 1.9	8 ± 1.2	5 ± 1.2	4 ± 0.7	6 ± 1.7
	33	4 ± 0.9	6 ± 2.2	7 ± 2.4	6 ± 1.5	7 ± 1.5	7 ± 0.7
	100	4 ± 1.5	4 ± 0.3	7 ± 0.3	7 ± 1.3	6 ± 1.2	8 ± 4.2
	333			7 ± 1.7	7 ± 0.9	6 ± 1.5	5 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		186 ± 19.4	157 ± 28.2	408 ± 11.7	354 ± 22.2	132 ± 20.3	114 ± 5.7
TA98	0	21 ± 1.5	16 ± 1.2	36 ± 2.5	36 ± 3.1	23 ± 2.3	20 ± 1.3
	1	18 ± 1.9	11 ± 3.2				
	3	18 ± 1.2	10 ± 2.6	30 ± 5.2	28 ± 2.0	31 ± 2.6	26 ± 5.2
	10	16 ± 2.4	10 ± 3.0	29 ± 1.2	24 ± 3.3	34 ± 3.8	27 ± 5.3
	33	19 ± 4.4	10 ± 2.1	28 ± 1.5	23 ± 2.2	35 ± 2.2	19 ± 3.5
	100	18 ± 1.5	11 ± 1.5	28 ± 5.2	26 ± 5.7	27 ± 3.8	20 ± 4.6
	333			24 ± 3.5	33 ± 4.8	25 ± 2.6	38 ± 2.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		475 ± 5.4	325 ± 9.7	1,629 ± 25.7	948 ± 61.4	867 ± 11.9	386 ± 14.6

[a] Study performed at SRI International. The detailed protocol and these data are presented in Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± standard error from three plates.
[c] 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, the positive controls were 4-nitro-*o*-phenylenediamine (TA98), sodium azide (TA100 and TA1535), and 9-aminoacridine (TA1537).

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Turmeric Oleoresin[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide								
		50	1,047	383	0.36	7.7	26.0	
Mitomycin-C								
	0.0008	50	1,050	509	0.48	10.2	26.0	32.52
	0.0050	10	210	289	1.37	28.9	26.0	276.21
Turmeric oleoresin								
	0.16	50	1,048	415	0.39	8.3	26.0	8.25
	0.50	50	1,042	417	0.40	8.3	26.0	9.40
	1.60	50	1,048	437	0.41	8.7	26.0	13.99
	5.00	50	1,049	488	0.46	9.8	26.0	27.17*
								P<0.001[c]
Trial 2								
Summary: Negative								
Dimethylsulfoxide								
		50	1,051	460	0.43	9.2	26.0	
Mitomycin-C								
	0.0005	50	1,049	559	0.53	11.2	26.0	21.75
	0.0050	210	10	261	1.24	26.1	26.0	183.97
Turmeric oleoresin								
	0.16	50	1,050	448	0.42	9.0	26.0	-2.52
	0.50	50	1,049	435	0.41	8.7	26.0	-5.25
	1.60	50	1,045	456	0.43	9.1	26.0	-0.30
	5.00	50	1,046	542	0.51	10.8	26.0	18.39
								P=0.005

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Turmeric Oleoresin
(continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)
+S9								
Trial 1								
Summary: Questionable								
Dimethylsulfoxide		50	1,049	434	0.41	8.7	26.0	
Cyclophosphamide	0.10	50	1,049	595	0.56	11.9	26.0	37.10
	0.60	10	209	251	1.20	25.1	26.0	190.28
Turmeric oleoresin	0.16	50	1,049	522	0.49	10.4	26.0	20.28*
	0.50	50	1,050	457	0.43	9.1	26.0	5.20
	1.60	50	1,050	497	0.47	9.9	26.0	14.41
	5.00	50	1,050	493	0.46	9.9	26.0	13.49
								P=0.093
Trial 2								
Summary: Positive								
Negative		50	1,050	391	0.37	7.8	26.0	
Cyclophosphamide	0.10	50	1,049	530	0.50	10.6	26.0	35.68
	0.60	10	211	237	1.12	23.7	26.0	201.63
Turmeric oleoresin	0.16	50	1,050	460	0.43	9.2	26.0	17.65
	0.50	50	1,051	427	0.40	8.5	26.0	9.10
	1.60	50	1,049	484	0.46	9.7	26.0	23.90*
	5.00	50	1,048	482	0.45	9.6	26.0	23.51*
								P=0.001

* Positive (≤0.01)
[a] Study performed at Environmental Health Research & Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. The detailed protocol is presented in Galloway *et al.* (1987).
[b] SCE's/chromosome of culture exposed to turmeric oleoresin relative to those of culture exposed to solvent.
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Turmeric Oleoresin[a]

-S9					+S9				
Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Trial 1 - Harvest time: 12.0 hours Summary: Weak positive					**Trial 1** - Harvest time: 13.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	1	0.01	0.5		200	5	0.03	1.5
Mitomycin-C					Cyclophosphamide				
0.0625	200	50	0.25	20.5	2.5	200	36	0.18	16.0
0.2500	50	20	0.40	32.0	7.5	50	25	0.50	42.0
Turmeric oleoresin					Turmeric oleoresin				
5.0	200	1	0.01	0.5	3.0	200	5	0.03	2.0
10.0	200	2	0.01	1.0	5.0	200	3	0.02	1.5
16.0	200	7	0.04	3.5*	10.0	200	4	0.02	2.0
				P=0.006[b]					P=0.396
Trial 2 - Harvest time: 12.0 hours Summary: Weak positive									
Dimethylsulfoxide									
	200	1	0.01	0.5					
Mitomycin-C									
0.0625	200	30	0.15	15.0					
0.2500	50	19	0.38	36.0					
Turmeric oleoresin									
5.0	200	2	0.01	1.0					
10.0	200	3	0.02	1.5					
16.0	200	8	0.04	4.0*					
				P=0.005					

* Significant increase ($P \leq 0.05$)
[a] Study performed at Environmental Health Research & Testing, Inc. Abs = aberrations. The detailed protocol is presented in Galloway *et al.* (1987).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.

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

TABLE F1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Turmeric Oleoresin 232

TABLE F2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin 233

TABLE F3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Turmeric Oleoresin 234

TABLE F4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin 235

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Turmeric Oleoresin[a]

	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
n	10	10	9	10	10	10
Necropsy body wt	349 ± 5	350 ± 5	343 ± 6	352 ± 8	345 ± 7	335 ± 6
Brain						
Absolute	1.900 ± 0.038	1.926 ± 0.027	1.933 ± 0.025[b]	1.918 ± 0.024	1.929 ± 0.017	1.929 ± 0.023
Relative	5.46 ± 0.13	5.51 ± 0.11	5.65 ± 0.11[b]	5.47 ± 0.10	5.61 ± 0.13	5.78 ± 0.09
Heart						
Absolute	0.959 ± 0.040[c]	0.961 ± 0.029	0.957 ± 0.019	0.954 ± 0.019	0.930 ± 0.020	0.927 ± 0.034
Relative	2.75 ± 0.09[c]	2.75 ± 0.08	2.79 ± 0.03	2.72 ± 0.06	2.70 ± 0.06	2.77 ± 0.07
R. Kidney						
Absolute	1.008 ± 0.029	1.028 ± 0.019	1.039 ± 0.022[b]	1.035 ± 0.017	1.008 ± 0.025	0.973 ± 0.035
Relative	2.89 ± 0.07	2.94 ± 0.06	3.03 ± 0.05[b]	2.95 ± 0.05	2.92 ± 0.06	2.90 ± 0.07
Liver						
Absolute	12.276 ± 0.279	12.079 ± 0.193	13.606 ± 0.187*[b]	13.677 ± 0.369**	13.116 ± 0.407	12.530 ± 0.268
Relative	35.19 ± 0.52	34.60 ± 0.80	39.74 ± 0.68**[b]	38.89 ± 0.54**	37.99 ± 0.67**	37.47 ± 0.64**
Lungs						
Absolute	1.415 ± 0.053[c]	1.602 ± 0.131	1.461 ± 0.067	1.363 ± 0.042	1.352 ± 0.056	1.375 ± 0.064
Relative	4.06 ± 0.15[c]	4.59 ± 0.40	4.25 ± 0.14	3.89 ± 0.14	3.92 ± 0.16	4.10 ± 0.17
R. Testis						
Absolute	1.427 ± 0.015	1.475 ± 0.024	1.460 ± 0.028	1.502 ± 0.022	1.504 ± 0.027	1.448 ± 0.032
Relative	4.09 ± 0.04	4.22 ± 0.08	4.26 ± 0.07	4.28 ± 0.07*	4.37 ± 0.07**	4.33 ± 0.05**
Thymus						
Absolute	0.275 ± 0.019[c]	0.291 ± 0.020	0.277 ± 0.025	0.279 ± 0.018	0.274 ± 0.013	0.264 ± 0.018
Relative	0.79 ± 0.05[c]	0.83 ± 0.05	0.80 ± 0.06	0.80 ± 0.06	0.79 ± 0.03	0.79 ± 0.05
Female						
n	10	10	10	10	10	10
Necropsy body wt	195 ± 3	203 ± 2	197 ± 3	201 ± 3	196 ± 3	191 ± 2
Brain						
Absolute	1.826 ± 0.032[c]	1.822 ± 0.022	1.767 ± 0.017	1.822 ± 0.025	1.800 ± 0.022	1.790 ± 0.018
Relative	9.42 ± 0.18[c]	8.98 ± 0.13	8.98 ± 0.11	9.06 ± 0.16	9.19 ± 0.16	9.38 ± 0.13
Heart						
Absolute	0.629 ± 0.015	0.632 ± 0.017	0.599 ± 0.012	0.605 ± 0.011	0.577 ± 0.007**	0.572 ± 0.012**
Relative	3.23 ± 0.07	3.11 ± 0.08	3.04 ± 0.07	3.01 ± 0.06*	2.94 ± 0.05**	3.00 ± 0.07**
R. Kidney						
Absolute	0.637 ± 0.009[c]	0.641 ± 0.009	0.617 ± 0.008	0.625 ± 0.014	0.601 ± 0.007*	0.601 ± 0.015*
Relative	3.28 ± 0.05[c]	3.16 ± 0.03	3.13 ± 0.05	3.10 ± 0.05*	3.06 ± 0.04*	3.14 ± 0.07*
Liver						
Absolute	6.450 ± 0.146	6.914 ± 0.114*	7.153 ± 0.158**	7.554 ± 0.192**	7.457 ± 0.118**	7.204 ± 0.124**
Relative	33.05 ± 0.50	34.07 ± 0.53	36.31 ± 0.64**	37.51 ± 0.83**	38.02 ± 0.52**	37.70 ± 0.45**
Lungs						
Absolute	1.110 ± 0.052	1.075 ± 0.043	0.950 ± 0.024**	0.973 ± 0.039*	0.921 ± 0.030**	0.960 ± 0.039**[c]
Relative	5.70 ± 0.27	5.29 ± 0.19	4.83 ± 0.11**	4.83 ± 0.18**	4.71 ± 0.18**	5.05 ± 0.20**[c]
Thymus						
Absolute	0.208 ± 0.005[c]	0.245 ± 0.012	0.228 ± 0.017	0.229 ± 0.013	0.222 ± 0.015	0.218 ± 0.013
Relative	1.07 ± 0.04[c]	1.21 ± 0.06	1.16 ± 0.08	1.14 ± 0.07	1.14 ± 0.09	1.14 ± 0.07

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=10
[c] n=9

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Male				
n	10	10	10	9
Necropsy body wt	479 ± 10	478 ± 8	477 ± 6	466 ± 10
Brain				
Absolute	2.127 ± 0.021	2.108 ± 0.015	2.123 ± 0.020	2.103 ± 0.014
Relative	4.46 ± 0.10	4.42 ± 0.06	4.45 ± 0.04	4.53 ± 0.11
R. Kidney				
Absolute	1.524 ± 0.028	1.542 ± 0.035	1.514 ± 0.015	1.502 ± 0.055
Relative	3.19 ± 0.07	3.22 ± 0.05	3.18 ± 0.03	3.21 ± 0.06
Liver				
Absolute	17.082 ± 0.606	17.546 ± 0.563	18.175 ± 0.355	17.189 ± 0.527
Relative	35.73 ± 1.17	36.63 ± 0.70	38.14 ± 0.75	36.85 ± 0.79
Female				
n	10	10	10	9
Necropsy body wt	311 ± 6	318 ± 6	305 ± 7	277 ± 7**
Brain				
Absolute	1.943 ± 0.015	1.883 ± 0.038	1.921 ± 0.017	1.921 ± 0.028
Relative	6.26 ± 0.12	5.93 ± 0.07	6.33 ± 0.15	6.98 ± 0.20**
R. Kidney				
Absolute	0.965 ± 0.017	0.919 ± 0.013	0.954 ± 0.023	0.914 ± 0.027
Relative	3.10 ± 0.03	2.90 ± 0.04	3.13 ± 0.05	3.32 ± 0.13*
Liver				
Absolute	10.560 ± 0.331	10.451 ± 0.233	11.475 ± 0.278*	11.312 ± 0.245*
Relative	33.89 ± 0.70	32.93 ± 0.68	37.64 ± 0.36**	40.99 ± 0.90**

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

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Turmeric Oleoresin[a]

	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
n	9	10	10	10	10	10
Necropsy body wt	32.3 ± 0.9	33.0 ± 0.8	32.9 ± 0.6	32.7 ± 0.9	32.6 ± 0.5	33.8 ± 0.6
Brain						
Absolute	0.459 ± 0.010	0.464 ± 0.007	0.461 ± 0.003	0.461 ± 0.010	0.456 ± 0.006	0.461 ± 0.003
Relative	14.24 ± 0.35	14.11 ± 0.24	14.06 ± 0.21	14.19 ± 0.44	14.00 ± 0.28	13.69 ± 0.29
Heart						
Absolute	0.154 ± 0.005	0.168 ± 0.005	0.155 ± 0.004	0.158 ± 0.004	0.153 ± 0.005	0.149 ± 0.002[b]
Relative	4.77 ± 0.12	5.12 ± 0.17	4.74 ± 0.17	4.83 ± 0.10	4.68 ± 0.12	4.43 ± 0.05[b]
R. Kidney						
Absolute	0.256 ± 0.012	0.281 ± 0.008	0.269 ± 0.005	0.258 ± 0.008	0.257 ± 0.008	0.249 ± 0.005
Relative	7.88 ± 0.21	8.57 ± 0.29	8.22 ± 0.26	7.91 ± 0.13	7.89 ± 0.20	7.38 ± 0.12
Liver						
Absolute	1.581 ± 0.038	1.673 ± 0.054	1.904 ± 0.051**	1.713 ± 0.067**	1.887 ± 0.054**	1.856 ± 0.070**
Relative	49.03 ± 1.05	50.68 ± 0.88	58.21 ± 2.35**	52.46 ± 1.68**	57.88 ± 1.42**	54.91 ± 1.64**
Lungs						
Absolute	0.222 ± 0.006	0.223 ± 0.008	0.222 ± 0.012	0.216 ± 0.012	0.186 ± 0.008*	0.195 ± 0.008*[b]
Relative	6.89 ± 0.24	6.76 ± 0.21	6.78 ± 0.43	6.64 ± 0.36	5.70 ± 0.23*	5.82 ± 0.20*[b]
R. Testis						
Absolute	0.116 ± 0.004	0.109 ± 0.003	0.118 ± 0.003	0.115 ± 0.002	0.113 ± 0.003[b]	0.117 ± 0.002[b]
Relative	3.58 ± 0.08	3.31 ± 0.08	3.61 ± 0.12	3.54 ± 0.09	3.44 ± 0.08[b]	3.50 ± 0.11[b]
Thymus						
Absolute	0.040 ± 0.005	0.038 ± 0.005	0.038 ± 0.003	0.033 ± 0.003	0.028 ± 0.001[b]	0.037 ± 0.004
Relative	1.23 ± 0.13	1.15 ± 0.15	1.14 ± 0.08	1.01 ± 0.07	0.86 ± 0.05	1.09 ± 0.10
Female						
n	10	10	10	10	9	10
Necropsy body wt	24.8 ± 0.8	26.0 ± 1.1	26.1 ± 1.1	26.1 ± 0.9	25.3 ± 0.7	25.5 ± 0.7
Brain						
Absolute	0.459 ± 0.010	0.472 ± 0.007	0.460 ± 0.012[b]	0.470 ± 0.012	0.469 ± 0.006	0.460 ± 0.006
Relative	18.73 ± 0.70	18.36 ± 0.54	18.25 ± 0.67[b]	18.06 ± 0.42	18.56 ± 0.37	18.11 ± 0.41
Heart						
Absolute	0.121 ± 0.004	0.123 ± 0.004	0.117 ± 0.004	0.120 ± 0.005	0.113 ± 0.007	0.121 ± 0.003
Relative	4.92 ± 0.15	4.76 ± 0.16	4.54 ± 0.16	4.61 ± 0.15	4.46 ± 0.24	4.74 ± 0.14
R. Kidney						
Absolute	0.170 ± 0.003	0.172 ± 0.004	0.165 ± 0.006	0.169 ± 0.005	0.161 ± 0.004	0.159 ± 0.004
Relative	6.91 ± 0.17	6.71 ± 0.24	6.36 ± 0.16*	6.50 ± 0.12*	6.37 ± 0.12*	6.25 ± 0.12**
Liver						
Absolute	1.192 ± 0.028	1.318 ± 0.024	1.372 ± 0.053*	1.448 ± 0.048**	1.544 ± 0.052**	1.526 ± 0.077**
Relative	48.36 ± 1.19	51.56 ± 2.38	52.71 ± 0.68	55.84 ± 2.41**	60.98 ± 1.63**	59.72 ± 2.51**
Lungs						
Absolute	0.194 ± 0.005	0.197 ± 0.008	0.189 ± 0.006	0.190 ± 0.011	0.190 ± 0.008	0.181 ± 0.009
Relative	7.86 ± 0.20	7.63 ± 0.28	7.32 ± 0.34	7.27 ± 0.38	7.51 ± 0.27	7.10 ± 0.35
Thymus						
Absolute	0.047 ± 0.004	0.040 ± 0.003	0.046 ± 0.002	0.044 ± 0.006	0.036 ± 0.004	0.042 ± 0.005
Relative	1.88 ± 0.14	1.54 ± 0.10	1.78 ± 0.09	1.67 ± 0.20	1.43 ± 0.15	1.64 ± 0.18

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin[a]

	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Male				
n	9	9	9	9
Necropsy body wt	47.0 ± 1.0	47.2 ± 0.7	48.6 ± 0.9	45.2 ± 1.4
Brain				
Absolute	0.460 ± 0.005	0.461 ± 0.006	0.464 ± 0.005	0.465 ± 0.009
Relative	9.82 ± 0.25	9.77 ± 0.17	9.57 ± 0.17	10.35 ± 0.33
R. Kidney				
Absolute	0.366 ± 0.009	0.377 ± 0.013	0.351 ± 0.004	0.327 ± 0.008**
Relative	7.79 ± 0.17	7.98 ± 0.28	7.24 ± 0.15	7.27 ± 0.18
Liver				
Absolute	2.006 ± 0.076	2.222 ± 0.126	2.847 ± 0.240**	2.655 ± 0.221**
Relative	42.58 ± 1.06	46.85 ± 2.09	58.99 ± 5.61**	58.08 ± 3.54**
Female				
n	10	10	9	10
Necropsy body wt	45.0 ± 1.4	42.4 ± 1.5	44.1 ± 1.2	38.3 ± 1.2**
Brain				
Absolute	0.478 ± 0.004	0.477 ± 0.004	0.478 ± 0.006	0.482 ± 0.004
Relative	10.70 ± 0.34	11.42 ± 0.48	10.92 ± 0.39	12.70 ± 0.42**
R. Kidney				
Absolute	0.223 ± 0.005	0.224 ± 0.004	0.225 ± 0.005	0.231 ± 0.006
Relative	4.99 ± 0.18	5.35 ± 0.23	5.15 ± 0.19	6.07 ± 0.20*
Liver				
Absolute	1.561 ± 0.033	1.587 ± 0.036	1.919 ± 0.081**	1.907 ± 0.041**
Relative	34.83 ± 0.81	37.74 ± 1.08	43.53 ± 1.19**	50.13 ± 1.55**

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

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1 Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Turmeric Oleoresin 238

TABLE G2 Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin 242

TABLE G3 Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Turmeric Oleoresin 244

TABLE G4 Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin 248

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Turmeric Oleoresin[a]

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
Hematology						
n	10	10	10	10	10	10
Hematocrit (%)	47.1 ± 0.8	48.1 ± 1.1	46.9 ± 1.5	48.6 ± 1.0	47.7 ± 0.9	46.3 ± 0.8
Hemoglobin (g/dL)	18.0 ± 0.3	17.9 ± 0.3	18.2 ± 0.4	17.6 ± 0.3	17.6 ± 0.3	17.7 ± 0.3
Erythrocytes ($10^6/\mu L$)	9.07 ± 0.41	9.14 ± 0.45	8.98 ± 0.39	9.21 ± 0.29	9.06 ± 0.30	9.40 ± 0.20
Mean cell volume (fL)	52.8 ± 2.6	53.5 ± 2.1	52.9 ± 2.3	51.3 ± 1.1[b]	53.0 ± 1.3	48.7 ± 0.3[b]
Mean cell hemoglobin (pg)	20.3 ± 1.1	19.9 ± 0.7	20.5 ± 0.9	18.7 ± 0.4[b]	19.6 ± 0.6	18.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)	38.2 ± 0.4	37.4 ± 0.7	38.8 ± 0.5	36.3 ± 0.4	37.0 ± 0.7	38.3 ± 0.5
Leukocytes ($10^3/\mu L$)	5.81 ± 0.20	5.85 ± 0.41	5.24 ± 0.20	5.31 ± 0.27	5.50 ± 0.17	5.53 ± 0.25
Segmented neutrophils ($10^3/\mu L$)	1.08 ± 0.11	1.03 ± 0.10	0.99 ± 0.10	1.34 ± 0.18	1.35 ± 0.06	1.56 ± 0.17*
Lymphocytes ($10^3/\mu L$)	4.31 ± 0.18	4.59 ± 0.35	3.98 ± 0.20	3.70 ± 0.21	3.93 ± 0.17	3.75 ± 0.25
Monocytes ($10^3/\mu L$)	0.24 ± 0.03	0.19 ± 0.03	0.19 ± 0.03	0.19 ± 0.04	0.17 ± 0.04	0.16 ± 0.04
Eosinophils ($10^3/\mu L$)	0.07 ± 0.02	0.05 ± 0.01	0.08 ± 0.02	0.07 ± 0.02	0.04 ± 0.02	0.03 ± 0.01[b]
Nucleated erythrocytes/100 leukocytes	1.10 ± 0.38	1.00 ± 0.33	0.90 ± 0.35	0.70 ± 0.26	1.10 ± 0.50	1.60 ± 0.43
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)	25.9 ± 0.8	23.6 ± 0.9	24.8 ± 0.7	23.8 ± 0.6	23.5 ± 0.5	22.1 ± 0.6**
Creatinine (mg/dL)	0.62 ± 0.04	0.57 ± 0.03	0.48 ± 0.04*	0.46 ± 0.04*	0.52 ± 0.04	0.48 ± 0.03*
Sodium (mEq/L)	146 ± 1	147 ± 1	147 ± 1	147 ± 1	147 ± 0	148 ± 0
Potassium (mEq/L)	3.3 ± 0.1	3.4 ± 0.1	3.4 ± 0.1	3.5 ± 0.0*	3.5 ± 0.1*	3.7 ± 0.1**
Chloride (mEq/L)	109 ± 1	109 ± 1	110 ± 1	110 ± 1	111 ± 1	112 ± 1*
Oxygen, partial pressure (mm Hg)	84 ± 8[b]	78 ± 2[c]	95 ± 10[d]	75 ± 1[c]	76 ± 3[c]	73 ± 2
Carbon dioxide, partial pressure (mm Hg)	44 ± 2[b]	47 ± 3[b]	46 ± 3[d]	49 ± 2[b]	47 ± 3[b]	51 ± 3
Carbon dioxide (mEq/L)	23 ± 1[b]	24 ± 1[b]	23 ± 2[d]	24 ± 1[b]	25 ± 1[b]	25 ± 1
Calcium (mg/dL)	11.09 ± 0.08	11.02 ± 0.09	11.07 ± 0.09	10.68 ± 0.10	10.86 ± 0.12	11.25 ± 0.12

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Turmeric Oleoresin (continued)

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male (continued)						
Clinical chemistry (continued)						
n	10	10	10	10	10	10
Phosphorus (mg/dL)	6.4 ± 0.2	5.9 ± 0.1	6.0 ± 0.2	6.2 ± 0.1	6.5 ± 0.1	6.9 ± 0.2
Total protein (g/dL)	6.9 ± 0.1	6.8 ± 0.1	6.8 ± 0.1	6.7 ± 0.2	6.6 ± 0.1	6.4 ± 0.1**
Albumin (g/dL)	4.6 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.5 ± 0.1
Globulin (g/dL)	2.3 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	2.0 ± 0.1*	2.0 ± 0.0**	1.9 ± 0.1**
A/G ratio	2.0 ± 0.1	2.1 ± 0.1	2.2 ± 0.1	2.4 ± 0.1**	2.4 ± 0.1**	2.4 ± 0.1**
Total bilirubin (mg/dL)	0.5 ± 0.0	0.4 ± 0.0	0.2 ± 0.0**	0.3 ± 0.0**	0.2 ± 0.0**	0.2 ± 0.0**
Direct bilirubin (mg/dL)	0.02 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.06 ± 0.01**	0.05 ± 0.01*
Alanine aminotransferase (IU/L)	48 ± 4	55 ± 5	48 ± 3[b]	35 ± 3**	38 ± 2*	35 ± 2**
Aspartate aminotransferase (IU/L)	99 ± 8[b]	97 ± 8	87 ± 4[b]	72 ± 4**	75 ± 4**	62 ± 2**
Lactate dehydrogenase (IU/L)	703 ± 66	611 ± 75	432 ± 51*	678 ± 60	536 ± 59	393 ± 49**
Ornithine carbamoyltransferase (IU/L)	16.0 ± 2.6	17.4 ± 2.1[b]	18.3 ± 2.4	11.0 ± 2.2	8.4 ± 1.3*	7.2 ± 1.1**
Sorbitol dehydrogenase (IU/L)	11 ± 1	11 ± 2	10 ± 1[b]	9 ± 1	9 ± 1	9 ± 2
Bicarbonate (IU/L)	22.0 ± 1.0[b]	22.5 ± 0.8[b]	21.6 ± 1.8[d]	22.9 ± 0.6[b]	23.1 ± 1.2[b]	23.1 ± 0.9
Cholinesterase (IU/L)	767.0 ± 33.3	810.0 ± 29.2	903.0 ± 47.3*	975.0 ± 51.9**	824.0 ± 45.0	968.0 ± 24.8**
pH	7.30 ± 0.02[b]	7.29 ± 0.02[b]	7.27 ± 0.02[d]	7.28 ± 0.03[b]	7.30 ± 0.04[b]	7.27 ± 0.02
Urinalysis						
n	10	10	10	10	10	10
Specific gravity	1.053 ± 0.002	1.059 ± 0.002	1.051 ± 0.003	1.055 ± 0.005	1.045 ± 0.004	1.049 ± 0.005

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Turmeric Oleoresin
(continued)

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Female						
Hematology						
n	10	10	10	10	10	10
Hematocrit (%)	46.6 ± 0.6	46.3 ± 1.3	43.8 ± 1.0*	44.1 ± 0.8*	43.8 ± 0.5*	44.1 ± 1.0*
Hemoglobin (g/dL)	16.8 ± 0.1	16.8 ± 0.2	16.8 ± 0.1	16.6 ± 0.2	16.7 ± 0.1	16.6 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.76 ± 0.18	8.19 ± 0.20	8.36 ± 0.30	8.08 ± 0.18	7.92 ± 0.40	8.44 ± 0.22
Mean cell volume (fL)	53.5 ± 1.4	56.8 ± 2.0	52.9 ± 1.6	55.0 ± 1.3	57.2 ± 3.9	52.5 ± 1.2
Mean cell hemoglobin (pg)	19.3 ± 0.4	20.6 ± 0.4	19.6 ± 0.4[b]	20.7 ± 0.5*	21.8 ± 1.5	19.8 ± 0.5
Mean cell hemoglobin concentration (g/dL)	36.2 ± 0.5	36.5 ± 1.1	38.5 ± 0.7*	37.8 ± 0.7	38.1 ± 0.4*	37.8 ± 0.6
Leukocytes ($10^3/\mu L$)	4.64 ± 0.17	4.93 ± 0.24	4.44 ± 0.20	4.92 ± 0.26	4.81 ± 0.25	5.14 ± 0.23[b]
Segmented neutrophils ($10^3/\mu L$)	0.84 ± 0.11	0.87 ± 0.07	0.93 ± 0.13	0.81 ± 0.12	1.01 ± 0.16	1.45 ± 0.19**[b]
Lymphocytes ($10^3/\mu L$)	3.62 ± 0.18	3.85 ± 0.23	3.38 ± 0.17	3.87 ± 0.21	3.54 ± 0.13	3.47 ± 0.19[b]
Monocytes ($10^3/\mu L$)	0.12 ± 0.02	0.15 ± 0.01	0.09 ± 0.02	0.14 ± 0.03	0.19 ± 0.04	0.16 ± 0.04[b]
Eosinophils ($10^3/\mu L$)	0.07 ± 0.02	0.06 ± 0.02	0.04 ± 0.01	0.09 ± 0.03	0.06 ± 0.01	0.06 ± 0.02[b]
Nucleated erythrocytes/100 leukocytes	1.60 ± 0.43	1.00 ± 0.37	0.40 ± 0.22	0.11 ± 0.11*[b]	0.60 ± 0.27	1.20 ± 0.36
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)	20.2 ± 1.2	22.4 ± 0.9	23.8 ± 0.9	22.4 ± 0.5	22.1 ± 0.4	19.2 ± 0.6
Creatinine (mg/dL)	0.60 ± 0.03	0.65 ± 0.05	0.51 ± 0.03	0.41 ± 0.04**	0.44 ± 0.04**	0.38 ± 0.02**
Sodium (mEq/L)	148 ± 0	148 ± 0	147 ± 0	148 ± 1	147 ± 1	147 ± 1
Potassium (mEq/L)	3.1 ± 0.0	3.1 ± 0.1	3.3 ± 0.1	3.1 ± 0.1	3.0 ± 0.0	3.2 ± 0.1
Chloride (mEq/L)	112 ± 0	113 ± 1	113 ± 1	113 ± 1	114 ± 1	112 ± 1
Oxygen, partial pressure (mm Hg)	83 ± 7[e]	84 ± 9[f]	111 ± 10[c]	111 ± 16[c]	117 ± 19[b]	88 ± 11[c]
Carbon dioxide, partial pressure (mm Hg)	46 ± 1[e]	45 ± 1[f]	41 ± 2[c]	44 ± 3[f]	45 ± 1[b]	47 ± 2[c]
Carbon dioxide (mEq/L)	27 ± 1[e]	24 ± 1*[f]	24 ± 1[c]	24 ± 1*[f]	20 ± 2**[b]	23 ± 1**[c]
Calcium (mg/dL)	10.37 ± 0.08	10.53 ± 0.16	10.34 ± 0.07[b]	10.18 ± 0.11	10.19 ± 0.13	10.07 ± 0.12
Phosphorus (mg/dL)	4.3 ± 0.2	4.1 ± 0.1	4.7 ± 0.2	4.6 ± 0.1	4.8 ± 0.1	4.8 ± 0.1*[b]

TABLE G1
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of Turmeric Oleoresin (continued)

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Female (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	10
Albumin (g/dL)	4.4 ± 0.1	4.5 ± 0.1	4.7 ± 0.1*	4.5 ± 0.1	4.5 ± 0.1	4.5 ± 0.1
Globulin (g/dL)	2.3 ± 0.1	2.4 ± 0.1	1.9 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	2.0 ± 0.1
A/G ratio	2.0 ± 0.1	1.9 ± 0.1	2.5 ± 0.1	2.1 ± 0.1	2.0 ± 0.1	2.3 ± 0.2
Total bilirubin (mg/dL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0*	0.1 ± 0.0**	0.1 ± 0.0**[b]
Direct bilirubin (mg/dL)	0.01 ± 0.01	0.00 ± 0.00[b]	0.00 ± 0.00	0.01 ± 0.00	0.02 ± 0.01	0.01 ± 0.01
Alanine aminotransferase (IU/L)	28 ± 3	30 ± 3	30 ± 1	26 ± 1[c]	24 ± 1[b]	26 ± 2
Aspartate aminotransferase (IU/L)	69 ± 3	76 ± 7	70 ± 2	79 ± 8	65 ± 6[b]	66 ± 4
Lactate dehydrogenase (IU/L)	567 ± 45	367 ± 35*	306 ± 21**	526 ± 38	354 ± 56*	504 ± 42
Ornithine carbamoyltransferase (IU/L)	6.8 ± 0.9	16.5 ± 3.5	7.7 ± 0.5[b]	8.4 ± 1.9[b]	5.3 ± 0.6[b]	4.8 ± 0.7
Sorbitol dehydrogenase (IU/L)	6 ± 1	6 ± 0	7 ± 0	5 ± 0[b]	6 ± 0[b]	7 ± 1
Bicarbonate (IU/L)	25.3 ± 0.6[e]	22.8 ± 0.8*[f]	22.6 ± 1.3[c]	22.5 ± 0.9*[f]	18.9 ± 1.7**[b]	22.0 ± 0.9**[c]
Cholinesterase (IU/L)	3,963.0 ± 164.0	4,181.0 ± 140.0	3,915.0 ± 137.0	4,250.0 ± 175.0	3,839.0 ± 278.0	3,674.0 ± 199.0
pH	7.34 ± 0.01[e]	7.30 ± 0.02[f]	7.34 ± 0.02[c]	7.31 ± 0.04[f]	7.19 ± 0.03**[b]	7.27 ± 0.01**[c]
Urinalysis						
n	10	10	10	10	10	10
Specific gravity	1.026 ± 0.003	1.023 ± 0.003	1.035 ± 0.004	1.021 ± 0.003	1.022 ± 0.003	1.041 ± 0.006

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; A/G ratio=albumin/globulin ratio.
[b] n=9
[c] n=8
[d] n=6
[e] n=5
[f] n=7

TABLE G2
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin[a]

Analysis	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Male				
Hematology				
n	10	10	10	8
Hematocrit (%)	44.3 ± 0.5	44.9 ± 1.2	44.0 ± 0.6	38.3 ± 1.7**
Hemoglobin (g/dL)	16.2 ± 0.4	16.1 ± 0.5	15.7 ± 0.2	13.4 ± 0.6**
Erythrocytes ($10^6/\mu L$)	8.67 ± 0.08	9.00 ± 0.21	8.57 ± 0.11	7.52 ± 0.18**
Mean cell volume (fL)	51.2 ± 0.5	49.7 ± 0.4	51.3 ± 0.3	50.8 ± 1.5
Mean cell hemoglobin (pg)	18.6 ± 0.3	17.8 ± 0.2	18.3 ± 0.1	17.8 ± 0.6
Mean cell hemoglobin concentration (g/dL)	36.4 ± 0.6	35.8 ± 0.3	35.6 ± 0.2	35.0 ± 0.3*
Platelets ($10^3/\mu L$)	551.1 ± 18.0	555.3 ± 42.2	562.4 ± 13.8	779.4 ± 49.9**
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0[b]	0.2 ± 0.0	0.5 ± 0.1*
Leukocytes ($10^3/\mu L$)	5.32 ± 0.31	6.00 ± 0.72	5.50 ± 0.19	5.98 ± 0.40
Segmented neutrophils ($10^3/\mu L$)	2.08 ± 0.20	2.19 ± 0.24	1.95 ± 0.19	3.08 ± 0.31*
Bands ($10^3/\mu L$)	0.10 ± 0.02	0.11 ± 0.03	0.10 ± 0.03	0.11 ± 0.03
Lymphocytes ($10^3/\mu L$)	2.84 ± 0.24	3.20 ± 0.44	3.10 ± 0.25	2.41 ± 0.30
Monocytes ($10^3/\mu L$)	0.27 ± 0.05	0.43 ± 0.16	0.31 ± 0.05	0.29 ± 0.04
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.02 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.05 ± 0.02	0.04 ± 0.01	0.05 ± 0.02	0.11 ± 0.03
Clinical Chemistry				
n	10	10	10	9
Urea nitrogen (mg/dL)	13.6 ± 0.5	13.3 ± 0.2[b]	14.0 ± 0.8	15.3 ± 0.4**
Creatinine (mg/dL)	0.47 ± 0.03	0.49 ± 0.05	0.47 ± 0.04	0.53 ± 0.05
Sodium (mEq/L)	149 ± 0	149 ± 1	147 ± 2	150 ± 2
Potassium (mEq/L)	3.1 ± 0.1	3.2 ± 0.1	3.0 ± 0.1	3.4 ± 0.1*
Chloride (mEq/L)	105 ± 1	105 ± 1	104 ± 1	107 ± 2
Calcium (mg/dL)	11.06 ± 0.24	11.24 ± 0.24	10.77 ± 0.11	10.64 ± 0.11
Phosphorus (mg/dL)	4.3 ± 0.1	4.3 ± 0.2	4.5 ± 0.1	4.9 ± 0.1**
Alkaline phosphatase (IU/L)	130 ± 5	121 ± 3	143 ± 5	134 ± 8
Alanine aminotransferase (IU/L)	82 ± 6	71 ± 6	68 ± 7	44 ± 2**
Sorbitol dehydrogenase (IU/L)	12 ± 1	10 ± 1	11 ± 1	7 ± 1**
Cholinesterase (IU/L)	1.0 ± 0.1	1.0 ± 0.1	1.1 ± 0.0	0.9 ± 0.0

TABLE G2
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin (continued)

Analysis	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Female				
Hematology				
n	10	10	10	9
Hematocrit (%)	42.9 ± 0.4	42.8 ± 0.3	43.6 ± 0.4	40.9 ± 0.4**
Hemoglobin (g/dL)	15.8 ± 0.2	15.8 ± 0.1	15.9 ± 0.1	15.1 ± 0.1**
Erythrocytes ($10^6/\mu L$)	7.86 ± 0.10	7.76 ± 0.08	7.94 ± 0.06	7.42 ± 0.10**
Mean cell volume (fL)	54.4 ± 0.3	55.3 ± 0.3*	54.8 ± 0.3	55.4 ± 0.5*
Mean cell hemoglobin (pg)	20.1 ± 0.2	20.4 ± 0.1	20.0 ± 0.1	20.3 ± 0.1
Mean cell hemoglobin concentration (g/dL)	36.9 ± 0.3	37.0 ± 0.1	36.5 ± 0.1	36.8 ± 0.2
Platelets ($10^3/\mu L$)	479.3 ± 23.4	497.2 ± 22.8	528.0 ± 8.3	583.9 ± 14.4**
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	3.17 ± 0.17	2.96 ± 0.15	3.58 ± 0.21	4.63 ± 0.29**
Segmented neutrophils ($10^3/\mu L$)	1.18 ± 0.12	1.00 ± 0.06	1.21 ± 0.11	2.28 ± 0.27**
Bands ($10^3/\mu L$)	0.05 ± 0.01	0.05 ± 0.01	0.08 ± 0.01	0.07 ± 0.02
Lymphocytes ($10^3/\mu L$)	1.78 ± 0.12	1.77 ± 0.13	2.12 ± 0.13	2.10 ± 0.12
Monocytes ($10^3/\mu L$)	0.11 ± 0.02	0.09 ± 0.02	0.14 ± 0.04	0.14 ± 0.03
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.00	0.00 ± 0.00*	0.00 ± 0.00**
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01	0.03 ± 0.01*	0.04 ± 0.02
Clinical Chemistry				
n	10	10	10	9
Urea nitrogen (mg/dL)	14.9 ± 0.5	15.5 ± 0.8	13.8 ± 0.4	15.7 ± 0.4
Creatinine (mg/dL)	0.41 ± 0.03	0.46 ± 0.04[b]	0.46 ± 0.03	0.43 ± 0.03
Sodium (mEq/L)	150 ± 1	147 ± 3	142 ± 5[c]	147 ± 4
Potassium (mEq/L)	2.9 ± 0.1	2.9 ± 0.1	2.9 ± 0.1[c]	2.9 ± 0.1
Chloride (mEq/L)	107 ± 1	105 ± 2	101 ± 3[c]	105 ± 3
Calcium (mg/dL)	11.25 ± 0.21	11.01 ± 0.19	10.76 ± 0.21	11.49 ± 0.23
Phosphorus (mg/dL)	3.4 ± 0.1	3.8 ± 0.2	3.3 ± 0.1	4.1 ± 0.3
Alkaline phosphatase (IU/L)	125 ± 4	130 ± 5	129 ± 7	138 ± 9
Alanine aminotransferase (IU/L)	54 ± 3	53 ± 8	45 ± 3	36 ± 2**
Sorbitol dehydrogenase (IU/L)	9 ± 0	7 ± 0	8 ± 0	7 ± 0
Cholinesterase (IU/L)	3.2 ± 0.1	3.2 ± 0.1	3.6 ± 0.2	3.2 ± 0.2

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[c] n=8

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Turmeric Oleoresin[a]

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male						
Hematology						
n	9	9	10	10	10	10
Hematocrit (%)	44.6 ± 1.0	42.2 ± 0.8	42.8 ± 1.1	43.8 ± 1.2	43.4 ± 1.1	47.2 ± 0.8
Hemoglobin (g/dL)	15.5 ± 0.3	15.0 ± 0.1	15.0 ± 0.2	14.9 ± 0.3	15.0 ± 0.1	15.3 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.64 ± 0.20	8.40 ± 0.50*[b]	8.75 ± 0.35	9.19 ± 0.23	9.38 ± 0.08[c]	9.33 ± 0.19
Mean cell volume (fL)	46.3 ± 0.8	49.1 ± 2.0[b]	49.8 ± 2.6	47.7 ± 0.9	47.1 ± 0.7[c]	50.9 ± 1.6*
Mean cell hemoglobin (pg)	16.1 ± 0.2	17.7 ± 0.8[b]	17.4 ± 0.8	16.3 ± 0.2	16.1 ± 0.1[c]	16.6 ± 0.5
Mean cell hemoglobin concentration (g/dL)	34.8 ± 0.7	35.9 ± 0.6[b]	35.2 ± 0.7	34.2 ± 0.6	34.9 ± 0.8	32.6 ± 0.6*
Leukocytes ($10^3/\mu L$)	5.13 ± 0.38	4.47 ± 0.40	3.66 ± 0.34**	3.12 ± 0.14**[c]	3.67 ± 0.29**	4.52 ± 0.58*
Segmented neutrophils ($10^3/\mu L$)	1.42 ± 0.10	1.99 ± 0.38	1.44 ± 0.30	0.98 ± 0.10[c]	1.41 ± 0.30	1.66 ± 0.40
Lymphocytes ($10^3/\mu L$)	3.60 ± 0.37	2.40 ± 0.07**	2.13 ± 0.20**	2.10 ± 0.11**[c]	2.18 ± 0.16**	2.73 ± 0.24**
Monocytes ($10^3/\mu L$)	0.07 ± 0.02	0.05 ± 0.02	0.03 ± 0.01	0.03 ± 0.01[c]	0.05 ± 0.02	0.08 ± 0.04
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.02 ± 0.01	0.06 ± 0.02	0.01 ± 0.01[c]	0.03 ± 0.02	0.04 ± 0.02
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry						
n	8	10	10	9	9	7
Urea nitrogen (mg/dL)	21.6 ± 2.0	26.5 ± 2.8[d]	24.7 ± 2.0	20.7 ± 0.9[b]	19.8 ± 0.8[b]	20.3 ± 1.5[c]
Creatinine (mg/dL)	0.51 ± 0.05	0.57 ± 0.05[c]	0.52 ± 0.04	0.39 ± 0.03	0.34 ± 0.03*[b]	0.28 ± 0.03**[c]
Sodium (mEq/L)	155 ± 1[e]	155 ± 0[e]	154 ± 1[c]	157 ± 1	157 ± 1	156 ± 2[d]
Potassium (mEq/L)	4.1 ± 0.1[e]	4.2 ± 0.1[e]	4.2 ± 0.1[c]	4.0 ± 0.1	4.1 ± 0.1	3.9 ± 0.1[d]
Chloride (mEq/L)	118 ± 1[e]	119 ± 1[e]	118 ± 1[c]	120 ± 1*	120 ± 1*	121 ± 2*[d]
Oxygen, partial pressure (mm Hg)	76 ± 9	63 ± 3	76 ± 8[d]	70 ± 2[e]	68 ± 1	70 ± 1
Carbon dioxide, partial pressure (mm Hg)	39 ± 3	47 ± 1	45 ± 2[d]	42 ± 1[e]	43 ± 1	43 ± 1
Carbon dioxide (mEq/L)	21 ± 1	24 ± 0	23 ± 1[d]	23 ± 1[e]	22 ± 0	22 ± 0
Phosphorus (mg/dL)	5.3 ± 0.2	5.3 ± 0.2[d]	5.6 ± 0.2	6.3 ± 0.2**[b]	6.4 ± 0.2**[b]	6.8 ± 0.1**[d]

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Turmeric Oleoresin (continued)

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male (continued)						
Clinical chemistry (continued)						
n	8	10	10	9	9	7
Total protein (g/dL)	4.4 ± 0.1	4.6 ± 0.1[d]	4.6 ± 0.1	4.3 ± 0.1	4.6 ± 0.1[b]	4.7 ± 0.1**[d]
Albumin (g/dL)	3.1 ± 0.1	3.4 ± 0.1[d]	3.7 ± 0.1**[c]	3.4 ± 0.1	3.4 ± 0.1	3.3 ± 0.1[d]
Globulin (g/dL)	1.2 ± 0.1	1.2 ± 0.1[d]	0.8 ± 0.1*[c]	1.0 ± 0.1	1.1 ± 0.1	1.5 ± 0.1
A/G ratio	2.6 ± 0.2	2.9 ± 0.2[d]	4.8 ± 0.5**[c]	3.7 ± 0.4	3.4 ± 0.3	2.3 ± 0.3
Alanine aminotransferase (IU/L)	24 ± 1[c]	22 ± 1[c]	19 ± 1[c]	27 ± 1[b]	26 ± 1[b]	27 ± 2[b]
Aspartate aminotransferase (IU/L)	57 ± 5[c]	68 ± 8	57 ± 8	71 ± 5[b]	57 ± 5[b]	59 ± 5[b]
Lactate dehydrogenase (IU/L)	520 ± 52[c]	546 ± 73	462 ± 43	682 ± 71[b]	475 ± 60[b]	299 ± 33**[c]
Ornithine carbamoyltransferase (IU/L)	2.6 ± 0.3[c]	3.2 ± 0.8[d]	3.5 ± 0.7	2.9 ± 0.2	2.7 ± 0.5[b]	4.0 ± 0.6[c]
Sorbitol dehydrogenase (IU/L)	20 ± 1[c]	24 ± 2	23 ± 1	27 ± 2*[b]	25 ± 1*[b]	26 ± 1*[b]
Bicarbonate (IU/L)	19.8 ± 1.3	22.9 ± 0.4	21.7 ± 0.8[d]	21.8 ± 0.5[e]	20.7 ± 0.4	20.8 ± 0.4
Cholinesterase (IU/L)	5,240 ± 203[c]	4,966 ± 139[c]	4,877 ± 151	6,057 ± 226*[b]	6,423 ± 266*[b]	6,593 ± 130**[b]
pH	7.32 ± 0.02	7.30 ± 0.01	7.29 ± 0.02[d]	7.32 ± 0.01[e]	7.29 ± 0.01	7.29 ± 0.01
Urinalysis						
n	10	10	10	10	10	9
Specific gravity	1.017 ± 0.005	1.040 ± 0.007	1.046 ± 0.007**	1.047 ± 0.005**	1.038 ± 0.007**	1.050 ± 0.007**

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Turmeric Oleoresin
(continued)

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Female						
Hematology						
n	9	10	10	10	8	10
Hematocrit (%)	50.5 ± 0.9	48.9 ± 1.4	47.9 ± 0.9	52.1 ± 1.3	52.2 ± 1.1	49.1 ± 1.8
Hemoglobin (g/dL)	15.3 ± 0.2	15.5 ± 0.1	15.2 ± 0.2	14.9 ± 0.2	15.4 ± 0.2	15.7 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.78 ± 0.15	9.09 ± 0.32	8.42 ± 0.48	9.95 ± 0.11[c]	9.97 ± 0.34	8.81 ± 0.64
Mean cell volume (fL)	51.8 ± 0.7	54.1 ± 1.6	58.4 ± 3.2	53.7 ± 1.1	52.9 ± 2.4	57.6 ± 3.0
Mean cell hemoglobin (pg)	15.7 ± 0.3	17.2 ± 0.6	18.7 ± 1.3	15.0 ± 0.2[c]	15.6 ± 0.6	18.9 ± 1.7
Mean cell hemoglobin concentration (g/dL)	30.3 ± 0.5	31.9 ± 0.9	31.8 ± 0.7	28.7 ± 0.5	29.6 ± 0.7	32.2 ± 1.2
Leukocytes ($10^3/\mu L$)	2.33 ± 0.17[d]	2.83 ± 0.21	1.86 ± 0.16	2.24 ± 0.29	2.56 ± 0.29	2.16 ± 0.17
Segmented neutrophils ($10^3/\mu L$)	0.57 ± 0.09[d]	0.85 ± 0.16	0.31 ± 0.04*	0.38 ± 0.04	0.59 ± 0.07	0.38 ± 0.06
Lymphocytes ($10^3/\mu L$)	1.73 ± 0.11[d]	1.95 ± 0.11	1.54 ± 0.14	1.84 ± 0.27	1.94 ± 0.25	1.75 ± 0.14
Monocytes ($10^3/\mu L$)	0.02 ± 0.01[d]	0.02 ± 0.01	0.01 ± 0.00	0.02 ± 0.01	0.04 ± 0.02	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)	0.01 ± 0.00[d]	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.23 ± 0.23
Nucleated erythrocytes/100 leukocytes	0.11 ± 0.11	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry						
n	10	10	7	10	7	8
Urea nitrogen (mg/dL)	23.9 ± 1.2	22.7 ± 1.1[c]	22.6 ± 1.3[b]	22.6 ± 1.3	22.0 ± 1.2[c]	18.3 ± 1.6*[c]
Creatinine (mg/dL)	0.42 ± 0.03	0.40 ± 0.04	0.27 ± 0.04*[b]	0.26 ± 0.02**	0.23 ± 0.03**	0.22 ± 0.04**[f]
Sodium (mEq/L)	156 ± 1[g]	155 ± 1[c]	154 ± 1	157 ± 2[g]	157 ± 2[g]	159 ± 2[h]
Potassium (mEq/L)	3.4 ± 0.1[g]	3.4 ± 0.1[c]	3.3 ± 0.0	3.4 ± 0.1[g]	3.4 ± 0.1[g]	3.4 ± 0.1[h]
Chloride (mEq/L)	128 ± 1[g]	126 ± 1[c]	127 ± 1	131 ± 2[g]	131 ± 2[g]	131 ± 1[h]
Oxygen, partial pressure (mm Hg)	83 ± 9[e]	85 ± 9[e]	80 ± 6	74 ± 1[d]	72 ± 2	79 ± 7
Carbon dioxide, partial pressure (mm Hg)	39 ± 2[e]	38 ± 1[e]	37 ± 3	41 ± 1[d]	42 ± 2	45 ± 2
Carbon dioxide (mEq/L)	20 ± 1[e]	20 ± 1[e]	18 ± 1	20 ± 1[d]	19 ± 1	20 ± 1
Phosphorus (mg/dL)	5.2 ± 0.4[d]	5.7 ± 0.2[c]	5.1 ± 0.2[d]	4.1 ± 0.5[g]	4.1 ± 0.5[g]	6.4 ± 0.4[f]
Total protein (g/dL)	4.6 ± 0.1[h]	4.9 ± 0.2[e]	4.9 ± 0.2	4.8 ± 0.7[i]	5.5[j]	5.5 ± 0.2*[k]

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of Turmeric Oleoresin (continued)

Analysis	0 ppm	1,000 ppm	5,000 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Female (continued)						
Clinical Chemistry (continued)						
n	10	10	7	10	7	8
Albumin (g/dL)	3.4 ± 0.2[f]	3.7 ± 0.1[e]	3.9 ± 0.1[g]	3.7[j]	4.0[j]	4.3 ± 0.2*[h]
Globulin (g/dL)	1.4 ± 0.4[k]	1.1 ± 0.3[g]	0.9 ± 0.2[g]	0.4[j]	1.5[j]	1.2 ± 0.4[k]
A/G ratio	3.1 ± 1.6[k]	4.3 ± 1.0[g]	5.3 ± 1.2[g]	9.3[j]	2.7[j]	4.3 ± 1.1[k]
Alanine aminotransferase (IU/L)	19 ± 1	20 ± 1	13 ± 1*[c]	19 ± 2	23 ± 2[c]	18 ± 1
Aspartate aminotransferase (IU/L)	45 ± 1	47 ± 2	35 ± 1*[d]	47 ± 4	51 ± 2[c]	49 ± 5[c]
Lactate dehydrogenase (IU/L)	267 ± 27	232 ± 24	231 ± 17[b]	201 ± 20	247 ± 29[c]	221 ± 44[b]
Ornithine carbamoyltransferase (IU/L)	3.3 ± 0.8[c]	4.9 ± 0.7	3.3 ± 0.7[c]	3.8 ± 0.6[d]	3.8 ± 0.5	5.0 ± 1.1
Sorbitol dehydrogenase (IU/L)	17 ± 1	14 ± 1	16 ± 2[c]	16 ± 1	17 ± 2[c]	23 ± 2[b]
Bicarbonate (IU/L)	19.2 ± 0.6[e]	19.2 ± 0.6[e]	17.4 ± 0.8	18.7 ± 0.8[d]	18.0 ± 0.9	18.5 ± 0.7
Cholinesterase (IU/L)	8,640 ± 328	7,523 ± 342	8,144 ± 351[b]	8,995 ± 360	9,538 ± 234[c]	9,419 ± 185[b]
pH	7.30 ± 0.01[e]	7.30 ± 0.01[e]	7.28 ± 0.02	7.26 ± 0.02[d]	7.24 ± 0.01*	7.22 ± 0.03*
Urinalysis						
n	8	5	9	8	7	10
Specific gravity	1.021 ± 0.006	1.029 ± 0.008	1.042 ± 0.008	1.039 ± 0.010	1.025 ± 0.009	1.029 ± 0.007

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error; A/G ratio = albumin/globulin ratio.
[b] n=10
[c] n=9
[d] n=8
[e] n=7
[f] n=5
[g] n=6
[h] n=4
[i] n=2
[j] n=1; no standard error calculated
[k] n=3

TABLE G4
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Turmeric Oleoresin[a]

Analysis	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Male				
Hematology				
n	9	9	8	9
Hematocrit (%)	44.0 ± 0.6	43.7 ± 0.6	44.6 ± 1.3	44.5 ± 0.6
Hemoglobin (g/dL)	15.1 ± 0.1	15.3 ± 0.2	15.7 ± 0.5	15.7 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.89 ± 0.17	8.83 ± 0.15	9.37 ± 0.36	9.22 ± 0.13
Mean cell volume (fL)	49.7 ± 0.6	49.4 ± 0.5	47.8 ± 0.5	48.6 ± 0.8
Mean cell hemoglobin (pg)	17.1 ± 0.2	17.4 ± 0.3	16.8 ± 0.2	17.0 ± 0.3
Mean cell hemoglobin concentration (g/dL)	34.4 ± 0.4	35.1 ± 0.5	35.2 ± 0.3	35.3 ± 0.4
Platelets ($10^3/\mu L$)	812.0 ± 11.8[b]	848.9 ± 40.5[c]	851.3 ± 36.7[c]	853.0 ± 26.0[d]
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0[b]	0.2 ± 0.0	0.3 ± 0.1	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	4.36 ± 0.26	6.79 ± 0.61**	5.31 ± 0.35	5.24 ± 0.78
Segmented neutrophils ($10^3/\mu L$)	1.97 ± 0.37	2.92 ± 0.58	1.70 ± 0.28	1.84 ± 0.44
Bands ($10^3/\mu L$)	0.11 ± 0.02	0.24 ± 0.04*	0.18 ± 0.02	0.14 ± 0.02
Lymphocytes ($10^3/\mu L$)	2.19 ± 0.37	3.52 ± 0.63	3.28 ± 0.32	3.20 ± 0.61
Monocytes ($10^3/\mu L$)	0.08 ± 0.03	0.08 ± 0.03	0.14 ± 0.05	0.06 ± 0.02
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.06 ± 0.04	0.02 ± 0.02	0.05 ± 0.04
Clinical Chemistry				
n	9	9	9	9
Urea nitrogen (mg/dL)	23.5 ± 1.8[b]	21.0 ± 2.5[e]	21.6 ± 1.6[c]	18.3 ± 2.1[d]
Creatinine (mg/dL)	0.28 ± 0.05[d]	0.30 ± 0.10[f]	0.28 ± 0.05[e]	0.22 ± 0.02[g]
Calcium (mg/dL)	8.26 ± 0.11[c]	9.03 ± 0.64[d]	9.59 ± 0.44**	8.84 ± 0.31*[b]
Phosphorus (mg/dL)	6.6 ± 0.5[b]	6.4 ± 0.4[g]	7.8 ± 0.6	8.2 ± 0.4[b]
Alkaline phosphatase (IU/L)	42 ± 3	53 ± 5	58 ± 3**	78 ± 10**
Alanine aminotransferase (IU/L)	38 ± 3[b]	43 ± 6[b]	66 ± 11	41 ± 7[b]
Sorbitol dehydrogenase (IU/L)	34 ± 2	38 ± 5[b]	35 ± 2	41 ± 4
Cholinesterase (IU/L)	7.6 ± 0.4	8.6 ± 0.4	9.2 ± 0.5*	9.2 ± 0.8*

TABLE G4
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluations in the 2-Year Feed Study of Turmeric Oleoresin (continued)

Analysis	0 ppm	2,000 ppm	10,000 ppm	50,000 ppm
Female				
Hematology				
n	10	10	9	10
Hematocrit (%)	44.8 ± 0.6	45.4 ± 0.5	44.1 ± 0.8	44.4 ± 0.5
Hemoglobin (g/dL)	15.4 ± 0.2	15.6 ± 0.2	15.2 ± 0.2	15.6 ± 0.3
Erythrocytes ($10^6/\mu L$)	9.26 ± 0.10	9.42 ± 0.11	9.33 ± 0.10	9.35 ± 0.10
Mean cell volume (fL)	48.3 ± 0.3	48.2 ± 0.2	47.1 ± 0.6	47.5 ± 0.6
Mean cell hemoglobin (pg)	16.6 ± 0.1	16.6 ± 0.1	16.3 ± 0.1	16.7 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.3 ± 0.1	34.3 ± 0.2	34.5 ± 0.4	35.1 ± 0.5
Platelets ($10^3/\mu L$)	728.9 ± 14.5[b]	677.8 ± 33.6	751.1 ± 24.2[b]	751.5 ± 19.0
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	3.55 ± 0.33	3.76 ± 0.33	3.93 ± 0.45	2.94 ± 0.32
Segmented neutrophils ($10^3/\mu L$)	1.53 ± 0.12	1.28 ± 0.13	1.37 ± 0.18	0.85 ± 0.12**
Bands ($10^3/\mu L$)	0.08 ± 0.01	0.09 ± 0.02	0.07 ± 0.02	0.03 ± 0.01*
Lymphocytes ($10^3/\mu L$)	1.85 ± 0.33	2.24 ± 0.27	2.31 ± 0.33	1.99 ± 0.21
Monocytes ($10^3/\mu L$)	0.06 ± 0.02	0.10 ± 0.02	0.08 ± 0.03	0.05 ± 0.01
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01
Clinical Chemistry				
n	9	10	9	10
Urea nitrogen (mg/dL)	25.1 ± 4.2	20.9 ± 5.1[c]	29.3 ± 2.3	18.9 ± 1.9
Creatinine (mg/dL)	0.64 ± 0.23[g]	0.80 ± 0.31[e]	0.30 ± 0.05[b]	0.33 ± 0.03[b]
Calcium (mg/dL)	9.32 ± 0.32	9.69 ± 0.58[c]	9.29 ± 0.47	9.25 ± 0.16
Phosphorus (mg/dL)	7.6 ± 0.6	7.8 ± 0.5[d]	6.8 ± 0.3	7.3 ± 0.4
Alkaline phosphatase (IU/L)	73 ± 3[h]	76 ± 7[i]	100 ± 6*	106 ± 6**
Alanine aminotransferase (IU/L)	36 ± 6	32 ± 6[b]	31 ± 4[b]	30 ± 5
Sorbitol dehydrogenase (IU/L)	24 ± 2[h]	28 ± 3	27 ± 3	39 ± 9
Cholinesterase (IU/L)	7.9 ± 0.6[h]	8.5 ± 0.3	9.0 ± 0.5[b]	8.5 ± 0.3[i]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=8
[c] n=7
[d] n=6
[e] n=4
[f] n=3
[g] n=5
[h] n=10
[i] n=9

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

PROCUREMENT AND CHARACTERIZATION OF TURMERIC OLEORESIN

Turmeric oleoresin was obtained from Kalsec, Incorporated (Kalamazoo, MI), in four lots (2173-A, 2327-A, 2452-A, and 2558-A). Lots 2173-A and 2327-A were used sequentially throughout the 13-week studies in rats and mice and lots 2452-A and 2558-A were used sequentially throughout the 2-year studies in rats and mice. The material was a purified oleoresin that was produced by extracting turmeric with acetone, followed by concentration and acid precipitation. Identity, characterization, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the turmeric oleoresin studies are on file at the National Institute of Environmental Health Sciences.

All lots of the purified extract, a yellow-orange crystalline powder, had infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopic characteristics expected for turmeric oleoresin as shown in Figures H1 and H2. The melting point was 173.5° to 174.5° C.

Lot 2173-A was divided into two batches, 01 and 02, and each batch was characterized by elemental analyses, Karl Fischer water analysis, non-aqueous titration, thin-layer chromatography, and high-performance liquid chromatography. Non-aqueous titration was performed by dissolving the sample in pyridine and titrating with 0.1 N tetrabutylammonium hydroxide in methanol:2-propanol (1:9). The titration was monitored potentiometrically using a glass indicating electrode versus a calomel reference electrode containing 1.0 M tetrabutylammonium chloride in methanol. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates using two solvent systems: 1) toluene:chloroform:95% ethanol (76:12:12) and 2) *n*-hexanes:acetone:*n*-propanol (60:30:10). Plates were examined under shortwave (254 nm) and longwave (366 nm) ultraviolet light and a spray of 5% molybdophosphoric acid in ethanol, followed by heating to 120° C. High-performance liquid chromatography was performed with a Hamilton PRP-1 C_{18} column (150 × 4.1 mm ID) and a mobile phase of two solvent systems: 1) water containing 1% (v/v) glacial acetic acid and 2) acetonitrile containing 1% (v/v) glacial acetic acid, with a solvent ratio of 63:37, at a flow rate of 2.5 mL/minute. Detection was with ultraviolet light at 254 nm and visible light at 436 nm.

Elemental analyses of batch 02 for carbon and both batches for hydrogen were in agreement with the theoretical values for turmeric oleoresin. The elemental analyses of batch 01 for carbon were slightly higher than the theoretical values for turmeric oleoresin. Karl Fischer water analysis indicated less than 0.03% water in batch 01 and less than 0.04% water in batch 02. Non-aqueous titration indicated purities of 102.3% ± 0.8% and 93.6% ± 0.9% for batch 01 and 102.2% ± 0.8% and 93.5% ± 1.5% for batch 02. Neither of these values provide an accurate determination of the curcumin content because of the presence of curcumin-like compounds. Thin-layer chromatography of batch 01 using system 1 indicated one major spot, three minor spots, and two trace spots; system 2 indicated a major spot, three minor spots, and a trace spot. Thin-layer chromatography of batch 02 using system 1 indicated a major spot, two minor spots, and three trace spots, while system 2 indicated a major spot, a minor spot, and three trace spots. High-performance liquid chromatography for batch 01 indicated six components at 436 nm, the three largest of which had peak areas of 16.9%, 3.1%, and 0.9% of the total peak areas. The remaining three components had a combined area of less than 0.3% relative to the total peak area. At 254 nm, a major peak and eight smaller peaks were observed, with the four largest peaks having areas of 17.1%, 3.6%, 3.6%, and 0.9% relative to the total peak area. The four remaining peaks had an area of 0.5% relative to the total peak area. High-performance liquid chromatography of batch 02 at 254 nm indicated a major peak and six smaller peaks with an area of 25.7% relative to the total peak area. At 436 nm, a major peak and four smaller peaks with an area 19.9% relative to the total peak area were observed. The overall composition of batches 01 and 02 was determined to be 79% curcumin,

with the two other components tentatively identified by ultraviolet/visible spectroscopy as 16.9% 1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione and 3.1% 1,7-bis(4-hydroxyphenyl)-1,6-hepatdiene-3,5-dione.

Lot 2327-A was characterized by elemental analyses, Karl Fischer water analysis, non-aqueous titration, thin-layer chromatography, and high-performance liquid chromatography. Non-aqueous titration was performed as for lot 2173-A. Thin-layer chromatography was performed using the same solvent systems as for lot 2173-A, but plates were heated to a temperature of 110° C. High-performance liquid chromatography was performed using the same systems as for lot 2173-A.

Elemental analyses of lot 2327-A for carbon and hydrogen were in agreement with the theoretical values for turmeric oleoresin. Karl Fischer water analysis indicated 0.11% ± 0.01% water. Non-aqueous titration indicated purities of 102.5% ± 0.4% and 94.3% ± 1.8%. Neither of these values provide an accurate determination of the curcumin content because of the presence of curcumin-like compounds. Thin-layer chromatography by system 1 indicated a major spot, two minor spots, and two trace spots, while system 2 indicated a major spot and one trace spot. High-performance liquid chromatography at a detection wavelength of 254 nm indicated a major peak and four smaller peaks with an area of 21.8% relative to the total peak area. Detection at a wavelength of 436 nm indicated a major peak and three smaller peaks with an area of 14.6% relative to the total peak area. The curcumin content of the lot was determined to be 85%.

The composition of lot 2452-A was determined by elemental analyses, Karl Fischer water analysis, non-aqueous titration, thin-layer chromatography, and high-performance liquid chromatography. Non-aqueous titration, thin-layer chromatography, and high-performance liquid chromatography were performed using the methods and systems described for lot 2173-A.

Elemental analyses of lot 2452-A for carbon were slightly greater than the theoretical values, while results for hydrogen were in agreement with the theoretical values for turmeric oleoresin. Karl Fischer water analysis indicated less than 0.1% water. Non-aqueous titration indicated purities of 103.8% ± 0.5% and 87.8% ± 1.7%. Neither of these values provide an accurate determination of the curcumin content because of the presence of curcumin-like compounds. Thin-layer chromatography by system 1 indicated a major spot, two minor spots, and two trace spots, while system 2 indicated a major spot, one minor spot, and two trace spots. High-performance liquid chromatography at a detection wavelength of 254 nm indicated a major peak and seven smaller peaks with an area of 35.3% relative to the total peak area. At a detection wavelength of 436 nm, a major peak and four smaller peaks with an area of 19.7% relative to the total peak area were observed. The curcumin content of the lot was determined to be 80%.

Lot 2558-A was divided into two batches, batch 05 and 06. The composition of each batch was determined by elemental analyses, Karl Fischer water analysis, non-aqueous titration, thin-layer chromatography, and high-performance liquid chromatography. Non-aqueous titration was performed following the methods described for lot 2173-A. Thin-layer chromatography was performed using the methods described for lot 2327-A. High-performance liquid chromatography was performed for both batches using the same methods and systems described for lot 2173-A, but with a solvent ratio of 65:35 for batch 05 and a solvent ratio of 64:36 for batch 06.

Elemental analyses for both batches of the lot for carbon and hydrogen were in agreement with the theoretical values for turmeric oleoresin. Karl Fischer water analysis for lot 05 indicated 0.12% ± 0.02% water, while batch 06 contained 0.19% ± 0.01% water. Non-aqueous titration indicated purities of 102.2% ± 0.5% and 87.3% ± 1.5% for batch 05 and a purity of 100% ± 1% for batch 06. Neither of these values provide an accurate determination of the curcumin content because of the presence of curcumin-like compounds. Thin-layer chromatography for batch 05 using system 1 indicated a major spot, two minor spots, and two trace spots, while system 2 indicated a major spot, two minor

spots, and a trace spot. Thin-layer chromatography of batch 06 using system 1 indicated a major spot, two minor spots, and four trace spots; system 2 indicated a major spot, two minor spots, and two trace spots. High-performance liquid chromatography of batch 05 indicated a major peak and five smaller peaks with an area of 19.5% relative to the total peak area at a detection wavelength of 254 nm; a major peak and three smaller peaks with an area of 13.5% relative to the total peak area were observed at a detection wavelength of 436 nm. For batch 06, a major peak and eight smaller peaks with an area of 21.2% relative to the total peak area were observed at a detection wavelength of 254 nm. High-performance liquid chromatography for batch 06 indicated a major peak and three smaller peaks with an area of 15.5% relative to the total peak area at a detection wavelength of 436 nm. The curcumin composition of batch 05 was determined to be 85%, while the curcumin composition for batch 06 was determined to be 82%.

Stability studies were performed by the analytical chemistry laboratory on lot 2173-A. High-performance liquid chromatography was performed using the methods described above except with a 60:40 solvent ratio and butyrophenone as an internal standard. These studies indicated that the composition of the turmeric oleoresin did not change when heated to 60° C for 2 weeks while being protected from light. The percent composition of the bulk chemical was monitored periodically at the study laboratory with non-aqueous titration and high-performance liquid chromatography methods similar to those described above. No change in the composition of the bulk chemical was observed.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing turmeric oleoresin with feed (w/w) in a blender (Patterson-Kelley Twin Shell with intensifier bar) for 15 minutes (Table H1). Dose formulations were prepared weekly during the 13-week and 2-year studies.

Studies to determine homogeneity and stability of the dosed feed preparations were conducted by the analytical chemistry laboratory. For homogeneity and stability analyses, turmeric oleoresin in feed (10,000 ppm) was extracted with 100 mL of methanol, centrifuged, and further diluted with methanol. The samples were filtered and then injected into a high-performance liquid chromatographic system equipped with a μBondapak C_{18} column. The mobile phase was a mixture of methanol:water:glacial acetic acid at a ratio of 80:19:1 and a flow rate of 1 mL/minute. Ultraviolet detection was at 405 nm. Homogeneity was confirmed and the stability of the dose formulations was established for at least 2 weeks when stored in the dark at temperatures up to 25° C and for 1 week when stored open to air and light.

Periodic analyses of the dose formulations of turmeric oleoresin were conducted at the study laboratory and the analytical chemistry laboratory using ultraviolet spectroscopy methods. The feed was extracted with methanol, then the extract was diluted further with methanol. The absorbance was determined at 420 nm. The concentration was estimated using a standard curve prepared from spiked feed. During the 13-week studies, the dose formulations were analyzed at the initiation, midpoint, and termination of the studies (Table H2). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks (Table H3). In the 2-year studies, 100% (81/81) of the dose formulations were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory were in good agreement with the results obtained by the study laboratory (Table H4).

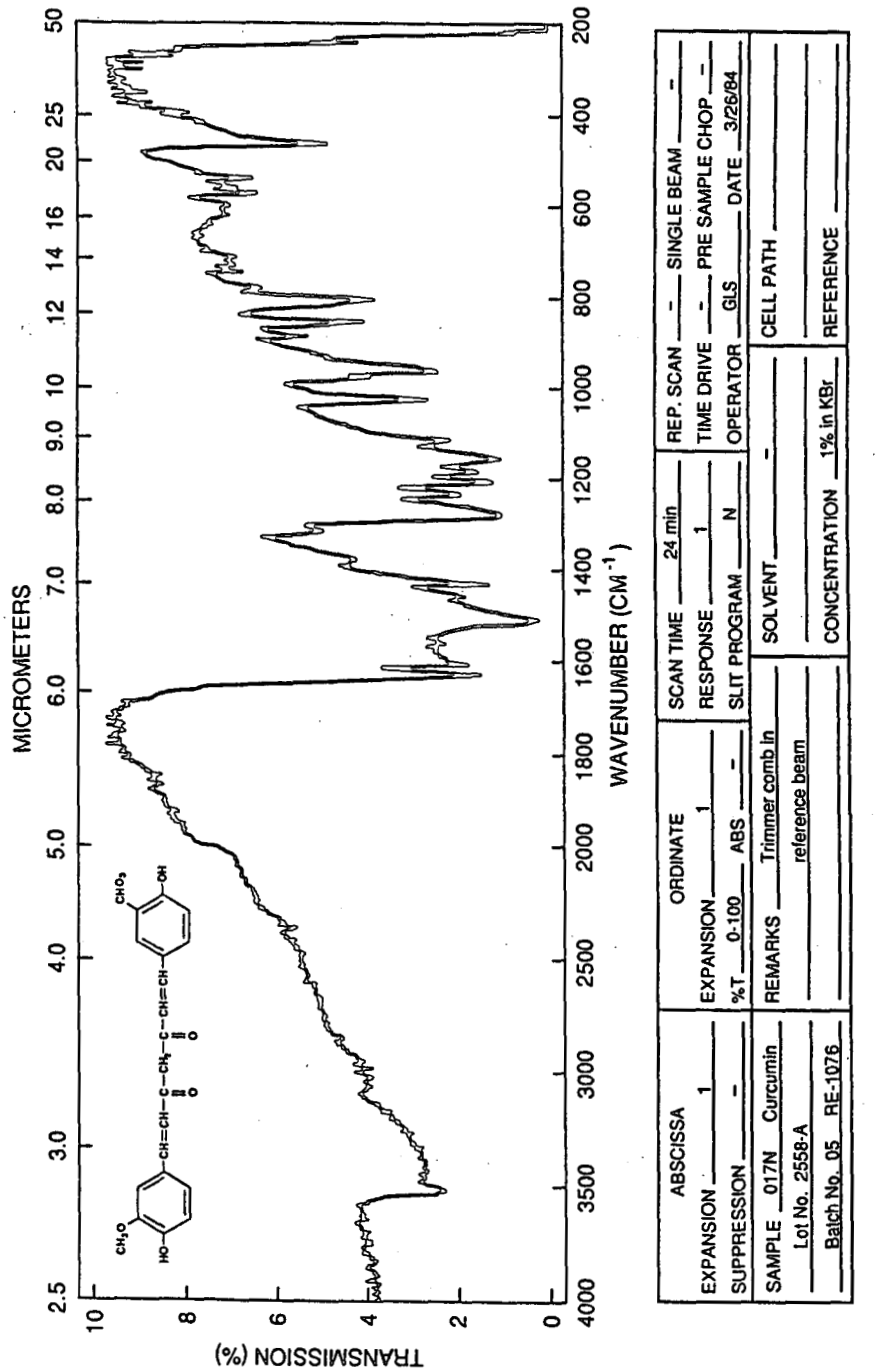

FIGURE H1
Infrared Absorption Spectrum of Turmeric Oleoresin

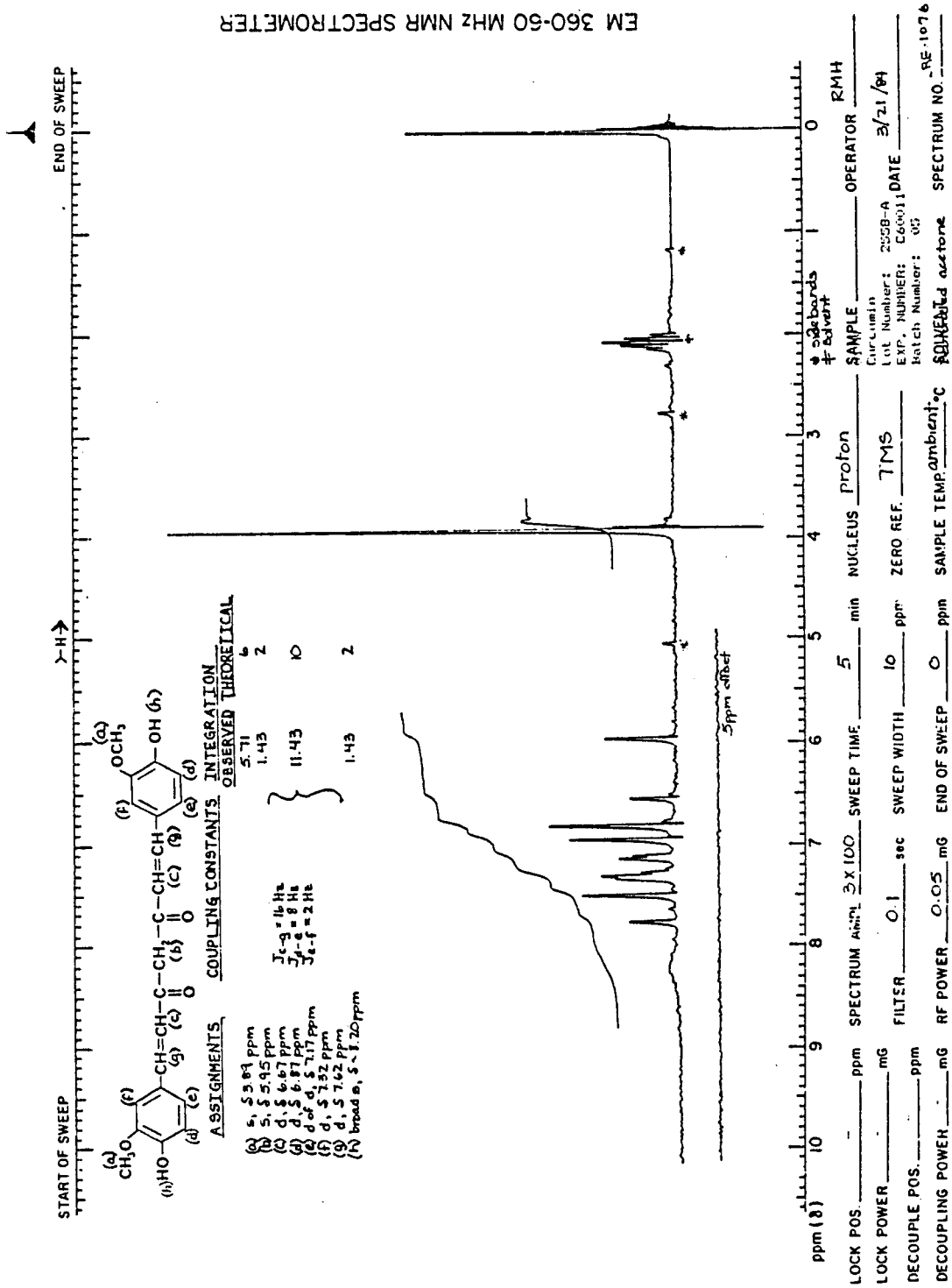

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Turmeric Oleoresin

TABLE H1
Preparation and Storage of Dose Formulations in the Feed Studies of Turmeric Oleoresin

13-Week Studies	2-Year Studies
Preparation	
Dose formulations were prepared weekly. Premix was prepared by mixing feed and turmeric oleoresin with mortar and pestle; premix and remaining feed were layered in a blender with an intensifier bar for 15 minutes. The intensifier bar was turned on for the first 5 minutes and turned off for the next 10 minutes.	Same as 13-week studies
Lot Number	
2173-A and 2327-A	2452-A and 2558-A
Maximum Storage Time	
14 days	Same as 13-week studies
Storage	
0° ± 5° C in labeled double plastic bags	Same as 13-week studies
Study Laboratory	
EG&G Mason Research Institute, Worcester, MA	Same as 13-week studies
Analytical Chemistry Laboratory	
Midwest Research Institute, Kansas City, MO	Same as 13-week studies

TABLE H2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of Turmeric Oleoresin

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
11 October 1982	12 October 1982	1,000	980[b]	-2
		1,000	1,020[c]	+2
		1,000	980[d]	-2
		5,000	4,980	0
	13 October 1982	10,000	10,100	+1
		25,000	25,000	0
		50,000	56,000[e]	+12[e]
		50,000	51,600[e]	+3
		50,000	49,200[e]	-2
14 October 1982	14 October 1982	50,000	51,200[b]	+2
		50,000	51,200[c]	+2
		50,000	50,500[d]	+1
8 December 1982	13 December 1982	1,000	980	-2
		5,000	4,900	-2
		10,000	9,840	-2
		25,000	25,100	0
		50,000	50,400	+1
19 January 1983	21 January 1983	1,000	1,000	0
		5,000	4,930	-1
		10,000	10,000	0
		25,000	25,000	0
		50,000	50,700	+1

[a] Results of duplicate analyses
[b] Sample taken from top left of blender
[c] Sample taken from top right of blender
[d] Sample taken from bottom of blender
[e] The 50,000 ppm dose formulation was remixed.

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Turmeric Oleoresin

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
12 July 1984	13 July 1984	2,000	1,970[b]	−1
		2,000	1,960[c]	−2
		2,000	2,030[d]	+2
	17 July 1984	10,000	9,950	0
		50,000	51,100[b]	+2
		50,000	51,100[c]	+2
		50,000	50,700[d]	+1
13 September 1984	13 September 1984	2,000	1,940	−3
		2,000	2,120	+6
	14 September 1984	10,000	9,600	−4
		10,000	10,000	0
		50,000	49,100	−2
		50,000	49,600	−1
1 November 1984	2 November 1984	2,000	1,990	0
		2,000	2,030	+2
	5 November 1984	10,000	9,900	−1
		10,000	9,900	−1
		50,000	49,800	0
		50,000	49,900	0
10 January 1985	11 January 1985	2,000	1,990	0
		2,000	1,900	−5
		10,000	9,720	−3
		10,000	9,950	0
		50,000	49,200	−2
		50,000	49,900	0
28 February 1985	1 March 1985	2,000	1,950	−2
		10,000	9,870	−1
		50,000	49,400	−1
17 April 1985	18 April 1985	2,000	2,000	0
		2,000	2,000	0
	19 April 1985	10,000	9,900	−1
		10,000	9,700	−3
		50,000	50,400	+1
		50,000	50,400	+1
20 June 1985	21 June 1985	2,000	1,880	−6
		2,000	1,960	−2
		10,000	9,990	0
		10,000	10,230	+2
		50,000	50,000	0
		50,000	49,300	−1

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Turmeric Oleoresin (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
8 August 1985	9 August 1985	2,000	1,940	-3
		2,000	1,920	-4
		10,000	9,630	-4
		10,000	9,950	0
		50,000	49,300	-1
		50,000	49,900	0
10 October 1985	14 October 1985	2,000	2,050	+3
		2,000	1,980	-1
	15 October 1985	10,000	9,500	-5
		10,000	9,180	-8
		50,000	47,600	-5
		50,000	47,600	-5
5 December 1985	9 December 1985	2,000	1,870	-6
		2,000	1,880	-6
		10,000	9,460	-5
		10,000	9,580	-4
		50,000	49,400	-1
		50,000	49,600	-1
23 January 1986	24 January 1986	2,000	2,070	+4
		2,000	2,090	+5
		10,000	10,110	+1
		10,000	9,780	-2
		50,000	50,400	+1
		50,000	50,200	0
20 March 1986	24 March 1986	2,000	2,030	+2
		2,000	2,040	+2
	25 March 1986	10,000	9,860	-1
		10,000	9,940	-1
		50,000	48,500	-3
		50,000	49,100	-2
22 May 1986	23 May 1986	2,000	2,020	+1
		2,000	2,020	+1
		10,000	10,090	+1
		10,000	10,130	+1
		50,000	51,000	+2
		50,000	51,600	+3
10 July 1986	14 July 1986	2,000	1,980	-1
		2,000	2,010	+1
		10,000	9,800	-2
		10,000	9,880	-1
		50,000	49,500	-1
		50,000	49,900	0

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Turmeric Oleoresin (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
4 September 1986	8 September 1986	2,000	2,170	+9
		10,000	9,820	−2
		50,000	48,700	−3

[a] Results of duplicate analyses
[b] Sample taken from top left of blender
[c] Sample taken from top right of blender
[d] Sample taken from bottom of blender

TABLE H4
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of Turmeric Oleoresin

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13 Weeks			
11 October 1982	10,000	10,100	9,970 ± 60
2 Years			
12 July 1984	2,000	1,980	2,010 ± 170[c]
10 January 1985	50,000	49,200	49,100 ± 600[d]
20 June 1985	10,000	9,990	10,000 ± 200
5 December 1985	2,000	1,870	1,970 ± 120
10 July 1986	50,000	49,500	50,300 ± 200

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard deviation)
[c] Results of seven analyses (mean ± standard deviation)
[d] Results of six analyses (mean ± standard deviation)

APPENDIX I
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF TURMERIC OLEORESIN

TABLE I1 Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Turmeric Oleoresin 264

TABLE I2 Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Turmeric Oleoresin 265

TABLE I3 Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Turmeric Oleoresin 266

TABLE I4 Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Turmeric Oleoresin 267

TABLE I1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Turmeric Oleoresin

	0 ppm		2,000 ppm			10,000 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	15.4	165	15.6	167	188	15.1	166	906	14.9	162	4,615
5	17.1	261	17.3	260	133	17.7	261	680	19.6	254	3,873
9	17.2	332	16.2	322	101	16.9	325	522	17.7	315	2,809
12			15.7	349	90	16.4	351	469	17.0	342	2,495
13	15.0	367	15.0	357	84	15.8	360	439	15.8	346	2,280
17	15.1	389	15.4	374	83	14.5	380	383	16.2	359	2,252
25	19.3	392	21.0	382	110	20.0	380	526	21.4	363	2,948
29	16.9	434	15.9	428	74	16.8	423	397	16.5	403	2,055
33	15.2	446	16.3	441	74	16.7	441	379	17.5	414	2,110
37	16.9	454	17.6	445	79	15.6	440	354	17.9	417	2,150
45	17.2	481	17.1	471	73	17.8	469	380	18.4	444	2,070
49	14.3	485	14.6	479	61	15.1	476	317	16.7	446	1,875
53	16.8	488	17.2	476	72	17.5	481	365	17.7	443	2,001
57	16.5	487	17.6	481	73	17.7	479	370	19.2	453	2,117
65	15.9	494	15.7	487	64	16.0	487	329	17.1	460	1,860
69	15.0	486	15.7	481	65	15.8	487	324	16.5	450	1,830
73	15.2	488	14.8	474	63	15.2	483	315	16.2	447	1,806
77	14.8	485	14.8	473	63	15.0	478	314	16.0	452	1,765
81	14.1	474	14.9	468	64	14.7	478	308	16.3	453	1,795
85	10.9	447	13.9	458	61	11.1	434	256	15.2	444	1,715
89	16.1	460	13.7	457	60	15.6	454	343	15.3	435	1,756
93	15.3	458	14.0	444	63	15.0	442	340	16.4	429	1,915
97	14.6	442	13.6	435	63	13.0	419	311	15.3	415	1,840
101	13.3	436	13.9	421	66	14.7	427	345	16.6	423	1,959
104	13.4	417	14.5	423	68	15.3	428	357	15.6	417	1,872
Mean for weeks											
1-13	16.1	281	16.0	275	119	16.4	278	603	17.0	270	3,214
14-52	16.4	433	16.9	423	79	16.6	422	391	17.8	400	2,209
53-104	14.8	468	14.9	461	65	15.1	462	329	16.4	442	1,864

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

TABLE I2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Turmeric Oleoresin

	0 ppm		2,000 ppm			10,00 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	11.6	130	11.6	127	184	11.1	128	865	10.5	124	4,246
5	11.1	167	11.1	165	135	11.5	163	702	11.6	160	3,631
9	10.3	192	10.9	192	114	11.1	190	581	12.2	187	3,248
13	9.7	204	9.0	199	91	9.5	200	477	10.4	196	2,649
17	10.7	210	10.2	207	99	10.4	207	501	10.5	199	2,635
21	10.0	218	10.2	211	96	10.2	208	491	10.8	202	2,661
25	11.2	225	11.6	219	106	11.5	215	535	11.6	211	2,764
29	11.2	230	9.9	226	88	9.7	221	440	10.6	215	2,457
33	10.8	240	9.9	236	84	9.5	228	415	11.3	224	2,534
37	10.6	246	10.4	242	86	10.7	231	463	11.5	225	2,565
40	11.4	258	11.6	252	92	11.6	243	478	12.4	232	2,672
44	11.5	266	11.2	257	88	11.0	247	445	11.6	236	2,454
48	11.5	277	11.1	269	82	11.8	262	451	12.5	248	2,522
52	12.5	288	13.5	280	96	11.7	270	431	12.1	256	2,369
56	11.4	291	11.6	284	82	11.0	269	408	12.0	254	2,372
60	11.5	303	11.2	298	75	11.5	283	408	12.7	266	2,395
64	11.0	308	10.9	304	72	11.2	288	388	12.4	273	2,269
69	11.6	315	10.5	304	69	11.7	292	401	12.9	278	2,321
72	11.4	319	11.8	311	76	12.5	302	416	13.1	287	2,278
77	11.4	323	11.9	318	75	11.2	308	365	12.8	295	2,163
81	12.3	332	11.7	326	72	11.7	314	373	13.3	305	2,172
84	11.9	338	12.2	331	74	11.6	319	362	13.7	314	2,190
88	11.6	342	10.5	328	64	11.5	319	361	13.0	313	2,078
92	11.2	342	12.4	335	74	10.6	319	334	13.1	318	2,058
96	11.5	338	11.8	335	70	11.9	324	367	12.6	313	2,003
101	12.1	343	11.6	341	68	12.8	328	390	12.9	320	2,026
103	11.9	343	12.2	338	72	11.8	320	370	13.0	314	2,081
Mean for weeks											
1-13	10.7	173	10.7	171	131	10.8	169	656	11.2	166	3,444
14-52	11.2	242	11.0	236	92	10.8	230	465	11.5	222	2,563
53-103	11.6	326	11.6	319	73	11.6	307	380	12.9	296	2,185

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

TABLE I3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Turmeric Oleoresin

	0 ppm		2,000 ppm			10,000 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2[c]	5.3	23.1	4.4	23.4	381	4.6	22.7	2,057	4.5	23.2	8,708
5	4.6	25.0	4.7	25.3	374	4.4	24.9	1,754	4.4	24.9	8,820
9	4.2	28.2	4.7	28.5	333	4.3	28.1	1,517	4.5	28.3	8,029
13	3.9	30.7	3.8	30.8	249	3.9	30.7	1,255	4.0	30.5	6,585
17	4.5	33.5	4.1	33.5	244	3.6	33.2	1,082	4.3	32.6	6,577
21	3.8	34.6	4.0	34.7	232	4.0	34.1	1,173	4.1	33.2	6,248
25	4.2	37.7	4.3	37.9	228	4.2	37.1	1,125	4.4	35.8	6,125
29	4.6	40.1	4.1	40.0	206	4.2	39.1	1,068	4.6	38.2	5,973
33	4.3	41.4	4.4	42.5	205	4.4	41.8	1,050	4.5	39.9	5,599
37	4.5	42.3	4.9	43.0	230	4.9	41.8	1,167	5.0	40.5	6,186
41	4.8	44.6	5.1	45.0	227	4.9	43.8	1,128	5.3	42.5	6,231
45	2.5	45.5	2.6	46.0	114	2.6	44.7	583	2.7	44.1	3,081
49	4.1	46.7	4.6	47.9	192	4.7	47.4	994	4.5	46.3	4,842
53	5.3	46.4	4.8	48.8	195	4.9	46.6	1,061	4.9	46.0	5,378
57	4.1	46.0	4.2	47.5	178	4.5	46.2	968	4.4	45.5	4,837
61	4.5	46.1	4.5	47.5	189	4.5	46.3	980	4.6	45.0	5,144
65	4.9	47.1	4.6	48.4	190	4.8	46.9	1,034	4.9	46.6	5,246
69	4.3	46.5	4.4	48.1	181	4.4	46.8	947	4.5	46.7	4,865
73	3.8	47.4	4.3	47.5	180	4.2	46.3	915	4.3	46.4	4,665
77	4.5	47.5	4.4	47.5	186	4.4	46.2	958	4.4	46.7	4,737
81	4.1	48.4	4.5	48.1	187	4.6	46.6	986	4.6	47.1	4,889
85	4.2	47.9	4.4	48.6	179	4.3	47.2	903	4.5	47.9	4,693
89	4.6	47.2	4.4	47.7	183	4.5	47.0	968	4.8	47.0	5,127
93	4.4	47.4	4.4	46.2	191	4.3	45.7	949	4.7	45.2	5,210
97	4.4	46.9	4.5	45.8	197	4.7	45.6	1,037	4.8	44.9	5,365
101	4.4	46.9	4.5	46.2	197	4.4	46.0	959	4.6	45.1	5,125
104	4.6	47.4	4.9	46.0	213	4.6	47.5	972	4.7	44.9	5,195
Mean for weeks											
1-13	5.8	26.8	5.6	27.0	430	5.5	26.6	2,160	5.5	26.7	10,712
14-52	4.1	40.7	4.2	41.2	209	4.2	40.3	1,041	4.4	39.2	5,651
53-104	4.4	47.1	4.5	47.4	189	4.5	46.5	974	4.6	46.1	5,034

[a] Grams of feed consumed per animal per day
[b] Milligrams of turmeric oleoresin consumed per day per kilogram body weight
[c] Average of feed consumption for weeks 1 and 2

TABLE I4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Turmeric Oleoresin

	0 ppm		2,000 ppm			10,000 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2[c]	6.7	8.6	6.3	17.3	728	6.1	16.5	3,760	4.6	16.6	13,478
5	4.8	20.1	4.8	19.8	488	4.7	19.8	2,360	4.7	19.9	11,812
13	5.6	24.3	5.2	24.2	433	5.3	24.7	2,137	5.2	23.9	10,821
17			4.8	27.3	354	4.6	26.3	1,746	4.9	25.8	9,488
21	4.3	27.9	4.0	27.4	292	4.8	28.4	1,683	4.9	27.8	8,795
25	5.8	31.7	5.7	31.0	368	5.2	30.5	1,708	5.7	29.0	9,865
29	5.4	33.4	5.3	32.6	325	4.9	31.9	1,545	6.3	30.3	10,391
33	5.3	35.2	5.4	34.8	312	5.2	33.9	1,537	5.7	31.7	9,009
37	5.3	37.9	5.7	36.5	310	5.7	35.2	1,622	5.9	33.5	8,857
41	5.1	39.2	5.2	38.4	273	5.0	37.9	1,326	6.0	34.9	8,528
45	4.6	40.6	4.7	40.8	232	4.6	40.5	1,138	4.8	37.4	6,474
49	4.5	42.5	4.6	43.1	214	4.4	43.5	1,015	4.5	39.4	5,725
53	4.3	44.3	4.7	43.8	213	4.7	42.7	1,110	4.7	40.4	5,814
57	4.7	44.0	4.5	44.5	204	4.5	42.9	1,053	4.7	40.1	5,817
61	4.8	44.3	5.2	45.0	233	5.2	43.3	1,204	5.3	41.0	6,497
65	4.8	45.6	4.9	46.1	214	4.9	44.4	1,113	4.9	41.6	5,866
69	4.6	46.3	5.0	45.9	217	4.5	45.2	1,004	4.9	41.9	5,891
73	4.6	46.7	4.5	45.5	199	4.5	43.5	1,038	4.6	40.8	5,665
77	4.7	45.6	4.6	45.0	204	4.7	43.5	1,085	4.9	40.6	6,004
81	6.0	47.1	6.2	46.9	265	5.7	45.3	1,258	6.1	42.9	7,114
85	4.9	47.4	5.2	47.1	219	5.1	45.8	1,109	5.4	42.8	6,289
89	4.6	47.0	4.6	45.8	203	4.8	43.2	1,107	4.6	41.6	5,566
93	4.6	45.4	5.1	45.1	224	4.7	42.6	1,098	5.3	41.6	6,324
97	4.9	45.0	5.4	44.5	243	5.1	41.7	1,229	5.5	40.6	6,792
101	5.1	45.0	5.3	44.5	238	5.4	42.1	1,279	5.6	40.8	6,921
104	5.1	45.2	5.5	44.1	248	5.2	42.3	1,234	5.3	40.6	6,505
Mean for weeks											
1-13	8.0	20.5	7.6	20.4	793	7.4	20.3	3,973	6.4	20.1	16,864
14-52	5.0	36.1	5.1	34.7	298	4.9	34.2	1,480	5.4	32.2	8,570
53-104	4.8	45.6	5.1	45.3	223	4.9	43.5	1,137	5.1	41.2	6,219

[a] Grams of feed consumed per animal per day
[b] Milligrams of turmeric oleoresin consumed per day per kilogram body weight
[c] Average of feed consumption for weeks 1 and 2

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

TABLE J1 Ingredients of NIH-07 Rat and Mouse Ration 270
TABLE J2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 270
TABLE J3 Nutrient Composition of NIH-07 Rat and Mouse Ration 271
TABLE J4 Contaminant Levels in NIH-07 Rat and Mouse Ration 272

TABLE J1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE J2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE J3
Nutrient Composition of NIH-07 Rat and Mouse Ration[a]

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.16 ± 0.52	21.0 – 23.2	20
Crude fat (% by weight)	5.65 ± 0.41	4.8 – 6.3	20
Crude fiber (% by weight)	3.50 ± 0.53	2.8 – 5.4	20
Ash (% by weight)	6.65 ± 0.44	6.0 – 7.9	20
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.060	1.210 – 1.390	8
Cystine	0.306 ± 0.084	0.181 – 0.400	8
Glycine	1.150 ± 0.047	1.060 – 1.210	8
Histidine	0.576 ± 0.024	0.531 – 0.607	8
Isoleucine	0.917 ± 0.029	0.881 – 0.944	8
Leucine	1.946 ± 0.055	1.850 – 2.040	8
Lysine	1.270 ± 0.058	1.200 – 1.370	8
Methionine	0.448 ± 0.128	0.306 – 0.699	8
Phenylalanine	0.987 ± 0.140	0.665 – 1.110	8
Threonine	0.877 ± 0.042	0.824 – 0.940	8
Tryptophan	0.236 ± 0.176	0.107 – 0.671	8
Tyrosine	0.676 ± 0.105	0.564 – 0.794	8
Valine	1.103 ± 0.040	1.050 – 1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830 – 2.570	7
Linolenic	0.280 ± 0.040	0.210 – 0.320	7
Vitamins			
Vitamin A (IU/kg)	9,360 ± 3,839	4,500 – 19,000	20
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.406	22.5 – 48.9	8
Thiamine (ppm)	21.40 ± 3.86	18.0 – 37.0	20
Riboflavin (ppm)	7.92 ± 0.87	6.10 – 9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0 – 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0 – 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60 – 14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80 – 3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19 – 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 – 65.0	8
Choline (ppm)	3,089 ± 328.69	2,400 – 3,430	8
Minerals			
Calcium (%)	1.11 ± 0.11	0.90 – 1.30	19
Phosphorus (%)	0.91 ± 0.06	0.81 – 1.00	20
Potassium (%)	0.883 ± 0.078	0.772 – 0.971	6
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.313 ± 0.390	0.258 – 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151 – 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208 – 0.420	8
Iron (ppm)	360.54 ± 100	255.0 – 523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70 – 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10 – 64.50	8
Copper (ppm)	11.06 ± 2.50	8.090 – 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52 – 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04 – 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490 – 0.780	4

[a] One lot milled on 14 August 1984 was not analyzed for calcium and the lot milled on 7 May 1985 was used for less than 4 weeks due to high concentrations of lead.

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

	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.70 ± 0.19	0.22 - 0.98	20
Cadmium (ppm)[b]	0.11 ± 0.03	<0.10 - 0.20	20
Lead (ppm)	0.52 ± 0.19	0.14 - 0.87	20
Mercury (ppm)	<0.05		20
Selenium (ppm)	0.37 ± 0.07	0.17 - 0.48	20
Aflatoxins (ppb)	<5.0		20
Nitrate nitrogen (ppm)[c]	15.41 ± 5.01	6.70 - 22.0	20
Nitrite nitrogen (ppm)[c]	0.27 ± 0.48	<0.10 - 2.10	20
BHA (ppm)[d]	2.45 ± 0.89	<2.00 - 5.00	20
BHT (ppm)[d]	2.00 ± 1.12	<1.00 - 4.00	20
Aerobic plate count (CFU/g)[e]	121,930 ± 146,182	3,900 - 450,000	20
Coliform (MPN/g)[f]	285 ± 567	<3.00 - 2,400	20
E. coli (MPN/g)	12.55 ± 33.55	<3.00 - 150.0	20
E. coli (MPN/g)[g]	5.31 ± 9.31	<3.00 - 43.0	19
Total nitrosoamines (ppb)[h]	6.25 ± 3.01	1.50 - 13.30	20
N-Nitrosodimethylamine (ppb)[h]	5.63 ± 2.78	1.20 - 13.0	20
N-Nitrosopyrrolidine (ppb)[h]	0.62 ± 0.61	0.30 - 2.70	20
Pesticides (ppm)			
α-BHC[i]	<0.01		20
β-BHC	<0.02		20
γ-BHC	<0.01		20
δ-BHC	<0.01		20
Heptachlor	<0.01		20
Aldrin	<0.01		20
Heptachlor epoxide	<0.01		20
DDE	<0.01		20
DDD	<0.01		20
DDT	<0.01		20
HCB	<0.01		20
Mirex	<0.01		20
Methoxychlor	<0.05		20
Dieldrin	<0.01		20
Endrin	<0.01		20
Telodrin	<0.01		20
Chlordane	<0.05		20
Toxaphene	<0.1		20
Estimated PCBs	<0.2		20
Ronnel	<0.01		20
Ethion	<0.02		20
Trithion	<0.05		20
Diazinon	<0.1		20
Methyl parathion	<0.02		20
Ethyl parathion	<0.02		20
Malathion[j]	0.26 ± 0.70	0.05 - 3.20	20
Endosulfan 1	<0.01		20
Endosulfan 2	<0.01		20
Endosulfan sulfate	<0.03		20

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

[a] For values less than the limit of detection, the detection limit is given as the mean.
[b] The lots milled on 9 May 1984 and 8 October 1985 contained 0.20 ppm.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony-forming unit
[f] MPN = most probable number
[g] Excludes one high value of 150 MPN/g obtained from the lot milled on 17 October 1984.
[h] All values corrected for percent recovery.
[i] BHC = hexachlorocyclohexane or benzene hexachloride
[j] Seven lots contained more than 0.05 ppm, including one lot milled on 7 May 1985 that contained 3.20 ppm.

APPENDIX K
SENTINEL ANIMAL PROGRAM

METHODS 276
TABLE K1 Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of Turmeric Oleoresin 278

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. The sentinel animals come from the same production source and weanling groups as animals used for the studies of chemical compounds, and these animals and the study animals are subject to identical environmental conditions.

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected, allowed to clot, and the serum separated. The serum was cooled and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times during the studies at which blood was collected for serological testing are also listed.

Test and Method	Time of Analysis
Rats	
13-Week Study	
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	Study termination
Sendai	Study termination
KRV (Kilham rat virus)	Study termination
H-1 (Toolan's H-1 virus)	Study termination
Complement Fixation	
RCV (rat coronavirus)	Study termination
2-Year Study	
Hemagglutination Inhibition	
KRV	6, 12, 18, and 24 months
H-1	6, 12, 18, and 24 months
ELISA	
Mycoplasma pulmonis	6, 12, 18, and 24 months
Mycoplasma arthritidis	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
RCV/SDA (rat coronavirus/sialodacryoadentitis virus)	6, 12, 18, and 24 months
CARB (cilia-associated respiratory bacillus)	24 months

Mice

13-Week Study

Hemagglutination Inhibition	
PVM	Study termination
Reovirus 3	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Polyoma virus	Study termination
Sendai	Study termination
MVM (minute virus of mice)	Study termination
Ectromelia virus (mouse pox)	Study termination
Complement Fixation	
Mouse adenoma virus	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
MHV (mouse hepatitis virus)	Study termination

2-Year Study

Hemagglutination Inhibition	
K (papovirus)	6, 12, 18 (females), 22, and 24 months
Polyoma virus	6, 12, 18 (females), 22, and 24 months
MVM	6, 12, 18 (females), 22, and 24 months
KRV	18 months (males)
H-1	18 months (males)
Complement Fixation	
LCM	6, 12, 18 (females), 22, and 24 months
ELISA	
M. pulmonis	6, 12, 18, 22, and 24 months
M. arthritidis	6, 12, 18, 22, and 24 months
PVM	6, 12, 18, 22, and 24 months
Sendai	6, 12, 18, 22, and 24 months
MHV	6, 12, 18 (females), 22, and 24 months
Ectromelia virus	6, 12, 18 (females), 22, and 24 months
GDVII	6, 12, 18 (females), 22, and 24 months
Reovirus 3	6, 12, 18 (females), 22, and 24 months
Mouse adenoma virus	6, 12, 18 (females), 22, and 24 months
RCV/SDA	18 months (males)
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	6, 12, 18 (females), 22, and 24 months

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of Turmeric Oleoresin

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies			
Rats	13 weeks	0/10	None positive
Mice	13 weeks	0/9	None positive
2-Year Studies			
Rats	6 months	10/10	RCV/SDA
	12 months	10/10	RCV/SDA
	18 months	2/10	KRV
		1/10	*M. arthritidis*
		10/10	RCV/SDA
	24 months	10/10	RCV/SDA
Mice			
	6 months	0/10	None positive
	12 months	0/10	None positive
	18 months	1/10	Sendai
	22 months	0/3	None positive
	24 months	1/10	*M. arthritidis*

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF AUGUST 1993

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

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF AUGUST 1993 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Hellow 4
434	1,3-Butadiene

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