NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of *trans*-Cinnamaldehyde (Microencapsulated) (CAS No. 14371-10-9) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies)

NTP TR 514

FEBRUARY 2004

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF *trans*-CINNAMALDEHYDE (MICROENCAPSULATED)

(CAS NO. 14371-10-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

February 2004

NTP TR 514

NIH Publication No. 04-4448

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

FOREWORD

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

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

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

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

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

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CONTENTS

SUMMARY

Background

trans-Cinnamaldehyde is used in foods, drinks, and cosmetics to give a cinnamon flavor and fragrance. We studied the effects of *trans*-cinnamaldehyde on male and female rats and mice to identify potential toxic or cancer-related hazards to humans.

Methods

Because *trans*-cinnamaldehyde can evaporate easily, we enclosed it in starch microcapsules and placed them in the feed of rats and mice for two years. The doses given were 1,000, 2,100, or 4,100 parts per million (ppm) *trans*-cinnamaldehyde (equivalent to 0.1%, 0.21%, or 0.41%). Control animals received empty starch microcapsules in their feed. Tissues from more than 40 sites were examined for every animal.

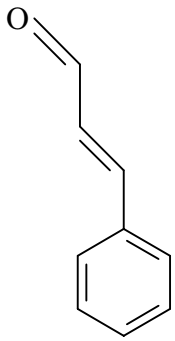
Results

Rats receiving 4,100 ppm *trans*-cinnamaldehyde and mice receiving 2,100 or 4,100 ppm weighed less on average than the control animals, although they ate the same amount of feed. No more tumors or other toxic effects were observed in the groups of rats or mice given *trans*-cinnamaldehyde compared with the animals that were not. Mice receiving 4,100 ppm *trans*-cinnamaldehyde developed pigmentation of the olfactory epithelium of the nose.

Conclusions

We conclude that *trans*-cinnamaldehyde did not cause cancer in male or female rats or in male or female mice.

ABSTRACT



***trans*-CINNAMALDEHYDE**

CAS No. 14371-10-9

Chemical Formula: C_9H_8O Molecular Weight: 132.16

Synonyms: *trans*-Benzenepropenal; (E)-cinnamaldehyde; cinnamaldehyde; *trans*-cinnamic aldehyde; (E)-cinnamyl aldehyde; *trans*-cinnamylaldehyde; (E)-3-phenylacrolein; (E)-3-phenylpropenal; *trans*-3-phenyl-2-propenal; (E)-3-phenylprop-2-enal; (E)-3-phenyl-2-propenal; *trans*-3-phenylpropenal; 2-propenal, 3-phenyl-, (E)-; 2-propenal, 3-phenyl

Cinnamaldehyde is used in foods, beverages, medical products, perfumes, cosmetics, soaps, detergents, creams, and lotions. Cinnamaldehyde has been used as a filtering agent and a rubber reinforcing agent and is used as a brightener in electroplating processes, as an animal repellent, as an insect attractant, and as an antifungal agent. *trans*-Cinnamaldehyde was nominated for study by the Food and Drug Administration based on its widespread use as a flavor and fragrance ingredient and its structural similarity to cinnamyl anthranilate and 3,4,5-trimethoxy cinnamaldehyde, two known rodent carcinogens. Male and female F344/N rats and B6C3F$_1$ mice were exposed to *trans*-cinnamaldehyde (at least 95% pure) in feed for 3 months or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, and mouse peripheral blood erythrocytes.

3-Month Study in Rats

Groups of 10 male and 10 female F344/N rats were fed diets containing 4,100, 8,200, 16,500, or 33,000 ppm microencapsulated *trans*-cinnamaldehyde (equivalent to average daily doses of approximately 275, 625, 1,300, or 4,000 mg *trans*-cinnamaldehyde/kg body weight to males and 300, 570, 1,090, or 3,100 mg/kg to females) for 3 months. Additional groups of 10 male and 10 female rats received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). All rats survived to the end of the study. Mean body weights of all exposed groups of males and 16,500 and 33,000 ppm females were significantly less than those of the vehicle controls, and 33,000 ppm males lost weight during the study. Feed consumption by exposed groups of males and females was less than that by the vehicle controls throughout the study. Clinical chemistry results of these studies indicated that

trans-cinnamaldehyde administration, at the doses selected, induced an increase in serum bile acid concentration that suggests a hepatic effect in both male and female rats. Gross lesions observed at necropsy included multifocal to diffuse white nodules of the forestomach mucosa in 8,200 ppm or greater males and females. Increased incidences of nonneoplastic lesions of the forestomach included squamous epithelial hyperplasia in 8,200 ppm or greater males and females and chronic active inflammation in 33,000 ppm males and 16,500 and 33,000 ppm females.

3-Month Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were fed diets containing 4,100, 8,200, 16,500, or 33,000 ppm microencapsulated *trans*-cinnamaldehyde (equivalent to average daily doses of approximately 650, 1,320, 2,550, and 5,475 mg/kg to males and 625, 1,380, 2,680, and 5,200 mg/kg to females) for 3 months. Additional groups of 10 male and 10 female mice received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). One vehicle control male, one 4,100 ppm male, and one 33,000 ppm male died during the first week of the study due to inanition that resulted from difficulty with the feeder. Five 16,500 ppm and eight 33,000 ppm male mice died during weeks 2 and 3 due to unpalatability of the dosed feed. Mean body weights of all exposed groups of males and of females exposed to 8,200 ppm or greater were significantly less than those of the vehicle controls. Feed consumption by 16,500 and 33,000 ppm mice was less than that by the vehicle controls during weeks 1 and 2. The incidence of squamous epithelial hyperplasia of the forestomach mucosa in 33,000 ppm females was significantly increased, and olfactory epithelial degeneration of the nasal cavity occurred in 16,500 and 33,000 ppm males and females.

2-Year Study in Rats

Groups of 50 male and 50 female F344/N rats were fed diets containing 1,000, 2,100, or 4,100 ppm microencapsulated *trans*-cinnamaldehyde for 2 years. Additional groups of 50 male and 50 female rats received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). Dietary concentrations of 1,000, 2,100, or 4,100 ppm delivered average daily doses of approximately 50, 100, or 200 mg/kg to males and females. Survival of 4,100 ppm males was greater than that of the vehicle controls. Mean body weights of 4,100 ppm males and females were generally less than those of the vehicle controls throughout the study. Feed consumption by 2,100 and 4,100 ppm males and 4,100 ppm females was less than that by the vehicle controls at the beginning and end of the study. There were no neoplasms or nonneoplastic lesions that were attributed to exposure to *trans*-cinnamaldehyde.

2-Year Study in Mice

Groups of 50 male and 50 female B6C3F$_1$ mice were fed diets containing 1,000, 2,100, or 4,100 ppm microencapsulated *trans*-cinnamaldehyde for 2 years. Additional groups of 50 male and 50 female mice received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). Dietary concentrations of 1,000, 2,100, or 4,100 ppm delivered average daily doses of approximately 125, 270, or 550 mg/kg to males and females. Survival of males in the 2,100 ppm group was less than that of the vehicle control group. Mean body weights of 2,100 and 4,100 ppm males and females were generally less than those of the vehicle controls throughout the study, and mean body weights of 1,000 ppm males were less after week 74. Feed consumption by exposed mice was similar to that by the vehicle controls. The incidences of olfactory epithelial pigmentation in 4,100 ppm males and in 2,100 and 4,100 females were significantly greater than those in vehicle controls. There were no neoplasms that were attributed to exposure to *trans*-cinnamaldehyde.

Genetic Toxicology

trans-Cinnamaldehyde was mutagenic in *S. typhimurium* strain TA100 in the presence of induced mouse liver S9 activation enzymes only. All other strain and activation combinations, including the standard rat and hamster-derived liver S9 fractions yielded negative results. *trans*-Cinnamaldehyde induced sister chromatid exchanges in Chinese hamster ovary cells with and without induced rat liver S9 activation. No significant increase in the frequency of chromosomal aberrations occurred in Chinese hamster ovary cells cultured with

trans-cinnamaldehyde, with or without induced rat liver S9. In tests for induction of germ cell genetic damage in male *Drosophila melanogaster*, *trans*-cinnamaldehyde induced a significant increase in the frequency of sex-linked recessive lethal mutations when administered by abdominal injection; however, no induction of reciprocal translocations occurred in germ cells of treated males. No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood of male or female mice administered *trans*-cinnamaldehyde in dosed feed for 3 months.

CONCLUSIONS

Under the conditions of this 2-year feed study, there was *no evidence of carcinogenic activity** of *trans*-cinnamaldehyde in male or female F344/N rats exposed to 1,000, 2,100, or 4,100 ppm. There was *no evidence of carcinogenic activity* of *trans*-cinnamaldehyde in male or female $B6C3F_1$ mice exposed to 1,000, 2,100, or 4,100 ppm.

Exposure to *trans*-cinnamaldehyde resulted in olfactory epithelial pigmentation in male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *trans*-Cinnamaldehyde

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in feed	Vehicle control, 1,000, 2,100, or 4,100 ppm	Vehicle control, 1,000, 2,100, or 4,100 ppm	Vehicle control, 1,000, 2,100, or 4,100 ppm	Vehicle control, 1,000, 2,100, or 4,100 ppm
Body weights	4,100 ppm group less than that of the vehicle control group	4,100 ppm group less than that of the vehicle control group	2,100 and 4,100 ppm groups less than that of the vehicle control group	2,100 and 4,100 ppm groups less than that of the vehicle control group
Survival rates	31/50, 36/50, 27/50, 41/50	36/50, 33/50, 35/49, 33/50	47/50, 46/50, 39/50, 49/50	41/50, 37/50, 44/50, 43/50
Nonneoplastic effects	None	None	Nose: olfactory epithelium, pigmentation (0/48, 0/48, 3/48, 26/50)	Nose: olfactory epithelium, pigmentation (0/50, 0/50, 8/50, 46/50)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA102, TA104, TA1535, and TA1537 with and without S9; positive in strain TA100 with mouse S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro:*	Positive with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro:*	Negative with and without S9			
Sex-linked recessive lethal mutations				
Drosophila melanogaster:	Positive			
Reciprocal translocations				
Drosophila melanogaster:	Negative			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo:*	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on *trans*-cinnamaldehyde on September 5, 2002, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

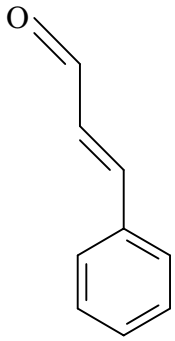
On September 5, 2002, the draft Technical report on the toxicology and carcinogenesis studies of *trans*-cinnamaldehyde (microencapsulated) received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. M. J. Hooth, NIEHS, introduced the toxicology and carcinogenesis studies of *trans*-cinnamaldehyde by describing its use as a flavoring agent and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related olfactory pigmentation. The proposed conclusions were *no evidence of carcinogenic activity* in male or female F344/N rats or B6C3F_1 mice.

The three principal reviewers, Drs. Vore, Boekelheide, and Ho, all agreed with the proposed conclusions. Dr. Elwell noted the decreases in liver tumor incidences in male and female mice and asked if these could be related to decreased body weights. Dr. Hooth replied that, extrapolating from known body weight relationships, the decrease in body weight in this study would account for some, but not all, of the liver tumor decrease. She also mentioned reports in the literature of antimutagenic and anticarcinogenic effects of *trans*-cinnmaldehyde and confirmed the one weakly positive mutagenic response in the *Salmonella* TA100 strain.

Dr. Vore moved that the conclusions be accepted as written, and Dr. Roberts seconded the motion, which was approved unanimously with 10 votes.

INTRODUCTION



***trans*-CINNAMALDEHYDE**

CAS No. 14371-10-9

Chemical Formula: C_9H_8O Molecular Weight: 132.16

Synonyms: *trans*-Benzenepropenal; (E)-cinnamaldehyde; cinnamaldehyde; *trans*-cinnamic aldehyde; (E)-cinnamyl aldehyde; *trans*-cinnamylaldehyde; (E)-3-phenylacrolein; (E)-3-phenylpropenal; *trans*-3-phenyl-2-propenal; (E)-3-phenylprop-2-enal; (E)-3-phenyl-2-propenal; *trans*-3-phenylpropenal; 2-propenal, 3-phenyl-, (E)-; 2-propenal, 3-phenyl

CHEMICAL AND PHYSICAL PROPERTIES

The studies conducted by the National Toxicology Program were on *trans*-cinnamaldehyde (CAS No. 14371-10-9). In the majority of the literature, the stereochemistry is not given by the author(s) in which case, cinnamaldehyde is assigned CAS No. 104-55-2 even though cinnamaldehyde contains more than 97% *trans*-cinnamaldehyde. *trans*-Cinnamaldehyde is generally produced commercially (*Kirk-Othmer,* 2001). Properties of cinnamaldehyde with and without the stereochemical designation are given in this section.

Cinnamaldehyde is a yellowish oily liquid with a strong odor of cinnamon and a sweet taste. It thickens and darkens in color upon exposure to air and light (*Merck Index*, 1996; *Hawley's,* 1997). It has a boiling point of 253° C, a melting point of –7.5° C, a vapor pressure of 1 mm Hg at 76° C, and a specific gravity of 1.048 to 1.052 at 25°/25° C. Cinnamaldehyde is soluble in ether and chloroform, and it is miscible with alcohol and oils. The solubility of cinnamaldehyde in water is 1.42 g/L at 25° C (*Merck Index*, 1996; HSDB, 2001).

trans-Cinnamaldehyde has a boiling point of 253° C, a melting point of –7.5° C, a vapor pressure of 49.0 mm Hg at 125° C, and a specific gravity of 1.0497 at 20°/4° C. *trans*-Cinnamaldehyde is soluble in ether, chloroform, and alcohol (Lide, 1999).

PRODUCTION, USE, AND HUMAN EXPOSURE

Cinnamaldehyde is the primary ingredient of cassia and cinnamon oils isolated from cinnamon trees found in China and other Asian countries. Cinnamaldehyde occurs naturally in Chinese cassia oil obtained from the leaves and twigs of *Cinnamomum cassia* (*Kirk-Othmer*, 2001). It has been identified in the leaves of cinnamon trees from Sri Lanka (*Cinnamomum zeylanicum*) and Madagascar and in the bark of cinnamon trees from Sri Lanka, Seychelles, and Japan (*Cinnamomum laureirii*) in varying amounts (0.1%-76%) (*Fenaroli's*, 1975). *trans*-Cinnamaldehyde is the major component of cinnamon cassia and cinnamon bark oils at concentrations of 81 and 62 mg/100 mL, respectively (Friedman *et al.*,

2000). Cinnamaldehyde has also been identified in the essential oils of hyacinth, myrrh, Bulgarian rose, patchouli, and other plants (*Fenaroli's*, 1975). It can be isolated from the wood-rotting fungus *Stereum subpileatum* (*Merck Index*, 1996).

Cinnamaldehyde is manufactured synthetically by the condensation of benzaldehyde and acetaldehyde in the presence of sodium hydroxide, calcium hydroxide, hydrochloric acid, or sodium ethylate or by the condensation of styrene with formylmethylaniline in the presence of phosphorus oxychloride. Cinnamaldehyde is also prepared from 2-chloroallylbenzene and by the oxidation of cinnamyl alcohol (*Merck Index*, 1996; HSDB, 2001).

Cinnamaldehyde is used primarily to impart a cinnamon flavor in foods and beverages (including liquors, cordials, and medicinals) and to impart a cinnamon fragrance in medical products, perfumes, and cosmetics. In food and beverages, it is found in concentrations of up to 7.7 ppm in ice cream and ices, 9 ppm in nonalcoholic beverages, 20 ppm in condiments, 60 ppm in meats, 700 ppm in candy, 2,000 ppm in baby food and desserts, 2,200 ppm in breakfast cereals, 3,500 ppm in baked goods, 4,900 ppm in chewing gum, and 6,400 ppm in fruits and juices (*Fenaroli's*, 1975; Blakemore and Thompson, 1983). It is also used in soaps (0.01%-0.2%), detergents (0.001%-0.02%), creams and lotions (0.003%-0.02%), and perfumes (0.1%-0.8%) (Opdyke, 1979).

trans-Cinnamaldehyde was extracted from commercial cinnamon-containing foods, including applesauces, breads, cereals, cookies, juices, and puddings, and quantitated by a gas chromatographic/mass spectrophotometric procedure (Friedman *et al.,* 2000). The cinnamaldehyde content ranged from trace amounts in apple and orange juices to 12.3 mg/100 g (123 ppm) in apple cinnamon cereals and 31.1 mg/100 g (311 ppm) in cinnamon swirl bread (highest value). Varying amounts of *trans*-cinnamaldehyde were found in similar food products; the *trans*-cinnamaldehyde values for five samples of cereals ranged from 1.8 to 21.9 mg/100 g. The amount of *trans*-cinnamaldehyde was also measured in three commercial brands of cinnamon powder and two brands of cinnamon sticks purchased in grocery stores. The concentration of *trans*-cinnamaldehyde varied widely in the samples, from 8.2 to 27.5 mg/g in the cinnamon powders and from 10.3 to 24.7 mg/g in the cinnamon sticks.

Cinnamaldehyde has been used as a filtering agent and a rubber reinforcing agent (HSDB, 2001). It is used as a brightener in electroplating processes, as an animal repellent, as an insect attractant, and as an antifungal agent (*Kirk-Othmer*, 2001). The Environmental Defense Scorecard (2001) lists 10 pesticidal/repellent products that contain cinnamaldehyde in concentrations ranging from 0.05% to 50% by mass. *trans*-Cinnamaldehyde purified from *Cinnamomum cassia* bark exhibited strong insecticidal and fumigant activities, producing 100% and 73% mortality against the oak nut weevil (*Mechoris ursulus* Roelofs) when tested by filter paper diffusion and fumigation methods, respectively (Park *et al.*, 2000).

Production estimates in the United States were 711,000 and 800,000 kg in 1972 and 1973, respectively (HSDB, 2001). Based on U.S. International Trade Commission figures, cinnamaldehyde production estimates were 850 and 975 metric tons in 1980 and 1990, respectively (*Kirk-Othmer*, 2001). Worldwide annual industrial usage of cinnamaldehyde was estimated to be 159 metric tons (Smith *et al.*, 2000). The consumption of cinnamaldehyde as a flavoring and fragrance ingredient in the United States was estimated to be 500,000 kg per year based on sales reported by the U.S. International Trade Commission (Blakemore and Thompson, 1983). In 1987, United States industries used 150,000 kg of cinnamaldehyde in food (NRC, 1989). Although no import or export information was available for cinnamaldehyde, approximately 333 metric tons of cassia oil were imported into the United States in 1990 (Clark, 1991).

Cinnamaldehyde is approved by the Food and Drug Administration for use in foods as a synthetic flavoring substance and adjuvant (21 CFR § 182.60). The Flavor and Extract Manufacturers' Association has given cinnamaldehyde Generally Recognized As Safe status (FEMA no. 2286) in the United States (*Kirk-Othmer*, 2001). Cinnamaldehyde has been used in some fragrance compositions, but the Research Institute for Fragrance Materials noted its potential for sensitization and limited its use in perfumes for skin contact at 1% in the formula (*Kirk-Othmer*, 2001).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

The metabolism of *trans*-[3-^{14}C]-cinnamaldehyde was investigated in male and female F344 rats and CD-1 mice at doses of 2 or 250 mg/kg body weight given by intraperitoneal injection and in male rats and mice at 250 mg/kg by gavage (Peters and Caldwell, 1994). More than 94% of the administered ^{14}C dose was recovered in the urine and feces 72 hours after dosing in both species with 70% to 90% present in the urine within 24 hours. Less than 2% of the administered dose was found in the carcasses 72 hours after dosing. In both species, the major urinary metabolites of *trans*-[3-^{14}C]-cinnamaldehyde coeluted with hippuric acid and benzoyl glucuronide and accounted for more than 70% of the ^{14}C in the urine within 24 hours. Other minor metabolites included 3-hydroxy-3-phenylpropionic acid and benzoic acid. Cinnamoylglycine was formed to a considerable extent only in mice. In addition, two unidentified urinary metabolites in the rats and three in the mice accounted for approximately 6% of the administered ^{14}C dose 24 hours after dosing. The unknown metabolites were identified subsequently as mercapturic acids derived from the direct conjugation of cinnamaldehyde with glutathione. The excretion pattern and metabolic profile (Figure 1) of *trans*-[3-^{14}C]-cinnamaldehyde in rats and mice were not significantly affected by sex, dose, or route of administration.

Toxicokinetic studies of cinnamaldehyde were conducted in male and female F344 rats (Yuan *et al.*, 1992a). Blood concentrations of cinnamaldehyde following intravenous administration of 5, 15, or 25 mg/kg decreased in a biphasic manner. The initial rapid phase (half-life of 4 to 5 minutes) correlated with the rapid appearance of cinnamic acid in the blood. The authors estimated that 37% to 60% of the cinnamaldehyde was oxidized to cinnamic acid in the first 30 minutes. An *in vitro* study determined a 4.5 minute half-life for cinnamaldehyde in rat blood (Yuan *et al.*, 1992b). The second phase (half-life of 1.7 hours) was hypothesized as release of cinnamaldehyde from protein adducts formed during the initial phase. Gavage administration of 50, 250, or 500 mg/kg cinnamaldehyde in corn oil produced much lower concentrations of cinnamaldehyde and cinnamic acid in blood than even the 5 mg/kg intravenous dose. Neither cinnamaldehyde [limit of quantitation (LOQ), 0.1 µg/mL] nor cinnamic acid (LOQ, 1 µg/mL) could be detected following the 50 mg/kg dose. The data for the two higher doses could not be modeled, but the bioavailability was estimated as less than 20% from comparison of the area under the concentration versus time curves. Hippuric acid was the major urinary metabolite. Excretion of hippuric acid was highly correlated (R=0.999) with the dose of cinnamaldehyde over the 50 to 500 mg/kg dose range, and urinary hippuric acid was proposed as an index of exposure to cinnamaldehyde.

A subsequent study evaluated the bioavailability of microencapsulated cinnamaldehyde (Yuan *et al.*, 1993). Rats were gavaged with cinnamaldehyde in corn oil using either microencapsulated or neat chemical at doses of 50, 250, or 500 mg/kg. No differences between the two formulations were observed in either the cinnamaldehyde blood concentration profiles or in the rate of urinary hippuric acid excretion. Similar toxicokinetic values (C_{max}, T_{max}, $t_{1/2}$, AUC, and bioavailability) were obtained for neat and microencapsulated cinnamaldehyde. The calculated oral bioavailability of cinnamaldehyde was less than 20% for the 250 and 500 mg/kg doses, and approximately 75% of the dose was metabolized to hippuric acid at 50 hours. Cinnamaldehyde concentrations were stable following microencapsulation and blending into rodent feed. These data indicate that microencapsulation of cinnamaldehyde does not affect its bioavailability or metabolism.

The absorption, distribution, and excretion of radiolabeled [^{14}C]-cinnamaldehyde were studied in male F344 rats following oral administration (acute and subacute) of 5, 50, or 500 mg/kg (Sapienza *et al.*, 1993). Cinnamaldehyde was labeled with [^{14}C] in the side chain (C-3 position). For the acute studies, rats were given a single radioactive dose of cinnamaldehyde in trioctanoin by gavage. For the subacute studies, rats were gavaged with unlabeled cinnamaldehyde once per day for 7 days at one of the dose concentrations followed by a single oral dose of [^{14}C]-cinnamaldehyde 24 hours after administration of the last unlabeled dose. Similar excretion patterns and tissue distribution of radiolabel were observed after single and multiple oral doses of [^{14}C]-cinnamaldehyde. In the acute study, averages of 83.5% and 4.1% of the administered dose were recovered in the urine and feces, respectively, after 24 hours. In the subacute study, averages of 81% and 5.9% of the administered dose were recovered in the urine and feces, respectively, after 24 hours. The cinnamaldehyde-derived radioactivity was distributed mainly into the gastrointestinal tract, liver, and kidney, but was rapidly

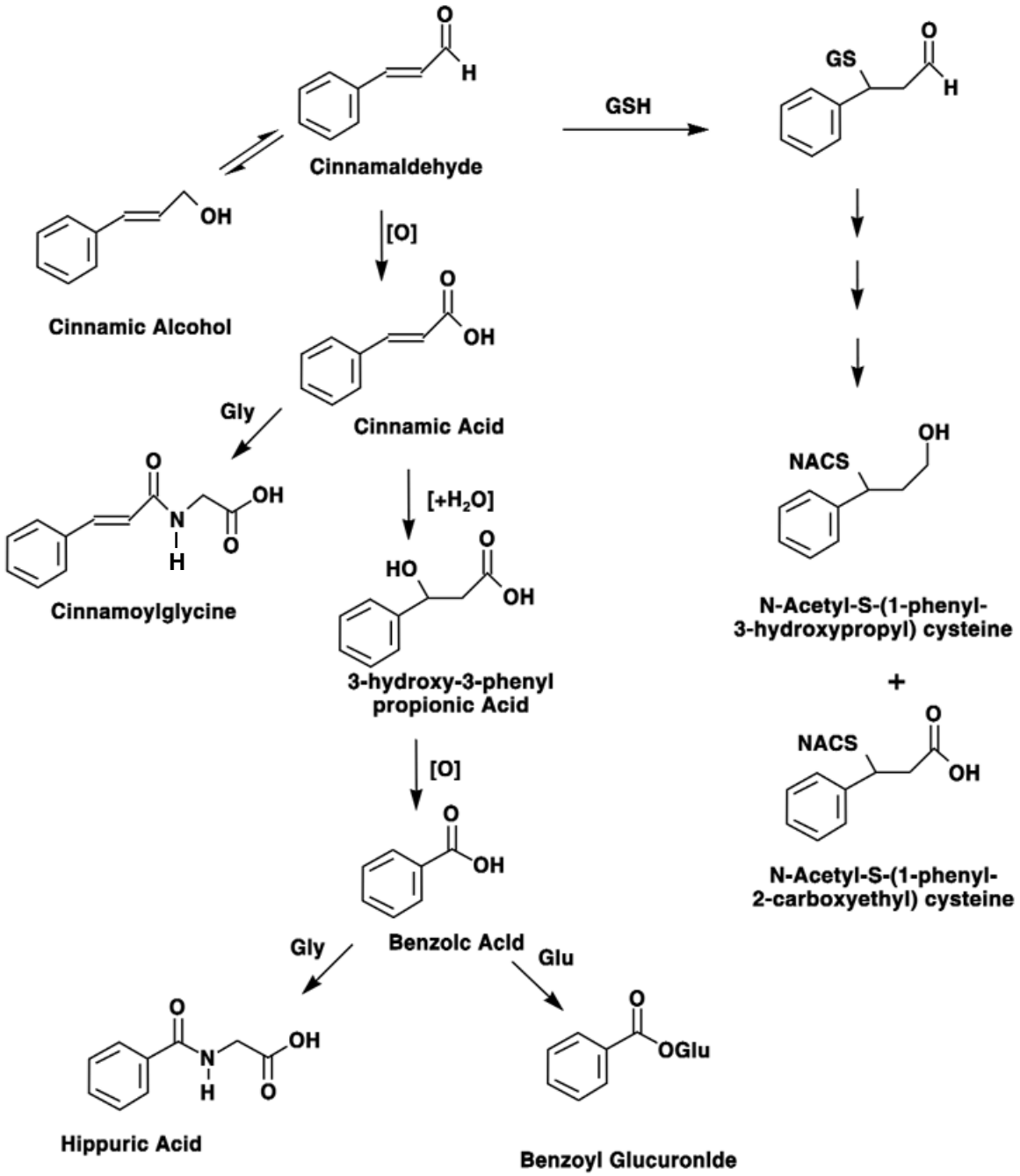


Figure 1
Proposed Metabolism of *trans*-Cinnamaldehyde (Delbressine *et al.*, 1981; Peters and Caldwell, 1994)

cleared from the liver and kidney after 24 hours. Cinnamaldehyde-derived radioactivity also distributed to the fat, but less than 0.3% of the administered dose was detected in the brain, heart, lung, spleen, and testes. Estimated whole blood levels of cinnamaldehyde-derived radioactivity averaged less than 0.15% of the administered dose after 24 hours for all doses tested. The elimination half-life for [^{14}C] was 5 to 9 hours for whole blood and liver and 5 to 8 hours for muscle. The elimination half-life of [^{14}C] from fat tissue was considerably longer, ranging from 17.3 hours at 5 mg/kg to 73 hours at 500 mg/kg. Hippuric acid was the major urinary metabolite after a single administration of each dose. After 7 consecutive daily 500 mg/kg doses of cinnamaldehyde, benzoic acid was the major urinary metabolite, indicating saturation of the conjugation pathway.

The elimination of cinnamaldehyde was studied in female Wistar rats after intraperitoneal administration of 250 mg/kg, 5 days per week for 2 weeks (Delbressine *et al.*, 1981). Two sulfur-containing metabolites were isolated from the urine and identified as *N*-acetyl-S-(1-phenyl-3-hydroxypropyl) cysteine and *N*-acetyl-S-(1-phenyl-2-carboxyethyl) cysteine in a 4:1 ratio. The hydroxypropyl mercapturic acid was also isolated from the urine of rats intraperitoneally dosed with 250 mg/kg cinnamic alcohol. The total mercapturic acid excretion in urine of rats dosed with cinnamaldehyde and cinnamic alcohol was 14.8% and 8.8% of the dose administered, respectively. Pretreatment of animals with 206 mg/kg pyrazole, an alcohol dehydrogenase inhibitor, diminished the mercapturic acid excretion of a cinnamic alcohol dose to 3.3% of the dose administered. These data suggest that cinnamaldehyde is an intermediate in the conversion of cinnamic alcohol to its mercapturic acid. The nuclear magnetic resonance spectra of the isolated mercapturic acids showed that glutathione addition occurred at the β-carbon atom of the double bond of cinnamaldehyde. The authors proposed that the conversion of the glutathione conjugate of cinnamaldehyde into the observed mercapturic acids involved either reduction of the aldehyde group to an alcohol or its oxidation to a carboxylic acid.

Humans

No information on the absorption, distribution, metabolism, or excretion of *trans*-cinnamaldehyde in humans was found in the literature. Presumably, cinnamaldehyde is oxidized *in vivo* to cinnamic acid, which is excreted in the urine as benzoic and hippuric acids (Williams, 1959). Oral administration of cinnamic acid in humans resulted in the excretion of hippuric acid in the urine (Hoskins, 1984). Monocinnamoylglucuronide has also been identified in human urine after exposure to cinnamic acid (Hoskins, 1984).

Cinnamaldehyde is a skin sensitizer and may in part be responsible for allergies to fragrances (Smith *et al.*, 2000). This has prompted several *in vitro* studies of the penetration of cinnamaldehyde through human skin. Very low penetration (0.175%) of cinnamaldehyde was observed in a study that used frozen human cadaver skin (Jimbo, 1983). No metabolites of cinnamaldehyde were detected in the receptor fluid. Weibel and Hansen (1989a) observed much higher penetration (approximately 4.5% of the applied dose) in fresh tissue from surgery. The absorbed dose in the receptor fluid was predominantly cinnamyl alcohol and cinnamic acid, but it also contained cinnamaldehyde. The difference in penetration in these two studies implies that the metabolism that occurs in viable tissue but not in tissue that has been frozen may enhance cinnamaldehyde dermal penetration. A second study that used fresh surgical tissue investigated the effect of metabolism on dermal penetration (Smith *et al.*, 2000). The authors determined that about 9% of the applied dose penetrated the skin as cinnamaldehyde or metabolites. Treatment of the skin with pyrazole, an inhibitor of alcohol dehydrogenase, resulted in no change in penetration of parent cinnamaldehyde, but the amounts of cinnamyl alcohol and cinnamic acid in the receptor fluid were significantly decreased.

TOXICITY

Experimental Animals

The oral LD_{50} for cinnamaldehyde is 2.22 to 3.4 g/kg for rats and mice (Opdyke, 1979). Observations included depression, diarrhea, and a thin appearance in rats, and convulsions, ataxia, and respiratory stimulation in mice. The oral LD_{50} in guinea pigs was 1.16 g/kg; coma was followed by death (Opdyke, 1979; RTECS, 2001). The LD_{50} of cinnamaldehyde after a single intravenous injection in F344 rats was less than 30 mg/kg (Yuan *et al.*, 1992a). Rats similarly dosed with 25 mg/kg showed an initial loss of blood pressure revealed by pale eye color and they had an irregular heartbeat that lasted for 1 minute prior to recovery. Mouse intravenous and intraperitoneal LD_{50} values were 75 mg/kg and 200 mg/kg, respectively (RTECS, 2001). The acute dermal LD_{50} in rabbits was 0.59 mL/kg (Opdyke, 1979).

Cinnamaldehyde is a sensitizing agent in multiple species. Cinnamaldehyde induced nonimmunologic contact urticaria (erythema and swelling) in the guinea pig, rat, and mouse following application of a 20% solution to the ears (Lahti and Maibach, 1985). Ear thickness was measured before, during, and after the application. Maximal ear swelling was observed 20 to 50 minutes after application and the swelling decreased progressively during the 3-hour observation period.

The contact sensitizing potential of amyl cinnamaldehyde was tested in female Balb/c mice maintained for 4 weeks on a diet supplemented with vitamin A acetate (Maisey and Miller, 1986). Ten mice were given six topical applications of a 30% amyl cinnamaldehyde solution to the shaved abdomen and thorax followed by topical challenge of a 15% amyl cinnamaldehyde solution to both ears a week later. Ear thickness was measured in 10 mice before challenge and 24 and 48 hours after challenge. After 24 hours, one mouse had an increase in ear thickness that was 100% greater than the largest increase in the control group. Six mice had increases in ear thickness that were 50% greater than the largest increase in the control group. Based on these studies, amyl cinnamaldehyde was classified as a contact sensitizer because it caused a significant increase ($P<0.01$) in ear thickness relative to the control group.

Systemic effects of cinnamaldehyde have been reported in various animal species following acute exposure (Harada and Yano, 1975). Reduced blood pressure and increased femoral blood flow were reported after intravenous administration of 5 or 10 mg/kg to male and female mongrel dogs and 1 mg/kg to male guinea pigs. Cinnamaldehyde inhibited intestinal propulsion in male DD strain mice dosed with 250 mg/kg by intraperitoneal injection and inhibited spontaneous gastric contraction in male Wistar rats dosed with 5 mg/kg by intravenous injection.

Cinnamaldehyde had inhibitory and excitatory effects on the central nervous system of mice (strain not specified). Intraperitoneal administration of cinnamaldehyde at doses greater than 100 mg/kg caused a transient excitation (running fit) followed by a depression in activity (Watanabe *et al.*, 1984).

The subacute toxicity of cinnamaldehyde was compared after administration by gavage or in dosed feed (Hébert *et al.*, 1994). Male and female F344/N rats and B6C3F$_1$ mice received cinnamaldehyde in corn oil by gavage daily for 2 weeks or in microencapsulated feed for 2 (rats) or 3 (mice) weeks. Daily gavage doses were 235, 470, 940, 1,880, or 3,750 mg/kg for rats and 656, 1,310, 2,620, 5,250, or 10,500 mg/kg for mice. In the feed study, diets contained 2,340, 4,690, 9,375, 18,750, or 37,500 ppm microencapsulated cinnamaldehyde equivalent to average daily doses of 188, 375, 750, 1,500, or 3,000 mg cinnamaldehyde/kg body weight to rats and 474, 948, 1,875, 3,750, or 7,500 mg/kg to mice. Rats gavaged with 940 mg/kg or greater and mice gavaged with 2,620 mg/kg or greater died or were killed moribund. All rats and mice that received microencapsulated cinnamaldehyde in feed survived. These results demonstrated that equivalent daily doses of cinnamaldehyde were more toxic when given by gavage than when given microencapsulated in feed. Cinnamaldehyde administered by either route caused hyperplasia of the forestomach epithelium in rats and mice. Hypoplastic changes in the reproductive organs and secondary sex glands were observed in male and female rats and female mice fed microencapsulated cinnamaldehyde.

When cinnamaldehyde was fed to 10 male and 10 female Osborne-Mendel rats at 10,000 ppm in the diet for 16 weeks, slight swelling of the hepatic cells and slight hyperkeratosis of the squamous portion of the stomach lining were observed (Hagan *et al.*, 1967). No effects were observed at 1,000 (macroscopic) or 2,500 ppm.

Humans

Data for the toxicity of cinnamaldehyde in humans are limited to its effect on the skin. Cinnamaldehyde is a strong sensitizer and a skin irritant.

Acute allergic reactions to cinnamaldehyde have been demonstrated by patch testing with 1% to 2% cinnamaldehyde in petrolatum (Schorr, 1975; Calnan, 1976; Forsbeck and Skog, 1977). Positive skin patch tests to 2% cinnamaldehyde were produced in 1 of 34 male patients and 5 of 55 female patients with contact dermatitis of unknown cause (Schorr, 1975).

In other closed-patch tests, cinnamaldehyde (2% or 5% in petroleum jelly or ointment) produced erythema in subjects with normal skin, and 0.2% cinnamaldehyde in ethanol or a cream base produced erythema in 4 of 156 patients with dermatoses (Fujii *et al.*, 1972).

Erythema and wheal formation occurred 30 minutes after exposure to 3% or 10% *trans*-cinnamaldehyde in

five of eight healthy subjects and in one patient suffering from eczema (Nater *et al.*, 1977). In another study, a 3% mixture of cinnamaldehyde in petrolatum was not found to cause skin irritation after a 48-hour closed-patch test (Opdyke, 1979). However, an 8% mixture was found to be severely irritating to the skin, and the concentration had to be reduced to 2% for the test to be completed.

Cinnamaldehyde caused contact urticaria in 12 of 40 children who were patch tested for skin reactions to a variety of fragrances and food additives (Rademaker and Forsyth, 1989). Children who developed palpable pruritic erythema 20 minutes after exposure to cinnamaldehyde were considered positive for contact urticaria reactions.

Numerous case reports describe the skin sensitization potential of cinnamaldehyde in humans. Skin sensitization has occurred after occupational and consumer exposures. Skin sensitization from cinnamaldehyde exposure has been reported among cinnamon workers (Uragoda, 1984), hairdressers (Lynde and Mitchell, 1982), and bakers (Malten, 1979). An employee in a deodorant manufacturing plant was treated for chronic contact dermatitis after exposure to cinnamaldehyde in the workplace (Nethercott *et al.*, 1983); positive patch test results confirmed that the skin reactions were due to cinnamaldehyde. Goodfield and Saihan (1988) examined the incidence of fragrance-related occupational dermatitis among a group of coal miners being treated for eczematous skin problems. The incidence of fragrance sensitivity in male miners (14%) was approximately twice that of male nonminers (7%). The increased incidence of chronic dermatitis among the coal workers was believed to be related to a highly perfumed body lotion used at the coal mine. A high incidence of occupationally related allergic skin reactions was reported among factory workers in a Danish spice manufacturing plant (Collins and Mitchell, 1975). Almost all of the workers exposed to high concentrations of cinnamaldehyde during the manufacture of cinnamon spice substitutes developed sensitivity to cinnamaldehyde.

Several cases have been reported of chronic contact dermatitis from consumer exposure to cinnamaldehyde in toothpaste (Kirton and Wilkinson, 1975; Magnusson and Wilkinson, 1975; Drake and Maibach, 1976), cosmetics (Eiermann *et al.*, 1982; Broeckx *et al.*, 1987), and fragrances (Larsen, 1977; Calnan *et al.*, 1980). A 25-year-old woman developed perioral leukoderma after using a toothpaste containing cinnamaldehyde (Mathias *et al.*, 1980), and an 82-year-old woman developed chronic cheilitis after using toothpaste and a sunscreen lipstick containing cinnamaldehyde (Maibach, 1986). Patients suffering from contact sensitization to cosmetics were patch tested with 22 fragrance raw materials (Malten *et al.*, 1984). Cinnamaldehyde produced positive results in seven of the 182 patients tested. In addition, cinnamaldehyde was identified in 8 of 79 cosmetic samples suspected by the patients or their physicians of causing the skin reactions.

Several studies have investigated the mechanism by which cinnamaldehyde causes skin sensitization; it is hypothesized that it penetrates the skin where it binds covalently to skin proteins forming an immunogenic complex. Majeti and Suskind (1977) proposed that skin sensitization involves the reaction of cinnamaldehyde with primary amines on protein side chains to form a Schiff base that initiates the allergenic response. Other studies suggest that cinnamaldehyde binds to proteins in the skin via the thiol groups of cysteine residues to form a cinnamaldehyde-protein conjugate that initiates sensitization (Weibel and Hansen, 1989b). Multiple studies confirmed that cinnamaldehyde reacts with the thiol group in glutathione both spontaneously and enzymatically (through glutathione S-transferases) *in vitro* and *in vivo* (Boyland and Chasseaud, 1970; Delbressine *et al.*, 1981; Swales and Caldwell, 1996).

Reproductive and Developmental Toxicity

Experimental Animals

Cinnamaldehyde did not affect body weight gain, reproductive ability, or the development and viability of offspring following administration (route not stated) of 2 mg on alternate days to two generations of rats (strain not specified) for 223 and 210 days, respectively (Opdyke, 1979).

The reproductive and developmental effects of *trans*-cinnamaldehyde were evaluated in pregnant CD-1 mice following daily administration of 1,200 mg/kg in corn oil by gavage on gestation days 7 to 14 (CDC, 1983). None of the reproductive parameters examined were significantly different from those in the control group, including the number of females producing viable, resorbed, or nonviable litters, the number of proven pregnant females, and the reproductive index. *trans*-Cinnamaldehyde had no effect on fetal viability, litter weight, or mean pup weight.

In another study, 49 pregnant CD-1 mice were given 1,200 mg/kg cinnamaldehyde in corn oil by gavage mid-pregnancy (days 6 to 13 of gestation) and were allowed to deliver litters (Hardin *et al.*, 1987). Litter viability, litter birth weight, survival of pups to postnatal day 3, and litter weight gain were used as indicators of potential developmental toxicity. No toxicity was observed in the dams or in their offspring.

Cinnamaldehyde was teratogenic in Sprague-Dawley rats administered 5, 25, or 250 mg/kg per day by gavage on days 7 to 17 of pregnancy (Mantovani *et al.*, 1989). Incidences of defective cranial ossification were increased significantly in all dose groups compared to that in controls. Reduced ossification of the tympanic bulla was increased significantly in the 25 and 250 mg/kg groups. Significant increases in the incidences of renal abnormalities (dilated pelvis, reduced papilla) and dilated ureters were observed in the 5 and 25 mg/kg groups. The incidence of abnormal sternebrae (two or more per fetus) was increased significantly in the 25 mg/kg group.

Cinnamaldehyde was embryotoxic and teratogenic in chick embryos (White Leghorn × Rhode Island Red) injected suprablastodermally on the third day of development with single doses of cinnamaldehyde ranging from 0.025 µM to 25.0 µM (Abramovici and Rachmuth-Roizman, 1983). The embryos were incubated until day 12 of development. The optimal teratogenic dose was 0.50 µM per embryo. At this concentration, the most common teratogenic effects were limb malformations, primarily limb size reduction, and malformations of the axial skeleton including spina bifida, anoura (tail absence), or haemisomia (absence of a lumbosacral region). Skeletal and limb malformations were observed in 56% of the embryos injected with 0.02 µM cinnamaldehyde.

Humans

No information on the reproductive or developmental toxicity of *trans*-cinnamaldehyde in humans was found in the literature.

CARCINOGENICITY

Experimental Animals

trans-Cinnamaldehyde in sterile trioctanoin was tested for hepatocarcinogenicity in preweanling male B6C3F_1 mice following intraperitoneal injections on days 1, 8, 15, and 22 for a total dose of 4.8 µmol per mouse (Wiseman *et al.*, 1987). Animals were maintained for 18 months. No hepatocarcinogenic response was observed in treated mice.

Cinnamaldehyde was evaluated for the ability to induce primary lung tumors in male and female A/He mice. Fifteen males and 15 females per group were given a total of 16 intraperitoneal injections of cinnamaldehyde in tricaprylin over an 8-week period for a total dose of 0.8 or 4.0 g/kg (Stoner *et al.*, 1973). After 24 weeks, the mice were necropsied. The tumor response after exposure to cinnamaldehyde was not significantly different from that in the vehicle controls.

The ability of *trans*-cinnamaldehyde to transform cells *in vitro* has been demonstrated in studies using Chinese hamster epithelial cells (CH-B241) (Kasamaki *et al.*, 1987). The CH-B241 cells were treated with 10 nM *trans*-cinnamaldehyde, and surviving cells were cultivated until they acquired characteristics of transformed cells, including increases in saturation density of the monolayer culture, plating efficiency at a low serum level, and colony-forming efficiency in soft agar medium. Transformed cells were assessed for their ability to produce tumors *in vivo* by subcutaneous injection of 1×10^6 cells into a suprascapular site in male nude mice. Nodule formation at the injection site was observed in six of seven injected mice. Liver and spleen nodules were present in one mouse, indicating metastasis. Cells isolated from these tumors were later shown to be transplantable and to metastasize to the spleen.

Morphological transformation of BALB/c-3T3 cells *in vitro* was evident after exposure to *trans*-cinnamaldehyde at concentrations of 0.0605 mM in one study and 0.0378 or 0.0567 mM in another study (Matthews *et al.*, 1993).

Cinnamaldehyde significantly enhanced the viral transformation of Syrian hamster embryo cells *in vitro* by simian adenovirus SA7 (Hatch *et al.*, 1986). In one experiment, 0.05 mM cinnamaldehyde resulted in enhanced transformation, but in another experiment, 0.19 mM was required to produce enhanced transformation.

Although no studies associate cinnamaldehyde with carcinogenic effects in animals, two related compounds, cinnamyl anthranilate and 3,4,5-trimethoxy-cinnamaldehyde, have been reported to induce tumors in

experimental animals. Cinnamyl anthranilate is a synthetic ester of cinnamyl alcohol and anthranilic acid and was used as a flavor and fragrance ingredient in food until 1985 (IARC, 2000). A carcinogenicity bioassay of cinnamyl anthranilate was conducted in male and female F344/N rats and B6C3F$_1$ mice (NCI, 1980). Cinnamyl anthranilate was administered in the feed at 0, 15,000, or 30,000 ppm for 103 weeks. Animals were observed an additional 2 or 3 weeks prior to necropsy. Dose-related increases in the incidences of hepatocellular adenoma and hepatocellular carcinoma occurred in male and female mice. Cinnamyl anthranilate also induced low incidences of acinar-cell adenoma or carcinoma (combined) of the pancreas and adenoma or adenocarcinoma (combined) of the renal cortex in male F344/N rats. Cinnamyl anthranilate was not carcinogenic in female F344/N rats. Because anthranilic acid was not found to be carcinogenic when tested in rats or mice (NCI, 1978), the cinnamyl moiety was hypothesized to play a role in the carcinogenicity of cinnamyl anthranilate.

Cinnamyl anthranilate produced a significant increase in lung tumors in male and female A/He mice given intraperitoneal injections three times per week for 8 weeks for a total dose of 12 g/kg (Stoner *et al.*, 1973); animals were necropsied 24 weeks after the first injection.

Cinnamyl anthraniliate at doses of 0.08, 0.12, or 0.16 µM significantly enhanced the viral transformation of Syrian hamster embryo cells *in vitro* by simian adenovirus SA7 (Hatch *et al.*, 1986).

The related compound 3,4,5-trimethoxy-cinnamaldehyde induced testicular and nasal tumors in male white rats given 150 mg/kg by intraperitoneal injection followed one week later by a subcutaneous dose of 100 mg/kg (Schoental and Gibbard, 1972). The four animals that survived 20 to 25 months after these treatments developed tumors. These tumors consisted of a sarcoma in the peritoneal cavity of one animal, a mesothelioma of the tunica albuginea of both testes in one animal, and nasal squamous carcinomas in two animals.

One lipomatous kidney tumor was produced when six male white rats were given a subcutaneous dose of 100 mg/kg 3,4,5-trimethoxy-cinnamaldehyde in 0.1 mL dimethylformamide (Schoental *et al.*, 1971). The animals survived for 17 months prior to necropsy.

Humans

No epidemiological studies in humans were found in the literature. *trans*-Cinnamaldehyde did not induce transformation of the human fibroblast cell line HAIN-55 following treatment with various concentrations ranging from 5 to 80 nM (Kasamaki *et al.*, 1987).

GENETIC TOXICOLOGY

Most of the published mutagenicity test data for specified *trans*-cinnamaldehyde comes from the NTP. The NTP found weakly positive results for *trans*-cinnamaldehyde (at near toxic doses of 200 to 300 µg/plate) in *Salmonella typhimurium* strain TA100, but only in the presence of induced B6C3F$_1$ mouse liver S9 enzymes (Dillon *et al.*, 1998). Mouse liver S9 is infrequently used in *Salmonella* tests, and additional tests with *trans*-cinnamaldehyde (doses ranging up to 333 µg/plate) in a variety of strains with and without the more traditional rat and hamster liver S9s gave uniformly negative results (Mortelmans *et al.*, 1986; Dillon *et al.*, 1998). Sister chromatid exchanges were significantly increased in cultured Chinese hamster ovary cells exposed to *trans*-cinnamaldehyde with and without S9, but no increase in chromosomal aberrations was induced in these cells by *trans*-cinnamaldehyde (Galloway *et al.*, 1987). In a brief abstract with no data, *trans*-cinnamaldehyde was reported to produce a questionable response in the mouse lymphoma assay for gene mutations in L5178Y TK$^{+/-}$ cells (Palmer, 1984). *trans*-Cinnamaldehyde was assessed for germ cell mutagenicity in *Drosophila melanogaster* assays (Woodruff *et al.*, 1985); when administered by injection to adult male flies, *trans*-cinnamaldehyde induced a significant increase in sex-linked recessive lethal mutations but not reciprocal translocations (heritable chromosomal changes).

There is additional mutagenicity literature for cinnamaldehyde and/or the unspecified isomer. The mutagenicity of cinnamaldehyde was recently reviewed by Neudecker (1992). As was reported for *trans*-cinnamaldehyde, cinnamaldehyde was not mutagenic in *S. typhimurium* in most cases (Florin *et al.*, 1980; Kasamaki *et al.*, 1982; Sekizawa and Shibamoto, 1982; Maron and Ames, 1983; Ishidate *et al.*, 1984) or *E. coli* (Sekizawa and Shibamoto, 1982). However, an isolated weak positive response was reported by Ishidate *et al.*, (1984) in *S. typhimurium* strain TA100 in the absence of S9 activation. In addition, there is one report of recombinational DNA repair detected in *Bacillus subtilis* after treatment with cinnamaldehyde (Sekizawa and Shibamoto, 1982). Reports of cinnamaldehyde-induced increases in chromosomal aberrations in mammalian cells *in vitro* (Kasamaki *et al.*, 1982; Ishidate *et al.*, 1984; Blazak *et al.*, 1986a,b) contrast with the negative results obtained in cultured CHO cells with *trans*-cinnamaldehyde cited above (Galloway *et al.*, 1987). Despite the *in vitro* evidence for cinnamaldehyde-induced chromosomal damage, no induction of micronuclei, an indicator of structural and/or numerical chromosomal damage *in vivo*, was observed in ddY mice (Hayashi *et al.*, 1984). The single doses administered to ddY mice ranged from 125 to 1,000 mg/kg and bone marrow was sampled at 5 time points from 18 to 72 hours posttreatment.

Several observations of antimutagenic activity by cinnamaldehyde *in vitro* in the presence of known mutagenic agents have been reported, and these are included in the review by Neudecker (1992). Rutten and Gocke (1988) and de Silva and Shankel (1987) showed that some interpretations of antimutagenicity using bacterial mutation systems may be the result of confounding toxicity in the form of growth inhibition (as reported in Neudecker, 1992). However, results of studies in which toxicity was controlled and well defined demonstrated a reduction in induced mutagenicity and suggested that recombinational DNA repair mechanisms are critical to the antimutagenic activity of cinnamaldehyde (Ohta *et al.*, 1983; MacPhee and Hafner, 1988; Imanishi *et al.*, 1990; Sasaki *et al.*, 1990). Recent experiments with *S. typhimurium* strain TA104 have provided some insight into the possible mechanistic aspects of cinnamaldehyde antimutagenic activity in this test system. Shaughnessy *et al.* (2001) reported that concentrations of 3 to 3.5 µmol (396 to 462 µg) cinnamaldehyde per plate reduced the spontaneous level of revertants to 50% of background, with only minimal toxicity. Molecular analyses of mutations showed that the antimutagenic effect was the result of a reduction in mutations at GC sites only and that it required functional SOS repair genes. The authors speculated that the inhibition by cinnamaldehyde of the error-prone SOS pathway, with an enhancement of the more accurate recombinational repair system, might be responsible for the observed reduction in spontaneous revertants. The data reported from NTP tests in *S. typhimurium* strain TA104 at a lower dose range (Dillon *et al.*, 1998) did not show a similar reduction in the level of spontaneous mutagenicity, but the contrasting results may be protocol dependent. Additional studies to characterize and interpret this observation of the reduction in spontaneous mutagenicity by cinnamaldehyde in TA104 are continuing (Shaughnessy *et al.*, 2001).

There is a single report of antimutagenic activity of cinnamaldehyde *in vivo*. Sasaki *et al.* (1990) reported that posttreatment of male ddY mice with cinnamaldehyde (250 to 500 mg/kg) reduced the level of micronuclei in bone marrow erythrocytes induced by X-radiation (200 rad) and stated that a clear dose-dependent suppression in micronuclei was seen, with the top dose of 500 mg/kg cinnamaldehyde producing a 58% decrease in the frequency of micronuclei compared to the untreated irradiated control mice. However, because the absolute micronucleus frequencies in these experiments were small (a change from 3.35% micronucleated erythrocytes in the control to 1.40% micronucleated erythrocytes in the highest dose group), these results ought to be interpreted cautiously.

Overall, the mutagenicity literature for cinnamaldehyde is complicated, consisting of reports of weak mutagenicity as well as antimutagenicity; its activity appears to be specific to cell type and test protocol and dependent upon particular DNA repair mechanisms.

Study Rationale

The Food and Drug Administration nominated *trans*-cinnamaldehyde. for carcinogenicity studies based on its widespread use as a flavor and fragrance ingredient and its structural similarity to cinnamyl anthranilate and 3,4,5-trimethoxy-cinnamaldehyde, two known rodent carcinogens. The 3-month and 2-year studies were conducted in male and female F344/N rats and B6C3F$_1$ mice to evaluate the toxicity and carcinogenicity of *trans*-cinnamaldehyde. The oral route of administration was used because it is the most likely route of human exposure through consumption of foods. Because *trans*-cinnamaldehyde oxidizes to cinnamic acid when exposed to air, procedures were developed for microencapsulation of *trans*-cinnamaldehyde for administration in feed.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *trans*-CINNAMALDEHYDE

trans-Cinnamaldehyde was obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI) in two lots. Lot 10120 TF was used in the 3-month studies and lot 13831AR was used in the 2-year studies. The chemical was microencapsulated by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and the loaded microcapsules were assigned separate lot numbers (3-month studies: DB 1-23-95; 2-year studies: 042497MC). Identity, purity, moisture content, and stability analyses of the neat and microencapsulated *trans*-cinnamaldehyde were conducted by the analytical chemistry laboratory. Reports on analyses performed in support of the *trans*-cinnamaldehyde studies are on file at the National Institute of Environmental Health Sciences.

Analyses of Neat Chemical

Both lots of the chemical, a pale yellow liquid, were identified as *trans*-cinnamaldehyde by the analytical chemistry laboratory using infrared and nuclear magnetic resonance spectroscopy. The purity of *trans*-cinnamaldehyde was determined by the analytical chemistry laboratory using free acid titration and high-performance liquid chromatography (HPLC) (lot 10120 TF) or free acid titration, thin-layer chromatography (TLC), and gas chromatography (GC) (lot 13831AR). The moisture content of lot 13831AR was determined using Karl Fischer titration.

For lot 10120 TF, free acid titration indicated 0.38% ± 0.02% free acid, present as cinnamic acid. HPLC indicated a major peak and four impurity peaks with a total area of 5.2% relative to the major peak area. The overall purity of lot 10120 TF was determined to be approximately 95%. For lot 13831AR, Karl Fischer titration indicated 0.04% ± 0.03% water. Free acid titration indicated 0.56% ± 0.01% free acid, present as cinnamic acid. TLC indicated one major spot and one minor spot. GC indicated one major peak and two impurities with a combined area of 1.07% (batch 1) relative to the major peak area. The overall purity of lot 13831AR was determined to be approximately 99%. Homogeneity analyses of batches 1 and 2 were performed by the analytical chemistry laboratory using GC. Homogeneity was confirmed; both samples were consistent with a *trans*-cinnamaldehyde standard (Aldrich Chemical Company, Inc.).

Stability analyses of lot M5016 of neat *trans*-cinnamaldehyde (not used in the current studies) were performed by the analytical chemistry laboratory using GC. Samples stored under a nitrogen headspace in amber glass vials, sealed with aluminum caps and Teflon®-lined septa were stable for at least 2 weeks at temperatures up to 60° C.

Microcapsule Formulation and Analyses

Microcapsules loaded with neat *trans*-cinnamaldehyde and placebos (empty microcapsules) were prepared by the analytical chemistry laboratory with a proprietary process using food-grade, modified corn starch and sucrose to produce dry microspheres; the outer surfaces of the microcapsules were coated with food-grade, hydrophobic, modified corn starch. Following microencapsulation, the analytical chemistry laboratory tested lot 042497MC of the microcapsules for conformance to specifications. The microcapsules were examined microscopically for appearance, and particle sizes were profiled. Particles were smooth, shiny, translucent or opaque white spheres, heavily coated with small, colorless particles. Only occasional particle fragments and no leaking capsules or foreign particles were observed. For particle size profiling, microcapsules were passed through U.S. standard sieves (numbers 30, 40, 60, 80, 100, and 120); 98.6% of the microcapsules were retained by the sieves.

The chemical loads of freshly prepared microcapsules (both lots) and the purity of lot 042497MC were determined by the analytical chemistry laboratory with HPLC. The chemical load for both lots of microcapsules was determined to be 30% to 34%. Lot DB 1-23-95 contained 1.58% cinnamic acid and no cinnamyl alcohol. Lot 042497MC contained approximately 0.4% cinnamic acid; one additional impurity peak with an area of

0.05% of the total peak area was identified. The study laboratory confirmed the chemical load of lot 042497MC to be 33% using HPLC.

Microcapsules were stored in amber glass bottles at approximately 5° C, protected from light. Stability was monitored by the study laboratory using HPLC. From July 1998 through the end of the studies, slight decreases (1% to 2%) in the *trans*-cinnamaldehyde load and increases in cinnamic acid concentrations in the microcapsules were observed.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared at least every 3 weeks by mixing microencapsulated *trans*-cinnamaldehyde with nonirradiated NTP-2000 feed during the 3-month studies and with irradiated NTP-2000 feed during the 2-year studies (Table I1). Placebo and/or loaded microcapsules were combined with feed to a concentration of 10% (3-month studies) or 1.25% (2-year studies) in the diet. Dose formulations were stored in plastic buckets at room temperature (3-month studies) or at approximately 5° C (2-year studies) for up to 5 weeks.

Homogeneity and stability studies of a 0.3% dose formulation prepared with nonirradiated feed and an approximately 0.447% dose formulation prepared with irradiated feed were conducted by the analytical chemistry laboratory using HPLC. Homogeneity was confirmed; stability was confirmed for up to 42 days for dose formulations stored in sealed containers in the dark at temperatures up to approximately 25° C or for 9 days under simulated animal room conditions, open to air and light at room temperature. The study laboratory also analyzed the dose formulation homogeneity and the stability under simulated and actual animal room conditions for the 2-year studies. Homogeneity was confirmed; dose formulations contaminated with urine and feces showed some losses of the chemical load, as did dose formulations collected from the feeders in the female mouse cages.

Periodic analyses of the dose formulations of *trans*-cinnamaldehyde used during the 3-month studies were conducted by the analytical chemistry laboratory using HPLC. The dose formulations were analyzed at the beginning, midpoint, and end of the studies; animal room samples of these dose formulations were also analyzed. Original acceptance criteria were based on the concentration of loaded microcapsules in the feed. Table I2 provides analysis results in both ppm and percent loaded microcapsules for clarity. Based on the original criteria, formulations were generally within 10% of the target concentration. Periodic analyses of the dose formulations used during the 2-year studies were conducted by the study laboratory using HPLC. During the 2-year studies, the dose formulations were analyzed approximately every 9 to 12 weeks; animal room samples of these dose formulations were also analyzed. Based on the original criteria, all formulations were within 10% of the target concentration (Table I3). During the 3-month and 2-year studies, problems with animal room samples were encountered due to the animals' ability to eat around the microcapsules (causing high animal room sample analyses results) and due to contamination of the feed with urine and feces which softened the microcapsules (causing low results). Both problems were more prevalent in the 3-month studies because the animals were younger and smaller and because of the higher concentrations of cinnamaldehyde in the feed.

3-Month Studies

The 3-month studies were conducted to evaluate the cumulative toxic effects of repeated exposure to *trans*-cinnamaldehyde and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were 5 weeks old. Rats were quarantined for 14 (males) or 15 (females) days and mice were quarantined for 12 (females) or 13 (males) days; rats and mice were approximately 7 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Serologic analyses were performed on five male and five female sentinel rats and mice 4 weeks after the study began and on five male and five female untreated control rats and mice at study termination using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female core study rats and mice and groups of 10 male and 10 female clinical pathology study rats were fed diets containing 4,100, 8,200, 16,500, or 33,000 ppm microencapsulated *trans*-cinnamaldehyde for 14 weeks. Additional groups

of 10 male and 10 female core study rats and mice and groups of 10 male and 10 female clinical pathology study rats received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). Feed and water were available *ad libitum*. Rats and female mice were housed five per cage, and male mice were housed individually. The animals were weighed initially, weekly thereafter, and at the end of the studies. Clinical findings were recorded on day 8 and weekly thereafter. Feed consumption was recorded once weekly (male mice) or twice weekly (rats and female mice). Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected from the retroorbital sinus of clinical pathology study rats under carbon dioxide anesthesia on days 5 and 22 and from all core study rats and mice surviving to the end of the studies for hematology and clinical chemistry (rats) analyses. Blood samples for hematology analyses were placed in microcollection tubes containing potassium EDTA. Erythrocyte, platelet, and leukocyte counts, hematocrit values, hemoglobin concentration, mean cell hemoglobin, and mean cell hemoglobin concentration were determined using a Serono-Baker System 9000 hematology analyzer (Serono-Baker Diagnostics, Allentown, PA) with reagents supplied by the manufacturer. Differential leukocyte counts and erythrocyte and platelet morphologies were determined microscopically from blood smears stained with a modified Wright-Giemsa stain on a Hema-Tek® slide stainer (Miles Laboratory, Ames Division, Elkhart, IN). A Miller disc was used to determine reticulocyte counts from smears prepared with blood stained with new methylene blue. For clinical chemistry analyses, blood samples from rats were placed into microcollection serum separator tubes and centrifuged; the serum samples were analyzed using a Hitachi 704® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using commercially available reagents (Sigma, St. Louis, MO; Boehringer Mannheim). The hematology and clinical chemistry parameters measured are listed in Table 1.

Five male and five female rats per core study group were randomly selected for urine collection at the end of the study. The rats were placed individually into metabolism cages for urine collection, and urine was collected over ice during a 24-hour period. The volume of urine was recorded, and urine creatinine concentrations were determined using a Hitachi 704® chemistry analyzer and reagents supplied by the manufacturer; the parameters measured are listed in Table 1. Urine samples were stored frozen at –20° C or less until they were shipped to CEDRA Corporation (Austin, TX) for determination of hippuric acid concentration. Hippuric acid was chosen as a biomarker to establish the correlation between exposure concentration and internal dose and to determine how metabolism of *trans*-cinnamaldehyde may change with chronic exposure and age. Urine samples were mixed with an ammonium formate/formic acid buffer. Metabolite concentrations were determined by high-performance liquid chromatography/mass spectrometry (HPLC/MS; Waters Corp., Milford, MA) with atmospheric-pressure chemical ionization. A Zorbax (Rockland Technologies; Newport, DC) SB C_{18} column (250 mm × 4.6 mm) was used with a mobile phase of 0.0125 M potassium phosphate:acetonitrile (80:20), adjusted to pH 3 with phosphoric acid, at a flow rate of 1.4 mL/minute. The detector wavelength was 230 nm. The HPLC/MS was calibrated against spiked urine standards containing known hippuric acid concentrations of 0.25 to 25 mg/mL, with deuterated hippuric acid (Aldrich Chemical Co., Milwaukee, WI) as the internal standard. Relative response was calculated as the ratio of the peak height from hippuric acid (m/z 178) to the peak height from hippuric acid (m/z 183). A linear calibration curve was derived by fitting a weighted linear least-squares regression curve to concentration and relative response data.

Necropsies were performed on all core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on all core study untreated control, vehicle control, 33,000 ppm rats and female mice, and 8,200 ppm or greater male mice. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats and mice were fed diets containing 1,000, 2,100, or 4,100 ppm microencapsulated *trans*-cinnamaldehyde for 104 to 105 (males) or 105 to 106 (females) weeks. Additional groups of 50 male and 50 female rats and mice received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls).

Source and Specification of Animals

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

Animal Maintenance

Male rats were housed two or three per cage, female rats and mice were housed five per cage, and male mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured over a 1-week period approximately every 4 weeks by cage. Animals were given irradiated feed; the feed was irradiated to reduce potential microbial contamination. Cages were changed once (male mice) or twice weekly; 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 K.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially, on day 8, day 36 (mice), every 4 weeks thereafter, and at the end of the studies. Clinical findings were recorded on day 36, every 4 weeks thereafter, and at the end of the studies. Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the pituitary gland, uterus, adrenal gland, lung, and mesentery of rats and forestomach, nose, bone, and thyroid gland of mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

Hippuric Acid – Biomarker of Exposure

Ten male and ten female rats from each group were randomly selected for urinary metabolite analysis at 2 weeks and 3, 12, and 18 months. Animals were placed in metabolism cages for 24 hours. Urine samples were placed on ice, urine volume and creatinine concentration were measured, and then the samples were frozen pending shipment to Battelle Toxicology Northwest (Richland, WA) for hippuric acid quantitation. Methods for hippuric acid quantitation were the same as those for the 3-month studies.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *trans*-Cinnamaldehyde

3-Month Studies	2-Year Studies
Study Laboratory	
Battelle Columbus Operations (Columbus, OH)	Battelle Columbus Operations (Columbus, OH)
Strain and Species	
F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice
Animal Source	
Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies	
Rats: 14 (males) or 15 (females) days Mice: 12 (females) or 13 (males) days	Rats: 11 (males) or 12 (females) days Mice: 13 (males) or 14 (females) days
Average Age When Studies Began	
7 weeks	5 to 6 weeks
Date of First Exposure	
Rats: May 4 (males) or 5 (females), 1995 Mice: May 2 (females) or 3 (males), 1995	Rats: September 8 (males) or 9 (females), 1997 Mice: September 24 (males) or 25 (females), 1997
Duration of Exposure	
14 weeks	Rats: 105 or 106 (females) weeks Mice: 104 (males) or 105 to 106 (females) weeks
Date of Last Exposure and Necropsy	
Rats: August 3 (males) or 4 (females), 1995 Mice: August 1 (females) or 2 (males), 1995	Rats: September 8-10 (males) or 13-15 (females), 1999 Mice: September 21-24 (males) or 27-30 (females), 1999
Average Age at Necropsy	
20 weeks	109 to 111 weeks
Size of Study Groups	
10 males and 10 females	50 males and 50 females
Method of Distribution	
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 3-month studies
Animals per Cage	
Rats: 5 Mice: 1 (males) or 5 (females)	Rats: 2 or 3 (males) or 5 (females) Mice: 1 (males) or 5 (females)
Method of Animal Identification	
Tail tattoo	Tail tattoo
Diet	
Nonirradiated NTP-2000 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 3-month studies, except feed was irradiated
Water	
Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Same as 3-month studies

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *trans*-Cinnamaldehyde

3-Month Studies	2-Year Studies
Cages	
Polycarbonate (Lab Products, Inc., Maywood, NJ) changed twice weekly (rats and female mice) or once weekly (male mice)	Same as 3-month studies
Bedding	
Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly (rats and female mice) or once weekly (male mice)	Same as 3-month studies
Cage Filters	
Dupont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks	Same as 3-month studies
Racks	
Stainless steel (Lab Products, Inc., Maywood, NJ), changed and rotated every 2 weeks	Same as 3-month studies
Animal Room Environment	
Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour
Exposure Concentrations	
0, 4,100, 8,200, 16,500, or 33,000 ppm, microencapsulated in feed	0, 1,000, 2,100, or 4,100 ppm, microencapsulated in feed
Type and Frequency of Observation	
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded on day 8 and weekly thereafter. Feed consumption was recorded twice weekly (rats and female mice) or weekly (male mice).	Observed twice daily; animals were weighed initially, on day 8, day 36 (mice), every 4 weeks thereafter, and at the end of the studies. Clinical findings were recorded on day 36, every 4 weeks thereafter, and at the end of the studies. Feed consumption was recorded by cage for a 1-week period approximately every 4 weeks.
Method of Sacrifice	
Carbon dioxide asphyxiation	Same as 3-month studies
Necropsy	
Necropsies were performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all animals.
Clinical Pathology	
Blood was collected from the retroorbital sinus of clinical pathology study rats on study days 5 and 22 and from all core study rats and mice surviving to the end of the studies for hematology and clinical chemistry (rats) analyses. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids	None

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *trans*-Cinnamaldehyde

3-Month Studies	2-Year Studies
Histopathology	
Complete histopathology was performed on untreated controls, vehicle controls, 33,000 ppm rats and female mice and male mice exposed to 4,100 (nose only), 8,200, 16,500, or 33,000 ppm. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart with aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the stomach (forestomach) of all core study rats and mice was examined.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart with aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and/or mesenteric), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Hippuric Acid – Biomarker of Exposure	
Urine was collected during a 24-hour period from five male and five female rats from each core study group at the end of the study. Parameters evaluated included creatinine and hippuric acid concentrations and volume.	Urine was collected during a 24-hour period from 10 male and 10 female rats from each group at 2 weeks and 3, 12, and 18 months. Parameters evaluated included creatinine and hippuric acid concentrations and volume.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B4, C1, C4, D1, and D4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend

test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

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

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

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, and urinalysis data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Linearity of the urinary *trans*-cinnamaldehyde data was analyzed as described in Neter and Wasserman (1974).

Historical Control Data

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

Significant differences in the incidences of some neoplasms and nonneoplastic lesions occurred between untreated and vehicle controls. In male rats, these lesions included subcutaneous skin fibroma, pheochromocytoma, mixed cell foci, cytoplasmic vacuolization of the liver, pancreatic acinar atrophy, and preputial gland hyperplasia; in female rats, these lesions included cardiomyopathy, pancreatic cyst, and thyroid gland C-cell hyperplasia. In female mice, the incidence of uturine inflammation in the vehicle controls was significantly greater than that in the untreated controls. The significant findings were examined using the NTP historical control database for neoplasms and a similar informal NTP database for nonneoplastic lesions to determine the relevance of these differences. Based on this review, it was determined that significant differences were likely due to individual animal variation and not due to ingestion of microcapsules. Furthermore, in the citral (CAS No. 5392-40-5) study where microcapsules were used as a vehicle, none of these lesions differed significantly between the untreated and vehicle controls, supporting the conclusion that these effects were not related to microencapsulation (NTP, 2003).

A similar analysis was conducted between exposed male and/or female rats and the vehicle controls for statistically significant differences in the incidences of nonneoplastic lesions. The decreased incidences of nonneoplastic lesions in the pancreas, bone marrow, prostate gland, liver, salivary gland, and mammary gland, and the increased incidences of nonneoplastic lesions in the clitoral gland were considered to be due to biological variation and, therefore, were unrelated to *trans*-cinnamaldehyde exposure.

Quality Assurance Methods

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

Genetic Toxicology

The genetic toxicity of *trans*-cinnamaldehyde was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium,* sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster,* and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

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

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

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage

and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

3-MONTH STUDY

All rats survived to the end of the study (Table 2). Final mean body weights and body weight gains of all exposed groups of males and of females exposed to 16,500 or 33,000 ppm were significantly less than those of the vehicle controls; males in the 33,000 ppm group lost weight during the study. Feed consumption was less by exposed groups of males and females than by the vehicle controls throughout the study, possibly due to poor palatability of the feed; feed consumption estimates for exposed groups were higher than actual throughout the study due to scattering. Dietary concentrations of 4,100, 8,200, 16,500, and 33,000 ppm resulted in average daily doses of approximately 275, 625, 1,300, and 4,000 mg *trans*-cinnamaldehyde/kg body weight to males and 300, 570, 1,090, and 3,100 mg/kg to females. There were no clinical findings related to exposure to *trans*-cinnamaldehyde other than thinness in 16,500 and 33,000 ppm males and females, which was attributed to the decreased feed consumption by those groups. Changes in organ weights appeared to be related to changes in body weights (Table H1).

The hematology and clinical chemistry data for rats in the 3-month toxicity study of *trans*-cinnamaldehyde are

TABLE 2
Survival, Body Weights, and Feed Consumption of Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 2	Week 14
Male							
Vehicle Control	10/10	146 ± 4	366 ± 6	220 ± 3		17.6	18.6
4,100	10/10	145 ± 3	346 ± 7**	201 ± 6**	94	15.7	17.3
8,200	10/10	146 ± 3	302 ± 4**	156 ± 5**	82	14.4	18.3
16,500	10/10	144 ± 3	247 ± 3**	103 ± 3**	67	13.3	17.3
33,000	10/10	146 ± 3	131 ± 5**	–14 ± 4**	36	8.9	15.9
Female							
Vehicle Control	10/10	120 ± 2	191 ± 2	71 ± 2		12.1	11.2
4,100	10/10	119 ± 2	189 ± 3	70 ± 3	99	11.6	10.5
8,200	10/10	119 ± 2	182 ± 3	63 ± 2	95	9.7	9.9
16,500	10/10	120 ± 2	157 ± 5**	37 ± 4**	82	5.9	9.3
33,000	10/10	119 ± 2	119 ± 6**	0 ± 5**	62	6.5	9.4

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' test
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

listed in Table F1. In treated animals, an increase in the erythron, evidenced by small (≤15%) increases in hemoglobin concentrations, hematocrit values, and erythrocyte counts, occurred on day 5 in the 16,500 and 33,000 ppm males and females. Evidence of the erythron increase was sustained throughout the study but ameliorated with time. By the end of the study, erythron values for the exposed animals were at or near values for the vehicle controls. Since it is considered that rats that do not eat also do not drink, the changes in the erythron would be consistent with a physiological hemoconcentration related to the decreased feed intake and, therefore, water consumption by the 33,000 ppm animals. On day 5 and at week 3 there were decreases in reticulocyte counts that would suggest a physiological decrease in red cell production or release in response to the hemoconcentration. At week 3 and study termination, there were increases in neutrophil counts in 16,500 ppm and/or 33,000 ppm rats. The neutrophilia would be consistent with the inflammatory process that was observed in the forestomach of 16,500 ppm and 33,000 ppm rats at study termination. Minimal (<10%) dose-related decreases in mean cell volume and mean cell hemoglobin values occurred primarily in female rats throughout the study and suggests that there was some minimal alteration in iron metabolism or hemoglobin production resulting in production of slightly smaller erythrocytes.

On day 3, *trans*-cinnamaldehyde administration resulted in increases in serum bile acid concentration in the 4,100 ppm or greater male and 8,200 ppm or greater females. The bile acid concentration increase persisted throughout the study, but the number of dose groups affected ameliorated and only the 33,000 ppm animals had increased serum concentrations by study termination. The severity of the bile acid concentration increase, however, progressed in the 33,000 ppm rats with time. For example, the 33,000 ppm male rats had an approximately 2.5-fold increase in bile acid concentration on day 3 that increased to approximately 6-fold at study termination. In general, increases in bile acid concentration and alkaline phosphatase activity are used as markers of cholestasis. In this study, the alkaline phosphatase activity demonstrated dose-related decreases that ameliorated with time. Thus, the increase in bile acid concentration and decrease in alkaline phosphatase activity would appear to be incongruous. It has been suggested that decreases in alkaline phosphatase activity may reflect decreases in feed intake and loss of the intestinal contribution to serum alkaline phosphatase activity (Travlos *et al.*, 1996). In this study, there was evidence of decreased feed consumption that could account for the decreased alkaline phosphatase activity. Thus, the increased bile acid concentration may suggest a cholestasis but could also be consistent with heptocellular injury or altered function (Hofmann, 1988). No histopathological lesions in the liver were observed.

At week 3 and study termination, alanine aminotransferase activity was increased in 33,000 ppm males and females. Increases in alanine aminotransferase activity are used as a marker of hepatocellular injury. In this study, however, sorbitol dehydrogenase activity, another marker of hepatocellular injury, was unaffected or decreased. Therefore, the increase in alanine aminotransferase activity in the 33,000 ppm animals may have been related to an enzyme induction rather than hepatocellular damage.

At study termination, a treatment-related decrease (approximately 10% or less) of serum albumin and/or total protein concentrations occurred in 16,500 and 33,000 ppm males and females and 8,200 ppm females. An altered nutritional status may have contributed to the decrease in serum protein concentrations and the severity of the decrease may have been masked somewhat by the apparent dehydration. A decrease in serum creatinine concentrations in the 16,500 and 33,000 ppm rats at study termination would be consistent with the lower body weights and, hence, less muscle mass. The small increases in urea nitrogen concentrations of the 33,000 ppm rats were not considered of renal origin and were probably related to hydration status.

Hippuric acid excretion in urine, expressed as the hippuric acid to creatinine ratio, was exposure concentration proportional for females (Tables 3 and G1). Data for males did not meet the test for dose proportionality or linearity, primarily due to the 16,500 ppm results. The ratio was nearly identical for males and females in the 33,000 ppm group. These data indicate that neither absorption, metabolism, nor excretion was saturated in female rats exposed to feed containing up to 33,000 ppm *trans*-cinnamaldehyde. There may have been saturation of one (or more) of these parameters in males exposed to between 8,200 and 16,500 ppm.

Gross lesions observed at necropsy included multifocal to diffuse white nodules of the forestomach mucosa in males and females exposed to 8,200 ppm or greater. Microscopically, the nodules were associated with forestomach squamous epithelial hyperplasia; the

TABLE 3
Urinary Hippuric Acid-Biomarker for *trans*-Cinnamaldehyde Exposure in Rats in the 3-Month Feed Study[a]

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
n	5	5	5	5	5	5
Male						
Hippuric acid/ creatinine ratio	1.14 ± 0.05	0.966 ± 0.057	5.23 ± 0.23	8.11 ± 0.71	12.9 ± 0.9	48.5 ± 5.4
Total hippuric acid excreted (mg)[b]	15.4 ± 0.6	12.2 ± 1.0	63.6 ± 3.4	81.2 ± 8.1	107 ± 8.6	169 ± 16
Female						
Hippuric acid/ creatinine ratio[b]	1.70 ± 0.10	1.50 ± 0.09	7.97 ± 0.36	11.9 ± 0.9	26.6 ± 1.84	50.1 ± 2.2
Total hippuric acid excreted (mg)[b]	10.8 ± 0.7	9.14 ± 0.76	45.5 ± 4.5	70.1 ± 5.6	117 ± 10	142 ± 7

[a] Data are presented as mean ± standard error.
[b] Linear and dose proportional

incidences were significantly increased in 8,200 ppm or greater males and females, and the severities were mild to marked (Table 4). Squamous epithelial hyperplasia was characterized at 8,200 ppm by multiple raised, broadly thickened, plaque-like areas of squamous epithelium with thick layers of abnormal keratin (Plates 1 and 2). The hyperplastic squamous epithelium covered upward folds of lamina propria. In the most severely affected forestomachs from the 16,500 and 33,000 ppm groups, the hyperplastic areas were confluent and had a papillary or villous appearance, irregular cords of basal cells, and elongated folds of lamina propria (Plate 3). In affected areas, the progression of squamous cell differentiation from basal layer to prickle layer then granular layer and finally horny layer of keratin was abnormal. Basal cells were numerous and formed irregular epithelial borders often composed of darkly basophilic stained cords between folds of the lamina propria. The prickle layer varied greatly in thickness and blended into the granular layer where cells underwent degeneration. Instead of normal, thin, flat cells with numerous prominent keratohyaline granules, granular cells were pale staining and markedly enlarged (hydropic degeneration). Abundant abnormal keratin that eosin stained pale to intensely red formed and ghosts of the large degenerated cells were seen. In affected areas, the lamina propria and submucosa had increased numbers of blood vessels, various numbers of inflammatory cells, and lymphoid cell infiltrates. Aggressive proliferation of the squamous epithelium resulted in extension of nodular hyperplastic lesions into the submucosa. The degenerated epithelium sometimes formed vacuoles with acute inflammation, microabscesses, and hemorrhages. Marked epithelial ulceration occurred in 16,500 ppm males and 33,000 ppm males and females (Plate 4).

Exposure Concentration Selection Rationale: Based on reduced body weights, decreased feed consumption, and increased incidences and severities of forestomach lesions, *trans*-cinnamaldehyde exposure concentrations selected for the 2-year feed study in rats were 1,000, 2,100, and 4,100 ppm.

TABLE 4
Incidences of Nonneoplastic Lesions of the Forestomach in Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde

	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Male					
Number Examined Microscopically	10	10	10	10	10
Epithelium, Hyperplasia, Squamous[a]	0	0	7** (2.1)[b]	10** (3.4)	10** (4.0)
Inflammation, Chronic Active	0	0	0	3 (1.3)	7** (1.3)
Epithelium, Ulcer	0	0	0	1 (4.0)	1 (4.0)
Female					
Number Examined Microscopically	10	10	10	10	10
Epithelium, Hyperplasia, Squamous	0	0	10** (3.4)	10** (3.9)	10** (3.6)
Inflammation, Chronic Active	0	0	0	8** (1.1)	8** (1.6)
Epithelium, Ulcer	0	0	0	0	3 (4.0)

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

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 2). Survival of 4,100 ppm males was greater than that of the vehicle control group; survival of other exposed groups of males and of exposed females was similar to that of the vehicle control groups.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 4,100 ppm males were less than those of the vehicle controls throughout the study, mean body weights of 2,100 ppm males were less after week 94, and mean body weights of 4,100 ppm females were less after week 18 (Figure 3; Tables 6 and 7). Feed consumption by 2,100 and 4,100 ppm males and 4,100 ppm females was less than that by the vehicle controls at the beginning and end of the study (Tables J1 and J2). Dietary concentrations of 1,000, 2,100, or 4,100 ppm delivered average daily doses of approximately 50, 100, or 200 mg/kg body weight to males and females. There were no clinical findings related to *trans*-cinnamaldehyde exposure.

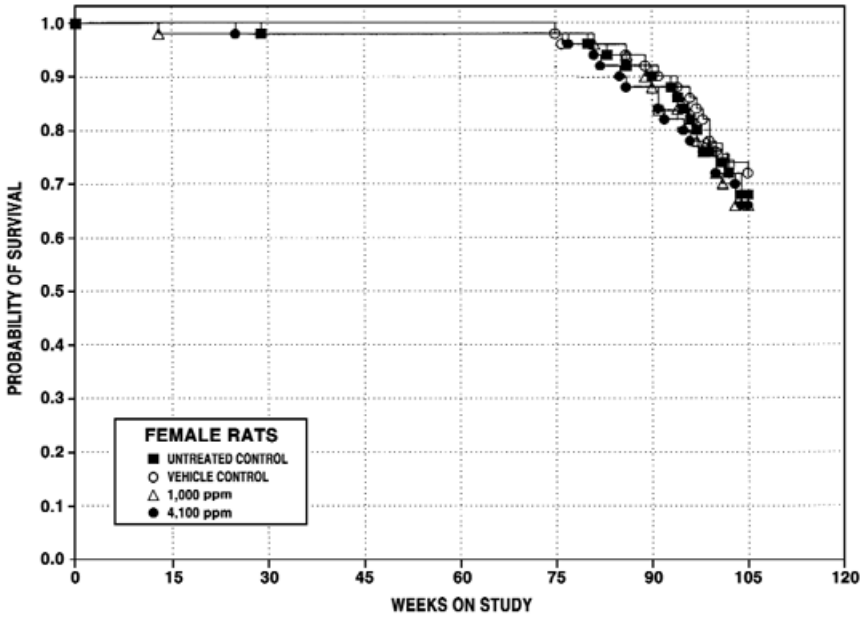
Hippuric Acid – Biomarker of Exposure

Hippuric acid excretion in urine expressed as the hippuric acid to creatinine ratio was proportional to dose (Tables 8 and G2), indicating that neither absorption, metabolism, nor excretion was saturated in either male or female rats exposed to dosed feed containing 1,000 to 4,100 ppm *trans*-cinnamaldehyde.

Table 5
Survival of Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	13	11	11	6
Natural deaths	6	3	12	3
Animals surviving to study termination	31	36	27	41
Percent probability of survival at end of study[a]	62	72	54	82
Mean survival (days)[b]	679	697	658	719
Survival analysis[c]	P=0.064N	P=0.284N	P=0.548	P=0.025N
Female				
Animals initially in study	50	50	50	50
Missing[d]	0	0	1	0
Moribund	10	13	10	10
Natural deaths	4	4	4	7
Animals surviving to study termination	36	33	35	33
Percent probability of survival at end of study	72	66	71	66
Mean survival (days)	711	698	691	695
Survival analysis	P=0.652	P=0.642	P=1.000	P=0.609

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



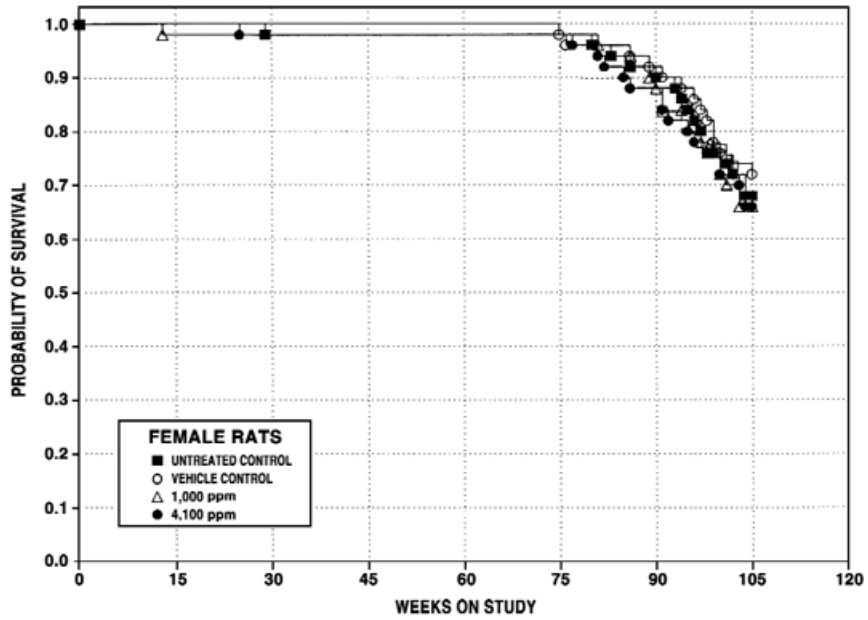


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to *trans*-Cinnamaldehyde in Feed for 2 Years

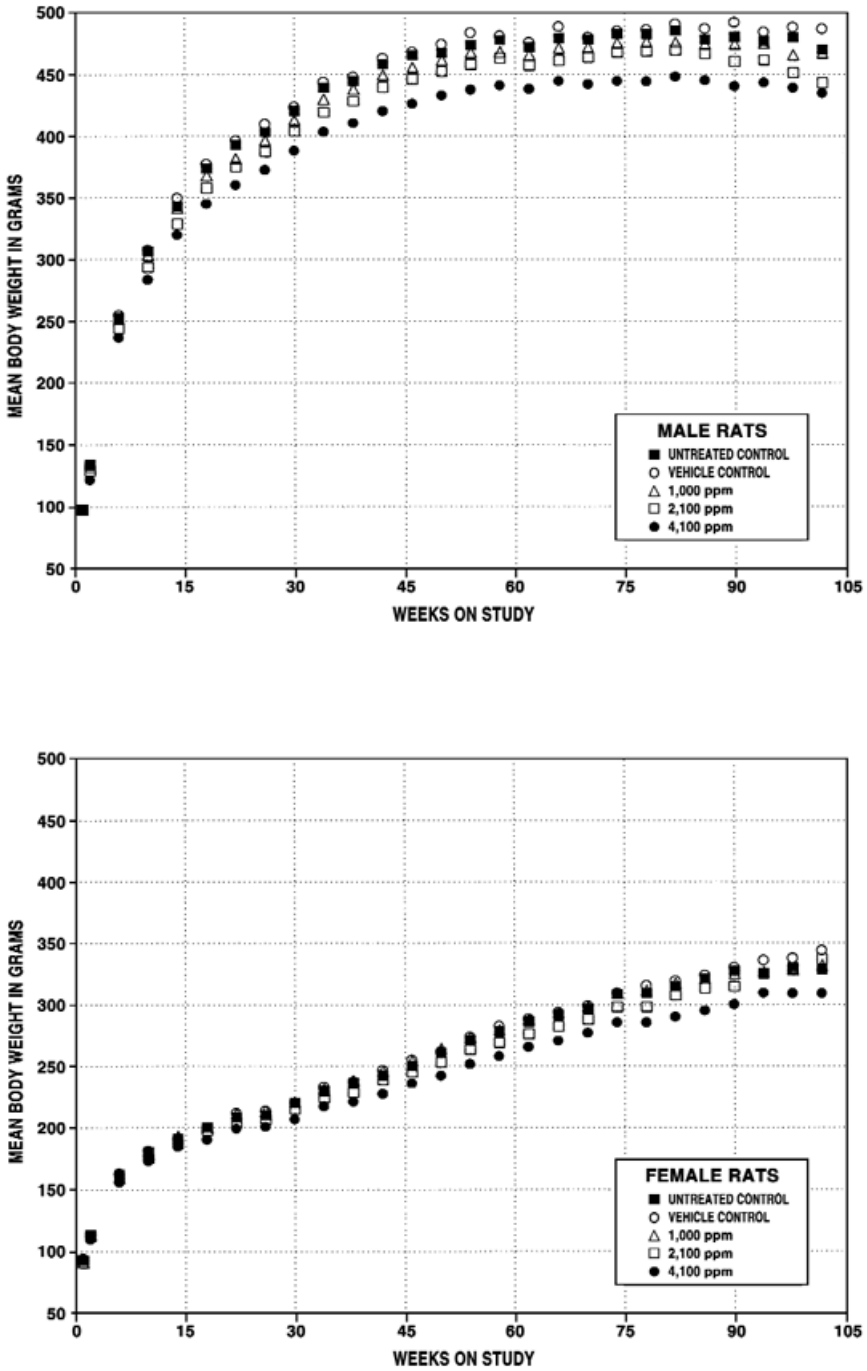


FIGURE 3
Growth Curves for Male and Female Rats Exposed to *trans*-Cinnamaldehyde in Feed for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Weeks on Study	Vehicle Control		1,000 ppm			2,100 ppm			4,100 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	97	50	98	101	50	98	100	50	98	101	50
2	134	50	132	99	50	129	96	50	122	91	50
6	255	50	252	99	50	244	96	50	237	93	50
10	308	50	304	99	50	294	96	50	284	92	50
14	350	50	342	98	50	329	94	50	320	92	50
18	378	50	368	98	50	358	95	50	345	91	50
22	397	50	382	96	50	375	95	49	361	91	50
26	410	50	397	97	49	387	95	49	373	91	50
30	424	50	413	98	49	404	95	48	388	92	50
34	444	50	430	97	49	420	95	48	404	91	50
38	448	50	438	98	49	429	96	48	411	92	50
42	463	50	449	97	49	440	95	48	421	91	50
46	468	50	456	97	49	446	95	48	427	91	50
50	475	50	462	97	49	453	95	48	433	91	50
54	484	50	468	97	49	458	95	48	438	91	50
58	482	50	468	97	49	463	96	48	441	92	50
62	476	50	466	98	48	457	96	48	438	92	50
66	489	49	471	96	48	461	94	48	445	91	50
70	480	49	472	98	48	464	97	48	442	92	50
74	485	46	475	98	48	468	97	46	445	92	49
78	486	46	476	98	48	469	96	44	444	91	49
82	491	45	476	97	48	470	96	43	448	91	49
86	487	42	474	98	46	467	96	40	445	91	49
90	492	37	475	96	45	460	94	35	440	90	49
94	485	35	475	98	43	461	95	33	444	92	48
98	488	33	466	95	42	451	92	30	439	90	45
102	487	32	467	96	38	443	91	28	435	89	43
Mean for weeks											
1-13	199		197	99		191	96		185	93	
14-52	426		414	97		404	95		388	91	
53-102	486		471	97		461	95		442	91	

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Weeks on Study	Vehicle Control		1,000 ppm			2,100 ppm			4,100 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	94	50	91	97	50	93	99	50	94	100	50
2	113	50	113	100	50	113	99	50	110	97	50
6	163	50	160	98	50	160	98	50	156	96	50
10	182	50	179	98	50	175	97	49	173	96	50
14	191	50	194	101	49	187	98	49	185	97	50
18	201	50	201	100	49	198	99	49	191	95	50
22	212	50	212	100	49	204	96	49	200	94	50
26	214	50	214	100	49	207	97	49	201	94	49
30	221	50	222	100	49	215	98	48	207	94	49
34	234	50	232	99	49	225	96	48	218	93	49
38	238	50	239	100	49	229	97	48	222	93	49
42	247	50	246	100	49	239	97	48	228	92	49
46	255	50	255	100	49	246	96	48	236	93	49
50	262	50	264	101	49	253	97	48	243	93	49
54	274	50	274	100	49	264	96	48	252	92	49
58	283	50	280	99	49	269	95	48	258	91	49
62	289	50	288	100	49	276	96	48	266	92	49
66	294	50	293	100	49	283	96	48	271	92	49
70	299	50	299	100	49	288	96	46	277	93	49
74	310	50	310	100	49	298	96	45	286	92	49
78	316	48	312	99	49	298	95	45	286	91	48
82	320	48	318	99	48	308	96	44	291	91	47
86	324	48	321	99	48	313	97	44	295	91	45
90	331	46	325	98	45	315	95	42	301	91	44
94	336	45	327	97	44	326	97	41	310	92	41
98	338	42	329	97	39	330	98	39	310	92	39
102	344	37	332	97	35	337	98	37	309	90	36
Mean for weeks											
1-13	138		136	99		135	98		133	96	
14-52	228		228	100		220	96		213	93	
53-102	312		308	99		300	96		286	92	

TABLE 8
Urinary Hippuric Acid-Biomarker for *trans*-Cinnamaldehyde Exposure in Rats in the in the 2-Year Feed Study[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Male					
n					
Week 2	9	10	10	10	10
Month 3	10	10	10	10	10
Month 12	10	10	10	10	10
Month 18	10	10	10	10	10
Hippuric acid/creatinine ratio[b]					
Week 2	2.01 ± 0.25	2.24 ± 0.09[c]	4.90 ± 0.14**	8.18 ± 0.42**	13.2 ± 0.9**
Month 3	0.92 ± 0.09	1.05 ± 0.05	2.20 ± 0.10**	3.18 ± 0.20**	5.25 ± 0.37**
Month 12	0.90 ± 0.03	0.85 ± 0.06	1.59 ± 0.08**	2.10 ± 0.14**	4.26 ± 0.33**
Month 18	1.02 ± 0.02	1.01 ± 0.06	1.61 ± 0.09**	2.50 ± 0.21**	4.36 ± 0.35**
Total hippuric acid excreted (mg)[b]					
Week 2	10.9 ± 1.7	10.0 ± 1.6	29.5 ± 1.8**	38.2 ± 2.7**	63.6 ± 3.7**
Month 3	12.3 ± 1.3	15.2 ± 0.9	30.1 ± 2.1**	40.3 ± 3.8**	61.7 ± 4.7**
Month 12	11.3 ± 1.0	11.3 ± 0.9	19.3 ± 1.3**	22.8 ± 3.0**	49.8 ± 4.9**
Month 18	12.1 ± 0.5	10.6 ± 1.0	20.1 ± 1.5**	24.7 ± 3.5**	47.5 ± 3.9**[c]
Female					
n					
Week 2	10	10	9	10	10
Month 3	10	10	10	10	10
Month 12	10	10	10	10	10
Month 18	10	10	10	10	10
Hippuric acid/creatinine ratio[b]					
Week 2	2.40 ± 0.12	2.48 ± 0.16	5.27 ± 0.21**	7.89 ± 0.27**	14.3 ± 0.8**
Month 3	1.24 ± 0.10	1.17 ± 0.05	3.05 ± 0.19**	4.35 ± 0.33**	6.84 ± 0.32**
Month 12	1.18 ± 0.06	1.07 ± 0.07	2.21 ± 0.11**	3.54 ± 0.19**	6.50 ± 0.43**
Month 18	1.36 ± 0.07	1.29 ± 0.06	2.68 ± 0.11**	4.17 ± 0.18**	6.80 ± 0.48**
Total hippuric acid excreted (mg)[b]					
Week 2	9.86 ± 0.70	9.03 ± 1.07	18.2 ± 1.7**	28.7 ± 2.6**	50.7 ± 3.0**
Month 3	8.33 ± 0.77	8.44 ± 0.59	21.0 ± 1.8**	33.4 ± 2.7**	47.5 ± 3.2**
Month 12	8.21 ± 0.63	8.18 ± 0.56	15.6 ± 1.5**	25.1 ± 3.0**	46.6 ± 4.7**
Month 18	11.8 ± 0.9	10.6 ± 0.7	23.7 ± 1.0**	37.8 ± 2.7**	63.3 ± 5.7**[c]

** Significantly different (P≤0.01) from the vehicle control group by Dunn's or Shirley's test; pairwise comparisons between the untreated control and other groups are not presented.
[a] Data are presented as mean ± standard error.
[b] Linear and dose proportional
[c] n=9

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms of the preputial and prostate glands and mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Preputial and Prostate Glands: The incidences of adenoma of the preputial gland (vehicle control, 5/50; 1,000 ppm, 1/49; 2,100 ppm, 2/50; 4,100 ppm, 0/50) and prostate gland (4/50, 0/49, 0/49, 0/50) in 4,100 ppm males were significantly decreased compared to those in the vehicle controls (Table A3). The incidences of preputial gland adenoma in the exposed and vehicle control groups were within the historical range in controls (all routes) given NTP-2000 diet [45/907 (4.2% ± 3.5%), range 0%-13%] (Table A4a). Similarly, the incidences of carcinoma of the preputial gland (1/50, 2/49, 3/50, 1/50) were within the historical range in controls given NTP-2000 diet [27/907 (3.3% ± 3.0%), range 0%-10%]. The incidence of prostate gland adenoma in the vehicle controls (4/50) exceeded the historical control range [13/906 (1.4% ± 1.7%), range 0%-4%] (Table A4b) (Suwa *et al.*, 2001). The incidences of preputial and prostate gland adenomas likely represent biologic variation unrelated to exposure to *trans*-cinnamaldehyde.

Mononuclear Cell Leukemia: The incidence of mononuclear cell leukemia in 4,100 ppm males was significantly decreased (18/50, 15/50, 21/50, 9/50; Table A3), was considered unrelated to *trans*-cinnamaldehyde exposure, and may have contributed to the increased survival in this group. The historical control incidence for vehicle controls given NTP-2000 diet is 401/909 (44.1% ± 11.8%) with a range of 22% to 68%. Mononuclear cell leukemia is one of the most common neoplasms of F344/N rats in 2-year studies.

MICE

3-MONTH STUDY

One vehicle control male, one 4,100 ppm male, and one 33,000 ppm male died during the first week of the study due to inanition that resulted from difficulty with the feeder; five 16,500 ppm and eight 33,000 ppm males died during weeks 2 and 3 due to initial difficulty with the feeder and unpalatability of the dosed feed (Table 9). All female mice survived to the end of the study. Final mean body weights and body weight gains of all exposed groups of males and of females exposed to 8,200 ppm or greater were significantly less than those of the vehicle controls. Feed consumption by 16,500 and 33,000 ppm mice was less than that by the vehicle controls during weeks 1 (females) and 2 (males) due to difficulty with the feeder; during weeks 2 and 4, additional feeders were used and feed consumption improved. Feed consumption by exposed mice (except 33,000 ppm females) was generally similar to that by the vehicle controls at the end of the study. Dietary concentrations of 4,100, 8,200, 16,500, and 33,000 ppm resulted in average daily doses of approximately 650, 1,320, 2,550, and 5,475 mg/kg body weight to males and 625, 1,380, 2,680, and 5,200 mg/kg to females. There were no clinical findings related to exposure to *trans*-cinnamaldehyde other than thinness and lethargy in 16,500 and 33,000 ppm males and thinness in females from those groups; these findings were attributed to the decreased feed consumption. Changes in organ weights appeared to be related to changes in body weights (Table H2).

TABLE 9
Survival, Body Weights, and Feed Consumption of Mice in the 3-Month Feed Study of *trans*-Cinnamaldehyde

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 2	Week 14
Male							
Vehicle Control	9/10[d]	20.9 ± 0.3	30.9 ± 0.8	10.0 ± 0.8		3.7	4.4
4,100	9/10[d]	20.8 ± 0.3	27.9 ± 0.5**	7.1 ± 0.6**	90	3.5	4.1
8,200	10/10	21.1 ± 0.4	27.2 ± 0.5**	6.1 ± 0.2**	88	3.5	4.0
16,500	5/10[e]	21.0 ± 0.3	26.3 ± 0.6**	5.1 ± 0.6**	85	2.4	4.0
33,000	1/10[f]	21.0 ± 0.3	19.1[g]	0.1[g]	62	3.2	3.8
Female						**Week 1**	**Week 14**
Vehicle Control	10/10	17.1 ± 0.3	27.7 ± 0.9	10.6 ± 0.7		2.5	3.9
4,100	10/10	17.0 ± 0.2	27.5 ± 0.9	10.5 ± 0.9	99	2.6	4.0
8,200	10/10	17.0 ± 0.3	25.4 ± 0.8*	8.4 ± 0.7*	92	2.4	3.9
16,500	10/10	16.9 ± 0.3	20.8 ± 0.2**	3.9 ± 0.3**	75	2.3	3.8
33,000	10/10	17.0 ± 0.2	17.6 ± 0.2**	0.6 ± 0.3**	63	1.5	3.2

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' test
** ($P \leq 0.01$)
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.
[d] Week of death: 1
[e] Week of death: 2, 2, 2, 2, 2
[f] Week of death: 1, 2, 2, 2, 2, 2, 2, 2, 3
[g] No standard error calculated due to high mortality

The hematology data for mice in the 3-month toxicity study of *trans*-cinnamaldehyde are listed in Table F2. Similar to the rat study, a minimal (≤9%) decrease in mean cell volume and mean cell hemoglobin values occurred in 16,500 and 33,000 ppm males and females and 8,200 ppm males. The 16,500 ppm males and the surviving 33,000 ppm male had decreased leukocyte counts that were attributed to a decrease in lymphocyte numbers. The decrease in lymphocyte count would be consistent with a stress-related lymphopenia and would be supported by the apparent decrease in circulating eosinophil numbers. The surviving 33,000 ppm male also had increases in hematocrit, hemoglobin concentration, and erythrocyte count that would be consistent with hemoconcentration.

The incidence of squamous epithelial hyperplasia of the forestomach mucosa in 33,000 ppm females was significantly greater than that in the vehicle controls (Table 10). One 16,500 ppm male and one 8,200 ppm female also had these lesions. The forestomach lesions consisted of diffuse thickening of the squamous epithelium due to increased numbers of cell layers (hyperplasia).

Olfactory epithelial degeneration of the nasal cavity occurred in 16,500 and 33,000 ppm males and females (Table 10). Olfactory degeneration was minimal to mild and was characterized by fewer layers of sensory cells (atrophy) and disorganization of the neuroepithelium, primarily at Level II adjacent to the dorsal meatus. At Level III, the olfactory epithelium was also affected in a patchy or multifocal pattern. Olfactory degeneration was diffuse in neuroepithelium lining the dorsal meatus at Level II and had an irregular multifocal distribution along the nasal septum and the tips of the ethmoid turbinates at Level III. Cross sections of the nasal cavity at Levels II and III are made using the following landmarks on the ventral surface of the cranium: Level II is taken through the incisive papilla anterior to the first palatial ridge while Level III is taken through the middle of the second molar teeth.

Exposure Concentration Selection Rationale: Based on reduced body weights in 8,200, 16,500, and 33,000 ppm males and females and increased incidences of forestomach lesions in 33,000 ppm females, *trans*-cinnamaldehyde exposure concentrations selected for the 2-year feed study in mice were 1,000, 2,100, and 4,100 ppm.

TABLE 10
Incidences of Selected Nonneoplastic Lesions in Mice in the 3-Month Feed Study of *trans*-Cinnamaldehyde

	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Male					
Stomach, Forestomach[a]	10	10	10	10	10
Epithelium, Hyperplasia, Squamous[b]	0	0	0	1 (1.0)[c]	0
Nose	10	10	10	10	10
Olfactory Epithelium, Degeneration	0	0	0	4* (1.0)	1 (2.0)
Female					
Stomach, Forestomach	10	10	10	10	10
Epithelium, Hyperplasia, Squamous	0	0	1 (1.0)	0	4* (1.3)
Nose	10	0	2	10	10
Olfactory Epithelium, Degeneration	0		2 (1.0)	10** (1.0)	10** (2.0)

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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 4). Survival of 2,100 ppm males was less than that of the vehicle control group; survival of other exposed groups of males and of exposed females was similar to that of the vehicle control groups.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 2,100 and 4,100 ppm males and females were generally less than those of the vehicle controls throughout the study, and mean body weights of 1,000 ppm males were less after week 74 (Tables 12 and 13; Figure 5). Feed consumption by exposed mice was similar to that by the vehicle controls (Tables J3 and J4). Dietary concentrations of 1,000, 2,100, or 4,100 ppm delivered average daily doses of approximately 125, 270, or 540 (males) or 570 (females) mg/kg body weight to males and females. There were no clinical findings related to *trans*-cinnamaldehyde exposure.

TABLE 11
Survival of Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	0	0	2	1
Natural deaths	3	4	9	0
Animals surviving to study termination	47[d]	46	39	49
Percent probability of survival at end of study[a]	94	92	78	98
Mean survival (days)[b]	712	710	695	725
Survival analysis[c]	P=0.712N	P=0.990	P=0.043	P=0.603N
Female				
Animals initially in study	50	50	50	50
Moribund	3	4	1	4
Natural deaths	6	9	5	3
Animals surviving to study termination	41	37[e]	44	43
Percent probability of survival at end of study	82	74	88	86
Mean survival (days)	707	703	719	706
Survival analysis	P=0.371N	P=0.485	P=0.556N	P=0.788N

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

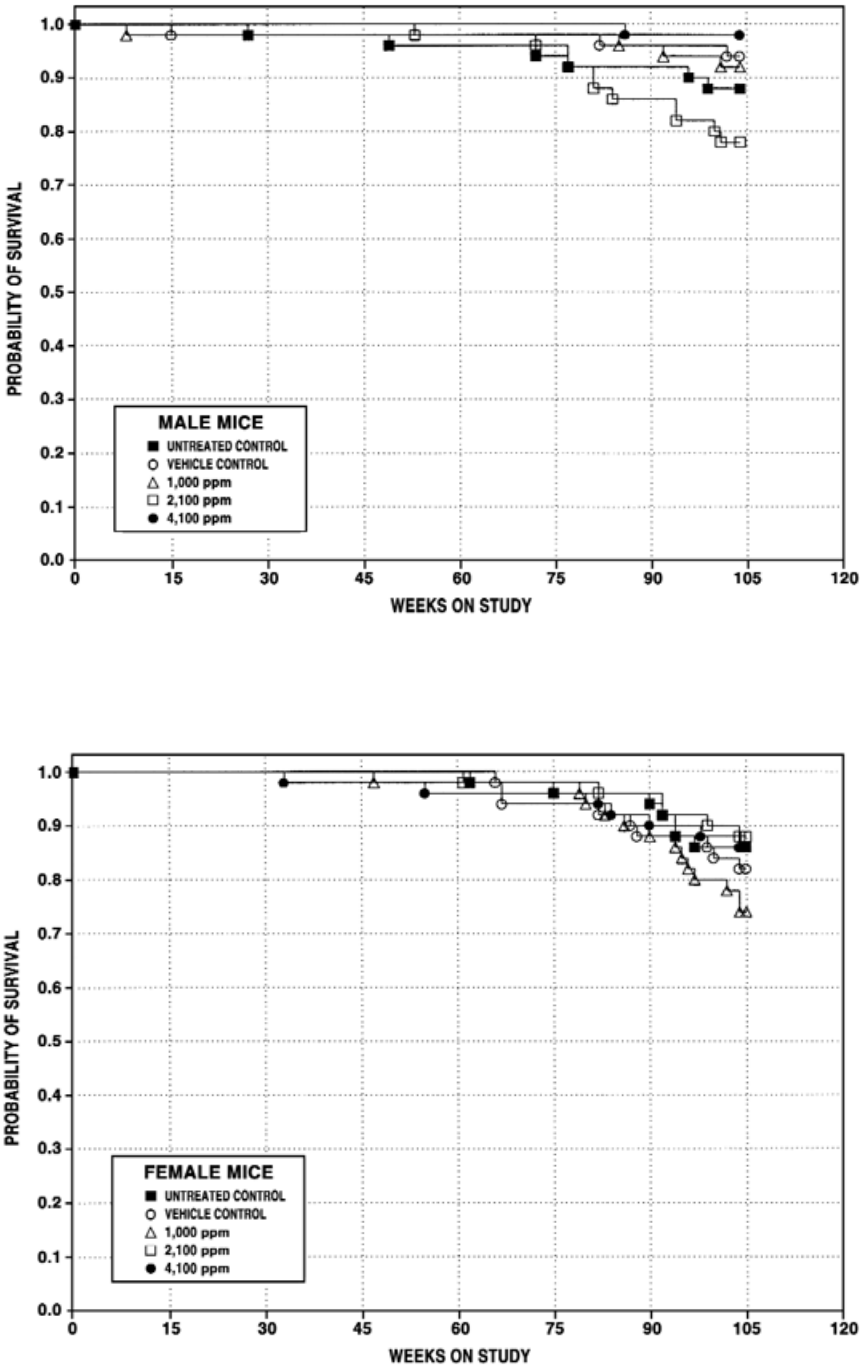


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to *trans*-Cinnamaldehyde in Feed for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Weeks on Study	Vehicle Control		1,000 ppm			2,100 ppm			4,100 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	21.1	50	20.8	99	50	20.6	98	50	20.6	98	50
2	22.8	50	22.4	98	50	22.0	97	50	22.0	97	50
6	25.8	50	25.9	100	50	25.3	98	50	24.5	95	50
9	29.9	50	29.2	98	49	28.3	95	50	27.5	92	50
13	32.3	50	31.5	98	49	30.3	94	50	29.0	90	50
18	35.4	49	34.5	98	49	32.4	92	50	31.8	90	50
22	36.9	49	36.7	100	49	34.4	93	50	33.2	90	50
26	39.1	49	39.0	100	49	36.4	93	50	35.7	91	50
30	40.6	49	40.5	100	49	38.2	94	50	36.8	91	50
34	42.5	49	42.4	100	49	39.9	94	50	38.1	90	50
38	42.6	49	42.2	99	49	40.1	94	50	38.1	89	50
42	43.0	49	42.6	99	49	40.0	93	50	38.1	89	50
46	43.7	49	43.2	99	49	40.7	93	50	38.6	88	50
50	45.4	49	44.6	98	49	42.4	93	50	40.3	89	50
54	46.0	49	45.3	99	49	43.1	94	49	41.0	89	50
58	46.5	49	45.9	99	49	43.2	93	49	40.9	88	50
62	46.1	49	45.1	98	49	42.1	91	49	40.1	87	50
66	45.1	49	44.0	98	49	41.1	91	49	39.0	87	50
70	44.8	49	43.8	98	49	40.5	90	49	38.2	85	50
74	43.8	49	42.4	97	49	39.0	89	48	36.3	83	50
78	40.5	49	38.3	95	49	35.0	86	46	32.8	81	50
82	38.9	49	36.8	95	49	33.6	86	44	32.0	82	50
86	37.9	48	35.6	94	48	32.6	86	43	31.6	83	50
90	35.4	48	33.4	94	48	32.1	91	43	32.3	91	49
94	35.9	48	33.7	94	47	32.6	91	41	32.1	89	49
98	36.0	48	33.2	92	47	32.2	89	41	32.0	89	49
102	35.6	47	33.1	93	46	32.3	91	39	32.1	90	49
Mean for weeks											
1-13	26.4		26.0	98		25.3	96		24.7	94	
14-52	41.0		40.6	99		38.3	93		36.7	90	
53-102	41.0		39.3	96		36.9	90		35.4	86	

TABLE 13
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Weeks on Study	Vehicle Control		1,000 ppm			2,100 ppm			4,100 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	17.9	50	17.6	98	50	17.9	100	50	17.9	100	50
2	18.8	50	18.4	98	50	18.5	98	50	18.5	98	50
6	20.6	50	21.5	104	50	20.5	100	50	21.1	102	50
9	24.6	50	24.4	99	50	23.9	97	50	23.8	97	50
13	27.4	50	27.1	99	50	26.5	97	50	25.7	94	50
18	31.5	50	31.1	99	50	29.7	94	50	28.6	91	50
22	33.8	50	33.4	99	50	32.5	96	50	30.5	90	50
26	36.5	50	36.1	99	50	35.5	97	50	33.1	91	50
30	36.2	50	36.3	100	50	35.3	98	50	33.7	93	50
34	39.5	50	38.9	99	50	38.4	97	50	35.9	91	49
38	40.0	50	38.8	97	50	38.3	96	50	36.3	91	49
42	40.8	50	39.7	97	50	38.9	95	50	36.7	90	49
46	41.8	50	40.4	97	50	39.2	94	50	37.0	89	49
50	43.2	50	41.7	97	49	40.1	93	50	38.5	89	49
54	44.2	50	43.2	98	49	41.8	95	50	39.5	89	49
58	45.2	50	44.1	98	49	42.7	95	50	38.8	86	48
62	45.4	50	44.0	97	49	41.9	92	49	38.3	84	48
66	43.4	49	43.2	100	49	40.9	94	49	37.8	87	48
70	44.8	47	43.3	97	49	40.7	91	49	38.3	86	48
74	46.0	47	43.9	95	49	40.9	89	49	37.7	82	48
78	42.7	47	41.2	97	49	37.1	87	49	34.8	82	48
82	40.2	47	39.9	99	47	34.8	87	49	33.3	83	48
86	40.0	46	39.6	99	45	34.1	85	48	33.1	83	46
90	39.2	44	38.3	98	45	34.1	87	48	33.3	85	46
94	39.0	44	37.7	97	44	34.7	89	46	33.5	86	45
98	40.9	44	39.2	96	40	35.5	87	46	33.6	82	45
102	40.4	42	39.0	97	40	35.0	87	45	34.2	85	44
Mean for weeks											
1-13	21.9		21.8	100		21.5	98		21.4	98	
14-52	38.1		37.4	98		36.4	96		34.5	91	
53-102	42.4		41.3	97		38.0	90		35.9	85	

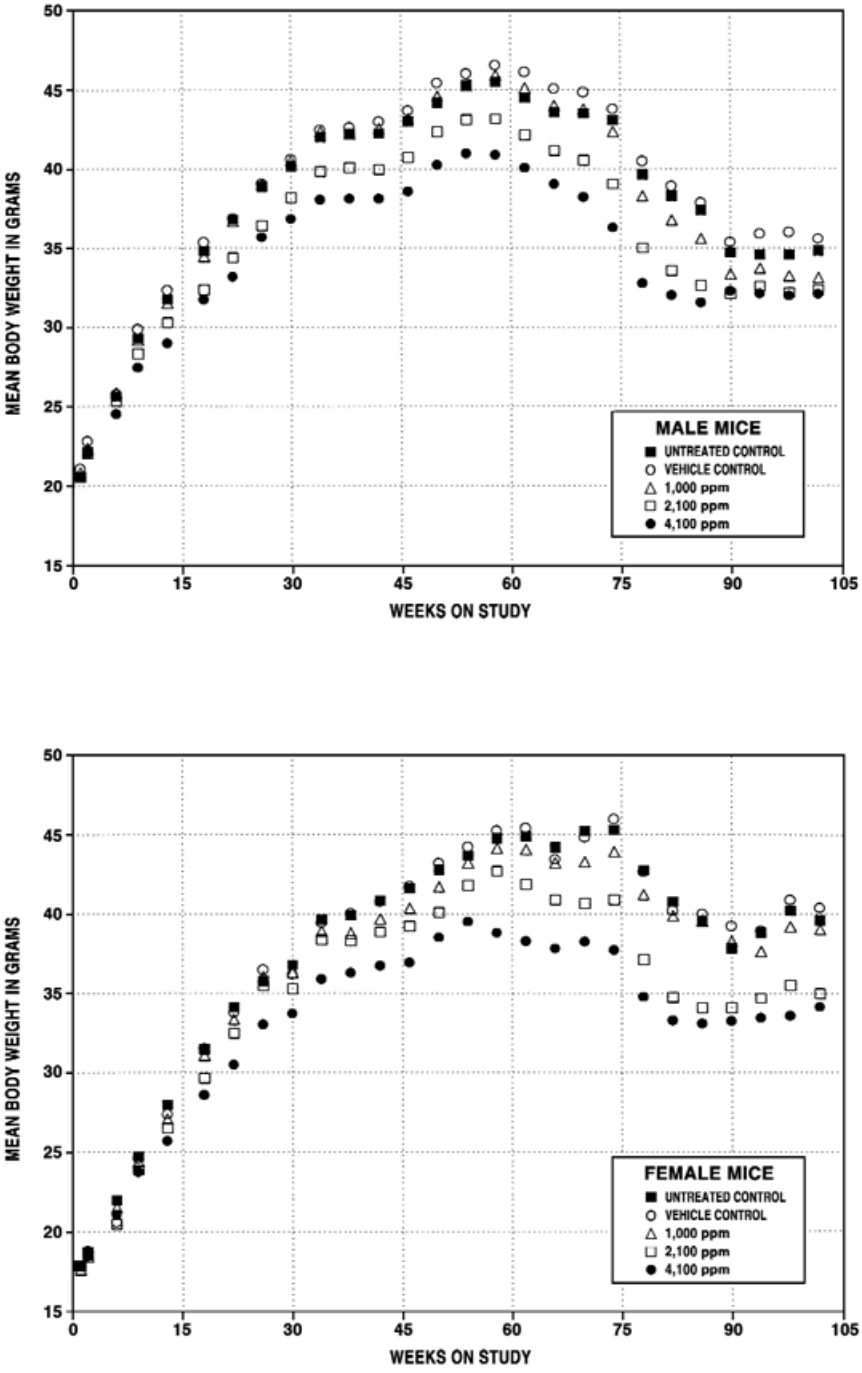


FIGURE 5
Growth Curves for Male and Female Mice Exposed to *trans*-Cinnamaldehyde in Feed for 2 Years

Pathology and Statistical Analyses

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

Forestomach: One male and three females in the 2,100 ppm groups had a squamous cell papilloma, and one male and one female in these groups had a squamous cell carcinoma (Tables C1, D1, and D3); one 4,100 ppm male and one untreated control female also had a squamous cell papilloma. The incidences of squamous cell papilloma and of squamous cell carcinoma in males and females were within the historical ranges in controls (all routes) given NTP-2000 diet [squamous cell papilloma: males, 12/959 (1.5% ± 1.9%), range 0%-6%, females, 14/959 (1.5% ± 1.9%), range 0%-6%; squamous cell carcinoma: males, 2/959 (0.3% ± 0.7%), range 0%-2%, females, 1/959 (0.1% ± 0.5%), range 0%-2%]. The combined incidence of squamous cell papilloma or carcinoma in 2,100 ppm females [4/50 (8%); Table D3] slightly exceeded the historical range [15/959 (1.7% ± 1.9%), range 0%-6%]. The forestomach neoplasms were not considered to be related to *trans*-cinnamaldehyde exposure because the combined incidences of benign or malignant neoplasms were not significantly increased, the incidences were generally within the historical control ranges, exposure-related responses were not seen in males or females, and there were no supportive preneoplastic lesions (hyperplasia).

Nose: The incidences of olfactory epithelial pigmentation in 4,100 ppm males (vehicle control, 0/48; 1,000 ppm, 0/48; 2,100 ppm, 3/48; 4,100 ppm, 26/50; Table C4) and in 2,100 and 4,100 ppm females (0/50, 0/50, 8/50, 46/50; Table D4) were significantly greater than those in the vehicle controls. Pigmentation was located in the basal cytoplasm of the olfactory epithelial cells in the dorsal meatus of Level II and was characterized by finely granular, golden brown pigment consistent with that of lipofuscin. The pigmentation was minimal, and the cellular detail within the olfactory epithelium was retained. Females in the 4,100 ppm group did not have hyaline degeneration of the olfactory epithelium, a spontaneous nonneoplastic lesion in mice; however, this lesion was observed in the vehicle control and lower exposure groups.

Bone: The incidence of myelofibrosis in 4,100 ppm females was significantly increased (27/50, 23/50, 34/50, 38/50, Table D4). Myelofibrosis was characterized by increased osteoclastic and osteoblastic activity with atrophy of trabeculae of long bones and skull and increased deposition of fibrous connective tissue. Myelofibrosis is commonly associated with hormonal changes, cystic ovaries, and endometrial hyperplasia in aged female $B6C3F_1$ mice and was not considered related to *trans*-cinnamaldehyde exposure. The incidences of myelofibrosis in this study are consistent with that of vehicle controls in NTP studies.

Liver: The incidences of hepatocellular adenoma or carcinoma (combined) in 2,100 and 4,100 ppm males were significantly decreased (16/50, 12/50, 7/50, 7/50; Table C3), and the combined incidence of these neoplasms occurred with a negative trend in females (5/49, 4/50, 2/50, 1/50; Table D3). The incidences in exposed groups of males and females were less than the historical ranges in controls (all routes) given NTP-2000 diet [males: 441/959 (48.4% ± 12.9%), range 26%-72%; females: 203/954 (22.6% ± 9.1%), range 9%-40%]. The decreased incidences of liver neoplasms in males and females were most likely related to the decreased body weights (Haseman *et al.*, 1997).

GENETIC TOXICOLOGY

trans-Cinnamaldehyde (1 to 333 µg/plate) was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of induced mouse liver S9 activation enzymes; no mutagenicity was seen in this strain with induced rat or hamster liver S9 enzymes or without activation (Table E1; Mortelmans *et al.*, 1986; Dillon *et al.*, 1998). Mutagenicity tests in all other strains (TA98, TA102, TA104, TA1535, TA1537), with or without mouse, hamster, or rat liver S9, yielded negative results. *trans*-Cinnamaldehyde induced sister chromatid exchanges in Chinese hamster ovary (CHO) cells, with and without induced rat liver S9 activation (Table E2; Galloway *et al.*, 1987). No significant increase in the frequency of chromosomal aberrations occurred in CHO cells cultured with *trans*cinnamaldehyde, with or without induced rat liver S9 (Table E3; Galloway *et al.*, 1987). In tests for induction of germ cell genetic

damage in male *Drosophila melanogaster*, *trans*-cinnamaldehyde induced a significant increase in the frequency of sex-linked recessive lethal mutations when administered by abdominal injection (Table E4; Woodruff *et al.*, 1985); however, no induction of reciprocal translocations occurred in germ cells of treated males (Table E5; Woodruff *et al*., 1985). Dietary concentrations of 4,100 to 33,000 ppm *trans*-cinnamaldehyde administered by feeding for 3 months did not increase the frequency of micronucleated normochromatic erythrocytes in the peripheral blood of male or female $B6C3F_1$ mice (Table E6).

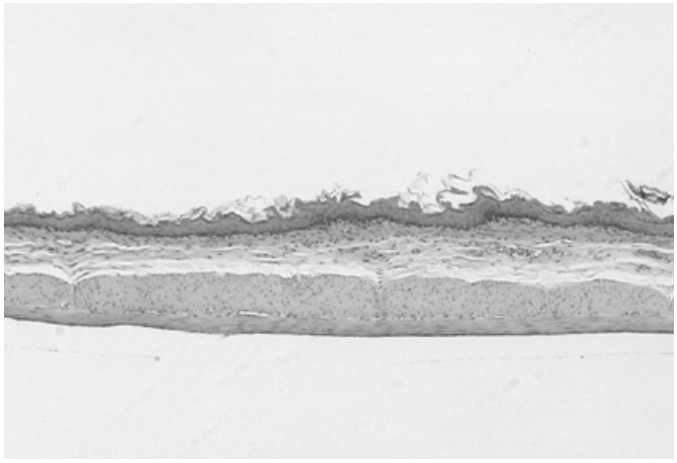


Plate 1
Forestomach of a control male F334/N rat in the 3-month feed study of *trans*-cinnamaldehyde. H&E; 20x

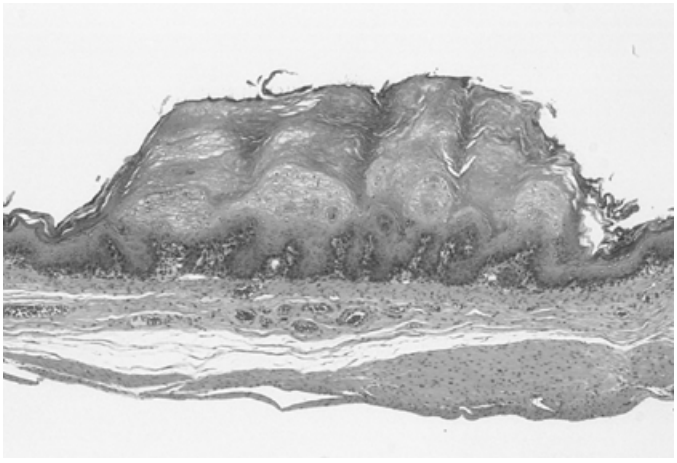


Plate 2
Squamous epithelial hyperplasia of the forestomach in a male F344/N rat exposed to 8,200 ppm *trans*-cinnamaldehyde in the feed for 3 months. Note the plaque-like area of thickened squamous epithelium with thick layers of abnormal keratin. Compare the squamous epithelial hyperplasia with normal squamous epithelium in Plate 1. H&E; 20x

Plate 3
Marked squamous epithelial hyperplasia of the forestomach in a female F344/N rat exposed to 33,000 ppm *trans*-cinnamaldehyde in the feed for 3 months. Note the prominent downgrowths of the basal layer and thick layers of abnormal keratin. H&E; 20x

Plate 4
Marked squamous epithelial hyperplasia of the forestomach in a female F344/N rat exposed to 33,000 ppm *trans*-cinnamaldehyde in the feed for 3 months. Note the hyperplastic squamous epithelium is ulcerated and associated with chronic active inflammation. H&E; 40x

DISCUSSION AND CONCLUSIONS

Cinnamaldehyde occurs naturally in several plant and cinnamon tree species and is the primary ingredient of cinnamon and cassia oils. It is used as a flavoring agent in foods and beverages and as a fragrance ingredient in a wide variety of consumer products including cosmetics, soaps, and detergents. Toxicology and carcinogenicity studies of *trans*-cinnamaldehyde were performed because of widespread human exposure through its use as a food and fragrance additive and because of its structural similarity to cinnamyl anthranilate and 3,4,5-trimethoxycinnamaldehyde (Figures 6 and 7), two known rodent carcinogens.

Because significant human exposure to relatively high concentrations of *trans*-cinnamaldehyde occurs through ingestion as a food additive, dosed feed was chosen as the most appropriate route of exposure for the current studies. *trans*-Cinnamaldehyde is a reactive conjugated allyl aldehyde and is rapidly oxidized to cinnamic acid when exposed to air. Microencapsulation was demonstrated to be an effective technique for administering cinnamaldehyde and other reactive aldehydes in the diet including citral, another flavor and fragrance ingredient (Melnick *et al.,* 1987; Kuhn *et al.,* 1991; Dieter *et al.,* 1993; Yuan *et al.*, 1993). In a stability study in NIH-07 diet, 41% of a dose formulation of 0.20 mg citral/kg body weight was lost after one day, and 92% was lost after seven days due to volatility and reactivity with components in the feed (Kuhn *et al.,* 1991); when citral was given in starch microcapsules mixed with the diet, the stability increased to 95% after seven days. Likewise, dose formulations of microencapsulated *trans*-cinnamaldehyde were stable (≥90%) for 9 days under simulated animal room conditions.

Comparative feed (microencapsulated) and corn oil gavage studies were performed to determine if the toxicity of *trans*-cinnamaldehyde was altered by microencapsulation (Hébert *et al.,* 1994). No mortality was observed in F344 rats or B6C3F$_1$ mice exposed to average daily doses of microencapsulated cinnamaldehyde up to 3,000 or 10,000 mg/kg, respectively. In the corn oil gavage study, doses of 2,620 mg/kg per day or greater in mice and 940 mg/kg or greater in rats resulted in nearly 100% mortality. Other studies revealed that the bioavailability and metabolism of *trans*-cinnamaldehyde were not altered when administered in microcapsules compared to corn oil gavage administration (Yuan *et al.,* 1993). Microencapsulated *trans*-cinnamaldehyde was chosen as the route of administration for long-term studies because chemical loss from the microcapsules would be minimal, higher doses of cinnamaldehyde could be used, and the bioavailability and toxicity of cinnamaldehyde would not be altered by microencapsulation. The exposure concentrations used in the present studies were equivalent to the amount of *trans*-cinnamaldehyde found in some food products, including desserts, breakfast cereals, and baked goods (Blakemore and Thompson, 1983).

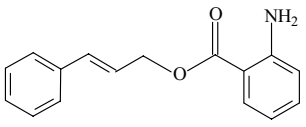


FIGURE 6
Cinnamyl anthranilate

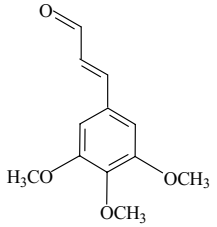


FIGURE 7
3, 4, 5-trimethoxycinnamaldehyde

A few significant differences in the incidences of some neoplasms and nonneoplastic lesions occurred between untreated and vehicle control groups in the 2-year studies. The significant findings were examined using the NTP historical control database for neoplasms and a similar informal NTP database for nonneoplastic lesions to determine the relevance of these differences. These incidences occurred at the frequencies expected by chance, suggesting that the differences were due to biologic variation and were not related to ingestion of microcapsules. In female rats, the incidence of cardiomyopathy in the vehicle controls was significantly greater than that in the untreated controls. Although this difference was also observed in the citral feed study (NTP, 2003), it was not related to microencapsulation in either study. Cardiomyopathy is a common degenerative myocardial disease of F344 rats (MacKenzie and Alison, 1990).

In the current 3-month study in rats, there were no exposure-related deaths. Exposure concentration-dependent decreases in mean body weights were observed in all exposed groups of males and in females exposed to 16,500 or 33,000 ppm. Reductions in body weight were a result of decreased feed consumption by these groups due to unpalatability of the dosed feed. In addition, the incidences of squamous epithelial hyperplasia of the forestomach were significantly increased in 8,200 ppm or greater males and females. Chronic active inflammation and epithelial ulceration of the forestomach also occurred in some males and females in the 16,500 and 33,000 ppm groups. Based on these results, the highest exposure concentration selected for the 2-year study was 4,100 ppm. Other investigators have observed forestomach lesions in rats following administration of cinnamaldehyde in the feed. In a 16-week dosed-feed study, Osborne-Mendel rats given 10,000 ppm cinnamaldehyde in the diet exhibited slight hyperkeratosis of the stomach lining (Hagan *et al.*, 1967). When microencapsulated cinnamaldehyde was administered in the diet to F344 rats, exposure concentration-related increases in the incidences and severity of forestomach epithelial hyperplasia occurred in males and females (Hébert *et al.,* 1994).

In the current 2-year rat study, no chemical-related neoplasms or nonneoplastic lesions occurred in males or females exposed to microencapsulated *trans*-cinnamaldehyde. Mean body weights of 4,100 ppm males and females were generally less than those of the vehicle controls. The incidences of preputial gland adenoma, prostate gland adenoma, and mononuclear cell leukemia were decreased in 4,100 ppm males compared to those in the vehicle controls. These decreases were considered unrelated to *trans*-cinnamaldehyde exposure, but the decreased incidence of mononuclear cell leukemia may have contributed to the increased survival of 4,100 ppm male rats.

Urinary hippuric acid served as a good biomarker for *trans*-cinnamaldehyde exposure in rats. In most cases, the hippuric acid to creatinine ratio was proportional to dose, indicating that absorption, metabolism, and excretion processes were not saturated. In the 2-year rat study, the ratio tended to decrease with time and was well correlated with the calculated *trans*-cinnamaldehyde doses at similar times (Tables J1 and J2). The dose of *trans*-cinnamaldehyde on a body weight basis tended to be higher in younger animals because their feed consumption was comparable to older animals, but their body weight was lower.

In the current 3-month study in mice, one vehicle control male and one 4,100 ppm male died during the first week of the study; five 16,500 ppm and nine 33,000 ppm males died during the first 3 weeks. These deaths were due to inanition that resulted from difficulty with the feeder coupled with unpalatability of the dosed feed. Minimal to mild squamous epithelial hyperplasia of the forestomach mucosa occurred in 33,000 ppm females. Although minimal forestomach hyperplasia occurred in male mice fed diets containing 37,500 ppm microencapsulated cinnamaldehyde (Hébert *et al.,* 1994), forestomach hyperplasia did not occur in any of the 33,000 ppm males in the current 3-month study due to the early deaths of these animals. Based on the exposure concentration-related decreases in mean body weights of males and females and the increased incidences of forestomach lesions in 33,000 ppm females, the highest exposure concentration selected for the 2-year study was 4,100 ppm.

In the current 2-year mouse study, the combined incidences of squamous cell papilloma and carcinoma of the forestomach in 2,100 ppm females slightly exceeded the historical range for controls given the NTP-2000 diet. However, the forestomach neoplasms were not considered related to *trans*-cinnamaldehyde exposure because the incidences of benign or malignant neoplasms were not significantly increased, the incidences were generally within the historical control ranges, there was no exposure-related response due to the lack of forestomach lesions in 4,100 ppm females, and there were no supportive preneoplastic lesions (hyperplasia).

The incidences of hepatocellular adenoma or carcinoma (combined) in 2,100 and 4,100 ppm male mice were significantly less than those in the vehicle controls and the combined incidence of these neoplasms occurred with a negative trend in females. The incidences in exposed groups of males and females were less than the historical ranges in controls (all routes) given NTP-2000 diet. The decreased incidences of liver neoplasms in male and female $B6C3F_1$ mice were most likely related to the decreased body weights. The control mice in the 2-year *trans*-cinnamaldehyde study weighed less than control mice in other studies in the current historical control database (with one exception in the females). At 52 weeks, the body weight of the 4,100 ppm males was approximately 11% less than that of the control males. Haseman *et al*., (1997) demonstrated that this body weight decrement would be associated with approximately an 8% to 12% reduction in liver tumor incidence, which is equivalent to four to six animals out of 50. Because 16 vehicle control males had liver neoplasms, approximately 10 to 12 males in the 4,100 ppm group would be predicted to have liver tumors, based on the reduced body weight. Seven neoplasms were seen in this group, thus the reduction in body weight accounts for most of the decrease in liver tumor incidence.

The decreased liver tumor incidences may suggest a weak antineoplastic effect of *trans*-cinnamaldehyde. There are numerous reports in the literature describing the antimutagenic effects of cinnamaldehyde in test systems with specific recombinational DNA repair mechanisms (reviewed by Neudecker, 1992), and there is at least one study that suggests cinnamaldehyde has anticarcinogenic effects (Imai *et al*., 2002). The effects of cinnamaldehyde on lung carcinogenesis were investigated in *ras*H2 transgenic and nontransgenic mice initiated with intraperitoneal injections of 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone, at a dose of 3 mg/mouse once a week for 2 weeks. Following initiation, animals were fed a diet containing 5,000 ppm cinnamaldehyde for 26 weeks. Cinnamaldehyde treatment significantly reduced the combined incidences of lung adenoma and carcinoma in *ras*H2 males and the multiplicity of lung tumors in *ras*H2 males and nontransgenic females.

In contrast to *trans*-cinnamaldehyde, cinnamyl anthranilate was carcinogenic in rodents and caused hepatocellular adenomas and carcinomas in male and female mice and adenomas and carcinomas of the pancreas and adenomas and adenocarcinomas of the kidney in male F344 rats (NCI, 1980). Because anthranilic acid was not carcinogenic in mice or rats (NCI, 1978), the cinnamyl moiety was thought to be responsible for the carcinogenicity of cinnamyl anthranilate. Based on the results of the current 2-year studies, it appears that the carcinogenic potential of cinnamyl anthranilate is a property of the entire molecule.

The comparative mutagenicity profiles of *trans*-cinnamaldehyde and cinnamyl anthranilate do not aid in the understanding of the activity shown by these two chemicals in the rodent bioassay. In fact, in a variety of mutagenicity assays, the carcinogenic cinnamyl anthranilate was less active than the noncarcinogenic *trans*-cinnamaldehyde. *trans*-Cinnamaldehyde was weakly mutagenic in *Salmonella typhimurium* strain TA100 in the presence of $B6C3F_1$ mouse liver S9, an unconventional source of activation enzymes (Dillon *et al.*, 1998). No mutagenic activity was seen in any other strain, or in TA100 with or without conventional S9 enzyme preparations from Syrian hamsters or Sprague-Dawley rats (Mortelmans *et al.*, 1986; Dillon *et al.*, 1998). *trans*-Cinnamaldehyde also induced sister chromatid exchanges in cultured Chinese hamster ovary cells (Galloway *et al.*, 1987) and gene mutations in germ cells of male *Drosophila melanogaster* when administered by injection (Woodruff *et al.*, 1985). Cinnamyl anthranilate, in contrast, was clearly inactive in all three of these mutation assays (Zeiger *et al.*, 1988; Foureman *et al.*, 1994; Gulati *et al.*, 1989). Neither compound induced micronucleated erythrocytes in treated mice (Appendix E; Shelby *et al*., 1993).

CONCLUSIONS

Under the conditions of this 2-year feed study, there was *no evidence of carcinogenic activity** of *trans*-cinnamaldehyde in male or female F344/N rats exposed to 1,000, 2,100, or 4,100 ppm. There was *no evidence of carcinogenic activity* of *trans*-cinnamaldehyde in male or female $B6C3F_1$ mice exposed to 1,000, 2,100, or 4,100 ppm.

Exposure to *trans*-cinnamaldehyde resulted in olfactory epithelial pigmentation in male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF *trans*-CINNAMALDEHYDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	14	13	11	11	6
Natural deaths	7	6	3	12	3
Survivors					
Terminal sacrifice	29	31	36	27	41
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(50)	(50)
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Intestine large, cecum	(50)	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Leiomyosarcoma					1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)	(50)
Cholangiocarcinoma	1 (2%)				
Fibrous histiocytoma, metastatic, skin			2 (4%)	1 (2%)	1 (2%)
Hepatocellular adenoma	1 (2%)	1 (2%)		1 (2%)	
Osteosarcoma, metastatic, uncertain primary site		1 (2%)			
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)		
Mesentery	(14)	(5)	(8)	(9)	(12)
Fibrous histiocytoma, metastatic, skin			1 (13%)		
Lipoma		1 (20%)			1 (8%)
Osteosarcoma, metastatic, uncertain primary site		1 (20%)			
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (13%)		
Oral mucosa	(13)	(13)	(14)	(12)	(24)
Gingival, squamous cell carcinoma		1 (8%)		1 (8%)	
Pancreas	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Mixed tumor benign		1 (2%)			
Osteosarcoma, metastatic, uncertain primary site		1 (2%)			
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)		
Acinus, adenoma	1 (2%)		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)	(50)
Carcinoma					1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)		
Squamous cell papilloma		1 (2%)			
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Tongue	(1)			(1)	
Squamous cell papilloma	1 (100%)			1 (100%)	
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Schwannoma 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 *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)	
Ganglioneuroma	1 (2%)				
Pheochromocytoma benign	5 (10%)		3 (6%)	4 (8%)	
Bilateral, pheochromocytoma benign			1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		1 (2%)	
Carcinoma					1 (2%)
Parathyroid gland	(47)	(45)	(48)	(46)	(42)
Adenoma			2 (4%)		
Pituitary gland	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, salivary glands					1 (2%)
Pars distalis, adenoma	13 (26%)	8 (16%)	10 (20%)	10 (20%)	8 (16%)
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Bilateral, C-cell, adenoma		1 (2%)	1 (2%)		
Bilateral, C-cell, carcinoma					1 (2%)
C-cell, adenoma	4 (8%)	7 (14%)	9 (18%)	3 (6%)	10 (20%)
C-cell, carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)	
Follicular cell, adenoma	1 (2%)				
Follicular cell, carcinoma	1 (2%)	2 (4%)	1 (2%)		
General Body System					
Peritoneum		(1)	(1)		(1)
Genital System					
Epididymis	(50)	(50)	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Preputial gland	(50)	(50)	(49)	(50)	(50)
Adenoma	2 (4%)	5 (10%)	1 (2%)	2 (4%)	
Carcinoma	3 (6%)	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Prostate	(50)	(50)	(49)	(49)	(50)
Adenoma		4 (8%)			
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(49)	(50)
Testes	(50)	(50)	(49)	(50)	(50)
Bilateral, interstitial cell, adenoma	34 (68%)	39 (78%)	44 (90%)	35 (70%)	47 (94%)
Interstitial cell, adenoma	11 (22%)	7 (14%)	3 (6%)	7 (14%)	3 (6%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Lymph node	(24)	(20)	(28)	(28)	(20)
Deep cervical, carcinoma, metastatic, thyroid gland				1 (4%)	1 (5%)
Mediastinal, carcinoma, metastatic, thyroid gland					1 (5%)
Mediastinal, fibrous histiocytoma, metastatic, skin			1 (4%)		
Pancreatic, fibrous histiocytoma, metastatic, skin			1 (4%)		
Lymph node, mandibular	(2)		(4)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Hematopoietic System (continued)					
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)		
Osteosarcoma, metastatic, uncertain primary site		1 (2%)			
Spleen	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)	
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)		
Thymus	(43)	(44)	(45)	(46)	(43)
Thymoma benign		1 (2%)			
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Fibroadenoma	2 (4%)	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)			
Basal cell carcinoma	1 (2%)		1 (2%)		
Keratoacanthoma	2 (4%)	2 (4%)	2 (4%)	3 (6%)	
Keratoacanthoma, multiple	1 (2%)		1 (2%)		
Squamous cell carcinoma				1 (2%)	
Trichoepithelioma		1 (2%)	3 (6%)		
Sebaceous gland, adenoma				1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	5 (10%)		2 (4%)	4 (8%)
Subcutaneous tissue, fibroma, multiple		1 (2%)	1 (2%)		
Subcutaneous tissue, fibrosarcoma	4 (8%)	2 (4%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrous histiocytoma			2 (4%)	1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma					1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)	
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)		
Skeletal muscle	(2)	(1)	(3)	(1)	(1)
Fibrous histiocytoma, metastatic, skin			2 (67%)		1 (100%)
Rhabdomyosarcoma			1 (33%)		
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone				1 (2%)	
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	6 (12%)	6 (12%)	1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)	
Carcinoma, metastatic, preputial gland	1 (2%)				
Carcinoma, metastatic, salivary glands					1 (2%)
Carcinoma, metastatic, thyroid gland	1 (2%)				
Carcinoma, metastatic, Zymbal's gland			1 (2%)		
Fibrosarcoma, metastatic, skin	1 (2%)	1 (2%)			
Fibrous histiocytoma, metastatic, skin			1 (2%)	1 (2%)	1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Respiratory System (continued)					
Lung (continued)	(50)	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, uncertain primary site		1 (2%)			
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)		
Squamous cell carcinoma			1 (2%)		
Squamous cell carcinoma, metastatic, oral mucosa		1 (2%)			
Mediastinum, fibrosarcoma, metastatic, skin	1 (2%)				
Mediastinum, osteosarcoma, metastatic, uncertain primary site		1 (2%)			
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)		
Nose	(50)	(50)	(50)	(50)	(50)
Fibroma				1 (2%)	
Squamous cell carcinoma, metastatic, oral mucosa		1 (2%)			
Trachea	(50)	(50)	(50)	(50)	(50)
Special Senses System					
Zymbal's gland	(1)		(1)		(2)
Adenoma					1 (50%)
Carcinoma			1 (100%)		
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin			1 (2%)	1 (2%)	
Renal tubule, adenoma, multiple				1 (2%)	
Urinary bladder	(50)	(50)	(49)	(49)	(50)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Leukemia mononuclear	22 (44%)	18 (36%)	15 (30%)	21 (42%)	9 (18%)
Mesothelioma malignant	3 (6%)	2 (4%)	5 (10%)		1 (2%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	50	50	49	48	50
Total primary neoplasms	119	121	122	112	95
Total animals with benign neoplasms	50	49	48	48	50
Total benign neoplasms	83	90	90	80	76
Total animals with malignant neoplasms	30	27	27	27	19
Total malignant neoplasms	36	31	32	32	19
Total animals with metastatic neoplasms	3	3	4	4	3
Total metastatic neoplasms	4	9	26	9	7
Total animals with malignant neoplasms of uncertain primary site		1			

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	508	524	583	588	598	603	615	631	659	673	676	690	696	703	709	733	799	700	711	700	711	711	724	731	731	731	731
Carcass ID Number	03 8	04 1	00 9	03 1	03 7	00 5	02 1	03 5	01 4	01 9	04 4	03 0	02 9	01 6	00 8	03 3	01 1	01 5	00 2	01 8	02 3	00 1	01 0	02 5	02 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma															X										
Hepatocellular adenoma																									
Mesentery		+	+								+		+		+					+				+	
Oral mucosa													+		+				+		+	+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																		+							
Squamous cell papilloma																		X							
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma															X										
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X					X							X		X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																							X		X
C-cell, carcinoma																X									
Follicular cell, adenoma								X																	
Follicular cell, carcinoma																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 *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 3 1	7 3 1 1	7 3 1 1	7 3 1 1	7 3 1 1	7 3 2 0	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 2 2	7 3 3 3	7 3 3 3	7 3 3 3	7 3 3 3	7 3 3 3	7 3 3 3	7 3 3 3	7 3 3 3	7 3 3 3	
Carcass ID Number	0 3 3 9	0 4 0 0	0 4 4 6	0 4 4 8	0 5 0 0	0 0 0 3	0 0 0 6	0 0 1 3	0 0 2 2	0 0 2 8	0 0 3 4	0 0 4 2	0 0 4 3	0 0 4 5	0 0 4 7	0 0 4 9	0 0 4 4	0 0 0 7	0 0 1 2	0 0 1 7	0 0 2 0	0 0 2 4	0 0 2 6	0 0 3 2	0 0 3 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hepatocellular adenoma						X																				1
Mesentery	+					+	+		+				+	+								+				14
Oral mucosa		+		+	+					+					+							+	+			13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																										1
Pheochromocytoma benign				X			X		X										X				X			5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X							X			X	X	X			X	X					13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X				X												4
C-cell, carcinoma																										1
Follicular cell, adenoma																										1
Follicular cell, carcinoma																										1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	5 0 8	5 2 4	5 8 3	5 8 6	5 9 8	6 0 3	6 1 5	6 3 1	6 5 9	6 7 3	6 7 6	6 9 0	6 9 6	7 0 3	7 0 9	7 0 9	7 1 0	7 1 0	7 1 1	7 1 1	7 2 4	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 3 8	0 4 1	0 0 9	0 3 1	0 3 7	0 0 5	0 2 1	0 3 5	0 1 4	0 1 9	0 4 4	0 3 0	0 2 9	0 1 6	0 0 8	0 3 3	0 1 1	0 1 5	0 2 2	0 1 8	0 2 3	0 1 0	0 1 2	0 2 7
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X											
Carcinoma																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X			X		X	X	X	X		X		X	X	X	X		X	X	X		X
Interstitial cell, adenoma	X	X			X	X									X									
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+						+	+	+	+	+	+		+	+	+	+			+		+
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	M	M	+	M	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																	X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma				X																				
Keratoacanthoma													X											
Keratoacanthoma, multiple																								
Subcutaneous tissue, fibroma																			X					
Subcutaneous tissue, fibrosarcoma						X			X			X												
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+												+									
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																					
Spinal cord			+																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 3 9	0 4 0	0 4 6	0 4 8	0 5 0	0 0 3	0 0 6	0 1 3	0 2 2	0 2 8	0 3 4	0 4 2	0 4 3	0 4 5	0 4 7	0 4 9	0 0 4	0 0 7	0 1 2	0 1 7	0 2 0	0 2 4	0 2 6	0 3 2	0 3 6	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								2
Carcinoma							X		X																X	3
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	34
Interstitial cell, adenoma		X									X		X		X		X			X						11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+						+	+	+	+						+			+	+		+	+		+	24
Lymph node, mandibular	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																								X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Keratoacanthoma															X											2
Keratoacanthoma, multiple																								X		1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																					X					4
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	508	524	583	588	598	603	615	631	659	673	676	690	696	703	709	709	711	710	711	711	724	731	731	731
Carcass ID Number	038	041	049	031	037	005	021	035	014	019	044	030	029	016	038	033	011	015	020	018	023	010	012	027
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X													
Carcinoma, metastatic, preputial gland																								
Carcinoma, metastatic, thyroid gland																X								
Fibrosarcoma, metastatic, skin									X															
Mediastinum, fibrosarcoma, metastatic, skin									X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								
Zymbal's gland									+															
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
Mesothelioma malignant												X											X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 3 9	0 4 0	0 4 6	0 4 8	0 5 0	0 0 3	0 0 6	0 1 3	0 2 2	0 2 8	0 3 4	0 4 2	0 4 3	0 4 5	0 4 7	0 4 9	0 0 4	0 0 7	0 1 2	0 1 7	0 2 0	0 2 4	0 2 6	0 3 2	0 3 6	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										2
Carcinoma, metastatic, preputial gland									X																	1
Carcinoma, metastatic, thyroid gland																										1
Fibrosarcoma, metastatic, skin																										1
Mediastinum, fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																								+		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye														+									+			2
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X	X				X					X			X			X	X			22
Mesothelioma malignant																						X				3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	4 2 9	4 9 9	5 0 5	5 0 8	5 5 4	5 7 7	5 7 7	5 7 7	5 9 8	6 0 6	6 0 6	6 0 6	6 2 4	6 3 7	6 4 7	6 5 3	6 5 5	7 0 7	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 8 7	0 6 2	0 7 8	0 9 2	0 6 4	0 7 5	0 8 0	0 9 8	0 7 2	0 5 3	0 8 3	0 8 8	0 6 3	0 7 3	0 5 6	0 7 9	0 9 1	0 7 0	0 5 1	0 5 5	0 6 0	0 6 5	0 6 6	0 6 7	0 7 4
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								
Osteosarcoma, metastatic, uncertain primary site																	X							
Mesentery																+	+					+		
Lipoma																								
Osteosarcoma, metastatic, uncertain primary site																	X							
Oral mucosa	+														+							+	+	+
Gingival, squamous cell carcinoma																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor benign																								
Osteosarcoma, metastatic, uncertain primary site																	X							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																								X
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X			X	X					X			X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																								
C-cell, adenoma																								
C-cell, carcinoma												X												
Follicular cell, carcinoma																		X						
General Body System																								
Peritoneum																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	731	731	731	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	07 76	09 93	09 95	06 88	06 89	07 07	08 76	08 89	09 94	09 96	09 97	09 99	05 52	05 54	05 57	05 58	05 59	06 01	07 11	08 11	08 12	08 24	08 45	09 00	10 00	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X																	1
Osteosarcoma, metastatic, uncertain primary site																										1
Mesentery								+					+													5
Lipoma								X																		1
Osteosarcoma, metastatic, uncertain primary site																										1
Oral mucosa								+	+	+				+				+				+		+		13
Gingival, squamous cell carcinoma																		X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor benign					X																					1
Osteosarcoma, metastatic, uncertain primary site																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant											X															2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X									X	X												8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma															X											1
C-cell, adenoma				X		X						X	X	X				X					X			7
C-cell, carcinoma																X										2
Follicular cell, carcinoma										X																2
General Body System																										
Peritoneum	+																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	4 2 9	4 9 9	5 0 5	5 0 8	5 5 4	5 7 7	5 7 7	5 7 7	5 9 8	6 0 6	6 0 6	6 0 6	6 2 4	6 3 7	6 4 7	6 5 3	6 5 5	7 0 7	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 8 7	0 6 2	0 7 8	0 9 2	0 6 4	0 7 5	0 8 0	0 9 8	0 7 2	0 5 3	0 8 3	0 8 8	0 6 3	0 7 3	0 5 6	0 7 9	0 9 1	0 7 0	0 5 1	0 5 5	0 6 0	0 6 5	0 6 6	0 6 7	0 7 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					X	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X			X	X	X		X	X	X		X		X	X		X	X	X	X	X	X
Interstitial cell, adenoma	X	X	X		X	X																			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+		+				+					+	+	+	+	+			+			+	
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																	X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	+	M	+
Thymoma benign																									X
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma										X									X						
Trichoepithelioma																									
Subcutaneous tissue, fibroma						X				X									X						
Subcutaneous tissue, fibroma, multiple																								X	
Subcutaneous tissue, fibrosarcoma																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve												+													
Spinal cord												+													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 7 6	0 9 3	0 9 5	0 6 8	0 6 9	0 7 7	0 8 6	0 8 9	0 9 4	0 9 6	0 9 7	0 9 9	0 5 2	0 5 4	0 5 7	0 5 8	0 5 9	0 6 1	0 7 1	0 8 1	0 8 2	0 8 4	0 8 5	0 9 0	1 0 0	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X			X																X	X			5
Carcinoma								X																		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X		X	4
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	39
Interstitial cell, adenoma													X									X				7
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+			+	+						+	+	+				+			+		+			20
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	44
Thymoma benign																										1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma					X																					1
Keratoacanthoma																										2
Trichoepithelioma															X											1
Subcutaneous tissue, fibroma										X						X										5
Subcutaneous tissue, fibroma, multiple																										1
Subcutaneous tissue, fibrosarcoma																		X								2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	4 2 9	4 9 9	5 0 5	5 0 8	5 5 4	5 7 7	5 7 7	5 7 7	5 9 8	6 0 6	6 0 6	6 0 6	6 2 4	6 3 7	6 4 7	6 5 3	6 5 5	7 0 7	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 8 7	0 6 2	0 7 8	0 9 2	0 6 4	0 7 5	0 8 0	0 9 8	0 7 2	0 5 3	0 8 3	0 8 8	0 6 3	0 7 3	0 5 6	0 7 9	0 9 1	0 7 0	0 5 1	0 5 5	0 6 0	0 6 5	0 6 6	0 6 7	0 7 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																	X								
Fibrosarcoma, metastatic, skin																			X						
Osteosarcoma, metastatic, uncertain primary site																	X								
Squamous cell carcinoma, metastatic, oral mucosa																									
Mediastinum, osteosarcoma, metastatic, uncertain primary site																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa																									
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							
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 0 7 6	0 0 9 3	0 0 9 5	0 0 6 8	0 0 6 9	0 0 7 7	0 0 8 6	0 0 8 9	0 0 9 4	0 0 9 6	0 0 9 7	0 0 9 9	0 0 5 2	0 0 5 4	0 0 5 7	0 0 5 8	0 0 5 9	0 0 6 1	0 0 7 1	0 0 8 1	0 0 8 2	0 0 8 4	0 0 8 5	0 0 9 0	1 0 0 0	Total Tissues/ Tumors
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X					X																		2
Alveolar/bronchiolar carcinoma																												1
Fibrosarcoma, metastatic, skin																												1
Osteosarcoma, metastatic, uncertain primary site																												1
Squamous cell carcinoma, metastatic, oral mucosa																		X										1
Mediastinum, osteosarcoma, metastatic, uncertain primary site																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, oral mucosa																		X										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																												
Eye				+																								1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X			X		X			X	X		X						X	X		X					18
Mesothelioma malignant	X																		X									2

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

Number of Days on Study	1 7 0	4 0 4	5 9 1	5 9 3	6 1 9	6 4 3	6 4 8	6 7 2	6 8 0	6 8 2	6 8 2	6 9 0	7 1 0	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 2 7	1 0 9	1 1 6	1 4 9	1 3 3	1 2 4	1 4 7	1 1 3	1 3 0	1 2 2	1 2 3	1 4 2	1 2 8	1 3 7	1 0 4	1 0 5	1 0 6	1 1 0	1 1 7	1 1 8	1 2 0	1 2 5	1 3 2	1 3 6	1 3 8
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X											X		
Rhabdomyosarcoma, metastatic, skeletal muscle									X															
Mesentery						+			+		+					+					+			
Fibrous histiocytoma, metastatic, skin											X													
Rhabdomyosarcoma, metastatic, skeletal muscle									X															
Oral mucosa		+												+						+			+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X													
Rhabdomyosarcoma, metastatic, skeletal muscle									X															
Acinus, adenoma																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma, metastatic, skeletal muscle									X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X													
Schwannoma malignant											X													
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X						
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X													
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X										X	X			X					X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X													
Bilateral, C-cell, adenoma																								
C-cell, adenoma							X					X	X	X			X			X		X		
C-cell, carcinoma																								
Follicular cell, carcinoma																								

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

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 3 9	1 4 6	1 5 0	1 0 1	1 0 8	1 1 1	1 1 4	1 2 6	1 3 5	1 4 4	1 4 8	1 0 2	1 0 3	1 0 7	1 1 2	1 1 5	1 1 9	1 2 1	1 2 9	1 3 1	1 3 4	1 4 0	1 4 1	1 4 3	1 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										2
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Mesentery								+										+			+					8
Fibrous histiocytoma, metastatic, skin																										1
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Oral mucosa	+	+	+	+			+		+		+				+			+			+					14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Acinus, adenoma									X																	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X			X																				3
Bilateral, pheochromocytoma benign								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Adenoma												X														2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X								X		X														10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Bilateral, C-cell, adenoma		X																								1
C-cell, adenoma				X													X									9
C-cell, carcinoma																					X					1
Follicular cell, carcinoma																		X								1

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

Number of Days on Study	1 7 0	4 0 4	5 9 1	5 9 3	6 1 9	6 4 3	6 4 8	6 7 2	6 8 0	6 8 2	6 8 2	6 9 0	7 1 0	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 2 7	1 0 9	1 1 6	1 4 9	1 3 3	1 2 4	1 4 7	1 1 3	1 3 0	1 2 2	1 2 3	1 4 2	1 2 8	1 3 7	1 0 4	1 0 5	1 0 6	1 1 0	1 1 7	1 1 8	1 2 0	1 2 5	1 3 2	1 3 6	1 3 8
General Body System																								
Peritoneum																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X													
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma		X						X																
Fibrous histiocytoma, metastatic, skin											X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X													
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma			X			X	X																	
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X													
Lymph node				+	+	+	+	+		+	+	+	+					+	+	+		+		+
Mediastinal, fibrous histiocytoma, metastatic, skin											X													
Pancreatic, fibrous histiocytoma, metastatic, skin											X													
Lymph node, mandibular	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma, metastatic, skeletal muscle									X															
Thymus	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																								
Keratoacanthoma															X									
Keratoacanthoma, multiple																								
Trichoepithelioma							X								X		X							
Subcutaneous tissue, fibroma, multiple																								
Subcutaneous tissue, fibrosarcoma																								
Subcutaneous tissue, fibrous histiocytoma											X											X		

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

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 3 9	1 4 6	1 5 0	1 0 1	1 0 8	1 1 1	1 1 4	1 2 6	1 3 5	1 4 4	1 4 8	1 0 2	1 0 3	1 0 7	1 1 2	1 1 5	1 1 9	1 2 1	1 2 9	1 3 1	1 3 4	1 4 0	1 4 1	1 4 3	1 4 5	Total Tissues/ Tumors
General Body System																										
Peritoneum																					+					1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, skin																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma														X												1
Carcinoma																										2
Fibrous histiocytoma, metastatic, skin																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, skin																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Interstitial cell, adenoma																										3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Lymph node	+	+	+	+					+	+				+				+	+	+		+	+	+	+	28
Mediastinal, fibrous histiocytoma, metastatic, skin																										1
Pancreatic, fibrous histiocytoma, metastatic, skin																										1
Lymph node, mandibular	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	4
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma					X				X																	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma		X																								1
Keratoacanthoma									X																	2
Keratoacanthoma, multiple											X															1
Trichoepithelioma																										3
Subcutaneous tissue, fibroma, multiple				X																						1
Subcutaneous tissue, fibrosarcoma				X																						1
Subcutaneous tissue, fibrous histiocytoma																										2

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

Number of Days on Study	170	404	591	593	619	643	648	672	680	682	682	682	690	710	725	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	12027	10029	11016	14049	13033	12024	14047	11013	13030	12022	12023	14042	12028	13037	10304	10055	10066	11010	11117	11118	12020	12025	13032	13036	13038
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma, metastatic, skeletal muscle									X																
Skeletal muscle									+		+												+		
Fibrous histiocytoma, metastatic, skin											X												X		
Rhabdomyosarcoma									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X		X							
Carcinoma, metastatic, Zymbal's gland														X											
Fibrous histiocytoma, metastatic, skin											X														
Rhabdomyosarcoma, metastatic, skeletal muscle									X																
Squamous cell carcinoma																									
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Zymbal's gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin											X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X	X	X			X		X	X						X			X		X	X
Mesothelioma malignant								X													X				

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

Number of Days on Study	731	731	731	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	13 39	14 46	15 00	10 01	10 08	11 11	11 14	12 26	13 35	14 44	14 48	10 02	10 03	10 07	11 12	11 15	11 19	12 21	12 29	13 11	13 34	14 40	14 41	14 43	14 45	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Skeletal muscle																										3
Fibrous histiocytoma, metastatic, skin																										2
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X		X	X					X	6
Carcinoma, metastatic, Zymbal's gland																										1
Fibrous histiocytoma, metastatic, skin																										1
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Squamous cell carcinoma				X																						1
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye													+													2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X								X				X											15
Mesothelioma malignant	X												X								X					5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	12 23	17 28	48 28	50 36	53 35	53 35	56 30	57 37	58 33	59 33	60 39	61 44	62 21	62 24	62 44	62 47	64 55	65 55	67 56	67 57	68 25	69 55	71 33	73 11
Carcass ID Number	19 52	19 23	17 53	15 33	16 67	19 00	17 07	16 69	19 44	17 88	19 77	18 81	15 15	15 56	17 67	15 77	20 04	15 02	19 93	16 32	18 26	16 66	18 11	15 60
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																						X		
Hepatocellular adenoma																								
Mesentery						+			+									+						
Oral mucosa			+		+	+																		+
Gingival, squamous cell carcinoma						X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																					+			
Squamous cell papilloma																					X			
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																						X		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																						X		
Pheochromocytoma benign																			X	X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X			
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X						X				X			X		X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X																
C-cell, carcinoma																								
General Body System																								
None																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 6 2	1 7 2	1 7 4	1 8 4	1 8 5	1 8 6	1 8 7	1 9 1	1 5 4	1 5 8	1 5 9	1 6 4	1 6 8	1 7 1	1 7 5	1 7 9	1 8 3	1 8 9	1 6 1	1 6 5	1 7 0	1 8 0	1 9 3	1 9 6	1 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Hepatocellular adenoma													X													1
Mesentery		+	+	+												+	+					+				9
Oral mucosa		+			+		+		+	+					+		+		+							12
Gingival, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																					X					1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Pheochromocytoma benign									X																X	4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X																		X			X		10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X							X									3
C-cell, carcinoma															X											1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	1 2 3	1 7 8	4 8 8	5 0 6	5 3 5	5 3 5	5 6 0	5 7 7	5 8 3	5 9 3	6 0 9	6 1 4	6 2 1	6 2 4	6 2 4	6 2 7	6 4 5	6 5 5	6 7 6	6 7 7	6 8 2	6 9 5	7 1 3	7 3 1	7 3 1
Carcass ID Number	1 9 5	1 9 2	1 7 3	1 5 3	1 6 7	1 9 0	1 7 7	1 6 9	1 9 4	1 7 8	1 9 7	1 8 8	1 5 1	1 5 5	1 7 6	1 5 7	2 0 0	1 5 2	1 1 9	1 6 3	1 8 2	1 6 6	1 8 1	1 5 6	1 6 0
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma								X							X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X	X	X	X		X	X	X			X	X	X				X	X	X
Interstitial cell, adenoma				X		X					X					X						X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+			+	+		+	+				+	+		+	+			+	+
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																						X			
Squamous cell carcinoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrous histiocytoma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle																		+							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 6 2	1 7 2	1 7 4	1 8 4	1 8 5	1 8 6	1 8 7	1 9 1	1 5 4	1 5 8	1 5 9	1 6 4	1 6 8	1 7 1	1 7 5	1 7 9	1 8 3	1 8 9	1 6 1	1 6 5	1 7 0	1 8 0	1 9 3	1 9 6	1 9 8	Total Tissues/ Tumors
Genital System																										
Coagulating gland								+																		1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				2
Carcinoma										X																3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X		X	X	X	X	35
Interstitial cell, adenoma									X			X														7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+		+	+		+		+			+	+	+	+		+	+	+		+	+	+		+	28
Deep cervical, carcinoma, metastatic, thyroid gland															X											1
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma											X											X				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma														X				X								3
Squamous cell carcinoma					X																					1
Sebaceous gland, adenoma													X													1
Subcutaneous tissue, fibroma															X											2
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																								X		1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																								X		1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	123	178	488	506	535	535	560	577	583	593	609	614	621	624	624	627	645	655	667	677	682	695	713	731	731
Carcass ID Number	195	192	173	153	167	190	177	169	194	178	197	188	151	155	176	157	200	152	199	163	182	166	181	156	160
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Fibrous histiocytoma, metastatic, skin																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Renal tubule, adenoma, multiple																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X	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 *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 6 2	1 7 2	1 7 4	1 8 4	1 8 5	1 8 6	1 8 7	1 9 1	1 5 4	1 5 8	1 5 9	1 6 4	1 6 8	1 7 1	1 7 5	1 7 9	1 8 3	1 8 9	1 6 1	1 6 5	1 7 0	1 8 0	1 9 3	1 9 6	1 9 8	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X			X					X						X									6
Alveolar/bronchiolar carcinoma												X										X				2
Alveolar/bronchiolar carcinoma, metastatic, lung																						X				1
Fibrous histiocytoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Renal tubule, adenoma, multiple														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X	X				X									X		X	X			X	21

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	4	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	9	3	6	7	7	9	9	0	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	3	6	2	5	1	8	9	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	2	0	2	4	1	2	1	1	3	0	0	1	1	2	2	2	3	3	3	4	4	4	5	0	0
	1	2	4	4	3	9	6	5	2	1	5	0	9	2	3	8	4	7	8	1	6	7	0	3	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																X									
Mesentery			+			+							+				+								
Lipoma			X																						
Oral mucosa			+				+			+				+		+	+	+	+	+	+	+		+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																				
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, salivary glands					X																				
Pars distalis, adenoma						X							X						X		X				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, carcinoma			X																						
C-cell, adenoma					X											X				X		X	X		
General Body System																									
Peritoneum																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Interstitial cell, adenoma	X	X						X																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 0 0 6	2 1 2	2 1 7	2 1 8	2 2 0	2 2 5	2 2 6	2 2 7	2 3 3	2 3 6	2 3 9	2 4 2	2 4 5	2 4 9	2 0 7	2 0 8	2 0 9	2 1 1	2 1 4	2 3 0	2 3 1	2 3 5	2 4 0	2 4 3	2 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																									X	1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Mesentery							+			+	+		+		+		+	+			+					12
Lipoma																										1
Oral mucosa		+			+		+		+		+	+		+				+					+	+	+	24
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X																					1
Parathyroid gland	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, salivary glands																										1
Pars distalis, adenoma				X							X									X						8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, carcinoma																										1
C-cell, adenoma													X	X				X			X				X	10
General Body System																										
Peritoneum																		+								1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
Interstitial cell, adenoma																										3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	4 9 9	6 3 3	6 6 6	6 7 2	6 7 5	6 9 1	6 9 8	7 0 9	7 1 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2
Carcass ID Number	2 2 1	2 0 2	2 2 4	2 4 4	2 1 3	2 2 9	2 1 6	2 1 5	2 3 2	2 0 1	2 0 5	2 1 0	2 1 9	2 2 2	2 2 3	2 2 8	2 3 4	2 3 7	2 3 8	2 4 1	2 4 6	2 4 7	2 5 0	2 0 3	2 0 4	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+				+	+	+			+					+		+	+			+	+
Deep cervical, carcinoma, metastatic, thyroid gland			X																							
Mediastinal, carcinoma, metastatic, thyroid gland			X																							
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma				X			X				X															
Subcutaneous tissue, fibrosarcoma														X												
Subcutaneous tissue, fibrous histiocytoma																X										
Subcutaneous tissue, sarcoma	X																									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+										
Fibrous histiocytoma, metastatic, skin																X										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma																				X						
Carcinoma, metastatic, salivary glands					X																					
Fibrous histiocytoma, metastatic, skin																X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Zymbal's gland					+																					
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		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 *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 0 6	2 1 2	2 1 7	2 1 8	2 2 0	2 2 5	2 2 6	2 2 7	2 3 3	2 3 6	2 3 9	2 4 2	2 4 5	2 4 9	2 0 7	2 0 8	2 0 9	2 1 1	2 1 4	2 3 0	2 3 1	2 3 5	2 4 0	2 4 3	2 4 8	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+			+	+		+		+			+	+		+		+				+				20
Deep cervical, carcinoma, metastatic, thyroid gland																												1
Mediastinal, carcinoma, metastatic, thyroid gland																												1
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	43
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																		X										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma														X														4
Subcutaneous tissue, fibrosarcoma																												1
Subcutaneous tissue, fibrous histiocytoma																												1
Subcutaneous tissue, sarcoma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																												1
Fibrous histiocytoma, metastatic, skin																												1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																					1
Alveolar/bronchiolar carcinoma																												1
Carcinoma, metastatic, salivary glands																												1
Fibrous histiocytoma, metastatic, skin																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																												
Zymbal's gland																+												2
Adenoma																X												1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																		X								9
Mesothelioma malignant																		X										1

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Adrenal Medulla: Benign Pheochromocytoma					
Overall rate[a]	5/50 (10%)	0/50 (0%)	4/50 (8%)	4/50 (8%)	0/50 (0%)
Adjusted rate[b]	11.3%	0.0%	8.9%	10.0%	0.0%
Terminal rate[c]	5/29 (17%)	0/31 (0%)	4/36 (11%)	2/27 (7%)	0/41 (0%)
First incidence (days)	731 (T)	—[e]	731 (T)	676	—[f]
Poly-3 test[d]		P=0.309N	P=0.071	P=0.055	—
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	2/50 (4%)	2/50 (4%)	6/50 (12%)	6/50 (12%)	1/50 (2%)
Adjusted rate	4.5%	4.8%	13.3%	15.0%	2.1%
Terminal rate	1/29 (3%)	2/31 (7%)	6/36 (17%)	5/27 (19%)	1/41 (2%)
First incidence (days)	676	731 (T)	731 (T)	624	731 (T)
Poly-3 test		P=0.190N	P=0.160	P=0.118	P=0.452N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	2/50 (4%)	3/50 (6%)	6/50 (12%)	8/50 (16%)	2/50 (4%)
Adjusted rate	4.5%	7.2%	13.3%	20.0%	4.2%
Terminal rate	1/29 (3%)	2/31 (7%)	6/36 (17%)	7/27 (26%)	2/41 (5%)
First incidence (days)	676	655	731 (T)	624	731 (T)
Poly-3 test		P=0.256N	P=0.279	P=0.082	P=0.440N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	13/50 (26%)	8/50 (16%)	10/50 (20%)	10/50 (20%)	8/50 (16%)
Adjusted rate	28.9%	18.7%	21.9%	23.6%	16.7%
Terminal rate	10/29 (35%)	4/31 (13%)	7/36 (19%)	3/27 (11%)	7/41 (17%)
First incidence (days)	631	606	591	488	691
Poly-3 test		P=0.396N	P=0.458	P=0.387	P=0.509N
Preputial Gland: Adenoma					
Overall rate	2/50 (4%)	5/50 (10%)	1/49 (2%)	2/50 (4%)	0/50 (0%)
Adjusted rate	4.5%	11.9%	2.3%	5.0%	0.0%
Terminal rate	1/29 (3%)	4/31 (13%)	1/36 (3%)	1/27 (4%)	0/41 (0%)
First incidence (days)	696	577	731 (T)	655	—
Poly-3 test		P=0.021N	P=0.090N	P=0.237N	P=0.021N
Preputial Gland: Carcinoma					
Overall rate	3/50 (6%)	1/50 (2%)	2/49 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	6.8%	2.4%	4.4%	7.4%	2.1%
Terminal rate	3/29 (10%)	1/31 (3%)	0/36 (0%)	1/27 (4%)	1/41 (2%)
First incidence (days)	731 (T)	731 (T)	404	577	731 (T)
Poly-3 test		P=0.515N	P=0.530	P=0.295	P=0.729N
Preputial Gland: Adenoma or Carcinoma					
Overall rate	5/50 (10%)	6/50 (12%)	3/49 (6%)	5/50 (10%)	1/50 (2%)
Adjusted rate	11.2%	14.2%	6.6%	12.3%	2.1%
Terminal rate	4/29 (14%)	5/31 (16%)	1/36 (3%)	2/27 (7%)	1/41 (2%)
First incidence (days)	696	577	404	577	731 (T)
Poly-3 test		P=0.049N	P=0.206N	P=0.522N	P=0.038N
Prostate Gland: Adenoma					
Overall rate	0/50 (0%)	4/50 (8%)	0/49 (0%)	0/49 (0%)	0/50 (0%)
Adjusted rate	0.0%	9.6%	0.0%	0.0%	0.0%
Terminal rate	0/29 (0%)	3/31 (10%)	0/36 (0%)	0/26 (0%)	0/41 (0%)
First incidence (days)	—	724	—	—	—
Poly-3 test		P=0.021N	P=0.052N	P=0.069N	P=0.045N

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Skin: Keratoacanthoma					
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	6.7%	4.8%	6.6%	7.5%	0.0%
Terminal rate	2/29 (7%)	0/31 (0%)	3/36 (8%)	2/27 (7%)	0/41 (0%)
First incidence (days)	696	606	731 (T)	695	—
Poly-3 test		P=0.128N	P=0.532	P=0.474	P=0.210N
Skin: Trichoepithelioma					
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	2.4%	6.6%	0.0%	0.0%
Terminal rate	0/29 (0%)	1/31 (3%)	2/36 (6%)	0/27 (0%)	0/41 (0%)
First incidence (days)	—	731 (T)	648	—	—
Poly-3 test		P=0.129N	P=0.337	P=0.510N	P=0.472N
Skin: Trichoepithelioma or Basal Cell Adenoma					
Overall rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	4.8%	6.6%	0.0%	0.0%
Terminal rate	0/29 (0%)	2/31 (7%)	2/36 (6%)	0/27 (0%)	0/41 (0%)
First incidence (days)	—	731 (T)	648	—	—
Poly-3 test		P=0.061N	P=0.540	P=0.248N	P=0.208N
Skin: Keratoacanthoma or Squamous Cell Carcinoma					
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted rate	6.7%	4.8%	6.6%	10.1%	0.0%
Terminal rate	2/29 (7%)	0/31 (0%)	3/36 (8%)	3/27 (11%)	0/41 (0%)
First incidence (days)	696	606	731 (T)	695	—
Poly-3 test		P=0.147N	P=0.532	P=0.311	P=0.210N
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma					
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.2%	4.8%	8.8%	0.0%	0.0%
Terminal rate	0/29 (0%)	2/31 (7%)	3/36 (8%)	0/27 (0%)	0/41 (0%)
First incidence (days)	586	731 (T)	648	—	—
Poly-3 test		P=0.048N	P=0.378	P=0.248N	P=0.208N
Skin: Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma					
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	4/50 (8%)	0/50 (0%)
Adjusted rate	8.9%	9.5%	13.2%	10.1%	0.0%
Terminal rate	2/29 (7%)	2/31 (7%)	5/36 (14%)	3/27 (11%)	0/41 (0%)
First incidence (days)	586	606	648	695	—
Poly-3 test		P=0.022N	P=0.419	P=0.613	P=0.046N
Skin (Subcutaneous Tissue): Fibroma					
Overall rate	1/50 (2%)	6/50 (12%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.3%	14.1%	2.2%	5.0%	8.3%
Terminal rate	0/29 (0%)	3/31 (10%)	1/36 (3%)	1/27 (4%)	2/41 (5%)
First incidence (days)	711	577	731 (T)	676	672
Poly-3 test		P=0.422N	P=0.047N	P=0.153N	P=0.295N
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma					
Overall rate	4/50 (8%)	2/50 (4%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	8.8%	4.8%	6.6%	2.5%	6.2%
Terminal rate	1/29 (3%)	1/31 (3%)	2/36 (6%)	0/27 (0%)	2/41 (5%)
First incidence (days)	603	724	682	713	499
Poly-3 test		P=0.535	P=0.539	P=0.517N	P=0.569

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma					
Overall rate	5/50 (10%)	7/50 (14%)	3/50 (6%)	3/50 (6%)	7/50 (14%)
Adjusted rate	11.0%	16.4%	6.6%	7.5%	14.3%
Terminal rate	1/29 (3%)	4/31 (13%)	2/36 (6%)	1/27 (4%)	4/41 (10%)
First incidence (days)	603	577	682	676	499
Poly-3 test		P=0.491	P=0.132N	P=0.182N	P=0.504N
Testes: Adenoma					
Overall rate	45/50 (90%)	46/50 (92%)	47/49 (96%)	42/50 (84%)	50/50 (100%)
Adjusted rate	91.0%	94.0%	99.6%	91.4%	100.0%
Terminal rate	27/29 (93%)	31/31 (100%)	36/36 (100%)	26/27 (96%)	41/41 (100%)
First incidence (days)	508	429	591	506	499
Poly-3 test		P=0.148	P=0.127	P=0.458N	P=0.091
Thyroid Gland (C-cell): Adenoma					
Overall rate	4/50 (8%)	8/50 (16%)	10/50 (20%)	3/50 (6%)	10/50 (20%)
Adjusted rate	9.0%	19.2%	21.9%	7.5%	20.8%
Terminal rate	4/29 (14%)	8/31 (26%)	6/36 (17%)	2/27 (7%)	9/41 (22%)
First incidence (days)	731 (T)	731 (T)	648	577	675
Poly-3 test		P=0.550	P=0.484	P=0.107N	P=0.530
Thyroid Gland (C-cell): Adenoma or Carcinoma					
Overall rate	5/50 (10%)	10/50 (20%)	11/50 (22%)	4/50 (8%)	11/50 (22%)
Adjusted rate	11.2%	23.8%	24.1%	10.0%	22.8%
Terminal rate	4/29 (14%)	9/31 (29%)	7/36 (19%)	3/27 (11%)	9/41 (22%)
First incidence (days)	709	606	648	577	666
Poly-3 test		P=0.463N	P=0.587	P=0.082N	P=0.554N
All Organs: Mononuclear Cell Leukemia					
Overall rate	22/50 (44%)	18/50 (36%)	15/50 (30%)	21/50 (42%)	9/50 (18%)
Adjusted rate	46.2%	39.1%	31.9%	46.3%	18.6%
Terminal rate	10/29 (35%)	9/31 (29%)	8/36 (22%)	7/27 (26%)	6/41 (15%)
First incidence (days)	524	429	593	506	633
Poly-3 test		P=0.027N	P=0.303N	P=0.313	P=0.021N
All Organs: Malignant Mesothelioma					
Overall rate	3/50 (6%)	2/50 (4%)	5/50 (10%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.7%	4.8%	11.0%	0.0%	2.1%
Terminal rate	2/29 (7%)	2/31 (7%)	4/36 (11%)	0/27 (0%)	1/41 (2%)
First incidence (days)	690	731 (T)	672	—	731 (T)
Poly-3 test		P=0.132N	P=0.252	P=0.248N	P=0.452N
All Organs: Benign Neoplasms					
Overall rate	50/50 (100%)	49/50 (98%)	48/50 (96%)	48/50 (96%)	50/50 (100%)
Adjusted rate	100.0%	98.6%	99.6%	100.0%	100.0%
Terminal rate	29/29 (100%)	31/31 (100%)	36/36 (100%)	27/27 (100%)	41/41 (100%)
First incidence (days)	508	429	591	488	499
Poly-3 test		P=0.365	P=0.744	P=0.672	P=0.655
All Organs: Malignant Neoplasms					
Overall rate	30/50 (60%)	27/50 (54%)	27/50 (54%)	27/50 (54%)	19/50 (38%)
Adjusted rate	61.7%	57.8%	55.6%	58.3%	38.3%
Terminal rate	14/29 (48%)	15/31 (48%)	15/36 (42%)	10/27 (37%)	13/41 (32%)
First incidence (days)	524	429	404	506	499
Poly-3 test		P=0.025N	P=0.499N	P=0.562	P=0.041N

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
All Organs: Benign or Malignant Neoplasms					
Overall rate	50/50 (100%)	50/50 (100%)	49/50 (98%)	48/50 (96%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%	100.0%
Terminal rate	29/29 (100%)	31/31 (100%)	36/36 (100%)	27/27 (100%)	41/41 (100%)
First incidence (days)	508	429	404	488	499
Poly-3 test		P=1.000	P=1.000N	P=1.000N	—

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

TABLE A4a
Historical Incidence of Preputial Gland Neoplasms in Control Male F344/N Rats

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
trans-Cinnamaldehyde (feed)	7/100	4/100	11/100
Citral (feed)	7/100	1/100	8/100
Decalin (inhalation)	0/50	0/50	0/50
p,p'-Dichlorodiphenyl sulfone (feed)	3/50	0/50	3/50
Dipropylene glycol (drinking water)	3/50	3/50	6/50
Elmiron® (gavage)	1/50	1/50	2/50
2,4-Hexadienal (gavage)	1/49	3/49	4/49
Indium phosphide (inhalation)	1/50	2/50	3/50
60-Hz Magnetic fields (whole body exposure)	13/100	0/100	13/100
Methacrylonitrile (gavage)	2/50	1/50	3/50
Naphthalene (inhalation)	3/48	3/48	6/48
o-Nitrotoluene (feed)	2/60	2/60	4/60
p-Nitrotoluene (feed)	2/50	2/50	4/50
Sodium nitrite (drinking water)	0/50	5/50	5/50
Vanadium pentoxide (inhalation)	0/50	0/50	0/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	45/907 (5.0%)	27/907 (3.0%)	72/907 (7.9%)
Mean ± standard deviation	4.2% ± 3.5%	3.3% ± 3.0%	7.4% ± 4.0%
Range	0%-13%	0%-10%	0%-13%

[a] Data as of January 31, 2002

TABLE A4b
Historical Incidence of Prostate Gland Adenoma in Control Male F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
trans-Cinnamaldehyde (feed)	4/100
Citral (feed)	0/100
Decalin (inhalation)	0/50
p,p′-Dichlorodiphenyl sulfone (feed)	0/50
Dipropylene glycol (drinking water)	1/48
Elmiron® (gavage)	0/50
2,4-Hexadienal (gavage)	2/49
Indium phosphide (inhalation)	1/50
60-Hz Magnetic fields (whole body exposure)	0/100
Methacrylonitrile (gavage)	1/50
Naphthalene (inhalation)	0/49
o-Nitrotoluene (feed)	2/60
p-Nitrotoluene (feed)	2/50
Sodium nitrite (drinking water)	0/50
Vanadium pentoxide (inhalation)	0/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	13/906 (1.4%)
Mean ± standard deviation	1.4% ± 1.7%
Range	0%-4%

[a] Data as of January 31, 2002

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	14	13	11	11	6
Natural deaths	7	6	3	12	3
Survivors					
Terminal sacrifice	29	31	36	27	41
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Parasite metazoan	3 (6%)	4 (8%)	3 (6%)	1 (2%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Parasite metazoan	10 (20%)	4 (8%)	5 (10%)	8 (16%)	4 (8%)
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		1 (2%)	
Basophilic focus	25 (50%)	26 (52%)	32 (64%)	23 (46%)	33 (66%)
Clear cell focus	1 (2%)	1 (2%)			3 (6%)
Eosinophilic focus	2 (4%)	1 (2%)		2 (4%)	
Hematopoietic cell proliferation	1 (2%)	1 (2%)		2 (4%)	
Hepatodiaphragmatic nodule	2 (4%)	2 (4%)	1 (2%)	5 (10%)	4 (8%)
Inflammation, chronic active	34 (68%)	38 (76%)	38 (76%)	31 (62%)	39 (78%)
Mixed cell focus	18 (36%)	29 (58%)	32 (64%)	20 (40%)	32 (64%)
Necrosis	2 (4%)	5 (10%)	2 (4%)	3 (6%)	5 (10%)
Pigmentation		1 (2%)			
Thrombosis			1 (2%)		
Bile duct, cyst	1 (2%)	1 (2%)			
Bile duct, hyperplasia	45 (90%)	46 (92%)	45 (90%)	43 (86%)	43 (86%)
Hepatocyte, degeneration, cystic	4 (8%)	7 (14%)	3 (6%)	4 (8%)	5 (10%)
Hepatocyte, hyperplasia	1 (2%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Hepatocyte, hypertrophy					1 (2%)
Hepatocyte, vacuolization cytoplasmic	23 (46%)	37 (74%)	36 (72%)	32 (64%)	34 (68%)
Portal, fibrosis	1 (2%)				
Mesentery	(14)	(5)	(8)	(9)	(12)
Fat, inflammation, chronic	11 (79%)	2 (40%)	3 (38%)	6 (67%)	9 (75%)
Fat, mineralization	8 (57%)	2 (40%)	2 (25%)	5 (56%)	6 (50%)
Fat, necrosis	11 (79%)	2 (40%)	3 (38%)	8 (89%)	10 (83%)
Oral mucosa	(13)	(13)	(14)	(12)	(24)
Foreign body	13 (100%)	12 (92%)	12 (86%)	10 (83%)	22 (92%)
Gingival, inflammation, chronic active	9 (69%)	4 (31%)	9 (64%)	6 (50%)	12 (50%)
Pancreas	(50)	(50)	(50)	(50)	(50)
Basophilic focus		1 (2%)	2 (4%)		
Inflammation, chronic active		1 (2%)	1 (2%)		1 (2%)
Metaplasia, hepatocyte			1 (2%)		
Pigmentation		1 (2%)			
Acinus, atrophy	13 (26%)	25 (50%)	20 (40%)	23 (46%)	16 (32%)
Acinus, hyperplasia			2 (4%)	1 (2%)	
Artery, inflammation, chronic active				1 (2%)	
Duct, cyst	2 (4%)	3 (6%)	7 (14%)	3 (6%)	10 (20%)

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

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Alimentary System (continued)					
Salivary glands	(50)	(50)	(50)	(50)	(50)
Atrophy	8 (16%)	5 (10%)	7 (14%)	6 (12%)	1 (2%)
Basophilic focus	16 (32%)	19 (38%)	10 (20%)	18 (36%)	24 (48%)
Hyperplasia	1 (2%)				
Inflammation, chronic active		1 (2%)			1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Diverticulum	1 (2%)				
Inflammation, chronic active	4 (8%)	3 (6%)	1 (2%)	1 (2%)	
Mineralization			1 (2%)		
Epithelium, hyperkeratosis	2 (4%)	1 (2%)	2 (4%)	3 (6%)	
Epithelium, hyperplasia	5 (10%)	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Epithelium, ulcer	5 (10%)	2 (4%)	1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)		1 (2%)
Mineralization	1 (2%)				1 (2%)
Epithelium, erosion		4 (8%)	2 (4%)		1 (2%)
Epithelium, hyperplasia			1 (2%)		
Epithelium, necrosis			1 (2%)		
Epithelium, ulcer	1 (2%)	1 (2%)			1 (2%)
Glands, ectasia	34 (68%)	34 (68%)	37 (74%)	27 (54%)	39 (78%)
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Aorta, mineralization	1 (2%)	1 (2%)			1 (2%)
Media, mineralization	1 (2%)				
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	44 (88%)	46 (92%)	46 (92%)	45 (90%)	50 (100%)
Inflammation, chronic active	1 (2%)				
Mineralization	1 (2%)			2 (4%)	1 (2%)
Atrium, thrombosis	1 (2%)	3 (6%)		1 (2%)	
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		2 (4%)	1 (2%)	2 (4%)
Angiectasis				1 (2%)	
Atypia cellular	1 (2%)				
Hematopoietic cell proliferation	1 (2%)	2 (4%)	5 (10%)	2 (4%)	7 (14%)
Hyperplasia	12 (24%)	9 (18%)	16 (32%)	14 (28%)	13 (26%)
Hypertrophy	2 (4%)	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Mineralization				1 (2%)	
Necrosis		2 (4%)		3 (6%)	1 (2%)
Vacuolization cytoplasmic	30 (60%)	27 (54%)	30 (60%)	33 (66%)	24 (48%)
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Hyperplasia	8 (16%)	9 (18%)	14 (28%)	8 (16%)	5 (10%)
Thrombosis			1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)			

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Endocrine System (continued)					
Pituitary gland	(50)	(50)	(50)	(50)	(50)
Pars distalis, angiectasis		1 (2%)			1 (2%)
Pars distalis, cyst	2 (4%)	4 (8%)	6 (12%)	3 (6%)	4 (8%)
Pars distalis, hemorrhage	1 (2%)				
Pars distalis, hyperplasia	16 (32%)	13 (26%)	16 (32%)	18 (36%)	21 (42%)
Pars distalis, inflammation, suppurative	1 (2%)				
Pars distalis, mineralization	1 (2%)				
Pars intermedia, angiectasis					1 (2%)
Pars intermedia, cyst	2 (4%)	2 (4%)		2 (4%)	
Pars intermedia, hyperplasia		1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Ultimobranchial cyst	3 (6%)	1 (2%)		2 (4%)	2 (4%)
C-cell, hyperplasia	17 (34%)	22 (44%)	20 (40%)	15 (30%)	23 (46%)
Follicle, cyst	2 (4%)	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Follicular cell, hyperplasia		3 (6%)			2 (4%)
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(49)	(50)	(50)
Granuloma sperm	3 (6%)	1 (2%)	6 (12%)	4 (8%)	5 (10%)
Inflammation, chronic active	1 (2%)			2 (4%)	
Preputial gland	(50)	(50)	(49)	(50)	(50)
Hyperplasia	7 (14%)		2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic, diffuse, suppurative		1 (2%)			
Inflammation, chronic active	49 (98%)	43 (86%)	47 (96%)	43 (86%)	49 (98%)
Mineralization	2 (4%)				1 (2%)
Duct, ectasia	5 (10%)	7 (14%)	7 (14%)	6 (12%)	9 (18%)
Prostate, NOS	(50)	(50)	(49)	(49)	(50)
Cyst	1 (2%)	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Degeneration	1 (2%)				
Inflammation, chronic active	21 (42%)	23 (46%)	20 (41%)	20 (41%)	15 (30%)
Mineralization	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Epithelium, hyperplasia	2 (4%)	4 (8%)	1 (2%)	8 (16%)	6 (12%)
Seminal vesicle	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active		1 (2%)	1 (2%)		
Testes	(50)	(50)	(49)	(50)	(50)
Atrophy	1 (2%)				
Cyst					1 (2%)
Mineralization	42 (84%)	38 (76%)	44 (90%)	36 (72%)	41 (82%)
Germinal epithelium, atrophy	4 (8%)	1 (2%)		3 (6%)	2 (4%)
Interstitial cell, hyperplasia	10 (20%)	8 (16%)	4 (8%)	7 (14%)	3 (6%)

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Hyperplasia	29 (58%)	33 (66%)	21 (42%)	26 (52%)	22 (44%)
Myeloid cell, hyperplasia			1 (2%)		
Lymph node	(24)	(20)	(28)	(28)	(20)
Ectasia	2 (8%)		1 (4%)		
Hyperplasia, lymphoid	1 (4%)				
Bronchial, ectasia			1 (4%)		
Bronchial, hyperplasia, lymphoid			1 (4%)		
Deep cervical, ectasia	3 (13%)		4 (14%)	4 (14%)	2 (10%)
Deep cervical, hyperplasia, lymphoid	3 (13%)	1 (5%)	4 (14%)	4 (14%)	3 (15%)
Mediastinal, ectasia	6 (25%)	10 (50%)	11 (39%)	11 (39%)	7 (35%)
Mediastinal, hyperplasia, lymphoid	7 (29%)	10 (50%)	10 (36%)	12 (43%)	12 (60%)
Mediastinal, pigmentation			1 (4%)		
Pancreatic, ectasia	1 (4%)				
Lymph node, mandibular	(2)		(4)		
Ectasia	2 (100%)		1 (25%)		
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(50)
Ectasia	2 (4%)			1 (2%)	1 (2%)
Inflammation, suppurative		1 (2%)			
Spleen	(50)	(50)	(50)	(50)	(50)
Congestion			2 (4%)		
Fibrosis	1 (2%)		3 (6%)		
Hematopoietic cell proliferation	2 (4%)	5 (10%)	10 (20%)	4 (8%)	6 (12%)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	2 (4%)	1 (2%)	5 (10%)
Infarct		1 (2%)	1 (2%)	1 (2%)	
Necrosis		1 (2%)			
Pigmentation		1 (2%)			
Lymphoid follicle, depletion cellular			1 (2%)		
Thymus	(43)	(44)	(45)	(46)	(43)
Ectopic parathyroid gland		2 (5%)	1 (2%)	2 (4%)	2 (5%)
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Cyst	1 (2%)				
Hyperplasia, cystic	45 (90%)	47 (94%)	41 (82%)	45 (90%)	47 (94%)
Inflammation, chronic active	1 (2%)				
Skin	(50)	(50)	(50)	(50)	(50)
Hyperkeratosis	1 (2%)		1 (2%)	1 (2%)	
Inflammation, chronic active	1 (2%)			1 (2%)	
Inflammation, granulomatous			1 (2%)		
Dermis, fibrosis				1 (2%)	
Epidermis, hyperplasia	1 (2%)			1 (2%)	
Hair follicle, sebaceous gland, atrophy				1 (2%)	
Subcutaneous tissue, mineralization				1 (2%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteopetrosis			1 (2%)		

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Compression	3 (6%)	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Hemorrhage	6 (12%)	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Hydrocephalus	4 (8%)	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Inflammation, chronic active	1 (2%)				
Inflammation, suppurative	1 (2%)				
Mineralization	1 (2%)				
Necrosis	3 (6%)				
Pigmentation	1 (2%)				
Thrombosis					1 (2%)
Spinal cord	(1)	(1)			
Hemorrhage	1 (100%)				
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Fibrosis					2 (4%)
Hemorrhage			1 (2%)	1 (2%)	
Inflammation, chronic active	26 (52%)	32 (64%)	31 (62%)	27 (54%)	36 (72%)
Metaplasia, osseous				1 (2%)	
Mineralization	45 (90%)	46 (92%)	47 (94%)	48 (96%)	49 (98%)
Necrosis	1 (2%)				
Pigmentation	30 (60%)	35 (70%)	32 (64%)	23 (46%)	35 (70%)
Thrombosis			1 (2%)		
Alveolar epithelium, hyperplasia	9 (18%)	10 (20%)	10 (20%)	9 (18%)	11 (22%)
Alveolar epithelium, metaplasia, focal, squamous	1 (2%)				
Alveolus, infiltration cellular, histiocyte	31 (62%)	36 (72%)	32 (64%)	24 (48%)	35 (70%)
Nose	(50)	(50)	(50)	(50)	(50)
Foreign body		2 (4%)	1 (2%)	4 (8%)	3 (6%)
Inflammation, chronic active	2 (4%)	4 (8%)	2 (4%)	3 (6%)	4 (8%)
Keratin cyst	1 (2%)				
Polyp inflammatory					1 (2%)
Thrombosis	1 (2%)	2 (4%)	3 (6%)	6 (12%)	2 (4%)
Nasolacrimal duct, inflammation, suppurative	12 (24%)	6 (12%)	4 (8%)	5 (10%)	9 (18%)
Special Senses System					
Eye	(2)	(1)	(2)	(1)	
Cornea, inflammation, chronic active			1 (50%)		
Cornea, inflammation, suppurative			1 (50%)		
Lens, cataract	1 (50%)	1 (100%)	1 (50%)	1 (100%)	
Lens, degeneration	1 (50%)				
Retina, degeneration	2 (100%)	1 (100%)		1 (100%)	

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)	1 (2%)		
Atrophy					1 (2%)
Cyst		1 (2%)			1 (2%)
Hydronephrosis	1 (2%)				
Infarct			1 (2%)	2 (4%)	
Inflammation, chronic active		1 (2%)			
Inflammation, suppurative					1 (2%)
Metaplasia, osseous					1 (2%)
Mineralization	38 (76%)	31 (62%)	30 (60%)	32 (64%)	38 (76%)
Necrosis		1 (2%)			1 (2%)
Nephropathy	47 (94%)	47 (94%)	49 (98%)	44 (88%)	45 (90%)
Cortex, medulla, fibrosis		1 (2%)			
Cortex, medulla, pigmentation		1 (2%)			
Cortex, medulla, pelvis, cyst		1 (2%)			
Medulla, necrosis	1 (2%)				
Medulla, renal tubule, dilatation		1 (2%)			
Urinary bladder	(50)	(50)	(49)	(49)	(50)
Hemorrhage	1 (2%)		1 (2%)		
Inflammation, chronic active	1 (2%)				

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF *trans*-CINNAMALDEHYDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	11	10	13	10	10
Natural deaths	5	4	4	4	7
Survivors					
Died last week of study	1				
Terminal sacrifice	33	36	33	35	33
Missing				1	
Animals examined microscopically	50	50	50	49	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(49)	(50)
Lipoma					1 (2%)
Intestine large, colon	(50)	(50)	(50)	(49)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(49)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(49)	(50)
Carcinoma			1 (2%)		
Leiomyosarcoma			1 (2%)		
Intestine small, ileum	(50)	(50)	(50)	(49)	(50)
Liver	(50)	(50)	(50)	(49)	(50)
Cholangiocarcinoma			1 (2%)		
Mesentery	(11)	(9)	(6)	(9)	(8)
Pancreas	(50)	(50)	(50)	(49)	(50)
Salivary glands	(50)	(50)	(49)	(49)	(50)
Stomach, forestomach	(50)	(50)	(50)	(49)	(50)
Stomach, glandular	(50)	(50)	(50)	(49)	(50)
Tongue			(1)	(1)	
Squamous cell papilloma			1 (100%)	1 (100%)	
Cardiovascular System					
Heart	(50)	(50)	(50)	(49)	(50)
Hemangiosarcoma					1 (2%)
Schwannoma malignant					1 (2%)
Squamous cell carcinoma, metastatic, lung	1 (2%)				
Thymoma malignant, metastatic, thymus	1 (2%)				
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(49)	(50)
Adenoma	1 (2%)				
Chondrosarcoma, metastatic, bone			1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(49)	(50)
Chondrosarcoma, metastatic, bone			1 (2%)		
Pheochromocytoma malignant	1 (2%)	1 (2%)			
Pheochromocytoma complex		1 (2%)		1 (2%)	
Pheochromocytoma benign			2 (4%)		
Bilateral, pheochromocytoma benign		1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Endocrine System (continued)					
Islets, pancreatic	(50)	(50)	(50)	(49)	(50)
Adenoma			1 (2%)		2 (4%)
Carcinoma	2 (4%)				
Pituitary gland	(50)	(50)	(50)	(49)	(50)
Pars distalis, adenoma	19 (38%)	16 (32%)	17 (34%)	15 (31%)	17 (34%)
Pars distalis, adenoma, multiple			1 (2%)		
Thyroid gland	(50)	(50)	(49)	(49)	(50)
C-cell, adenoma	5 (10%)	6 (12%)	3 (6%)	4 (8%)	5 (10%)
C-cell, carcinoma	3 (6%)			3 (6%)	
Follicular cell, adenoma		1 (2%)			
General Body System					
None					
Genital System					
Clitoral gland	(49)	(50)	(50)	(49)	(50)
Adenoma	3 (6%)		4 (8%)	1 (2%)	2 (4%)
Carcinoma	3 (6%)	6 (12%)	1 (2%)	2 (4%)	2 (4%)
Bilateral, adenoma	1 (2%)				
Ovary	(50)	(50)	(50)	(49)	(50)
Cystadenoma		1 (2%)			
Granulosa cell tumor benign			1 (2%)		
Uterus	(50)	(50)	(50)	(49)	(50)
Leiomyoma			1 (2%)		
Polyp stromal	6 (12%)	7 (14%)	5 (10%)	8 (16%)	12 (24%)
Polyp stromal, multiple			3 (6%)		
Bilateral, polyp stromal	1 (2%)				
Endometrium, carcinoma			1 (2%)		
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(49)	(50)
Lymph node	(30)	(25)	(26)	(24)	(27)
Deep cervical, carcinoma, metastatic, thyroid gland	1 (3%)				
Mediastinal, carcinoma, metastatic, thyroid gland	2 (7%)				
Lymph node, mandibular	(1)	(2)		(1)	(2)
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(50)
Spleen	(50)	(50)	(49)	(49)	(50)
Thymus	(43)	(49)	(47)	(48)	(47)
Thymoma malignant	1 (2%)				
Integumentary System					
Mammary gland	(50)	(50)	(50)	(49)	(50)
Adenolipoma				1 (2%)	
Adenoma, multiple		1 (2%)			
Carcinoma	1 (2%)			3 (6%)	
Fibroadenoma	17 (34%)	22 (44%)	18 (36%)	16 (33%)	16 (32%)
Fibroadenoma, multiple	8 (16%)	8 (16%)	9 (18%)	5 (10%)	5 (10%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Integumentary System (continued)					
Skin	(50)	(50)	(50)	(49)	(50)
Basal cell carcinoma			1 (2%)		
Keratoacanthoma			2 (4%)		1 (2%)
Neural crest tumor	1 (2%)				
Subcutaneous tissue, fibroma		1 (2%)			
Subcutaneous tissue, fibrosarcoma				1 (2%)	
Subcutaneous tissue, lipoma			1 (2%)		
Musculoskeletal System					
Bone	(50)	(50)	(50)	(49)	(50)
Chondrosarcoma			1 (2%)		
Osteosarcoma		1 (2%)			
Skeletal muscle		(1)	(1)		(1)
Chondrosarcoma, metastatic, bone			1 (100%)		
Lipoma		1 (100%)			
Nervous System					
Brain	(50)	(50)	(50)	(49)	(50)
Astrocytoma malignant	1 (2%)				
Spinal cord				(1)	
Respiratory System					
Lung	(50)	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	4 (8%)	2 (4%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)				
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)				
Carcinoma, metastatic, thyroid gland	1 (2%)				
Chondrosarcoma, metastatic, bone			1 (2%)		
Pheochromocytoma complex, metastatic, adrenal medulla				1 (2%)	
Squamous cell carcinoma	1 (2%)				
Squamous cell carcinoma, metastatic, lung	1 (2%)				
Thymoma malignant, metastatic, thymus	1 (2%)				
Mediastinum, squamous cell carcinoma, metastatic, lung	1 (2%)				
Nose	(50)	(50)	(50)	(49)	(50)
Special Senses System					
Zymbal's gland	(1)		(2)		
Adenoma	1 (100%)				
Carcinoma			1 (50%)		
Urinary System					
Kidney	(50)	(50)	(50)	(49)	(50)
Renal tubule, adenoma				1 (2%)	
Urinary bladder	(50)	(50)	(50)	(49)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(49)	(50)
Adenolipoma				1 (2%)	
Leukemia mononuclear	9 (18%)	12 (24%)	8 (16%)	7 (14%)	9 (18%)
Lymphoma malignant	1 (2%)				
Neoplasm Summary					
Total animals with primary neoplasms[c]	45	47	42	44	42
Total primary neoplasms	89	90	87	71	76
Total animals with benign neoplasms	39	39	37	38	38
Total benign neoplasms	64	69	71	54	63
Total animals with malignant neoplasms	21	18	14	16	13
Total malignant neoplasms	24	21	16	17	13
Total animals with metastatic neoplasms	6		1	1	
Total metastatic neoplasm	10		4	1	
Total animals with uncertain neoplasms–benign or malignant	1				
Total uncertain neoplasms	1				

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	203	257	576	597	624	649	652	660	666	676	690	690	702	708	723	723	735	735	735	735	735	735	735	735	735
Carcass ID Number	270	269	286	251	263	289	256	261	290	268	281	292	272	273	258	298	253	259	262	267	274	275	280	283	293
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+				+		+				+						+		+				
Oral mucosa				+											+	+		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung														X											
Thymoma malignant, metastatic, thymus									X																
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																		
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X				X		X					X			X	X	X				X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X											
C-cell, carcinoma																X								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 B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 9 4	2 9 5	2 9 9	2 5 2	2 5 7	2 6 0	2 6 6	2 7 8	2 7 9	2 8 2	2 8 4	2 8 5	2 8 7	2 8 8	3 0 0	2 5 4	2 5 5	2 6 4	2 6 5	2 7 1	2 7 6	2 7 7	2 9 1	2 9 6	2 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+				+							+			+							+	11
Oral mucosa	+			+			+					+			+			+		+		+				12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, lung																										1
Thymoma malignant, metastatic, thymus																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant												X														1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									X	2
Parathyroid gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X					X	X			X	X		X				X	X			X				19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X	X					X				X	5
C-cell, carcinoma								X																		3
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	203	257	576	597	624	649	652	660	666	676	690	690	702	708	723	723	735	735	735	735	735	735	735	735	735
Carcass ID Number	270	269	286	251	263	289	256	261	290	268	281	292	272	273	258	298	253	259	262	267	274	275	280	283	293
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma				X											X										
Bilateral, adenoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X													X						
Bilateral, polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+	+	+		+		+	+	+	+	+	+	+				+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland																X									
Mediastinal, carcinoma, metastatic, thyroid gland																X									
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	
Thymoma malignant									X																
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma										X	X	X	X			X		X	X						X
Fibroadenoma, multiple						X	X										X							X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neural crest tumor																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 9 4	2 9 5	2 9 9	2 5 2	2 5 7	2 6 0	2 6 6	2 7 8	2 7 9	2 8 2	2 8 4	2 8 5	2 8 7	2 8 8	3 0 0	2 5 4	2 5 5	2 6 4	2 6 5	2 6 6	2 7 1	2 7 6	2 7 7	2 9 1	2 9 6	2 9 7	Total Tissues/ Tumors
Genital System																											
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X														X											3
Carcinoma							X																				3
Bilateral, adenoma																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal										X										X	X			X			6
Bilateral, polyp stromal											X																1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+	+	+	+	+	+	+	+					+	+	+	+	+	+							30
Deep cervical, carcinoma, metastatic, thyroid gland																											1
Mediastinal, carcinoma, metastatic, thyroid gland								X																			2
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Thymoma malignant																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																				X							1
Fibroadenoma	X	X				X						X			X		X					X		X	X		17
Fibroadenoma, multiple					X				X		X							X									8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neural crest tumor								X																			1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant												X															1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	203	257	576	597	624	649	652	660	666	676	690	690	702	708	723	723	735	735	735	735	735	735	735	735	735
Carcass ID Number	270	269	286	255	263	289	256	261	290	268	281	292	272	273	258	299	253	259	262	267	274	275	280	283	293
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Carcinoma, metastatic, thyroid gland																								X	
Squamous cell carcinoma														X											
Squamous cell carcinoma, metastatic, lung														X											
Thymoma malignant, metastatic, thymus									X																
Mediastinum, squamous cell carcinoma, metastatic, lung														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																							+		
Zymbal's gland			+																						
Adenoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X				X	X		X			X				X	X	X								
Lymphoma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 9 4	2 9 5	2 9 9	2 5 2	2 5 7	2 6 0	2 6 6	2 7 8	2 7 9	2 8 2	2 8 4	2 8 5	2 8 7	2 8 8	3 0 0	2 5 4	2 5 5	2 6 4	2 6 5	2 7 1	2 7 6	2 7 7	2 9 1	2 9 6	2 9 7	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X				X												2
Alveolar/bronchiolar carcinoma					X																					1
Alveolar/bronchiolar carcinoma, metastatic, lung					X																					1
Carcinoma, metastatic, thyroid gland																										1
Squamous cell carcinoma																										1
Squamous cell carcinoma, metastatic, lung																										1
Thymoma malignant, metastatic, thymus																										1
Mediastinum, squamous cell carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X											9
Lymphoma malignant				X																						1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 0 9	3 1 5	3 1 6	3 2 0	3 2 5	3 2 6	3 2 7	3 3 0	3 3 1	3 3 6	3 3 9	3 4 2	3 4 3	3 4 4	3 5 0	3 0 1	3 0 7	3 1 1	3 1 7	3 2 1	3 2 2	3 3 4	3 3 7	3 4 5	3 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+			+			+				+				+						+		9
Oral mucosa							+			+								+	+		+	+	+			11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																							X			1
Pheochromocytoma complex																										1
Bilateral, pheochromocytoma benign												X														1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	M	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X							X	X	X		X			X									X	16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X				X											X			X			X		6
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X		X							X						6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma														X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X																						X			7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	5 2 3	5 2 6	5 9 7	6 2 0	6 3 2	6 5 2	6 7 0	6 7 9	6 8 3	6 9 0	6 9 0	6 9 5	7 0 2	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6
Carcass ID Number	3 3 5	3 0 3	3 0 6	3 3 3	3 1 3	3 1 8	3 1 0	3 2 2	3 4 0	3 0 8	3 4 8	3 2 9	3 4 6	3 4 1	3 0 2	3 0 5	3 1 2	3 1 4	3 1 9	3 2 3	3 2 4	3 2 8	3 3 8	3 4 9	3 0 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+			+		+		+	+					+	+	+	+	+				+	
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple																									
Fibroadenoma							X	X		X		X	X	X						X	X	X			X	
Fibroadenoma, multiple					X	X											X							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																				X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma				X																							
Skeletal muscle																									
Lipoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X					X	X		X				X				X					X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	7 3 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 0 9	3 1 5	3 1 6	3 2 0	3 2 5	3 2 6	3 2 7	3 3 0	3 3 1	3 3 6	3 3 9	3 4 2	3 4 3	3 4 4	3 5 0	3 0 1	3 0 7	3 1 1	3 1 7	3 2 1	3 2 2	3 3 4	3 3 7	3 4 5	3 4 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+			+	+		+	+			+	+			+		+		+			+	+	25
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, multiple										X																	1
Fibroadenoma			X	X	X				X	X	X				X				X		X	X	X	X			22
Fibroadenoma, multiple							X							X				X								X	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																											1
Skeletal muscle																							+				1
Lipoma																							X				1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X				X												X				X						4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X					X							X			12

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

Number of Days on Study	0 8 5	5 6 1	5 9 7	6 1 8	6 2 0	6 2 6	6 5 2	6 5 2	6 7 1	6 7 5	6 7 5	6 8 1	6 9 7	6 9 7	7 0 1	7 1 8	7 1 8	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 8 2	3 6 5	3 9 4	3 9 1	3 5 4	3 7 0	3 9 2	3 9 6	3 5 8	3 6 4	3 7 2	3 8 8	3 6 6	3 9 8	3 6 8	3 7 6	3 8 1	3 5 1	3 5 3	3 5 5	3 5 6	3 7 1	3 7 3	3 7 4	3 7 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma									X																
Mesentery									+	+				+		+		+							
Oral mucosa	+	+			+		+		+							+	+		+	+	+			+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue		M																							
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondrosarcoma, metastatic, bone							X																		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondrosarcoma, metastatic, bone							X																		
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X							X		X	X		X	X	X			X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X						X													
General Body System																									
None																									

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

Number of Days on Study	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	37878	38833	38836	38867	38899	39090	35252	35577	35599	36060	37555	37799	38844	38855	39097	36611	36622	36633	36677	36699	38800	39033	39955	39990	40000	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Leiomyosarcoma											X															1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Mesentery	+																									6
Oral mucosa	+	+				+	+	+		+		+	+			+	+		+	+			+			24
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																								+		1
Squamous cell papilloma																								X		1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondrosarcoma, metastatic, bone																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondrosarcoma, metastatic, bone																										1
Pheochromocytoma benign						X																X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X		X		X										X	X	X						17
Pars distalis, adenoma, multiple																X										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma							X																			3
General Body System																										
None																										

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

Number of Days on Study	0 8 5	5 6 1	5 9 7	6 1 8	6 2 0	6 2 6	6 5 2	6 5 2	6 7 1	6 7 5	6 7 5	6 8 1	6 9 7	6 9 7	7 0 1	7 1 8	7 1 8	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 8 2	3 6 5	3 9 4	3 9 1	3 5 4	3 7 0	3 9 2	3 9 6	3 5 8	3 6 4	3 7 2	3 8 8	3 6 6	3 9 8	3 6 8	3 7 6	3 8 1	3 5 1	3 5 3	3 5 5	3 5 6	3 7 1	3 7 3	3 7 4	3 7 7
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma														X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Polyp stromal									X																
Polyp stromal, multiple			X																	X					
Endometrium, carcinoma					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+		+				+	+				+	+	+	+		+	+	+		+
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma										X	X		X				X					X			
Fibroadenoma, multiple												X						X		X	X		X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma			X																						
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondrosarcoma							X																		
Skeletal muscle							+																		
Chondrosarcoma, metastatic, bone							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Chondrosarcoma, metastatic, bone							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 7 8	3 8 3	3 8 6	3 8 7	3 8 9	3 9 0	3 5 2	3 5 7	3 5 9	3 6 0	3 7 5	3 7 9	3 8 4	3 8 5	3 9 7	3 6 1	3 6 2	3 6 3	3 6 7	3 6 9	3 8 0	3 9 3	3 9 5	3 9 9	4 0 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X	X	X														4
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																		X								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma	X																									1
Polyp stromal	X				X														X	X						5
Polyp stromal, multiple																					X					3
Endometrium, carcinoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+	+			+		+			+		+	+	+		+		+					+	26
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma	X	X	X	X	X					X	X	X			X			X		X		X			X	18
Fibroadenoma, multiple						X	X	X															X			9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																X										1
Keratoacanthoma												X														2
Subcutaneous tissue, lipoma					X																					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondrosarcoma																										1
Skeletal muscle																										1
Chondrosarcoma, metastatic, bone																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											2
Chondrosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7		
Carcass ID Number	3 7 8	3 8 3	3 8 6	3 8 7	3 8 9	3 9 0	3 5 2	3 5 7	3 5 9	3 6 0	3 7 5	3 7 9	3 8 4	3 8 5	3 9 7	3 6 1	3 6 2	3 6 3	3 6 7	3 6 9	3 8 0	3 9 3	3 9 5	3 9 9	4 0 0	Total Tissues/ Tumors	
Special Senses System																											
Eye																				+						3	
Zymbal's gland																										2	
Carcinoma																										1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear																		X	X							8	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 4 0	4 5 0	4 1 9	4 2 0	4 2 3	4 2 4	4 2 8	4 3 1	4 3 3	4 3 5	4 3 7	4 4 1	4 4 6	4 0 1	4 0 4	4 0 6	4 0 8	4 1 2	4 1 6	4 2 2	4 2 5	4 3 4	4 4 2	4 4 3	4 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery										+				+								+			+	9
Oral mucosa	+	+						+	+		+	+			+				+		+				+	18
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma complex																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X					X	X				X	X				X				X				15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma							X					X														4
C-cell, carcinoma														X			X									3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									X	1
Carcinoma																		X								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal									X										X		X		X	X		8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	1 7 7	4 5 9	4 7 0	4 9 8	5 4 3	6 1 0	6 1 3	6 3 2	6 5 2	6 5 2	6 8 1	7 0 2	7 0 9	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	4 0 9	4 2 9	4 0 7	4 4 5	4 1 5	4 2 1	4 3 2	4 4 7	4 1 8	4 3 6	4 4 9	4 0 5	4 4 4	4 3 0	4 0 2	4 0 3	4 1 0	4 1 1	4 1 3	4 1 4	4 1 7	4 2 7	4 3 8	4 3 9
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+				+	+	+			+	+		+	+		+		+	+	+		+
Lymph node, mandibular	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenolipoma																		X							
Carcinoma																							X		
Fibroadenoma			X						X		X	X	X		X							X			X
Fibroadenoma, multiple										X						X			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma															X										
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+																		
Spinal cord							+																		
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Pheochromocytoma complex, metastatic, adrenal medulla				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye									+																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenolipoma																		X							
Leukemia mononuclear		X					X		X	X				X									X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 4 0	4 5 0	4 1 9	4 2 0	4 2 3	4 2 4	4 2 8	4 3 1	4 3 3	4 3 5	4 3 7	4 4 1	4 4 6	4 0 1	4 0 4	4 0 6	4 0 8	4 1 2	4 1 6	4 2 2	4 2 5	4 3 4	4 4 2	4 4 3	4 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node		+	+			+		+			+	+		+						+	+		+		24
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenolipoma																										1
Carcinoma				X																X						3
Fibroadenoma							X				X				X		X	X		X		X	X			16
Fibroadenoma, multiple													X			X										5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma		X																	X							2
Pheochromocytoma complex, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenolipoma																										1
Leukemia mononuclear																							X			7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	1 7 2	5 3 6	5 6 4	5 6 8	5 9 0	5 9 7	6 3 4	6 3 5	6 4 3	6 6 5	6 6 9	6 8 1	6 9 4	6 9 7	7 1 8	7 2 3	7 2 6	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	4 4 7 1	4 6 9	4 7 9	4 6 3	4 8 9	4 5 3	4 5 9	4 6 1	4 9 3	4 8 8	4 8 2	4 7 0	4 6 4	4 6 8	4 9 8	4 8 7	4 7 4	4 5 1	4 5 2	4 5 7	4 5 8	4 6 2	4 7 3	4 8 0	4 8 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma															X									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																				+				
Oral mucosa										+			+			+					+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X							
Schwannoma malignant																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X											
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X		X	X	X		X					X		X					X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								X
General Body System																								
Peritoneum																						+		
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Carcinoma							X									X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct																			+					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X							X								X	X	X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	735	735	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	48485	49491	45404	46467	47472	47676	47878	48383	48686	49094	49497	45055	45606	46007	46605	46606	47505	47707	47804	49005	49202	49505	49606	49909	50000	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery					+	+			+		+				+									+	+		8
Oral mucosa																										+	5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Schwannoma malignant																	X										1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										X	2
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X				X		X				X	X		X						X				17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X					X					X												X				5
General Body System																											
Peritoneum																											1
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X												2
Carcinoma																											2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oviduct																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X	X						X		X	X	X											X				12

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 8 5	4 9 1	4 5 4	4 6 7	4 7 2	4 7 6	4 7 8	4 8 3	4 8 6	4 9 4	4 9 7	4 5 5	4 5 6	4 6 0	4 6 5	4 6 6	4 7 5	4 7 7	4 8 4	4 9 0	4 9 2	4 9 5	4 9 6	4 9 9	5 0 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+				+		+			+	+	+	+	+	+				+		+	+	+	+	27
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma				X				X	X		X				X	X	X						X	X	X	16
Fibroadenoma, multiple			X										X									X				5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+															1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																							+	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X						X															9

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Adrenal Medulla: Benign, Malignant, or Complex Pheochromocytoma					
Overall rate[a]	1/50 (2%)	3/50 (6%)	2/50 (4%)	1/49 (2%)	0/50 (0%)
Adjusted rate[b]	2.2%	6.5%	4.5%	2.3%	0.0%
Terminal rate[c]	1/34 (3%)	2/36 (6%)	2/33 (6%)	0/35 (0%)	0/33 (0%)
First incidence (days)	735 (T)	690	735 (T)	498	—[e]
Poly-3 test[d]		P=0.065N	P=0.514N	P=0.325N	P=0.126N
Clitoral Gland: Adenoma					
Overall rate	4/49 (8%)	0/50 (0%)	4/50 (8%)	1/49 (2%)	2/50 (4%)
Adjusted rate	9.1%	0.0%	8.9%	2.3%	4.5%
Terminal rate	3/33 (9%)	0/36 (0%)	3/33 (9%)	1/35 (3%)	2/33 (6%)
First incidence (days)	723	—	697	735 (T)	735 (T)
Poly-3 test		P=0.399	P=0.057	P=0.487	P=0.228
Clitoral Gland: Carcinoma					
Overall rate	3/49 (6%)	6/50 (12%)	1/50 (2%)	2/49 (4%)	2/50 (4%)
Adjusted rate	6.7%	13.0%	2.2%	4.7%	4.5%
Terminal rate	1/33 (3%)	4/36 (11%)	0/33 (0%)	2/35 (6%)	0/33 (0%)
First incidence (days)	597	683	697	735 (T)	634
Poly-3 test		P=0.139N	P=0.061N	P=0.158N	P=0.145N
Clitoral Gland: Adenoma or Carcinoma					
Overall rate	7/49 (14%)	6/50 (12%)	5/50 (10%)	3/49 (6%)	4/50 (8%)
Adjusted rate	15.7%	13.0%	11.1%	7.0%	9.0%
Terminal rate	4/33 (12%)	4/36 (11%)	3/33 (9%)	3/35 (9%)	2/33 (6%)
First incidence (days)	597	683	697	735 (T)	634
Poly-3 test		P=0.299N	P=0.519N	P=0.280N	P=0.393N
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	2/50 (4%)	4/50 (8%)	2/50 (4%)	2/49 (4%)	2/50 (4%)
Adjusted rate	4.4%	8.7%	4.5%	4.7%	4.5%
Terminal rate	2/34 (6%)	4/36 (11%)	2/33 (6%)	2/35 (6%)	1/33 (3%)
First incidence (days)	735 (T)	735 (T)	735 (T)	735 (T)	694
Poly-3 test		P=0.303N	P=0.349N	P=0.368N	P=0.354N
Mammary Gland: Fibroadenoma					
Overall rate	25/50 (50%)	30/50 (60%)[f]	27/50 (54%)	21/49 (43%)	21/50 (42%)
Adjusted rate	53.9%	63.2%	59.2%	46.9%	46.0%
Terminal rate	18/34 (53%)	22/36 (61%)	22/33 (67%)	15/35 (43%)	16/33 (49%)
First incidence (days)	649	632	675	470	536
Poly-3 test		P=0.037N	P=0.427N	P=0.083N	P=0.068N
Mammary Gland: Carcinoma					
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	3/49 (6%)	0/50 (0%)
Adjusted rate	2.2%	0.0%	0.0%	7.0%	0.0%
Terminal rate	1/34 (3%)	0/36 (0%)	0/33 (0%)	3/35 (9%)	0/33 (0%)
First incidence (days)	735 (T)	—	—[g]	735 (T)	—
Poly-3 test		P=0.520		P=0.107	—
Mammary Gland: Adenoma or Carcinoma					
Overall rate	1/50 (2%)	1/50 (2%)	0/50 (0%)	3/49 (6%)	0/50 (0%)
Adjusted rate	2.2%	2.2%	0.0%	7.0%	0.0%
Terminal rate	1/34 (3%)	1/36 (3%)	0/33 (0%)	3/35 (9%)	0/33 (0%)
First incidence (days)	735 (T)	735 (T)	—	735 (T)	—
Poly-3 test		P=0.513N	P=0.505N	P=0.282	P=0.508N

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma					
Overall rate	26/50 (52%)	30/50 (60%)	27/50 (54%)	23/49 (47%)	21/50 (42%)
Adjusted rate	56.0%	63.2%	59.2%	51.4%	46.0%
Terminal rate	19/34 (56%)	22/36 (61%)	22/33 (67%)	17/35 (49%)	16/33 (49%)
First incidence (days)	649	632	675	470	536
Poly-3 test		P=0.042N	P=0.427N	P=0.172N	P=0.068N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	19/50 (38%)	16/50 (32%)	18/50 (36%)	15/49 (31%)	17/50 (34%)
Adjusted rate	40.6%	34.5%	39.5%	34.1%	36.5%
Terminal rate	14/34 (41%)	14/36 (39%)	14/33 (42%)	11/35 (31%)	10/33 (30%)
First incidence (days)	557	632	626	610	536
Poly-3 test		P=0.525	P=0.388	P=0.576N	P=0.504
Skin: Keratoacanthoma or Basal Cell Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/49 (0%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	6.6%	0.0%	2.3%
Terminal rate	0/34 (0%)	0/36 (0%)	2/33 (6%)	0/35 (0%)	1/33 (3%)
First incidence (days)	—	—	597	—	735 (T)
Poly-3 test		P=0.616	P=0.116	—	P=0.492
Thyroid Gland (C-Cell): Adenoma					
Overall rate	5/50 (10%)	6/50 (12%)	3/49 (6%)	4/49 (8%)	5/50 (10%)
Adjusted rate	11.1%	13.0%	6.7%	9.3%	11.3%
Terminal rate	4/34 (12%)	5/36 (14%)	1/33 (3%)	4/35 (11%)	5/33 (15%)
First incidence (days)	708	670	626	735 (T)	735 (T)
Poly-3 test		P=0.557N	P=0.256N	P=0.415N	P=0.531N
Thyroid Gland (C-Cell): Carcinoma					
Overall rate	3/50 (6%)	0/50 (0%)	0/49 (0%)	3/49 (6%)	0/50 (0%)
Adjusted rate	6.7%	0.0%	0.0%	7.0%	0.0%
Terminal rate	2/34 (6%)	0/36 (0%)	0/33 (0%)	3/35 (9%)	0/33 (0%)
First incidence (days)	723	—	—	735 (T)	—
Poly-3 test		P=0.520	—	P=0.107	—
Thyroid Gland (C-Cell): Adenoma or Carcinoma					
Overall rate	8/50 (16%)	6/50 (12%)	3/49 (6%)	7/49 (14%)	5/50 (10%)
Adjusted rate	17.7%	13.0%	6.7%	16.3%	11.3%
Terminal rate	6/34 (18%)	5/36 (14%)	1/33 (3%)	7/35 (20%)	5/33 (15%)
First incidence (days)	708	670	626	735 (T)	735 (T)
Poly-3 test		P=0.514	P=0.256N	P=0.445	P=0.531N
Uterus: Stromal Polyp					
Overall rate	7/50 (14%)	7/50 (14%)	8/50 (16%)	8/49 (16%)	12/50 (24%)
Adjusted rate	15.4%	15.0%	17.6%	18.3%	26.7%
Terminal rate	6/34 (18%)	3/36 (8%)	6/33 (18%)	6/35 (17%)	10/33 (30%)
First incidence (days)	649	632	597	543	564
Poly-3 test		P=0.091	P=0.475	P=0.442	P=0.128
All Organs: Mononuclear Cell Leukemia					
Overall rate	9/50 (18%)	12/50 (24%)	8/50 (16%)	7/49 (14%)	9/50 (18%)
Adjusted rate	19.0%	24.9%	17.2%	15.6%	19.5%
Terminal rate	2/34 (6%)	6/36 (17%)	2/33 (6%)	2/35 (6%)	3/33 (9%)
First incidence (days)	203	523	561	459	564
Poly-3 test		P=0.340N	P=0.252N	P=0.199N	P=0.352N

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

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
All Organs: Benign Neoplasms					
Overall rate	39/50 (78%)	39/50 (78%)	37/50 (74%)	38/49 (78%)	38/50 (76%)
Adjusted rate	81.5%	82.1%	78.5%	82.4%	79.6%
Terminal rate	28/34 (82%)	31/36 (86%)	27/33 (82%)	29/35 (83%)	26/33 (79%)
First incidence (days)	557	632	597	470	536
Poly-3 test		P=0.477N	P=0.424N	P=0.599	P=0.476N
All Organs: Malignant Neoplasms					
Overall rate	21/50 (42%)	18/50 (36%)	14/50 (28%)	16/49 (33%)	13/50 (26%)
Adjusted rate	43.4%	36.9%	29.5%	35.2%	27.9%
Terminal rate	10/34 (29%)	10/36 (28%)	5/33 (15%)	10/35 (29%)	4/33 (12%)
First incidence (days)	203	523	561	459	564
Poly-3 test		P=0.255N	P=0.291N	P=0.518N	P=0.236N
All Organs: Benign or Malignant Neoplasms					
Overall rate	45/50 (90%)	47/50 (94%)	42/50 (84%)	44/49 (90%)	42/50 (84%)
Adjusted rate	90.0%	94.0%	85.8%	91.6%	86.1%
Terminal rate	29/34 (85%)	33/36 (92%)	27/33 (82%)	31/35 (89%)	27/33 (82%)
First incidence (days)	203	523	561	459	536
Poly-3 test		P=0.209N	P=0.154N	P=0.476N	P=0.161N

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	11	10	13	10	10
Natural deaths	5	4	4	4	7
Survivors					
Died last week of study	1				
Terminal sacrifice	33	36	33	35	33
Missing				1	
Animals examined microscopically	50	50	50	49	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic			1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(49)	(50)
Parasite metazoan	1 (2%)	5 (10%)		4 (8%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(49)	(50)
Parasite metazoan		4 (8%)	1 (2%)	3 (6%)	1 (2%)
Intestine large, cecum	(50)	(49)	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)				
Intestine small, duodenum	(50)	(50)	(50)	(49)	(50)
Mineralization	1 (2%)				
Parasite metazoan			1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active			1 (2%)		
Intestine small, ileum	(50)	(50)	(50)	(49)	(50)
Parasite metazoan					1 (2%)
Liver	(50)	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)				
Basophilic focus	42 (84%)	44 (88%)	42 (84%)	43 (88%)	44 (88%)
Clear cell focus	1 (2%)	2 (4%)	2 (4%)		
Eosinophilic focus		1 (2%)			1 (2%)
Fibrosis	1 (2%)				1 (2%)
Hematopoietic cell proliferation	3 (6%)	2 (4%)	3 (6%)		1 (2%)
Hepatodiaphragmatic nodule	4 (8%)	5 (10%)	12 (24%)	9 (18%)	7 (14%)
Infarct	1 (2%)				
Inflammation, chronic active	44 (88%)	41 (82%)	42 (84%)	42 (86%)	43 (86%)
Mixed cell focus	26 (52%)	25 (50%)	24 (48%)	27 (55%)	20 (40%)
Necrosis	5 (10%)	3 (6%)	4 (8%)	1 (2%)	6 (12%)
Pigmentation		1 (2%)	1 (2%)		
Thrombosis			1 (2%)		
Bile duct, hyperplasia	21 (42%)	25 (50%)	28 (56%)	21 (43%)	18 (36%)
Hepatocyte, degeneration, cystic	1 (2%)	1 (2%)			
Hepatocyte, hyperplasia	1 (2%)	1 (2%)	2 (4%)		
Hepatocyte, vacuolization cytoplasmic	31 (62%)	32 (64%)	25 (50%)	14 (29%)	18 (36%)
Mesentery	(11)	(9)	(6)	(9)	(8)
Hemorrhage					1 (13%)
Inflammation, chronic			1 (17%)		
Fat, inflammation, chronic	4 (36%)	8 (89%)	4 (67%)	8 (89%)	7 (88%)
Fat, mineralization	8 (73%)	5 (56%)	2 (33%)	5 (56%)	3 (38%)
Fat, necrosis	9 (82%)	7 (78%)	5 (83%)	9 (100%)	7 (88%)
Fat, pigmentation					1 (13%)

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Alimentary System (continued)					
Oral mucosa	(12)	(11)	(24)	(18)	(5)
Foreign body	11 (92%)	9 (82%)	24 (100%)	17 (94%)	4 (80%)
Gingival, hyperplasia, squamous		1 (9%)			
Gingival, inflammation, chronic active	5 (42%)	8 (73%)	8 (33%)	3 (17%)	1 (20%)
Gingival, necrosis					1 (20%)
Pancreas	(50)	(50)	(50)	(49)	(50)
Basophilic focus				1 (2%)	
Inflammation, chronic active				2 (4%)	1 (2%)
Acinus, atrophy	12 (24%)	14 (28%)	14 (28%)	5 (10%)	11 (22%)
Acinus, hyperplasia		1 (2%)	1 (2%)		1 (2%)
Duct, cyst		8 (16%)	4 (8%)	4 (8%)	1 (2%)
Salivary glands	(50)	(50)	(49)	(49)	(50)
Atrophy	11 (22%)	19 (38%)	8 (16%)	5 (10%)	11 (22%)
Basophilic focus	10 (20%)	7 (14%)	6 (12%)	6 (12%)	3 (6%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)		
Mineralization			1 (2%)		
Vacuolization cytoplasmic				1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)			2 (4%)	1 (2%)
Mineralization	1 (2%)				
Epithelium, hyperkeratosis			2 (4%)	1 (2%)	1 (2%)
Epithelium, hyperplasia	1 (2%)		2 (4%)	2 (4%)	
Epithelium, ulcer	1 (2%)			2 (4%)	
Stomach, glandular	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active				2 (4%)	
Mineralization	1 (2%)				
Epithelium, erosion	2 (4%)				1 (2%)
Epithelium, hyperplasia	1 (2%)				
Epithelium, ulcer				2 (4%)	
Glands, ectasia	39 (78%)	36 (72%)	36 (72%)	39 (80%)	38 (76%)
Cardiovascular System					
Heart	(50)	(50)	(50)	(49)	(50)
Cardiomyopathy	36 (72%)	45 (90%)	45 (90%)	43 (88%)	44 (88%)
Mineralization	1 (2%)		1 (2%)	1 (2%)	
Atrium, thrombosis	1 (2%)				
Valve, thrombosis				1 (2%)	
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(49)	(50)
Accessory adrenal cortical nodule	1 (2%)	2 (4%)	1 (2%)		1 (2%)
Angiectasis		1 (2%)			
Hematopoietic cell proliferation	2 (4%)	1 (2%)	5 (10%)	2 (4%)	1 (2%)
Hyperplasia	10 (20%)	17 (34%)	9 (18%)	12 (24%)	10 (20%)
Hypertrophy	1 (2%)	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Necrosis		1 (2%)	2 (4%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic	20 (40%)	18 (36%)	25 (50%)	19 (39%)	20 (40%)
Adrenal medulla	(50)	(50)	(50)	(49)	(50)
Hyperplasia	3 (6%)	6 (12%)	3 (6%)	3 (6%)	3 (6%)
Islets, pancreatic	(50)	(50)	(50)	(49)	(50)
Hyperplasia		1 (2%)			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Endocrine System (continued)					
Pituitary gland	(50)	(50)	(50)	(49)	(50)
Pars distalis, angiectasis	2 (4%)	2 (4%)	3 (6%)	1 (2%)	
Pars distalis, cyst	30 (60%)	27 (54%)	27 (54%)	19 (39%)	22 (44%)
Pars distalis, hemorrhage					1 (2%)
Pars distalis, hyperplasia	24 (48%)	19 (38%)	21 (42%)	23 (47%)	21 (42%)
Pars distalis, mineralization			1 (2%)		
Pars intermedia, angiectasis	1 (2%)				
Pars intermedia, cyst	2 (4%)				
Pars intermedia, hyperplasia	1 (2%)	1 (2%)			
Thyroid gland	(50)	(50)	(49)	(49)	(50)
Ectopic thymus	1 (2%)				
Inflammation, chronic			1 (2%)		
Ultimobranchial cyst			1 (2%)	2 (4%)	1 (2%)
C-cell, hyperplasia	23 (46%)	33 (66%)	23 (47%)	28 (57%)	21 (42%)
Follicle, cyst		2 (4%)		1 (2%)	
Follicular cell, hyperplasia			2 (4%)	1 (2%)	1 (2%)
General Body System					
None					
Genital System					
Clitoral gland	(49)	(50)	(50)	(49)	(50)
Hyperplasia	11 (22%)	11 (22%)	17 (34%)	11 (22%)	7 (14%)
Inflammation, chronic active	13 (27%)	9 (18%)	21 (42%)	15 (31%)	12 (24%)
Mineralization	1 (2%)				1 (2%)
Duct, cyst	11 (22%)	16 (32%)	7 (14%)	9 (18%)	11 (22%)
Ovary	(50)	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)				
Atrophy			1 (2%)		
Cyst	9 (18%)	5 (10%)	5 (10%)	4 (8%)	2 (4%)
Mineralization			1 (2%)	1 (2%)	
Granulosa cell, hyperplasia		1 (2%)			
Interstitial cell, hyperplasia			1 (2%)		
Uterus	(50)	(50)	(50)	(49)	(50)
Hemorrhage			1 (2%)		
Hydrometra	2 (4%)	2 (4%)	5 (10%)	5 (10%)	3 (6%)
Inflammation, chronic active			1 (2%)	1 (2%)	
Metaplasia, squamous	1 (2%)				
Cervix, cyst, squamous	1 (2%)				
Cervix, epithelium, hyperplasia		1 (2%)			
Endometrium, hyperplasia, cystic	2 (4%)	5 (10%)	2 (4%)	4 (8%)	4 (8%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(49)	(50)
Hyperplasia	15 (30%)	16 (32%)	13 (26%)	11 (22%)	13 (26%)
Myelofibrosis	3 (6%)	2 (4%)	2 (4%)		4 (8%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Hematopoietic System (continued)					
Lymph node	(30)	(25)	(26)	(24)	(27)
Deep cervical, ectasia	1 (3%)		1 (4%)	3 (13%)	
Deep cervical, hyperplasia, lymphoid			1 (4%)	3 (13%)	3 (11%)
Deep cervical, inflammation, chronic			1 (4%)		
Deep cervical, pigmentation				1 (4%)	
Lumbar, ectasia	1 (3%)				
Mediastinal, ectasia	15 (50%)	17 (68%)	21 (81%)	20 (83%)	21 (78%)
Mediastinal, hyperplasia, lymphoid	19 (63%)	20 (80%)	21 (81%)	20 (83%)	22 (81%)
Mediastinal, inflammation, chronic			1 (4%)		
Mediastinal, pigmentation	1 (3%)		4 (15%)	1 (4%)	2 (7%)
Lymph node, mandibular	(1)	(2)		(1)	(2)
Ectasia	1 (100%)				
Hyperplasia, lymphoid	1 (100%)				
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(50)
Ectasia	2 (4%)	1 (2%)			
Hyperplasia, lymphoid	1 (2%)				
Spleen	(50)	(50)	(49)	(49)	(50)
Atrophy		1 (2%)			
Hematopoietic cell proliferation	12 (24%)	5 (10%)	8 (16%)	3 (6%)	6 (12%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)			1 (2%)
Infarct		1 (2%)			
Pigmentation	1 (2%)	1 (2%)			2 (4%)
Thymus	(43)	(49)	(47)	(48)	(47)
Ectopic parathyroid gland	4 (9%)	4 (8%)	3 (6%)	2 (4%)	6 (13%)
Inflammation, chronic active	1 (2%)				
Integumentary System					
Mammary gland	(50)	(50)	(50)	(49)	(50)
Cyst	5 (10%)	3 (6%)	3 (6%)	3 (6%)	
Cyst, multiple		1 (2%)			
Hyperplasia, cystic	43 (86%)	47 (94%)	45 (90%)	37 (76%)	42 (84%)
Skin	(50)	(50)	(50)	(49)	(50)
Cyst epithelial inclusion					1 (2%)
Fibrosis		1 (2%)			
Inflammation, chronic active		1 (2%)			1 (2%)
Epidermis, hyperplasia		1 (2%)			
Epidermis, ulcer		1 (2%)			
Musculoskeletal System					
Bone	(50)	(50)	(50)	(49)	(50)
Osteopetrosis			1 (2%)		
Nervous System					
Brain	(50)	(50)	(50)	(49)	(50)
Compression	2 (4%)	3 (6%)	3 (6%)	2 (4%)	5 (10%)
Hemorrhage	2 (4%)			2 (4%)	3 (6%)
Hydrocephalus	2 (4%)	5 (10%)	10 (20%)	5 (10%)	8 (16%)
Inflammation, chronic active				1 (2%)	
Necrosis					1 (2%)
Meninges, inflammation, chronic active					1 (2%)
Spinal cord				(1)	
Hemorrhage				1 (100%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Respiratory System					
Lung	(50)	(50)	(50)	(49)	(50)
Congestion			1 (2%)		
Fibrosis	1 (2%)				1 (2%)
Inflammation, chronic active	31 (62%)	36 (72%)	40 (80%)	37 (76%)	33 (66%)
Metaplasia, squamous	1 (2%)				
Mineralization	45 (90%)	45 (90%)	47 (94%)	45 (92%)	44 (88%)
Pigmentation	44 (88%)	47 (94%)	44 (88%)	44 (90%)	44 (88%)
Alveolar epithelium, hyperplasia	12 (24%)	12 (24%)	15 (30%)	13 (27%)	9 (18%)
Alveolar epithelium, metaplasia, focal,squamous		1 (2%)			
Alveolus, infiltration cellular, histiocyte	44 (88%)	47 (94%)	44 (88%)	44 (90%)	45 (90%)
Nose	(50)	(50)	(50)	(49)	(50)
Foreign body					1 (2%)
Inflammation, chronic active	4 (8%)	1 (2%)			2 (4%)
Thrombosis	2 (4%)	3 (6%)		1 (2%)	
Nasolacrimal duct, inflammation, suppurative	4 (8%)	5 (10%)	3 (6%)	6 (12%)	2 (4%)
Trachea	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic			1 (2%)		
Special Senses System					
Eye	(1)		(3)	(1)	(2)
Lens, cataract	1 (100%)		3 (100%)		2 (100%)
Retina, degeneration	1 (100%)		3 (100%)		2 (100%)
Retina, hemorrhage				1 (100%)	
Zymbal's gland	(1)		(2)		
Cyst			1 (50%)		
Urinary System					
Kidney	(50)	(50)	(50)	(49)	(50)
Accumulation, hyaline droplet	1 (2%)				
Atrophy		1 (2%)			
Cyst	1 (2%)	1 (2%)			
Hydronephrosis		1 (2%)			
Infarct			1 (2%)		1 (2%)
Infiltration cellular, lipocyte					1 (2%)
Mineralization	30 (60%)	38 (76%)	28 (56%)	33 (67%)	30 (60%)
Nephropathy	39 (78%)	43 (86%)	41 (82%)	38 (78%)	40 (80%)
Pigmentation	1 (2%)	1 (2%)			
Pelvis, inflammation, suppurative		1 (2%)			
Urinary bladder	(50)	(50)	(50)	(49)	(50)
Transitional epithelium, hyperplasia				1 (2%)	
Transitional epithelium, metaplasia, squamous				1 (2%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF *trans*-CINNAMALDEHYDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund				2	1
Natural deaths	6	3	4	9	
Survivors					
Died last week of study	1	2			
Terminal sacrifice	43	45	46	39	49
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Intestine large, cecum	(50)	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)	(49)
Polyp adenomatous		1 (2%)	1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)				
Histiocytic sarcoma			1 (2%)		
Liver	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)	
Hepatocellular carcinoma	6 (12%)	7 (14%)	7 (14%)	4 (8%)	3 (6%)
Hepatocellular adenoma	5 (10%)	7 (14%)	5 (10%)	5 (10%)	4 (8%)
Hepatocellular adenoma, multiple		2 (4%)			
Histiocytic sarcoma			1 (2%)	2 (4%)	
Mesentery	(2)			(1)	
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (100%)	
Oral mucosa		(1)			
Pharyngeal, squamous cell papilloma		1 (100%)			
Pancreas	(50)	(50)	(50)	(50)	(50)
Hemangioma		1 (2%)			
Salivary glands	(50)	(50)	(50)	(49)	(50)
Stomach, forestomach	(49)	(50)	(50)	(48)	(50)
Squamous cell carcinoma				1 (2%)	
Squamous cell papilloma				1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)	
Histiocytic sarcoma				1 (2%)	
Endocrine System					
Adrenal cortex	(49)	(50)	(50)	(49)	(50)
Subcapsular, adenoma	1 (2%)	1 (2%)	2 (4%)		1 (2%)
Pituitary gland	(48)	(50)	(49)	(50)	(49)
Pars intermedia, adenoma	1 (2%)				
Thyroid gland	(50)	(49)	(50)	(50)	(50)
Follicular cell, adenoma		1 (2%)	1 (2%)	1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)			
Histiocytic sarcoma			1 (2%)	2 (4%)	
Preputial gland	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)	
Prostate	(50)	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)			
Histiocytic sarcoma				1 (2%)	
Interstitial cell, adenoma	1 (2%)		1 (2%)	1 (2%)	1 (2%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)	
Lymph node	(3)	(2)	(2)	(3)	(2)
Lumbar, histiocytic sarcoma			1 (50%)		
Mediastinal, histiocytic sarcoma			1 (50%)	1 (33%)	
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach				1 (33%)	
Renal, fibrous histiocytoma			1 (50%)		
Renal, histiocytic sarcoma			1 (50%)		
Lymph node, mandibular	(49)	(49)	(49)	(46)	(48)
Histiocytic sarcoma			1 (2%)		
Lymph node, mesenteric	(48)	(49)	(46)	(46)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (2%)			
Histiocytic sarcoma			1 (2%)		
Plasma cell tumor malignant		1 (2%)			
Spleen	(50)	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)		
Histiocytic sarcoma			1 (2%)	2 (4%)	
Thymus	(44)	(43)	(44)	(44)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)			
Integumentary System					
Skin	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)		
Histiocytic sarcoma				1 (2%)	
Squamous cell papilloma		1 (2%)			
Subcutaneous tissue, hemangioma	2 (4%)				
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Rib, fibrosarcoma					1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Nervous System					
None					
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	6 (12%)	7 (14%)	1 (2%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			1 (2%)	
Alveolar/bronchiolar carcinoma	2 (4%)	5 (10%)	1 (2%)	2 (4%)	6 (12%)
Carcinoma, metastatic, harderian gland			1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)		3 (6%)	2 (4%)	
Histiocytic sarcoma			1 (2%)	1 (2%)	
Nose	(48)	(48)	(48)	(48)	(50)
Histiocytic sarcoma				1 (2%)	
Pleura		(1)			(1)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)			
Special Senses System					
Harderian gland	(4)	(4)	(4)	(1)	(3)
Adenoma	4 (100%)	4 (100%)	3 (75%)	1 (100%)	2 (67%)
Carcinoma			1 (25%)		
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)	
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	2 (4%)	
Lymphoma malignant	4 (8%)	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	23	34	27	17	22
Total primary neoplasms	31	44	34	23	28
Total animals with benign neoplasms	14	23	16	9	15
Total benign neoplasms	17	25	20	11	16
Total animals with malignant neoplasms	12	16	14	11	12
Total malignant neoplasms	14	19	14	12	12
Total animals with metastatic neoplasms	1	1	4	4	
Total metastatic neoplasms	1	3	4	6	

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

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

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	03 30	04 00	04 44	04 49	00 04	00 08	02 22	02 23	02 24	03 02	03 38	04 45	04 47	05 00	05 05	01 00	01 13	01 15	01 18	02 01	02 25	02 28	03 33	03 35	04 48	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																X										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma										X										X					X	6
Hepatocellular adenoma																									X	5
Mesentery	+													+												2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcapsular, adenoma																						X				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS																			+							1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 3 0	0 4 0	0 4 4	0 4 9	0 0 4	0 0 8	0 2 2	0 2 3	0 2 4	0 3 2	0 3 8	0 4 5	0 4 7	0 5 0	0 0 5	0 1 0	0 1 3	0 1 5	0 1 8	0 2 1	0 2 5	0 2 8	0 3 3	0 3 5	0 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+												3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	44
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																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																						X		2
Alveolar/bronchiolar adenoma, multiple	X																									1
Alveolar/bronchiolar carcinoma		X					X																			2
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland			+													+										4
Adenoma			X													X										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																				X						4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	1 0 0	5 7 2	7 0 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	0 5 6	0 9 3	0 5 3	0 5 1	0 6 3	0 6 6	0 6 9	0 7 2	0 7 4	0 7 6	0 7 9	0 8 8	0 5 4	0 5 8	0 6 4	0 6 7	0 7 0	0 7 1	0 7 5	0 7 7	0 8 7	0 8 9	0 9 8	1 0 0	0 5 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X										X		X	X									
Hepatocellular adenoma					X						X														X
Hepatocellular adenoma, multiple																				X	X				
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 5 7	0 6 0	0 7 3	0 8 0	0 8 5	0 8 9	0 9 1	0 9 4	0 9 5	0 9 7	0 9 9	0 5 5	0 5 9	0 6 1	0 6 2	0 6 5	0 6 8	0 7 8	0 8 1	0 8 2	0 8 3	0 8 4	0 8 6	0 9 2	0 9 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous											X															1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X				X														X		7
Hepatocellular adenoma		X													X					X					X	7
Hepatocellular adenoma, multiple																										2
Oral mucosa																+										1
Pharyngeal, squamous cell papilloma																X										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																							+			1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma									X																	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma															X											1
General Body System																										
Tissue NOS						+																				1
Genital System																										
Coagulating gland				+																						1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	1 0 0	5 7 2	7 0 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	0 5 6	0 9 3	0 5 3	0 5 1	0 6 3	0 6 6	0 6 9	0 7 2	0 7 4	0 7 6	0 7 9	0 8 8	0 5 4	0 5 8	0 6 4	0 6 7	0 7 0	0 7 1	0 7 5	0 7 7	0 8 7	0 8 9	0 9 8	1 0 0	0 5 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Plasma cell tumor malignant																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X		X																					
Alveolar/bronchiolar carcinoma			X	X		X							X				X								
Nose	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura			+																						
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland								+																	
Adenoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant					X				X													X			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 5 7	0 6 0	0 7 3	0 8 0	0 8 5	0 8 9	0 9 1	0 9 4	0 9 5	0 9 7	0 9 9	0 9 5	0 5 5	0 5 9	0 6 1	0 6 2	0 6 5	0 6 8	0 7 8	0 8 1	0 8 2	0 8 3	0 8 4	0 8 6	0 9 2	0 9 6	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node															+												2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																											1
Plasma cell tumor malignant				X																							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X		X										X			X						6
Alveolar/bronchiolar carcinoma																											5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pleura																											1
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland										+		+							+								4
Adenoma										X		X							X								4
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant															X												4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	0 5 0	5 9 4	6 4 4	7 0 1	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 3 2	1 0 9	1 0 8	1 0 3	1 0 2	1 1 0	1 1 3	1 1 4	1 2 1	1 2 3	1 2 6	1 2 9	1 3 0	1 3 1	1 3 3	1 4 0	1 4 5	1 0 4	1 1 1	1 1 7	1 1 9	1 2 0	1 3 4	1 3 5	1 3 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous															X										
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X														X		X		
Hepatocellular adenoma						X		X									X		X						
Histiocytic sarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma												X													
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	M	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma															X										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	13 38	14 41	14 42	14 01	14 05	14 16	14 18	14 24	14 36	14 44	14 49	15 00	14 06	14 07	14 12	14 15	14 22	14 25	14 27	14 28	14 39	14 43	14 46	14 47	14 48	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X	X							X		X											7
Hepatocellular adenoma																		X								5
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma																							X			2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	41
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																		X								1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	13 38	14 41	14 42	10 01	10 05	11 06	11 18	12 24	13 36	14 44	14 49	15 00	10 06	10 07	11 12	11 15	12 22	12 25	12 27	12 28	13 39	14 33	14 46	14 47	14 48	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node																										2
Lumbar, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Renal, fibrous histiocytoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
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
Hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X			X					X									7
Alveolar/bronchiolar carcinoma																X										1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver													X													3
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland		+																		+						4
Adenoma		X																								3
Carcinoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	13 8	14 1	14 2	10 1	00 5	11 6	11 8	12 4	13 6	14 4	14 9	15 0	10 6	10 7	11 2	11 5	12 2	12 5	12 7	12 8	13 9	14 3	14 6	14 7	14 8	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant			X																							1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	365	498	533	533	561	566	588	652	652	699	702	728	728	728	728	728	728	728	728	728	728	728	728	729	729
Carcass ID Number	15 57	16 61	15 59	16 62	16 60	19 00	17 02	15 53	17 57	19 53	17 53	15 51	16 67	17 71	17 75	18 81	18 86	18 89	19 92	19 96	19 97	19 99	20 00	15 54	15 56
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Hepatocellular carcinoma		X					X																		
Hepatocellular adenoma		X					X							X				X						X	
Histiocytic sarcoma						X			X																
Mesentery											+														
Squamous cell carcinoma, metastatic, stomach, forestomach											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X														
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+																								
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Histiocytic sarcoma									X																
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X									
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	15 58	16 63	16 64	17 44	18 88	19 98	15 55	16 65	16 69	17 00	17 76	17 78	18 00	18 02	18 83	18 44	19 44	19 55	15 52	16 66	16 68	17 99	18 55	18 57	19 91	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma											X									X						4
Hepatocellular adenoma																										5
Histiocytic sarcoma																										2
Mesentery																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma																										1
Squamous cell papilloma																			X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	365	498	533	533	561	566	588	652	652	699	702	728	728	728	728	728	728	728	728	728	728	728	728	729	729
Carcass ID Number	15057	16161	15519	16262	16620	19100	17722	15353	17737	19313	17733	15511	16667	17715	17755	18161	18616	18892	19226	19676	19917	19999	20060	15474	15656
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X			X																
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Interstitial cell, adenoma																							X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymph node								+	+		+														
Mediastinal, histiocytic sarcoma									X																
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach											X														
Lymph node, mandibular	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X			X																
Thymus	M	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar adenoma, multiple																	X								
Alveolar/bronchiolar carcinoma									X	X															
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma									X																
Nose	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	15 58	16 63	16 64	17 44	18 88	19 88	15 55	16 65	16 69	17 00	17 66	17 78	18 00	18 02	18 83	18 44	19 44	19 55	15 52	16 66	16 68	17 99	18 85	18 87	19 91	Total Tissues/ Tumors
Genital System																										
Coagulating gland											+															1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node																										3
Mediastinal, histiocytic sarcoma																										1
Mediastinal, squamous cell carcinoma, metastatic, stomach, forestomach																										1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	44
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	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										2
Hepatocellular carcinoma, metastatic, liver											X									X						2
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	15 58	16 63	16 64	17 44	18 88	19 88	15 55	16 55	16 69	17 00	17 76	17 78	18 00	18 02	18 33	18 44	19 44	19 95	15 52	16 66	16 68	17 99	18 55	18 77	19 91	Total Tissues/ Tumors
Special Senses System																										
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	596	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	233	206	212	114	116	119	223	225	229	243	449	505	003	004	005	007	010	011	220	221	226	227	234	237	238
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																X									
Hepatocellular adenoma					X	X							X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																					+				
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma															X										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	23 39	24 1	21 3	21 7	21 8	22 2	22 8	23 0	23 1	23 2	23 5	24 2	24 6	24 8	20 1	20 2	20 8	20 9	21 5	21 24	23 6	24 0	24 4	24 5	24 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																	X								3
Hepatocellular adenoma												X														4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X																							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																								+		2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma																								X		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS														+								+				2
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	596	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	233	206	212	114	116	119	223	225	229	243	249	250	203	204	205	207	210	211	220	221	226	227	234	237	238
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, fibrosarcoma																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X				X			X									X			X				
Alveolar/bronchiolar carcinoma	X				X											X							X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																	+									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland																			+							
Adenoma																			X							
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 3 9	2 4 1	2 1 3	2 1 7	2 1 8	2 2 2	2 2 8	2 3 0	2 3 1	2 3 2	2 3 5	2 4 2	2 4 6	2 4 8	2 0 1	2 0 2	2 0 8	2 0 9	2 1 5	2 2 4	2 3 6	2 4 0	2 4 4	2 4 5	2 4 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+												+											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, fibrosarcoma				X																						1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																X								7
Alveolar/bronchiolar carcinoma																							X	X		6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																						+	+			3
Adenoma																						X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X												X											2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Harderian Gland: Adenoma					
Overall rate[a]	4/50 (8%)	4/50 (8%)	3/50 (6%)[e]	1/50 (2%)	2/50 (4%)
Adjusted rate[b]	8.6%	8.3%	6.2%	2.2%	4.0%
Terminal rate[c]	4/44 (9%)	4/47 (9%)	3/46 (7%)	1/39 (3%)	2/49 (4%)
First incidence (days)	728 (T)	728 (T)	728 (T)	728 (T)	728 (T)
Poly-3 test[d]		P=0.220N	P=0.503N	P=0.203N	P=0.327N
Liver: Hepatocellular Adenoma					
Overall rate	5/50 (10%)	9/50 (18%)	5/50 (10%)	5/50 (10%)	4/50 (8%)
Adjusted rate	10.6%	18.6%	10.4%	10.9%	8.1%
Terminal rate	4/44 (9%)	9/47 (19%)	5/46 (11%)	3/39 (8%)	4/49 (8%)
First incidence (days)	498	728 (T)	728 (T)	498	728 (T)
Poly-3 test		P=0.102N	P=0.197N	P=0.222N	P=0.108N
Liver: Hepatocellular Carcinoma					
Overall rate	6/50 (12%)	7/50 (14%)	7/50 (14%)	4/50 (8%)	3/50 (6%)
Adjusted rate	12.7%	14.4%	14.5%	8.7%	6.1%
Terminal rate	4/44 (9%)	6/47 (13%)	7/46 (15%)	2/39 (5%)	3/49 (6%)
First incidence (days)	538	708	728 (T)	498	728 (T)
Poly-3 test		P=0.082N	P=0.607	P=0.292N	P=0.150N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	10/50 (20%)	16/50 (32%)	12/50 (24%)	7/50 (14%)	7/50 (14%)
Adjusted rate	20.9%	33.0%	24.9%	15.2%	14.1%
Terminal rate	7/44 (16%)	15/47 (32%)	12/46 (26%)	5/39 (13%)	7/49 (14%)
First incidence (days)	498	708	728 (T)	498	728 (T)
Poly-3 test		P=0.012N	P=0.259N	P=0.036N	P=0.023N
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	3/50 (6%)	6/50 (12%)	7/50 (14%)	2/50 (4%)	7/50 (14%)
Adjusted rate	6.5%	12.3%	14.5%	4.4%	14.1%
Terminal rate	3/44 (7%)	5/47 (11%)	6/46 (13%)	1/39 (3%)	7/49 (14%)
First incidence (days)	728 (T)	572	644	699	728 (T)
Poly-3 test		P=0.531	P=0.492	P=0.162N	P=0.510
Lung: Alveolar/bronchiolar Carcinoma					
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	4.3%	10.3%	2.1%	4.4%	12.0%
Terminal rate	2/44 (5%)	4/47 (9%)	1/46 (2%)	0/39 (0%)	5/49 (10%)
First incidence (days)	728 (T)	708	728 (T)	652	596
Poly-3 test		P=0.263	P=0.104N	P=0.245N	P=0.521
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	4/50 (8%)	10/50 (20%)	8/50 (16%)	3/50 (6%)	13/50 (26%)
Adjusted rate	8.6%	20.4%	16.5%	6.6%	26.0%
Terminal rate	4/44 (9%)	8/47 (17%)	7/46 (15%)	1/39 (3%)	12/49 (25%)
First incidence (days)	728 (T)	572	644	652	596
Poly-3 test		P=0.244	P=0.408N	P=0.049N	P=0.338
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	6.5%	4.1%	4.1%	2.2%	0.0%
Terminal rate	3/44 (7%)	1/47 (2%)	1/46 (2%)	1/39 (3%)	0/49 (0%)
First incidence (days)	728 (T)	572	644	728 (T)	—[f]
Poly-3 test		P=0.126N	P=0.690	P=0.530N	P=0.235N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
All Organs: Malignant Lymphoma					
Overall rate	4/50 (8%)	4/50 (8%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rate	8.5%	8.3%	2.1%	4.4%	4.0%
Terminal rate	3/44 (7%)	4/47 (9%)	1/46 (2%)	0/39 (0%)	2/49 (4%)
First incidence (days)	538	728 (T)	728 (T)	561	728 (T)
Poly-3 test		P=0.339N	P=0.181N	P=0.364N	P=0.327N
All Organs: Benign Neoplasms					
Overall rate	14/50 (28%)	23/50 (46%)	16/50 (32%)	9/50 (18%)	15/50 (30%)
Adjusted rate	29.7%	47.0%	33.0%	19.5%	30.3%
Terminal rate	13/44 (30%)	22/47 (47%)	15/46 (33%)	6/39 (15%)	15/49 (31%)
First incidence (days)	498	572	644	498	728 (T)
Poly-3 test		P=0.052N	P=0.115N	P=0.003N	P=0.066N
All Organs: Malignant Neoplasms					
Overall rate	12/50 (24%)	16/50 (32%)	14/50 (28%)	11/50 (22%)	12/50 (24%)
Adjusted rate	25.4%	32.7%	28.8%	23.0%	24.0%
Terminal rate	10/44 (23%)	14/47 (30%)	12/46 (26%)	3/39 (8%)	11/49 (22%)
First incidence (days)	538	572	644	498	596
Poly-3 test		P=0.184N	P=0.426N	P=0.202N	P=0.233N
All Organs: Benign or Malignant Neoplasms					
Overall rate	23/50 (46%)	34/50 (68%)	27/50 (54%)	17/50 (34%)	22/50 (44%)
Adjusted rate	48.0%	69.4%	55.6%	35.5%	44.0%
Terminal rate	20/44 (46%)	32/47 (68%)	25/46 (54%)	9/39 (23%)	21/49 (43%)
First incidence (days)	498	572	644	498	596
Poly-3 test		P=0.005N	P=0.116N	P<0.001N	P=0.008N

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund				2	1
Natural deaths	6	3	4	9	
Survivors					
Died last week of study	1	2			
Terminal sacrifice	43	45	46	39	49
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(50)	(50)
Hyperkeratosis	4 (8%)	2 (4%)	2 (4%)	4 (8%)	
Gallbladder	(50)	(50)	(50)	(50)	(49)
Inflammation	2 (4%)	4 (8%)	2 (4%)	2 (4%)	4 (8%)
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Epithelium, hyperplasia			1 (2%)		
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Edema			1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(50)	(50)
Lymphoid tissue, hyperplasia					1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)	(49)
Epithelium, hyperplasia				1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Atrophy				1 (2%)	
Cyst		1 (2%)			
Diverticulum				1 (2%)	
Hyperplasia, lymphoid		1 (2%)			
Inflammation	1 (2%)				
Peyer's patch, hyperplasia	2 (4%)				
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Peyer's patch, hyperplasia	1 (2%)				
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)			
Basophilic focus	2 (4%)	1 (2%)	1 (2%)		1 (2%)
Clear cell focus	2 (4%)	3 (6%)	3 (6%)	1 (2%)	
Cyst	1 (2%)				
Eosinophilic focus	3 (6%)	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Fatty change	3 (6%)	3 (6%)	4 (8%)	4 (8%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	1 (2%)	
Inflammation	26 (52%)	33 (66%)	34 (68%)	28 (56%)	27 (54%)
Mitotic alteration					1 (2%)
Mixed cell focus	3 (6%)	5 (10%)	3 (6%)	3 (6%)	6 (12%)
Necrosis	3 (6%)	6 (12%)	4 (8%)	4 (8%)	3 (6%)
Pigmentation	1 (2%)		1 (2%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic					1 (2%)
Bile duct, cyst					1 (2%)
Centrilobular, degeneration				1 (2%)	
Portal, infiltration cellular, lymphocyte	1 (2%)	3 (6%)	6 (12%)	8 (16%)	3 (6%)

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Alimentary System (continued)					
Mesentery	(2)			(1)	
Fat, inflammation	1 (50%)				
Fat, necrosis	1 (50%)				
Pancreas	(50)	(50)	(50)	(50)	(50)
Atrophy		1 (2%)			
Cyst	2 (4%)				
Inflammation	8 (16%)	10 (20%)	8 (16%)	14 (28%)	10 (20%)
Salivary glands	(50)	(50)	(50)	(49)	(50)
Atrophy		3 (6%)		1 (2%)	
Inflammation	30 (60%)	31 (62%)	33 (66%)	26 (53%)	29 (58%)
Mineralization				2 (4%)	
Stomach, forestomach	(49)	(50)	(50)	(48)	(50)
Hyperkeratosis	2 (4%)		2 (4%)	3 (6%)	
Hyperplasia	1 (2%)	1 (2%)		1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Mineralization					1 (2%)
Ulcer				1 (2%)	
Tooth		(1)		(1)	(2)
Malformation		1 (100%)		1 (100%)	2 (100%)
Cardiovascular System					
Blood vessel	(50)	(49)	(50)	(50)	(50)
Aorta, inflammation	1 (2%)			1 (2%)	
Aorta, thrombosis	1 (2%)				
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Inflammation	1 (2%)		1 (2%)	1 (2%)	
Mineralization				5 (10%)	
Artery, inflammation	1 (2%)			1 (2%)	2 (4%)
Endocrine System					
Adrenal cortex	(49)	(50)	(50)	(49)	(50)
Fibrosis				1 (2%)	
Hyperplasia				1 (2%)	
Hypertrophy	23 (47%)	23 (46%)	22 (44%)	24 (49%)	19 (38%)
Subcapsular, hyperplasia	39 (80%)	46 (92%)	43 (86%)	44 (90%)	42 (84%)
Adrenal medulla	(49)	(50)	(50)	(49)	(50)
Hyperplasia			1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Atrophy	1 (2%)				
Hyperplasia	4 (8%)	4 (8%)	5 (10%)	3 (6%)	4 (8%)
Pituitary gland	(48)	(50)	(49)	(50)	(49)
Angiectasis	1 (2%)				
Cyst	2 (4%)	1 (2%)	3 (6%)		
Pars distalis, hyperplasia	5 (10%)	5 (10%)	6 (12%)	4 (8%)	5 (10%)
Thyroid gland	(50)	(49)	(50)	(50)	(50)
Inflammation			1 (2%)	1 (2%)	
Follicle, cyst	6 (12%)	4 (8%)	4 (8%)	5 (10%)	5 (10%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
General Body System					
None					
Genital System					
Coagulating gland		(1)		(1)	
Inflammation		1 (100%)		1 (100%)	
Epididymis	(50)	(50)	(50)	(50)	(50)
Inflammation		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Mineralization		3 (6%)		2 (4%)	2 (4%)
Preputial gland	(50)	(50)	(50)	(50)	(50)
Inflammation	26 (52%)	29 (58%)	31 (62%)	27 (54%)	22 (44%)
Duct, ectasia	15 (30%)	20 (40%)	27 (54%)	17 (34%)	13 (26%)
Duct, hyperplasia, squamous				1 (2%)	
Testes	(50)	(50)	(50)	(50)	(50)
Mineralization	1 (2%)		3 (6%)	3 (6%)	1 (2%)
Germinal epithelium, degeneration	1 (2%)				
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Hyperplasia	17 (34%)	14 (28%)	19 (38%)	20 (40%)	13 (26%)
Necrosis				1 (2%)	
Lymph node	(3)	(2)	(2)	(3)	(2)
Mediastinal, hyperplasia	1 (33%)				
Lymph node, mandibular	(49)	(49)	(49)	(46)	(48)
Atrophy			1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, plasma cell		1 (2%)			
Infiltration cellular, histiocyte			1 (2%)		
Pigmentation, hemosiderin					1 (2%)
Lymph node, mesenteric	(48)	(49)	(46)	(46)	(50)
Angiectasis				1 (2%)	
Atrophy	3 (6%)	1 (2%)		2 (4%)	
Ectasia	1 (2%)				
Hematopoietic cell proliferation		2 (4%)		1 (2%)	1 (2%)
Hemorrhage					1 (2%)
Hyperplasia	2 (4%)				1 (2%)
Infiltration cellular, mast cell	1 (2%)				
Infiltration cellular, plasma cell			1 (2%)	1 (2%)	1 (2%)
Inflammation				1 (2%)	1 (2%)
Mineralization	1 (2%)				
Spleen	(50)	(50)	(50)	(49)	(50)
Hematopoietic cell proliferation	7 (14%)	8 (16%)	10 (20%)	8 (16%)	5 (10%)
Hemorrhage					1 (2%)
Hyperplasia				1 (2%)	1 (2%)
Lymphoid follicle, atrophy		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Thymus	(44)	(43)	(44)	(44)	(49)
Atrophy		2 (5%)	3 (7%)	3 (7%)	1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Integumentary System					
Skin	(50)	(50)	(50)	(50)	(50)
Inflammation				1 (2%)	
Subcutaneous tissue, edema			1 (2%)	2 (4%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Myelofibrosis	1 (2%)	1 (2%)	1 (2%)		1 (2%)
Skeletal muscle			(1)		
Inflammation			1 (100%)		
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)	
Infiltration cellular, lymphocyte					1 (2%)
Cerebellum, necrosis					1 (2%)
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Inflammation	1 (2%)		1 (2%)	3 (6%)	1 (2%)
Inflammation, granulomatous				1 (2%)	
Metaplasia, osseous				1 (2%)	
Pigmentation, hemosiderin				1 (2%)	
Alveolar epithelium, hyperplasia	4 (8%)	2 (4%)	7 (14%)		5 (10%)
Perivascular, infiltration cellular, mononuclear cell				1 (2%)	
Nose	(48)	(48)	(48)	(48)	(50)
Foreign body	1 (2%)	1 (2%)	3 (6%)		3 (6%)
Inflammation	3 (6%)	2 (4%)	6 (13%)		4 (8%)
Nasolacrimal duct, foreign body			2 (4%)	1 (2%)	
Nasolacrimal duct, inflammation		2 (4%)	2 (4%)	1 (2%)	3 (6%)
Olfactory epithelium, degeneration, hyaline		2 (4%)	1 (2%)		
Olfactory epithelium, pigmentation				3 (6%)	26 (52%)
Olfactory epithelium, respiratory epithelium, degeneration			1 (2%)		
Trachea	(50)	(50)	(50)	(50)	(50)
Inflammation				1 (2%)	
Special Senses System					
Harderian gland	(4)	(4)	(4)	(1)	(3)
Inflammation	1 (25%)				

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Atrophy			1 (2%)		
Cyst	2 (4%)	3 (6%)		3 (6%)	3 (6%)
Cytoplasmic alteration					1 (2%)
Fibrosis				1 (2%)	
Infarct	2 (4%)	5 (10%)	2 (4%)	2 (4%)	
Infiltration cellular, lymphocyte	39 (78%)	39 (78%)	42 (84%)	40 (80%)	44 (88%)
Inflammation	2 (4%)			2 (4%)	1 (2%)
Metaplasia, osseous	2 (4%)		1 (2%)	3 (6%)	2 (4%)
Mineralization	42 (84%)	44 (88%)	49 (98%)	45 (90%)	46 (92%)
Nephropathy	46 (92%)	47 (94%)	46 (92%)	38 (76%)	42 (84%)
Artery, inflammation		1 (2%)		1 (2%)	
Glomerulus, dilatation			1 (2%)		
Renal tubule, dilatation	6 (12%)	7 (14%)	5 (10%)	8 (16%)	9 (18%)
Renal tubule, hyperplasia	1 (2%)	1 (2%)			
Renal tubule, pigmentation			1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)	(50)
Inflammation	20 (40%)	16 (32%)	20 (40%)	18 (36%)	21 (42%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF *trans*-CINNAMALDEHYDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	2	3	4	1	4
Natural deaths	5	6	9	5	3
Survivors					
Died last week of study	1		1		
Terminal sacrifice	42	41	36	44	43
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Gallbladder	(50)	(50)	(50)	(50)	(50)
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, skin				1 (2%)	
Intestine large, cecum	(50)	(50)	(50)	(49)	(50)
Intestine small, duodenum	(50)	(49)	(50)	(50)	(50)
Polyp adenomatous			1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)			
Liver	(50)	(49)	(50)	(50)	(50)
Carcinoma, metastatic, uterus				1 (2%)	
Hepatocellular carcinoma	1 (2%)	2 (4%)			
Hepatocellular adenoma	4 (8%)	3 (6%)	4 (8%)	2 (4%)	1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)	
Osteosarcoma, metastatic, uncertain primary site			1 (2%)		
Mesentery	(3)	(4)	(5)	(4)	(1)
Carcinoma, metastatic, uterus				1 (25%)	
Fibrosarcoma	1 (33%)				
Hemangioma	1 (33%)				
Histiocytic sarcoma			1 (20%)	1 (25%)	
Rhabdomyosarcoma, metastatic, skeletal muscle	1 (33%)				
Pancreas	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)	
Salivary glands	(48)	(50)	(48)	(49)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)	
Squamous cell carcinoma				1 (2%)	
Squamous cell papilloma	1 (2%)			3 (6%)	
Tooth		(2)		(1)	(1)
Cardiovascular System					
Heart	(49)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)		
Hemangioma			1 (2%)		
Histiocytic sarcoma		1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Subcapsular, adenoma					1 (2%)
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Pheochromocytoma malignant		1 (2%)			
Pheochromocytoma benign				1 (2%)	1 (2%)
Pituitary gland	(48)	(49)	(50)	(49)	(50)
Pars distalis, adenoma	5 (10%)	6 (12%)	1 (2%)	4 (8%)	2 (4%)
Pars intermedia, adenoma				1 (2%)	
Thyroid gland	(48)	(50)	(49)	(50)	(50)
Follicular cell, adenoma		1 (2%)			
General Body System					
Tissue NOS				(1)	
Genital System					
Clitoral gland	(50)	(49)	(50)	(49)	(50)
Carcinoma		1 (2%)			
Ovary	(50)	(50)	(50)	(49)	(50)
Cystadenoma	2 (4%)		2 (4%)	1 (2%)	1 (2%)
Granulosa cell tumor benign		1 (2%)			1 (2%)
Hemangioma	1 (2%)				
Hemangiosarcoma		1 (2%)		1 (2%)	1 (2%)
Luteoma	1 (2%)	1 (2%)	1 (2%)		1 (2%)
Thecoma benign		1 (2%)			
Oviduct	(1)	(1)	(2)	(3)	(4)
Histiocytic sarcoma				1 (33%)	
Uterus	(50)	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)	
Hemangioma		1 (2%)			
Histiocytic sarcoma			1 (2%)	1 (2%)	
Leiomyosarcoma		1 (2%)			
Polyp stromal	1 (2%)				1 (2%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Mast cell tumor malignant	1 (2%)				
Lymph node	(7)	(5)	(7)	(10)	(7)
Lumbar, histiocytic sarcoma				1 (10%)	
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (14%)		
Mediastinal, carcinoma, metastatic, uterus				1 (10%)	
Pancreatic, histiocytic sarcoma				1 (10%)	
Pancreatic, osteosarcoma, metastatic, uncertain primary site			1 (14%)		
Pancreatic, rhabdomyosarcoma, metastatic, skeletal muscle	1 (14%)				
Lymph node, mandibular	(46)	(47)	(45)	(49)	(47)
Mast cell tumor malignant	1 (2%)				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Hematopoietic System (continued)					
Lymph node, mesenteric	(49)	(49)	(50)	(49)	(50)
Carcinoma, metastatic, clitoral gland		1 (2%)			
Hemangiosarcoma				2 (4%)	
Histiocytic sarcoma				1 (2%)	
Spleen	(48)	(49)	(50)	(50)	(50)
Hemangiosarcoma				2 (4%)	1 (2%)
Thymus	(46)	(47)	(46)	(47)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)		
Histiocytic sarcoma		1 (2%)			
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Adenoma				1 (2%)	
Fibroadenoma			1 (2%)		
Skin	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)			1 (2%)	
Subcutaneous tissue, fibrosarcoma	2 (4%)	2 (4%)	3 (6%)		
Subcutaneous tissue, hemangioma		1 (2%)			
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		1 (2%)	
Subcutaneous tissue, schwannoma malignant	1 (2%)	1 (2%)			1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Vertebra, osteosarcoma		1 (2%)			
Skeletal muscle	(1)				
Rhabdomyosarcoma	1 (100%)				
Nervous System					
None					
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	1 (2%)		
Alveolar/bronchiolar carcinoma	2 (4%)		2 (4%)	1 (2%)	1 (2%)
Carcinoma, metastatic, clitoral gland		1 (2%)			
Carcinoma, metastatic, harderian gland			1 (2%)		
Carcinoma, metastatic, uncertain primary site		1 (2%)			
Carcinoma, metastatic, uterus				1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)				
Histiocytic sarcoma		1 (2%)			
Osteosarcoma, metastatic, bone		1 (2%)			
Osteosarcoma, metastatic, uncertain primary site	1 (2%)		1 (2%)		
Rhabdomyosarcoma, metastatic, skeletal muscle	1 (2%)				
Squamous cell carcinoma, metastatic, skin				1 (2%)	
Nose	(49)	(50)	(50)	(50)	(50)
Pleura	(1)				
Rhabdomyosarcoma, metastatic, skeletal muscle	1 (100%)				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Special Senses System					
Harderian gland	(2)	(1)	(4)	(5)	
Adenoma	1 (50%)	1 (100%)	3 (75%)	3 (60%)	
Carcinoma	1 (50%)		1 (25%)	2 (40%)	
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, uterus				1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)	(50)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)	1 (2%)	1 (2%)	
Lymphoma malignant	13 (26%)	10 (20%)	6 (12%)	8 (16%)	14 (28%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	32	29	21	24	21
Total primary neoplasms	43	41	28	36	27
Total animals with benign neoplasms	17	15	10	14	7
Total benign neoplasms	18	18	15	16	9
Total animals with malignant neoplasms	23	22	12	16	16
Total malignant neoplasms	25	23	13	20	18
Total animals with metastatic neoplasms	3	3	3	2	
Total metastatic neoplasms	6	4	7	7	
Total animals with malignant neoplasms of uncertain primary site	1	1	1		

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	4 2 9	5 2 0	6 2 7	6 3 8	6 5 2	6 5 2	6 7 5	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	2 8 1	2 6 6	2 8 5	2 5 2	2 7 2	2 8 9	2 7 3	2 5 5	2 5 8	2 6 0	2 6 9	2 7 4	2 7 9	2 8 8	2 9 0	2 9 8	2 9 9	2 5 1	2 5 3	2 5 9	2 6 2	2 6 5	2 6 7	2 7 0	2 7 1
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma															X											
Hepatocellular adenoma										X					X	X						X				
Mesentery					+																					
Fibrosarcoma																										
Hemangioma																										
Rhabdomyosarcoma, metastatic, skeletal muscle					X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X												X								
Thyroid gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																										
None																										

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 8 3	2 8 4	2 9 1	2 9 2	2 9 7	2 6 1	2 6 4	2 7 7	2 7 8	2 8 0	2 8 2	2 8 6	2 8 7	2 9 3	2 9 6	2 5 4	2 5 6	2 5 7	2 6 3	2 6 8	2 7 5	2 7 6	2 9 4	2 9 5	3 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma																										4
Mesentery					+								+													3
Fibrosarcoma													X													1
Hemangioma					X																					1
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma														X					X						X	5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	4 2 9	5 2 0	6 2 7	6 3 8	6 5 2	6 5 2	6 7 5	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	2 8 1	2 6 6	2 8 5	2 5 2	2 7 2	2 8 9	2 7 3	2 5 5	2 5 8	2 6 0	2 6 9	2 7 4	2 7 9	2 8 8	2 9 0	2 9 8	2 9 9	2 5 1	2 5 3	2 5 9	2 6 2	2 6 5	2 6 7	2 7 0	2 7 1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma							X																			
Hemangioma								X																		
Luteoma																										
Oviduct																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																										
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																										
Lymph node					+		+	+		+																
Pancreatic, rhabdomyosarcoma, metastatic, skeletal muscle					X																					
Lymph node, mandibular	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																										
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma				X																						
Subcutaneous tissue, fibrosarcoma																			X							
Subcutaneous tissue, schwannoma malignant			X																							
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																					
Rhabdomyosarcoma					X																					
Nervous System																										
Brain	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma																										
Hepatocellular carcinoma, metastatic, liver															X											
Osteosarcoma, metastatic, uncertain primary site	X																									
Rhabdomyosarcoma, metastatic, skeletal muscle					X																					
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura					+																					
Rhabdomyosarcoma, metastatic, skeletal muscle					X																					
Trachea	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	28383	28484	29091	29292	29297	26261	26464	26777	26778	28080	28282	28626	28787	29093	29696	25544	25566	25577	26263	26688	27555	27676	29944	29955	30300	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma				X																						2
Hemangioma																										1
Luteoma																					X					1
Oviduct										+																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X																					1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																									X	1
Lymph node										+	+									+						7
Pancreatic, rhabdomyosarcoma, metastatic, skeletal muscle																										1
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Mast cell tumor malignant																									X	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma							X																			2
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X															1
Alveolar/bronchiolar carcinoma																X		X								2
Hepatocellular carcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura																										1
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Untreated Control

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 8 3	2 8 4	2 9 1	2 9 2	2 9 7	2 6 1	2 6 4	2 7 7	2 7 8	2 8 0	2 8 2	2 8 6	2 8 7	2 9 3	2 9 6	2 5 4	2 5 6	2 5 7	2 6 3	2 6 8	2 7 5	2 7 6	2 9 4	2 9 5	3 0 0	Total Tissues/ Tumors
Special Senses System																										
Harderian gland		+								+																2
Adenoma										X																1
Carcinoma		X																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant					X				X	X			X		X					X		X				13

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	4 5 6	4 6 3	4 6 3	5 7 0	6 0 9	6 1 4	6 9 3	6 9 8	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 3 4	7 4 4	7 4 4	7 4 4	7 3 4
Carcass ID Number	3 0 7	3 3 5	3 4 6	3 2 8	3 1 9	3 2 0	3 1 6	3 2 1	3 2 3	3 0 2	3 1 2	3 1 4	3 1 5	3 3 1	3 3 2	3 3 4	3 3 7	3 3 8	3 0 3	3 0 6	3 1 8	3 2 5	3 2 7	3 3 9	3 4 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																X									
Hemangiosarcoma								X																	
Luteoma						X																			
Thecoma benign																									
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Leiomyosarcoma							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+				+												+	+			
Lymph node, mandibular	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, clitoral gland						X																			
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Histiocytic sarcoma	X																								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma														X											
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, histiocytic sarcoma																									
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Carcinoma, metastatic, clitoral gland						X																			
Carcinoma, metastatic, uncertain primary site					X																				
Histiocytic sarcoma	X																								
Osteosarcoma, metastatic, bone				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 4 8	3 4 9	3 5 0	3 0 4	3 0 8	3 0 9	3 1 0	3 1 7	3 2 4	3 2 6	3 2 9	3 3 3	3 4 0	3 4 1	3 4 4	3 4 5	3 0 1	3 0 5	3 1 1	3 1 3	3 2 2	3 3 0	3 3 6	3 4 2	3 4 7	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Hemangiosarcoma																										1
Luteoma																										1
Thecoma benign		X																								1
Oviduct												+														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma									X																	1
Leiomyosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																		+								5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, clitoral gland																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																							X			2
Subcutaneous tissue, hemangioma								X																		1
Subcutaneous tissue, histiocytic sarcoma												X														1
Subcutaneous tissue, schwannoma malignant		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																								2
Carcinoma, metastatic, clitoral gland																										1
Carcinoma, metastatic, uncertain primary site																										1
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: Vehicle Control

Number of Days on Study	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	
Carcass ID Number	34848	34949	35050	30404	30088	30209	31010	31177	32424	32626	32929	33330	34041	34411	34445	34501	30155	31151	32232	33306	33462	34247	34447	Total Tissues/ Tumors	
Special Senses System																										
Harderian gland											+															1
Adenoma											X															1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X														2
Lymphoma malignant			X								X				X			X	X							10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	3 2 5	5 5 1	5 5 8	5 7 5	5 9 6	6 2 8	6 5 2	6 6 3	6 6 8	6 7 3	7 0 8	7 2 3	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4
Carcass ID Number	3 7 2	3 8 3	3 9 0	3 6 2	3 7 7	3 7 9	3 5 6	3 7 3	3 6 6	3 6 8	3 7 0	3 8 9	3 8 1	3 5 5	3 6 3	3 6 4	3 6 9	3 7 4	3 7 5	3 7 8	3 8 2	3 8 5	4 0 0	3 5 1	3 5 3
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous											X													
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X					X					X			
Histiocytic sarcoma			X																					
Osteosarcoma, metastatic, uncertain primary site						X																		
Mesentery			+									+												
Histiocytic sarcoma			X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X											
Hemangioma																X								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X																				
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma											X											X		
Luteoma																					X			
Oviduct												+												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 5 4	3 7 6	3 8 0	3 8 4	3 8 6	3 8 7	3 9 1	3 9 4	3 9 5	3 9 7	3 5 2	3 5 7	3 5 8	3 5 9	3 6 1	3 8 8	3 9 2	3 9 3	3 9 6	3 9 8	3 6 0	3 6 5	3 6 7	3 7 1	3 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X											4
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Mesentery						+	+					+														5
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangioma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										2
Luteoma																										1
Oviduct												+														2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	325	551	558	575	596	628	655	663	668	673	708	723	728	733	733	733	733	733	733	733	733	733	733	744	733
Carcass ID Number	372	383	390	362	377	779	596	573	666	668	700	789	811	855	963	664	969	744	775	778	782	825	400	501	553
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+						+	+												
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung													X												
Pancreatic, osteosarcoma, metastatic, uncertain primary site						X																			
Lymph node, mandibular	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			X																						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma													X						X						
Carcinoma, metastatic, harderian gland																									
Osteosarcoma, metastatic, uncertain primary site						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland						+														+					
Adenoma						X														X					
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Lymphoma malignant												X					X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 1,000 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 5 4	3 7 6	3 8 0	3 8 4	3 8 6	3 8 7	3 9 1	3 9 4	3 9 5	3 9 7	3 5 2	3 5 7	3 5 8	3 5 9	3 6 1	3 8 8	3 9 2	3 9 3	3 9 6	3 9 8	3 6 0	3 6 5	3 6 7	3 7 1	3 9 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+		+					+				+					7
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Pancreatic, osteosarcoma, metastatic, uncertain primary site																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	46
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma												X				X										3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										2
Carcinoma, metastatic, harderian gland			X																							1
Osteosarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye															+											1
Harderian gland			+												+											4
Adenoma															X											3
Carcinoma			X																							1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant										X		X					X				X					6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	4 2 5	5 6 8	6 3 8	6 4 2	6 9 1	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 3 4
Carcass ID Number	4 2 6	4 4 4	4 3 3	4 5 0	4 4 5	4 3 8	4 0 3	4 1 7	4 2 1	4 2 3	4 2 4	4 2 9	4 3 2	4 3 7	4 4 0	4 4 6	4 4 8	4 0 6	4 0 7	4 0 9	4 1 2	4 1 4	4 1 6	4 2 8	4 4 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin									X																
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus						X																			
Hepatocellular adenoma																		X							
Histiocytic sarcoma				X																					
Mesentery				+	+	+																			
Carcinoma, metastatic, uterus						X																			
Histiocytic sarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Squamous cell carcinoma																									
Squamous cell papilloma											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+												
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X									
Pars intermedia, adenoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS	+																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 4 2	4 4 3	4 4 4	4 4 0	4 1 1	4 1 9	4 2 0	4 3 0	4 3 1	4 3 4	4 3 5	4 3 9	4 0 1	4 0 2	4 0 5	4 0 8	4 1 1	4 1 3	4 1 5	4 1 8	4 2 2	4 2 5	4 2 7	4 3 6	4 4 7	4 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, skin																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uterus																										1
Hepatocellular adenoma	X																									2
Histiocytic sarcoma																										1
Mesentery							+																			4
Carcinoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Squamous cell carcinoma															X											1
Squamous cell papilloma				X									X													3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	M	+	+	M	M	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					X															X				X		4
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	4 2 5	5 6 8	6 3 8	6 4 2	6 9 1	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4
Carcass ID Number	4 2 6	4 4 4	4 3 3	4 5 0	4 4 5	4 3 8	4 0 3	4 1 7	4 2 1	4 2 3	4 2 4	4 2 9	4 3 2	4 3 7	4 4 0	4 4 6	4 4 8	4 0 6	4 0 7	4 0 9	4 1 2	4 1 4	4 1 6	4 2 8	4 4 1
Genital System																									
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma													X												
Hemangiosarcoma																									
Oviduct			+	+	+																				
Histiocytic sarcoma				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Histiocytic sarcoma				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+	+				+	+												+		
Lumbar, histiocytic sarcoma				X																					
Mediastinal, carcinoma, metastatic, uterus						X																			
Pancreatic, histiocytic sarcoma				X																					
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma									X																
Subcutaneous tissue, histiocytic sarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma		X																							
Carcinoma, metastatic, uterus						X																			
Squamous cell carcinoma, metastatic, skin									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 4 4 2	4 4 4 3	4 4 0 4	4 4 1 0	4 4 1 9	4 4 2 0	4 4 3 0	4 4 3 1	4 4 3 4	4 4 3 5	4 4 3 9	4 4 0 1	4 4 0 2	4 4 0 5	4 4 0 8	4 4 1 1	4 4 1 3	4 4 1 5	4 4 1 8	4 4 2 2	4 4 2 5	4 4 2 7	4 4 3 6	4 4 4 7	4 4 4 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																										1
Hemangiosarcoma														X												1
Oviduct																										3
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+		+																				10
Lumbar, histiocytic sarcoma																										1
Mediastinal, carcinoma, metastatic, uterus																										1
Pancreatic, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma		X							X																	2
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X					X												2
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, uterus																										1
Squamous cell carcinoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 2,100 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 4 2	4 4 3	4 4 4	4 1 0	4 1 9	4 2 0	4 3 0	4 3 1	4 3 4	4 3 5	4 3 9	4 0 1	4 0 2	4 0 5	4 0 8	4 1 1	4 1 3	4 1 5	4 1 8	4 2 2	4 2 5	4 2 7	4 3 6	4 4 7	4 4 9	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland						+												+								5
Adenoma						X												X								3
Carcinoma																										2
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uterus																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant				X		X																				8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 7 8	4 8 8	4 9 6	4 5 1	4 5 4	4 6 7	4 6 8	4 7 4	4 7 9	4 8 1	4 9 2	4 9 5	4 5 3	4 5 8	4 6 0	4 6 2	4 6 5	4 7 0	4 7 6	4 7 7	4 8 0	4 8 5	4 8 7	4 9 0	4 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+																									1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																								X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma																									X	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Granulosa cell tumor benign																									X	1
Hemangiosarcoma																	X									1
Luteoma																					X					1
Oviduct			+										+			+										4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																								X		1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	2 2 6	3 7 9	5 6 8	5 8 7	6 2 7	6 8 0	7 2 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	4 4 9 4	4 8 3	4 6 9	4 5 5	4 8 4	4 6 6	4 9 1	4 5 2	4 5 9	4 6 1	4 7 1	4 7 2	4 8 2	4 8 6	4 8 9	4 9 3	4 9 8	4 9 9	5 0 0	4 5 6	4 5 7	4 6 3	4 6 4	4 7 3	4 7 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+			+	+									+					+			
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve					+																				
Spinal cord					+																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant			X	X			X	X									X			X		X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde: 4,100 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 7 8	4 8 8	4 9 6	4 5 1	4 5 4	4 6 7	4 6 8	4 7 4	4 7 9	4 8 1	4 9 2	4 9 5	4 5 3	4 5 8	4 6 0	4 6 2	4 6 5	4 7 0	4 7 6	4 7 7	4 8 0	4 8 5	4 8 7	4 9 0	4 9 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node												+								+						7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			1
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, schwannoma malignant																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X			X						X				X				X			X	X		14

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Harderian Gland: Adenoma					
Overall rate[a]	1/50 (2%)	1/50 (2%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate[b]	2.1%	2.2%	6.6%	6.3%	0.0%
Terminal rate[c]	1/43 (2%)	1/41 (2%)	2/37 (5%)	3/44 (7%)	0/43 (0%)
First incidence (days)	733 (T)	733 (T)	628	733 (T)	—[e]
Poly-3 test[d]		P=0.273N	P=0.303	P=0.319	P=0.498N
Harderian Gland: Adenoma or Carcinoma					
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)	0/50 (0%)
Adjusted rate	4.3%	2.2%	8.7%	10.5%	0.0%
Terminal rate	2/43 (5%)	1/41 (2%)	3/37 (8%)	5/44 (11%)	0/43 (0%)
First incidence (days)	733 (T)	733 (T)	628	733 (T)	—
Poly-3 test		P=0.282N	P=0.177	P=0.110	P=0.498N
Liver: Hepatocellular Adenoma					
Overall rate	4/50 (8%)	3/49 (6%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.5%	6.6%	8.8%	4.2%	2.2%
Terminal rate	4/43 (9%)	3/41 (7%)	3/37 (8%)	2/44 (5%)	1/43 (2%)
First incidence (days)	733 (T)	733 (T)	708	733 (T)	733 (T)
Poly-3 test		P=0.153N	P=0.504	P=0.475N	P=0.295N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	4/50 (8%)	5/49 (10%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.5%	11.1%	8.8%	4.2%	2.2%
Terminal rate	4/43 (9%)	5/41 (12%)	3/37 (8%)	2/44 (5%)	1/43 (2%)
First incidence (days)	733 (T)	733 (T)	708	733 (T)	733 (T)
Poly-3 test		P=0.048N	P=0.496N	P=0.194N	P=0.095N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.4%	4.3%	6.6%	2.1%	2.1%
Terminal rate	3/43 (7%)	2/41 (5%)	2/37 (5%)	0/44 (0%)	0/43 (0%)
First incidence (days)	733 (T)	733 (T)	728	568	680
Poly-3 test		P=0.272N	P=0.494	P=0.483N	P=0.495N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	5/48 (10%)	6/49 (12%)	1/50 (2%)	4/49 (8%)	2/50 (4%)
Adjusted rate	10.9%	13.3%	2.2%	8.6%	4.3%
Terminal rate	4/42 (10%)	5/41 (12%)	0/37 (0%)	4/43 (9%)	2/43 (5%)
First incidence (days)	652	698	575	733 (T)	733 (T)
Poly-3 test		P=0.168N	P=0.053N	P=0.348N	P=0.124N
Skin (Subcutaneous Tissue): Fibrosarcoma					
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	4.3%	4.3%	6.6%	0.0%	0.0%
Terminal rate	2/43 (5%)	2/41 (5%)	2/37 (5%)	0/44 (0%)	0/43 (0%)
First incidence (days)	733 (T)	733 (T)	668	—	—
Poly-3 test		P=0.070N	P=0.496	P=0.229N	P=0.235N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Stomach (Forestomach): Squamous Cell Papilloma					
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.1%	0.0%	0.0%	6.3%	0.0%
Terminal rate	1/43 (2%)	0/41 (0%)	0/37 (0%)	3/44 (7%)	0/43 (0%)
First incidence (days)	733 (T)	—	—[f]	733 (T)	—
Poly-3 test		P=0.547	—	P=0.126	—
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma					
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	2.1%	0.0%	0.0%	8.4%	0.0%
Terminal rate	1/43 (2%)	0/41 (0%)	0/37 (0%)	4/44 (9%)	0/43 (0%)
First incidence (days)	733 (T)	—	—	733 (T)	—
Poly-3 test		P=0.508	—	P=0.065	—
All Organs: Hemangiosarcoma					
Overall rate	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	2.2%	0.0%	6.3%	4.3%
Terminal rate	0/43 (0%)	0/41 (0%)	0/37 (0%)	3/44 (7%)	2/43 (5%)
First incidence (days)	—	698	—	733 (T)	733 (T)
Poly-3 test		P=0.248	P=0.503N	P=0.318	P=0.503
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.3%	6.5%	2.2%	6.3%	4.3%
Terminal rate	2/43 (5%)	2/41 (5%)	1/37 (3%)	3/44 (7%)	2/43 (5%)
First incidence (days)	733 (T)	698	733 (T)	733 (T)	733 (T)
Poly-3 test		P=0.514N	P=0.311N	P=0.646N	P=0.497N
All Organs: Malignant Lymphoma					
Overall rate	13/50 (26%)	10/50 (20%)	6/50 (12%)	8/50 (16%)	14/50 (28%)
Adjusted rate	27.6%	21.5%	13.2%	16.3%	29.4%
Terminal rate	13/43 (30%)	8/41 (20%)	5/37 (14%)	5/44 (11%)	11/43 (26%)
First incidence (days)	733 (T)	609	723	425	568
Poly-3 test		P=0.115	P=0.219N	P=0.349N	P=0.260
All Organs: Benign Neoplasms					
Overall rate	17/50 (34%)	15/50 (30%)	10/50 (20%)	14/50 (28%)	7/50 (14%)
Adjusted rate	35.8%	32.2%	21.3%	29.3%	15.0%
Terminal rate	15/43 (35%)	13/41 (32%)	6/37 (16%)	14/44 (32%)	7/43 (16%)
First incidence (days)	652	614	558	733 (T)	733 (T)
Poly-3 test		P=0.061N	P=0.169N	P=0.467N	P=0.042N
All Organs: Malignant Neoplasms					
Overall rate	24/50 (48%)	22/50 (44%)	13/50 (26%)	16/50 (32%)	16/50 (32%)
Adjusted rate	49.1%	45.4%	27.9%	32.0%	33.5%
Terminal rate	20/43 (47%)	15/41 (37%)	8/37 (22%)	10/44 (23%)	12/43 (28%)
First incidence (days)	429	456	558	425	568
Poly-3 test		P=0.222N	P=0.058N	P=0.124N	P=0.163N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
All Organs: Benign or Malignant Neoplasms					
Overall rate	33/50 (66%)	29/50 (58%)	21/50 (42%)	24/50 (48%)	21/50 (42%)
Adjusted rate	66.9%	59.8%	44.4%	48.0%	43.9%
Terminal rate	27/43 (63%)	22/41 (54%)	14/37 (38%)	18/44 (41%)	17/43 (40%)
First incidence (days)	429	456	558	425	568
Poly-3 test		P=0.117N	P=0.095N	P=0.166N	P=0.087N

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	2	3	4	1	4
Natural deaths	5	6	9	5	3
Survivors					
Died last week of study	1		1		
Terminal sacrifice	42	41	36	44	43
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(50)	(50)
Hyperkeratosis	2 (4%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Gallbladder	(50)	(50)	(50)	(50)	(50)
Cyst	1 (2%)				
Inflammation	3 (6%)	6 (12%)	5 (10%)	5 (10%)	3 (6%)
Intestine small, duodenum	(50)	(49)	(50)	(50)	(50)
Necrosis		1 (2%)			
Regeneration		1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Ulcer	1 (2%)				
Epithelium, atrophy		1 (2%)			
Peyer's patch, hyperplasia			1 (2%)		
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)				
Inflammation	1 (2%)				
Necrosis		1 (2%)			
Liver	(50)	(49)	(50)	(50)	(50)
Angiectasis				1 (2%)	
Atrophy	1 (2%)				
Basophilic focus	1 (2%)				
Clear cell focus	1 (2%)	4 (8%)	2 (4%)	1 (2%)	
Eosinophilic focus	3 (6%)	1 (2%)	2 (4%)		
Fatty change	5 (10%)	4 (8%)	8 (16%)	4 (8%)	7 (14%)
Hematopoietic cell proliferation	4 (8%)	6 (12%)	3 (6%)	2 (4%)	5 (10%)
Infiltration cellular, lymphocyte		1 (2%)		1 (2%)	
Inflammation	39 (78%)	42 (86%)	36 (72%)	38 (76%)	41 (82%)
Mixed cell focus	2 (4%)	1 (2%)	3 (6%)		
Necrosis	6 (12%)	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Pigmentation	2 (4%)	3 (6%)	4 (8%)	2 (4%)	4 (8%)
Vacuolization cytoplasmic	1 (2%)	1 (2%)	2 (4%)		1 (2%)
Portal, infiltration cellular, lymphocyte	26 (52%)	32 (65%)	25 (50%)	31 (62%)	26 (52%)
Mesentery	(3)	(4)	(5)	(4)	(1)
Inflammation		1 (25%)			
Fat, mineralization			2 (40%)		1 (100%)
Fat, necrosis		3 (75%)	2 (40%)	1 (25%)	1 (100%)
Pancreas	(50)	(50)	(50)	(50)	(50)
Cyst	1 (2%)			1 (2%)	1 (2%)
Inflammation	21 (42%)	25 (50%)	16 (32%)	24 (48%)	18 (36%)

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Alimentary System (continued)					
Salivary glands	(48)	(50)	(48)	(49)	(50)
Atrophy					1 (2%)
Inflammation	25 (52%)	32 (64%)	27 (56%)	27 (55%)	27 (54%)
Mineralization					1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Hyperkeratosis	3 (6%)	1 (2%)	1 (2%)	2 (4%)	
Hyperplasia			1 (2%)	1 (2%)	
Inflammation			1 (2%)		
Ulcer	1 (2%)				2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Inflammation					1 (2%)
Mineralization	1 (2%)	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Tooth		(2)		(1)	(1)
Malformation		1 (50%)		1 (100%)	1 (100%)
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Aorta, inflammation	1 (2%)			1 (2%)	1 (2%)
Heart	(49)	(50)	(50)	(50)	(50)
Cardiomyopathy		1 (2%)	1 (2%)		2 (4%)
Inflammation	1 (2%)	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Mineralization	1 (2%)	1 (2%)		1 (2%)	1 (2%)
Artery, inflammation		1 (2%)			2 (4%)
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	2 (4%)	1 (2%)			
Hyperplasia	2 (4%)	2 (4%)	6 (12%)	2 (4%)	2 (4%)
Hypertrophy	4 (8%)	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Pigmentation	32 (64%)	34 (68%)	26 (52%)	32 (64%)	29 (58%)
Vacuolization cytoplasmic	36 (72%)	34 (68%)	31 (62%)	37 (74%)	33 (66%)
Subcapsular, hyperplasia	50 (100%)	49 (98%)	50 (100%)	50 (100%)	49 (98%)
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	1 (2%)	3 (6%)	2 (4%)	
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	3 (6%)	4 (8%)		2 (4%)
Parathyroid gland	(41)	(44)	(40)	(41)	(44)
Cyst		1 (2%)			
Pituitary gland	(48)	(49)	(50)	(49)	(50)
Angiectasis	1 (2%)				
Cyst	1 (2%)		1 (2%)	2 (4%)	
Inflammation					1 (2%)
Pars distalis, hyperplasia	5 (10%)	5 (10%)	6 (12%)	2 (4%)	4 (8%)
Thyroid gland	(48)	(50)	(49)	(50)	(50)
Inflammation		2 (4%)			
Follicle, cyst	7 (15%)	3 (6%)	4 (8%)	10 (20%)	4 (8%)
Follicular cell, hyperplasia					1 (2%)
General Body System					
None					

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Genital System					
Clitoral gland	(50)	(49)	(50)	(49)	(50)
Cyst		1 (2%)			
Inflammation	32 (64%)	35 (71%)	30 (60%)	36 (73%)	33 (66%)
Inflammation, suppurative	1 (2%)				
Ovary	(50)	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)		1 (2%)		1 (2%)
Cyst	13 (26%)	9 (18%)	8 (16%)	11 (22%)	11 (22%)
Cyst, multiple		1 (2%)			
Inflammation	1 (2%)			1 (2%)	
Inflammation, suppurative			1 (2%)		
Mineralization	1 (2%)	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Oviduct	(1)	(1)	(2)	(3)	(4)
Inflammation		1 (100%)			1 (25%)
Uterus	(50)	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)		1 (2%)
Hydrometra	1 (2%)			1 (2%)	
Inflammation	1 (2%)	7 (14%)	3 (6%)	2 (4%)	6 (12%)
Ulcer		1 (2%)			
Endometrium, hyperplasia, cystic	43 (86%)	42 (84%)	46 (92%)	41 (82%)	48 (96%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Hyperplasia	11 (22%)	10 (20%)	10 (20%)	12 (24%)	12 (24%)
Infiltration cellular, lymphocyte	1 (2%)				
Lymph node	(7)	(5)	(7)	(10)	(7)
Lumbar, infiltration cellular, plasma cell	1 (14%)				
Renal, ectasia	1 (14%)				
Lymph node, mandibular	(46)	(47)	(45)	(49)	(47)
Atrophy	2 (4%)				
Hemorrhage	1 (2%)				
Hyperplasia			1 (2%)		1 (2%)
Lymph node, mesenteric	(49)	(49)	(50)	(49)	(50)
Angiectasis			1 (2%)		
Atrophy		1 (2%)			
Ectasia	1 (2%)				
Hemorrhage				1 (2%)	
Hyperplasia				1 (2%)	
Infiltration cellular, plasma cell				1 (2%)	
Inflammation			1 (2%)		
Spleen	(48)	(49)	(50)	(50)	(50)
Hematopoietic cell proliferation	11 (23%)	16 (33%)	15 (30%)	9 (18%)	11 (22%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)		
Infiltration cellular, plasma cell			1 (2%)		
Pigmentation			1 (2%)		
Lymphoid follicle, atrophy			2 (4%)	2 (4%)	
Lymphoid follicle, hyperplasia	2 (4%)	4 (8%)	1 (2%)		4 (8%)
Thymus	(46)	(47)	(46)	(47)	(47)
Atrophy	5 (11%)	2 (4%)	3 (7%)	2 (4%)	1 (2%)
Hyperplasia				1 (2%)	
Inflammation	1 (2%)				

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)				1 (2%)
Inflammation				1 (2%)	
Duct, dilatation			1 (2%)	1 (2%)	1 (2%)
Skin	(50)	(50)	(50)	(50)	(50)
Hyperkeratosis					1 (2%)
Subcutaneous tissue, inflammation	1 (2%)				
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Myelofibrosis	24 (48%)	27 (54%)	23 (46%)	34 (68%)	38 (76%)
Nervous System					
Brain	(49)	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocyte					1 (2%)
Choroid plexus, infiltration cellular, lymphocyte			1 (2%)		
Choroid plexus, inflammation					1 (2%)
Medulla, degeneration					1 (2%)
Meninges, infiltration cellular, lymphocyte		1 (2%)		1 (2%)	
Meninges, inflammation	2 (4%)				
Spinal cord					(1)
Degeneration					1 (100%)
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocyte	1 (2%)			1 (2%)	
Inflammation		1 (2%)		3 (6%)	
Inflammation, granulomatous	1 (2%)				
Metaplasia, osseous	1 (2%)				
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)		2 (4%)	1 (2%)
Perivascular, infiltration cellular, mononuclear cell			1 (2%)		1 (2%)
Nose	(49)	(50)	(50)	(50)	(50)
Foreign body	1 (2%)	1 (2%)			
Inflammation	2 (4%)	5 (10%)	3 (6%)	4 (8%)	2 (4%)
Glands, inflammation, focal, granulomatous		1 (2%)			
Nasolacrimal duct, inflammation	2 (4%)	1 (2%)			
Olfactory epithelium, degeneration, hyaline	17 (35%)	23 (46%)	25 (50%)	22 (44%)	
Olfactory epithelium, pigmentation				8 (16%)	46 (92%)
Trachea	(48)	(50)	(49)	(50)	(50)
Inflammation					1 (2%)
Special Senses System					
Eye			(1)	(1)	
Cornea, hyperplasia			1 (100%)		
Cornea, inflammation			1 (100%)	1 (100%)	
Harderian gland	(2)	(1)	(4)	(5)	
Inflammation	2 (100%)		1 (25%)	2 (40%)	
Lacrimal gland				(1)	
Inflammation				1 (100%)	

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Atrophy				1 (2%)	1 (2%)
Cyst					1 (2%)
Hydronephrosis	1 (2%)	1 (2%)		1 (2%)	
Infarct	1 (2%)	1 (2%)			2 (4%)
Infiltration cellular, lymphocyte	37 (74%)	44 (88%)	39 (78%)	42 (84%)	37 (74%)
Inflammation	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous		1 (2%)	1 (2%)	3 (6%)	1 (2%)
Mineralization	4 (8%)	4 (8%)	1 (2%)	2 (4%)	6 (12%)
Necrosis	1 (2%)				
Nephropathy	7 (14%)	11 (22%)	4 (8%)	12 (24%)	8 (16%)
Artery, inflammation					1 (2%)
Papilla, necrosis				1 (2%)	
Renal tubule, dilatation	24 (48%)	25 (50%)	30 (60%)	22 (44%)	32 (64%)
Urinary bladder	(50)	(50)	(50)	(50)	(50)
Inflammation	34 (68%)	33 (66%)	39 (78%)	33 (66%)	33 (66%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986) and Dillon *et al.* (1998). *trans*-Cinnamaldehyde 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, TA102, TA104, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat, Syrian hamster, or B6C3F$_1$ mouse 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 *trans*-cinnamaldehyde. The high dose was limited by toxicity. All trials were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). *trans*-Cinnamaldehyde 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 *trans*-cinnamaldehyde; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 25.5 hours with *trans*-cinnamaldehyde in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 25.5 hours, the medium containing *trans*-cinnamaldehyde 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 *trans*-cinnamaldehyde, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no *trans*-cinnamaldehyde. Incubation proceeded for an additional 25.5 to 28.8 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen in the third trial without S9 at 11.91 µg/mL, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells; however, this dose of *trans*-cinnamaldehyde was cytostatic.

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 ($P<0.005$) 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 *trans*-cinnamaldehyde for 8.5 to 9 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 *trans*-cinnamaldehyde and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 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. One 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 ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted 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.

DROSOPHILA MELANOGASTER TEST PROTOCOLS

The assays for induction of sex-linked recessive lethal (SLRL) mutations and chromosomal reciprocal translocations (RTs) were performed with adult flies as described by Woodruff *et al.* (1985). *trans*-Cinnamaldehyde was supplied as a coded aliquot by Radian Corporation.

Sex-Linked Recessive Lethal Mutation Test: *trans*-Cinnamaldehyde was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, *trans*-cinnamaldehyde was retested by injection into adult males.

To administer *trans*-cinnamaldehyde by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament, and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 µL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector that automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of *trans*-cinnamaldehyde at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on a 5% sucrose solution of *trans*-cinnamaldehyde dissolved in 40% ethanol. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of *trans*-cinnamaldehyde dissolved in 40% ethanol/0.7% saline and allowed to recover for 24 hours. A concurrent ethanol/saline control group was also included. Treated males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings was treated at successively earlier postmeiotic stages). F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental

male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. One cluster was removed from the feeding experiment. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls (Mason *et al.,* 1992) using a normal approximation to the binomial test (Margolin *et al.,* 1983). A test result was considered positive if the P value was less than or equal to 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or if the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

Reciprocal Translocation Test: Because the injection route produced a positive result in the SLRL test, *trans*-cinnamaldehyde was assayed for induction of RTs using the same exposure method. The treatment regimen was essentially the same as that for the SLRL test, except that Canton-S males were mated *en masse* to marker (*bw;st*) females. The females were transferred to fresh medium every 3 to 4 days for a period of about 3 weeks to produce a total of six broods. The results of the SLRL test were used to determine the germ cell stages most likely to be affected by *trans*-cinnamaldehyde. F_1 heterozygous males were backcrossed individually to *bw;st* females, and the F_2 progeny were screened for pseudolinkage, which results from the induction of a translocation in a germ cell of the parental male. Flies suspected of carrying reciprocal translocations were retested to confirm the findings. The translocation data were compared to the concurrent and historical controls, and significance was analyzed according to the conditional binomial response of Kastenbaum and Bowman (1970).

Mouse Peripheral Blood Micronucleus Test Protocol

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

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single exposed group is less than or equal to 0.025 divided by the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results of the 3-month study were accepted without repeat tests, because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

Evaluation Protocol

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

Results

trans-Cinnamaldehyde (1 to 333 µg/plate) was mutagenic in *S. typhimurium* strain TA100 in the presence of induced mouse liver S9 activation enzymes; no mutagenicity was seen in this strain with induced rat or hamster liver S9 enzymes or without activation (Table E1; Mortelmans *et al.*, 1986; Dillon *et al.*, 1998). Mutagenicity tests in all other strains (TA98, TA102, TA104, TA1535, TA1537), with or without mouse, hamster, or rat liver S9, yielded negative results. *trans*-Cinnamaldehyde induced SCEs in CHO cells, with and without induced rat liver S9 activation (Table E2; Galloway *et al.*, 1987). No significant increase in the frequency of Abs occurred in CHO cells cultured with *trans*-cinnamaldehyde, with or without induced rat liver S9 (Table E3; Galloway *et al.*, 1987). In tests for induction of germ cell genetic damage in male *D. melanogaster*, *trans*-cinnamaldehyde induced a significant increase in the frequency of SLRL mutations when administered by abdominal injection (Table E4; Woodruff *et al.*, 1985); however, no induction of reciprocal translocations occurred in germ cells of injected males (Table E5; Woodruff *et al.*, 1985). Dietary concentrations of 4,100 to 33,000 ppm *trans*-cinnamaldehyde administered by feeding for 3 months did not increase the frequency of micronucleated normochromatic erythrocytes in the peripheral blood of male or female B6C3F_1 mice (Table E6).

TABLE E1
Mutagenicity of *trans*-Cinnamaldehyde in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b]					
		–S9		+10% hamster S9		+10% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
Study performed at Case Western Reserve University							
TA100	0.0	130 ± 9.9	140 ± 6.7	157 ± 4.2	157 ± 7.5	179 ± 31.0	154 ± 19.9
	1.0		140 ± 9.3		178 ± 4.7		127 ± 4.0
	3.3	133 ± 8.2	136 ± 4.6	180 ± 0.7	178 ± 2.2	171 ± 19.4	132 ± 8.1
	10.0	127 ± 7.9	132 ± 2.3	210 ± 9.0	170 ± 20.0	144 ± 5.3	112 ± 14.0
	33.0	99 ± 3.3	114 ± 14.8	144 ± 3.2	137 ± 5.5	132 ± 10.8	111 ± 15.6
	100.0	102 ± 7.9	99 ± 10.7	158 ± 8.7	156 ± 10.4	143 ± 4.6	105 ± 15.2
	333.0	2 ± 0.9		14 ± 3.5		121 ± 3.8	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		745 ± 9.9	776 ± 27.8	1,634 ± 39.3	2,122 ± 27.4	1,236 ± 19.6	940 ± 117.9
TA1535	0.0	10 ± 1.3	7 ± 1.5	12 ± 1.7	10 ± 1.5	10 ± 1.2	7 ± 1.8
	1.0		6 ± 0.6		7 ± 1.5		6 ± 0.0
	3.3	7 ± 1.8	6 ± 1.3	10 ± 0.7	9 ± 0.3	10 ± 0.6	11 ± 1.9
	10.0	5 ± 0.0	5 ± 0.6	10 ± 0.9	6 ± 1.2	11 ± 1.7	10 ± 1.5
	33.0	10 ± 0.7	5 ± 1.7	12 ± 2.1	8 ± 1.5	7 ± 1.5	5 ± 0.5
	100.0	8 ± 1.2	5 ± 0.7	11 ± 1.3	10 ± 0.6	8 ± 0.0	6 ± 0.6
	333.0	4 ± 0.6		4 ± 0.7		11 ± 3.5	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		728 ± 9.6	703 ± 23.9	111 ± 7.5	108 ± 3.4	106 ± 5.6	48 ± 2.6
TA1537	0.0	7 ± 0.7	8 ± 0.9	10 ± 0.3	12 ± 1.0	11 ± 0.7	12 ± 1.2
	1.0		9 ± 2.0		13 ± 0.0		10 ± 2.4
	3.3	8 ± 0.7	9 ± 1.0	9 ± 2.0	10 ± 0.7	11 ± 1.8	13 ± 2.3
	10.0	6 ± 0.3	9 ± 2.2	11 ± 0.9	10 ± 1.8	12 ± 0.9	13 ± 1.5
	33.0	7 ± 0.7	7 ± 1.3	13 ± 2.9	10 ± 3.5	10 ± 0.3	9 ± 1.0
	100.0	10 ± 0.6	8 ± 2.3	8 ± 0.0	9 ± 0.6	8 ± 1.2	8 ± 0.9
	333.0	4 ± 1.5		8 ± 2.9		12 ± 3.5	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		534 ± 6.7	483 ± 60.0	108 ± 14.6	112 ± 12.0	79 ± 8.8	52 ± 2.5
TA98	0.0	15 ± 3.2	17 ± 1.0	25 ± 1.5	24 ± 1.0	19 ± 3.2	21 ± 1.0
	1.0		19 ± 1.9		20 ± 3.1		26 ± 2.2
	3.3	15 ± 1.7	19 ± 3.3	23 ± 1.5	23 ± 1.5	29 ± 0.9	26 ± 4.3
	10.0	13 ± 2.3	14 ± 1.3	31 ± 1.0	27 ± 4.3	20 ± 2.3	26 ± 3.0
	33.0	10 ± 2.6	16 ± 2.4	22 ± 2.3	20 ± 2.9	15 ± 0.5	19 ± 0.9
	100.0	23 ± 3.8	21 ± 4.2	23 ± 0.9	22 ± 1.5	17 ± 1.2	21 ± 2.0
	333.0	7 ± 2.0		11 ± 0.6		9 ± 2.9	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		614 ± 31.9	787 ± 55.6	1,101 ± 57.6	1,518 ± 15.0	962 ± 12.8	1,096 ± 31.6

TABLE E1
Mutagenicity of *trans*-Cinnamaldehyde in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate –S9 Trial 1	–S9 Trial 2	+10% mouse S9 Trial 1	+10% mouse S9 Trial 2	+10% mouse S9 Trial 3	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at Inveresk Research International								
TA102	0.0	273 ± 27.2	261 ± 14.6	285 ± 30.1	241 ± 9.8	321 ± 1.5	287 ± 2.7	315 ± 26.7
	25.0	291 ± 18.9	250 ± 5.5	305 ± 15.1	244 ± 7.9	296 ± 23.7	267 ± 30.1	347 ± 15.9
	50.0	301 ± 15.3	225 ± 5.5	348 ± 3.8	245 ± 22.6	297 ± 20.1	253 ± 27.4	321 ± 16.9
	100.0	248 ± 24.5	245 ± 2.3	264 ± 21.0	235 ± 8.0	265 ± 30.5	276 ± 23.3	308 ± 7.8
	200.0	231 ± 3.5[d]	203 ± 1.0[d]	273 ± 29.4	248 ± 4.1	296 ± 9.9	284 ± 8.5[d]	303 ± 23.5[d]
	300.0	180 ± 1.9[d]	203 ± 0.0[d]	294 ± 1.9[d]	228 ± 13.9	257 ± 32.1[d]	279 ± 9.8[d]	282 ± 15.1[d]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		942 ± 44.5	1,756 ± 20.7	405 ± 7.9	402 ± 0.6	751 ± 33.0	432 ± 6.4	851 ± 26.6
TA104	0.0	343 ± 23.3	365 ± 27.6	494 ± 20.9	433 ± 16.6		482 ± 21.7	459 ± 2.5
	25.0	336 ± 8.0	366 ± 8.0	476 ± 63.4	402 ± 34.6		524 ± 12.2	484 ± 13.4
	50.0	329 ± 13.6	362 ± 14.0	505 ± 16.3	448 ± 22.6		528 ± 11.3	480 ± 8.2
	100.0	281 ± 4.7	332 ± 17.2	479 ± 8.4	432 ± 28.2		475 ± 23.4	478 ± 12.3
	200.0	313 ± 14.4	348 ± 3.8[d]	490 ± 23.0[d]	407 ± 5.7[d]		453 ± 25.8[d]	457 ± 11.9[d]
	300.0	324 ± 10.0	243 ± 3.8[d]	419 ± 6.1[d]	362 ± 12.7[d]		473 ± 3.8[d]	432 ± 18.1[d]
Trial summary		Negative	Negative	Negative	Negative		Negative	Negative
Positive control		721 ± 26.3	820 ± 12.7	1,447 ± 75.6	1,216 ± 97.6		1,094 ± 18.8	1,007 ± 43.8

		–S9 Trial 1	–S9 Trial 2	–S9 Trial 3	+10% mouse S9 Trial 1	+10% mouse S9 Trial 2	+10% mouse S9 Trial 3	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0.0	75 ± 8.4	86 ± 4.5	111 ± 4.9	92 ± 8.8	93 ± 0.9	102 ± 8.4	92 ± 2.5	107 ± 4.0
	25.0	79 ± 1.8	79 ± 0.3	106 ± 7.5	83 ± 7.3	82 ± 1.7	100 ± 4.1	104 ± 2.0	105 ± 3.2
	50.0	76 ± 3.3	70 ± 0.3	108 ± 1.9	95 ± 5.8	108 ± 4.4	91 ± 4.4	80 ± 7.8	99 ± 4.2
	100.0	79 ± 5.4	78 ± 2.3	100 ± 4.4	112 ± 5.5	120 ± 8.1	123 ± 2.0	106 ± 9.5	98 ± 7.0
	200.0	82 ± 0.9	81 ± 9.7	105 ± 5.5	168 ± 6.1	127 ± 10.1	127 ± 2.1	116 ± 4.0	112 ± 3.1
	300.0	79 ± 1.5	101 ± 1.2	118 ± 2.6	162 ± 4.7	180 ± 16.6	158 ± 4.2	110 ± 4.3	126 ± 4.1
Trial summary		Negative	Negative	Negative	Weakly Positive	Weakly Positive	Equivocal	Negative	Negative
Positive control		164 ± 11.5[e]	288 ± 4.7	346 ± 12.0	493 ± 43.6	1,010 ± 52.9	1,235 ± 89.8	427 ± 15.4	679 ± 28.9

[a] The detailed protocol and the data from the Case Western Reserve University study are presented by Mortelmans *et al.* (1986); the detailed protocol and the data from the Inveresk Research International study are presented by Dillon *et al.* (1998). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), 4-nitro-*o*-phenylenediamine (TA98), mitomycin-C (TA102), and methyl methanesulfonate (TA104). The positive control for metabolic activation with all strains was 2-aminoanthracene, and 2-aminoanthracine or sterigmatocystin was used for TA102.
[d] Slight toxicity
[e] Slight toxicity and precipitation on plate

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *trans*-Cinnamaldehyde[a]

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
–S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide[c]		50	1,047	398	0.38	8.0	25.5	
trans-Cinnamaldehyde	0.34	50	1,051	530	0.50	10.6	25.5	32.66*
	1.02	50	1,050	697	0.66	13.9	25.5	74.62*
	3.4	Toxic					25.5	
					P<0.001[d]			
Mitomycin-C[e]	0.005	50	1,048	1,261	1.20	25.2	25.5	216.53
Trial 2								
Summary: Negative								
Dimethylsulfoxide		50	1,048	388	0.37	7.8	25.5	
trans-Cinnamaldehyde	2.04	50	1,050	450	0.42	9.0	25.5	15.76
	2.55	50	1,044	420	0.40	8.4	25.5	8.66
	3.06	50	1,047	452	0.43	9.0	25.5	16.61
					P=0.039			
Mitomycin-C	0.01	50	1,050	1,682	1.60	33.6	25.5	332.69
Trial 3								
Summary: Weakly Positive								
Dimethylsulfoxide		50	1,041	484	0.46	9.7	25.5	
trans-Cinnamaldehyde	3.4	50	1,036	528	0.50	10.6	25.5	9.62
	5.1	50	1,025	515	0.50	10.3	25.5	8.07
	6.8	50	1,039	657	0.63	13.1	25.5[f]	36.01*
	11.91	Toxic					31.3	
					P<0.001			
Mitomycin-C	0.005	50	1,046	1,597	1.52	31.9	25.5	228.38

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *trans*-Cinnamaldehyde

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9								
Trial 1								
Summary: Weakly Positive								
Dimethylsulfoxide		50	1,015	419	0.41	8.4	25.5	
trans-Cinnamaldehyde	3.4	50	1,029	427	0.41	8.5	25.5	0.52
	10.2	50	1,033	428	0.41	8.6	25.5	0.37
	34.0	50	1,025	565	0.55	11.3	25.5	33.53*
					P<0.001			
Cyclophosphamide[e]	1.5	50	1,032	1,514	1.46	30.3	25.5	255.39
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,028	443	0.43	8.9	25.5	
trans-Cinnamaldehyde	71.4	50	1,027	447	0.43	8.9	25.5	1.00
	81.6	50	1,028	551	0.53	11.0	25.5	24.38*
	91.8	50	1,033	624	0.60	12.5	28.8	40.18*
					P<0.001			
Cyclophosphamide	1.50	50	1,044	1,753	1.67	35.1	25.5	289.65

* Positive response (≥20% increase over solvent control)
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol and these data are presented by Galloway *et al.* (1987).
[b] SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[c] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[d] Solvent control
[e] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose
[f] Positive control
Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis; however, this concentration was cytostatic.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *trans*-Cinnamaldehyde[a]

Compound	Dose (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
–S9					
Trial 1					
Harvest time: 10.5 hours					
Summary: Weakly Positive					
Dimethylsulfoxide[b]		100	0	0.00	0.0
trans-Cinnamaldehyde	6.02	100	1	0.01	1.0
	7.96	100	4	0.04	4.0
	10.21	18	1	0.06	5.0*
					P=0.010[c]
Triethylenemelamine[d]	0.75	100	24	0.24	19.0
Trial 2					
Harvest time: 11.0 hours					
Summary: Negative					
Dimethylsulfoxide		100	3	0.03	1.0
trans-Cinnamaldehyde	6.4	100	3	0.03	3.0
	12.8	100	2	0.02	2.0
	18.3	100	3	0.03	3.0
					P=0.241
Triethylenemelamine	0.75	100	31	0.31	23.0
+S9					
Trial 1					
Harvest time: 10.5 hours					
Summary: Negative					
Dimethylsulfoxide		100	2	0.02	2.0
trans-Cinnamaldehyde	50.2	100	2	0.02	2.0
	74.8	100	2	0.02	2.0
	100.3	32	0	0.00	0.0
					P=0.676
Cyclophosphamide[d]	25	100	44	0.44	27.0

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol and these data are presented by Galloway *et al.* (1987).
[b] Solvent control
[c] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose
[d] Positive control

TABLE E4
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by *trans*-Cinnamaldehyde[a]

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Feeding	800	25	0	3/3,261	1/2,240	1/1,725	5/7,226 (0.07%)
	0			3/4,277	2/2,558	2/2,026	7/8,861 (0.08%)
							P=0.500[c]
Injection	20,000	0	0	4/2,337	2/2,195	9/2,077	15/6,609 (0.23%)
	0[d]			1/2,193	0/2,028	4/1,775	5/5,996 (0.08%)
							P<0.001

[a] Study was performed at Bowling Green State University. The detailed protocol and these data are presented by Woodruff *et al.* (1985).
[b] The mean mutant frequency from 518 negative control experiments is 0.074% (Mason *et al.,* 1992).
[c] Total number of lethal mutations/total number of X chromosomes tested for three mating trials
[d] Significance of total number of lethal mutations/total number of X chromosomes tested by a normal approximation to the binomial test (Margolin *et al.,* 1983).
40% ethanol/0.7% saline

TABLE E5
Induction of Reciprocal Translocations in *Drosophila melanogaster* by *trans*-Cinnamaldehyde[a]

Route of Exposure	Dose (ppm)	Translocations/Total F_1 Tested					No. of Tests	Total No. of Translocations	Total Translocations (%)
		1	2	3	4	5			
Injection	20,000	0/969	0/1,062	0/1,063	0/1,081	0/945	5,120	0	0.00
	Concurrent control[b]						23,686	1	0.00
	Historical control						116,163	2	0.00

[a] Study was performed at Bowling Green State University. The detailed protocol and these data are presented by Woodruff *et al.* (1985).
[b] Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).
40% ethanol/0.7% saline

TABLE E6
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Administration of *trans*-Cinnamaldehyde in Feed for 3 Months[a]

Compound	Dose (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male					
Feed[d]		5	1.20 ± 0.25		2.1
trans-Cinnamaldehyde	4,100	5	0.70 ± 0.25	0.8744	1.9
	8,200	5	0.80 ± 0.44	0.8146	1.9
	16,500	5	1.30 ± 0.12	0.4207	2.0
	33,000	1	0.50[e]	0.8075	1.7
			P=0.296[f]		
Female					
Feed		5	0.70 ± 0.20		1.9
trans-Cinnamaldehyde	4,100	5	0.70 ± 0.20	0.5000	1.5
	8,200	5	1.00 ± 0.35	0.2333	1.8
	16,500	5	0.10 ± 0.10	0.9831	1.9
	33,000	5	0.70 ± 0.12	0.5000	1.4
			P=0.713		

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by MacGregor *et al.* (1990).
[b] NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control; significant at P≤0.006 (ILS, 1990)
[e] Vehicle control
[f] No standard error calculated due to high mortality; not included in trend test analysis
Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Male						
Hematology						
n						
Day 5	10	10	10	10	9	10
Week 3	10	10	10	10	10	10
Month 3	10	10	9	10	10	10
Hematocrit (%)						
Day 5	42.4 ± 0.8	43.9 ± 0.5	43.3 ± 0.7	45.1 ± 0.5	46.0 ± 0.6*	48.1 ± 0.4**
Week 3	47.2 ± 0.5	47.4 ± 0.6	48.2 ± 0.8	47.7 ± 0.5	47.9 ± 0.5	50.6 ± 0.9*
Month 3	48.5 ± 0.4	46.9 ± 0.2	47.0 ± 0.5	47.9 ± 0.4	48.8 ± 0.3**	48.7 ± 0.5**
Hemoglobin (g/dL)						
Day 5	13.9 ± 0.3	14.3 ± 0.2	14.2 ± 0.2	14.8 ± 0.1	15.1 ± 0.2**	15.6 ± 0.2**
Week 3	15.4 ± 0.2	15.5 ± 0.2	15.5 ± 0.2	15.5 ± 0.2	15.4 ± 0.2	16.3 ± 0.2
Month 3	16.1 ± 0.1	15.5 ± 0.1	15.6 ± 0.1	15.8 ± 0.1*	16.0 ± 0.1**	15.8 ± 0.1**
Erythrocytes (10^6/μL)						
Day 5	6.94 ± 0.12	7.25 ± 0.07	7.26 ± 0.14	7.52 ± 0.08*	7.73 ± 0.09**	8.05 ± 0.07**
Week 3	7.88 ± 0.06	7.90 ± 0.09	8.06 ± 0.13	7.97 ± 0.10	8.21 ± 0.08*	8.95 ± 0.16**
Month 3	9.14 ± 0.07	8.88 ± 0.06	8.92 ± 0.10	9.05 ± 0.07	9.15 ± 0.05*	9.07 ± 0.11
Reticulocytes (10^6/μL)						
Day 5	0.27 ± 0.02	0.22 ± 0.02	0.20 ± 0.01	0.15 ± 0.01*	0.10 ± 0.01**	0.10 ± 0.00**
Week 3	0.11 ± 0.01	0.12 ± 0.01	0.12 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.05 ± 0.01**
Month 3	0.09 ± 0.01	0.13 ± 0.01	0.10 ± 0.01*	0.10 ± 0.01*	0.10 ± 0.01*	0.10 ± 0.00**
Nucleated erythrocytes (10^3/μL)						
Day 5	0.01 ± 0.01	0.03 ± 0.02	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02
Week 3	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)						
Day 5	61.3 ± 0.4	60.6 ± 0.3	59.7 ± 0.4	60.0 ± 0.3	59.6 ± 0.3	59.7 ± 0.4
Week 3	60.5 ± 0.5	60.0 ± 0.3	59.9 ± 0.3	59.8 ± 0.3	58.3 ± 0.4**	56.5 ± 0.3**
Month 3	53.3 ± 0.3	52.9 ± 0.2	52.9 ± 0.2	52.8 ± 0.2	53.4 ± 0.2	53.8 ± 0.1**
Mean cell hemoglobin (pg)						
Day 5	20.0 ± 0.1	19.7 ± 0.2	19.6 ± 0.2	19.6 ± 0.1	19.5 ± 0.1	19.4 ± 0.2
Week 3	19.8 ± 0.1	19.6 ± 0.1	19.2 ± 0.1*	19.4 ± 0.1	18.7 ± 0.1**	18.2 ± 0.1**
Month 3	17.6 ± 0.1	17.4 ± 0.1	17.5 ± 0.1	17.5 ± 0.1	17.5 ± 0.1	17.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.7 ± 0.3	32.5 ± 0.2	32.8 ± 0.2	32.7 ± 0.1	32.8 ± 0.2	32.5 ± 0.2
Week 3	32.6 ± 0.2	32.7 ± 0.1	32.1 ± 0.3	32.4 ± 0.2	32.2 ± 0.3	32.3 ± 0.2
Month 3	33.1 ± 0.3	33.0 ± 0.2	33.1 ± 0.2	33.1 ± 0.1	32.9 ± 0.2	32.4 ± 0.1
Platelets (10^3/μL)						
Day 5	942.6 ± 14.0	957.0 ± 18.2	979.5 ± 12.8	962.4 ± 16.6	995.7 ± 24.9	1111.0 ± 24.0**
Week 3	766.6 ± 14.3	739.2 ± 7.6	753.5 ± 13.1	730.3 ± 10.3	724.1 ± 13.8	604.9 ± 15.5**
Month 3	647.1 ± 9.7	654.4 ± 8.5	633.3 ± 16.1	661.7 ± 5.1	616.5 ± 10.8	640.1 ±12.9
Leukocytes (10^3/μL)						
Day 5	8.55 ± 0.83	9.34 ± 0.77	9.87 ± 0.71	10.63 ± 0.60	11.37 ± 0.57	11.75 ± 0.97
Week 3	9.30 ± 0.48	9.84 ± 0.64	10.41 ± 0.41	9.47 ± 0.67	9.60 ± 0.56	12.19 ± 0.91
Month 3	13.25 ± 0.45	11.22 ± 0.73	11.83 ± 0.84	11.51 ± 0.56	11.63 ± 0.48	9.44 ± 0.46
Segmented neutrophils (10^3/μL)						
Day 5	1.03 ± 0.17	1.11 ± 0.12	1.10 ± 0.24	1.18 ± 0.20	1.25 ± 0.18	1.33 ± 0.14
Week 3	0.76 ± 0.06	0.94 ± 0.10	1.12 ± 0.09	1.25 ± 0.12*	1.43 ± 0.12**	2.54 ± 0.28**
Month 3	1.57 ± 0.18	1.62 ± 0.19	1.43 ± 0.15	1.87 ± 0.21	2.03 ± 0.18	2.79 ± 0.27**

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Male						
Hematology (continued)						
n						
Day 5	10	10	10	10	9	10
Week 3	10	10	10	10	10	10
Month 3	10	10	9	10	10	10
Bands (10^3/μL)						
Day 5	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)						
Day 5	7.34 ± 0.71	8.16 ± 0.69	8.65 ± 0.61	9.32 ± 0.49	9.91 ± 0.51	10.29 ± 0.92
Week 3	8.35 ± 0.47	8.73 ± 0.57	9.11 ± 0.36	8.01 ± 0.57	8.00 ± 0.54	9.40 ± 0.73
Month 3	11.34 ± 0.47	9.28 ± 0.76	10.17 ± 0.88	9.45 ± 0.52	9.39 ± 0.35	6.52 ± 0.39**
Monocytes (10^3/μL)						
Day 5	0.12 ± 0.03	0.06 ± 0.02	0.07 ± 0.03	0.11 ± 0.02	0.13 ± 0.03	0.11 ± 0.04
Week 3	0.13 ± 0.02	0.13 ± 0.03	0.13 ± 0.03	0.16 ± 0.04	0.09 ± 0.02	0.18 ± 0.04
Month 3	0.23 ± 0.06	0.18 ± 0.06	0.14 ± 0.04	0.10 ± 0.03	0.14 ± 0.04	0.11 ± 0.04
Basophils (10^3/μL)						
Day 5	0.00 ± 0.00	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 3	0.00 ± 0.00	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Month 3	0.00 ± 0.00	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)						
Day 5	0.06 ± 0.02	0.01 ± 0.01	0.05 ± 0.02	0.02 ± 0.01	0.08 ± 0.03	0.02 ± 0.01
Week 3	0.06 ± 0.02	0.05 ± 0.02	0.06 ± 0.03	0.05 ± 0.02	0.08 ± 0.03	0.08 ± 0.03
Month 3	0.11 ± 0.04	0.14 ± 0.05	0.09 ± 0.03	0.08 ± 0.03	0.07 ± 0.02	0.03 ± 0.02
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	11.7 ± 0.5	11.1 ± 0.6	12.0 ± 0.3	12.3 ± 0.5	11.6 ± 0.4	16.4 ± 0.7**
Week 3	17.6 ± 0.6	13.7 ± 0.4	13.2 ± 0.4	13.8 ± 0.4	15.6 ± 0.4*	19.3 ± 1.1**
Month 3	17.6 ± 0.5	14.6 ± 0.3	14.1 ± 0.2	14.5 ± 0.3	14.9 ± 0.4	17.4 ± 0.6**
Creatinine (mg/dL)						
Day 5	0.60 ± 0.00	0.60 ± 0.00	0.61 ± 0.01	0.61 ± 0.01	0.63 ± 0.02	0.60 ± 0.02
Week 3	0.62 ± 0.01	0.63 ± 0.02	0.62 ± 0.01	0.60 ± 0.00	0.61 ± 0.01	0.60 ± 0.00
Month 3	0.71 ± 0.01	0.71 ± 0.02	0.70 ± 0.00	0.70 ± 0.00	0.66 ± 0.02**	0.62 ± 0.02**
Total protein (g/dL)						
Day 5	5.9 ± 0.1	5.9 ± 0.1	5.7 ± 0.1	5.6 ± 0.1	5.6 ± 0.1	5.6 ± 0.1
Week 3	6.3 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.1 ± 0.1	6.1 ± 0.1	6.0 ± 0.1*
Month 3	6.9 ± 0.1	6.9 ± 0.0	7.0 ± 0.1	6.8 ± 0.1	6.7 ± 0.1*	6.2 ± 0.1**
Albumin (g/dL)						
Day 5	4.4 ± 0.1	4.4 ± 0.0	4.3 ± 0.1	4.2 ± 0.1	4.3 ± 0.1	4.3 ± 0.0
Week 3	4.6 ± 0.0	4.7 ± 0.0	4.7 ± 0.0	4.6 ± 0.0	4.6 ± 0.1	4.6 ± 0.1
Month 3	4.8 ± 0.0	4.8 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	4.9 ± 0.0	4.6 ± 0.1

TABLE F1
Hematology and Clinical Chemistry for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Male (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	10
Alanine aminotransferase (IU/L)						
Day 5	64 ± 2	68 ± 2	75 ± 2	69 ± 2	69 ± 2	58 ± 4
Week 3	73 ± 1	68 ± 2	71 ± 1	66 ± 1	74 ± 3	102 ± 6**
Month 3	109 ± 9	97 ± 6	83 ± 4	76 ± 2*	90 ± 3	111 ± 7
Alkaline phosphatase (IU/L)						
Day 5	1566 ± 22	1665 ± 45	1628 ± 36	1416 ± 42**	1216 ± 21**	1049 ± 20**
Week 3	1180 ± 18	1120 ± 16	1144 ± 23	1059 ± 30	921 ± 21**	626 ± 53**
Month 3	635 ± 14	565 ± 8	550 ± 27	545 ± 14	602 ± 12	494 ± 12*
Creatine kinase (IU/L)						
Day 5	373 ± 39	429 ± 61	480 ± 95	369 ± 38	590 ± 93	369 ± 52
Week 3	242 ± 27	260 ± 22	189 ± 12	259 ± 33	260 ± 29	312 ± 55
Month 3	204 ± 39	223 ± 36	241 ± 51	220 ± 29	293 ± 35	271 ± 43
Sorbitol dehydrogenase (IU/L)						
Day 5	22 ± 1	24 ± 1	20 ± 1	20 ± 1	23 ± 1	24 ± 2
Week 3	25 ± 1	23 ± 1	19 ± 1*	20 ± 1	21 ± 1	18 ± 1*
Month 3	36 ± 5	34 ± 2	28 ± 2	23 ± 0**	22 ± 1**	18 ± 2**
Bile acids (µmol/L)						
Day 5	21.2 ± 1.8	25.8 ± 2.3	36.1 ± 4.1*	37.7 ± 1.9**	54.9 ± 3.3**	58.6 ± 6.8**
Week 3	28.8 ± 2.4	31.4 ± 3.3	34.0 ± 3.4	36.6 ± 2.0	45.6 ± 4.7*	82.5 ± 11.2**
Month 3	21.3 ± 1.6	27.8 ± 3.1	35.4 ± 6.7	30.5 ± 1.7	37.2 ± 5.3	158.5 ± 24.9**
Female						
Hematology						
n						
Day 5	10	10	10	10	8	9
Week 3	10	10	10	10	10	10
Month 3	10	10	9	10	10	10
Hematocrit (%)						
Day 5	44.7 ± 0.6	43.7 ± 0.5	47.0 ± 1.5	44.8 ± 0.4	46.9 ± 0.8**	47.8 ± 0.8**
Week 3	47.7 ± 0.4	49.2 ± 0.9	50.8 ± 0.7	49.6 ± 0.5	50.0 ± 0.6	52.6 ± 1.0
Month 3	45.8 ± 0.5	46.4 ± 0.5	46.0 ± 0.4	46.2 ± 0.4	45.9 ± 0.3	48.2 ± 0.6
Hemoglobin (g/dL)						
Day 5	14.4 ± 0.2	14.1 ± 0.2	15.2 ± 0.5	14.7 ± 0.2	15.4 ± 0.2**	15.8 ± 0.3**
Week 3	15.3 ± 0.2	15.7 ± 0.3	16.0 ± 0.2	16.1 ± 0.2	16.2 ± 0.2	17.1 ± 0.3**
Month 3	15.0 ± 0.1	15.1 ± 0.1	15.1 ± 0.1	15.0 ± 0.1	15.0 ± 0.1	15.8 ± 0.2
Erythrocytes (10^6/µL)						
Day 5	7.27 ± 0.10	7.12 ± 0.10	7.74 ± 0.26	7.45 ± 0.06	7.86 ± 0.15**	7.93 ± 0.13**
Week 3	7.78 ± 0.08	7.97 ± 0.15	8.25 ± 0.12	8.26 ± 0.09	8.63 ± 0.09**	9.19 ± 0.17**
Month 3	8.05 ± 0.08	8.07 ± 0.08	8.19 ± 0.06	8.20 ± 0.06	8.27 ± 0.06	8.84 ± 0.12**

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Female (continued)						
Hematology (continued)						
n						
Day 5	10	10	10	10	8	9
Week 3	10	10	10	10	10	10
Month 3	10	10	9	10	10	10
Reticulocytes (10^6/μL)						
Day 5	0.10 ± 0.02	0.18 ± 0.02	0.12 ± 0.02	0.11 ± 0.02*	0.06 ± 0.01**	0.06 ± 0.01**
Week 3	0.09 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.03 ± 0.00**
Month 3	0.11 ± 0.01	0.12 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.08 ± 0.01
Nucleated erythrocytes (10^3/μL)						
Day 5	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fl)						
Day 5	61.6 ± 0.2	61.5 ± 0.3	60.7 ± 0.3*	60.4 ± 0.4*	59.8 ± 0.3**	60.4 ± 0.3**
Week 3	61.5 ± 0.3	62.0 ± 0.3	61.6 ± 0.4	60.2 ± 0.3**	58.0 ± 0.3**	57.3 ± 0.3**
Month 3	56.9 ± 0.2	57.3 ± 0.2	56.3 ± 0.2**	56.2 ± 0.1**	55.5 ± 0.3**	54.6 ± 0.2**
Mean cell hemoglobin (pg)						
Day 5	19.8 ± 0.1	19.8 ± 0.1	19.6 ± 0.1	19.7 ± 0.1	19.6 ± 0.1	19.9 ± 0.1
Week 3	19.7 ± 0.1	19.7 ± 0.1	19.4 ± 0.1	19.5 ± 0.1	18.8 ± 0.1**	18.6 ± 0.2**
Month 3	18.6 ± 0.1	18.8 ± 0.1	18.4 ± 0.1*	18.3 ± 0.1**	18.2 ± 0.1**	17.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.2 ± 0.2	32.3 ± 0.3	32.3 ± 0.2	32.8 ± 0.3	32.8 ± 0.2	33.0 ± 0.2*
Week 3	32.0 ± 0.2	31.9 ± 0.1	31.5 ± 0.2	32.4 ± 0.2	32.4 ± 0.1*	32.5 ± 0.4*
Month 3	32.8 ± 0.2	32.7 ± 0.2	32.8 ± 0.1	32.5 ± 0.3	32.7 ± 0.2	32.9 ± 0.1
Platelets (10^3/μL)						
Day 5	858.6 ± 28.2	888.5 ± 18.6	905.3 ± 33.2	867.8 ± 19.2	868.8 ± 34.8	980.3 ± 19.8
Week 3	741.3 ± 16.2	744.8 ± 13.9	758.0 ± 20.2	724.3 ± 18.7	747.0 ± 11.4	587.9 ± 19.7**
Month 3	684.3 ± 9.3	687.7 ± 9.2	659.0 ± 8.1*	645.3 ± 11.6**	627.2 ± 8.6**	609.9 ± 11.1**
Leukocytes (10^3/μL)						
Day 5	9.88 ± 0.71	9.64 ± 0.27	9.79 ± 0.46	11.34 ± 0.50*	11.56 ± 0.39*	10.73 ± 0.73
Week 3	11.70 ± 0.80	12.72 ± 0.63	12.06 ± 0.50	11.62 ± 0.74	12.70 ± 0.70	14.32 ± 0.90
Month 3	8.65 ± 0.40	8.71 ± 0.23	8.16 ± 0.26	9.32 ± 0.48	10.70 ± 0.42**	8.91 ± 0.45
Segmented neutrophils (10^3/μL)						
Day 5	0.98 ± 0.12	0.99 ± 0.07	1.21 ± 0.15	1.23 ± 0.21	1.06 ± 0.13	1.01 ± 0.18
Week 3	1.18 ± 0.14	1.16 ± 0.11	1.30 ± 0.13	1.19 ± 0.15	1.42 ± 0.10	1.96 ± 0.22**
Month 3	1.21 ± 0.13	1.41 ± 0.09	1.03 ± 0.07	1.29 ± 0.14	1.89 ± 0.17	1.68 ± 0.16
Bands (10^3/μL)						
Day 5	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)						
Day 5	8.69 ± 0.64	8.50 ± 0.26	8.28 ± 0.44	9.82 ± 0.44*	10.24 ± 0.32**	9.49 ± 0.84*
Week 3	10.30 ± 0.74	11.28 ± 0.59	10.49 ± 0.47	10.18 ± 0.72	10.99 ± 0.69	12.13 ± 0.88
Month 3	7.24 ± 0.27	7.21 ± 0.18	7.02 ± 0.24	7.87 ± 0.43	8.59 ± 0.27*	7.18 ± 0.47
Monocytes (10^3/μL)						
Day 5	0.16 ± 0.05	0.11 ± 0.05	0.20 ± 0.05	0.16 ± 0.03	0.16 ± 0.04	0.15 ± 0.04
Week 3	0.14 ± 0.03	0.21 ± 0.05	0.20 ± 0.03	0.17 ± 0.04	0.19 ± 0.04	0.15 ± 0.04
Month 3	0.09 ± 0.02	0.05 ± 0.03	0.06 ± 0.03	0.10 ± 0.04	0.11 ± 0.03	0.03 ± 0.02

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Female (continued)						
Hematology (continued)						
n						
Day 5	10	10	10	10	8	9
Week 3	10	10	10	10	10	10
Month 3	10	10	9	10	10	10
Basophils ($10^3/\mu L$)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.012 ± 0.012	0.000 ± 0.000	0.000 ± 0.000
Week 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Month 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)						
Day 5	0.05 ± 0.02	0.04 ± 0.02	0.10 ± 0.03	0.12 ± 0.05	0.11 ± 0.03	0.09 ± 0.03
Week 3	0.08 ± 0.03	0.08 ± 0.03	0.07 ± 0.02	0.07 ± 0.03	0.10 ± 0.03	0.08 ± 0.03
Month 3	0.12 ± 0.04	0.04 ± 0.03	0.06 ± 0.02	0.07 ± 0.03	0.11 ± 0.04	0.02 ± 0.01
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	14.0 ± 0.3	11.3 ± 0.8	19.5 ± 2.8	10.1 ± 0.2	11.4 ± 0.5	16.6 ± 0.8**
Week 3	16.2 ± 0.5	16.8 ± 0.6	20.8 ± 0.9	13.5 ± 0.6	12.9 ± 0.3*	19.9 ± 2.0
Month 3	15.6 ± 0.4	14.0 ± 0.6	13.7 ± 0.4	13.5 ± 0.6	14.7 ± 0.5	20.5 ± 1.0**
Creatinine (mg/dL)						
Day 5	0.60 ± 0.00	0.61 ± 0.01	0.67 ± 0.03	0.60 ± 0.00	0.62 ± 0.01	0.63 ± 0.02
Week 3	0.63 ± 0.02	0.62 ± 0.01	0.65 ± 0.02	0.65 ± 0.02	0.64 ± 0.02	0.62 ± 0.01
Month 3	0.75 ± 0.02	0.76 ± 0.02	0.74 ± 0.02	0.77 ± 0.05	0.70 ± 0.02*	0.64 ± 0.02**
Total protein (g/dL)						
Day 5	5.8 ± 0.1	5.7 ± 0.1	5.8 ± 0.1	5.6 ± 0.0	5.6 ± 0.1	5.5 ± 0.1
Week 3	6.1 ± 0.0	6.1 ± 0.1	6.2 ± 0.1	6.1 ± 0.1	6.0 ± 0.1	5.8 ± 0.1
Month 3	6.7 ± 0.1	6.5 ± 0.1	6.5 ± 0.1	6.3 ± 0.1*	5.9 ± 0.0**	6.1 ± 0.1**
Albumin (g/dL)						
Day 5	4.5 ± 0.05	4.4 ± 0.1	4.5 ± 0.1	4.4 ± 0.0	4.4 ± 0.1	4.3 ± 0.1
Week 3	4.6 ± 0.03	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.6 ± 0.1
Month 3	5.1 ± 0.1	5.0 ± 0.1	4.9 ± 0.1	4.7 ± 0.0**	4.6 ± 0.0**	4.7 ± 0.0**
Alanine aminotransferase (IU/L)						
Day 5	61 ± 2	59 ± 3	50 ± 4	67 ± 2	74 ± 5*	60 ± 4
Week 3	67 ± 2	57 ± 2	61 ± 3	69 ± 4*	88 ± 4**	111 ± 6**
Month 3	74 ± 5	77 ± 5	76 ± 6	72 ± 4	88 ± 5	128 ± 12**
Alkaline phosphatase (IU/L)						
Day 5	1,099 ± 27	1,138 ± 28	966 ± 35**	1,032 ± 19**	869 ± 14**	755 ± 26**
Week 3	888 ± 22	650 ± 37	591 ± 16	814 ± 24*	655 ± 8	437 ± 27*
Month 3	494 ± 15	540 ± 12	491 ± 15	495 ± 10	547 ± 11	577 ± 21
Creatine kinase (IU/L)						
Day 5	281 ± 35[b]	302 ± 39[b]	318 ± 40	374 ± 54	496 ± 139[b]	384 ± 65
Week 3	275 ± 45	260 ± 39	262 ± 47	245 ± 11	462 ± 97*	373 ± 42*
Month 3	209 ± 45	147 ± 22	264 ± 64	197 ± 33	155 ± 20	281 ± 47

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Female (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	10
Sorbitol dehydrogenase (IU/L)						
Day 5	20 ± 1	19 ± 1	24 ± 3	17 ± 1	21 ± 3	22 ± 2
Week 3	20 ± 2	19 ± 1	19 ± 1	20 ± 1	24 ± 1**	20 ± 1
Month 3	21 ± 2	22 ± 2	22 ± 2	17 ± 1	17 ± 1	19 ± 1
Bile acids (µmol/L)						
Day 5	22.5 ± 2.8	20.1 ± 1.8	22.2 ± 1.6	32.4 ± 2.1**	46.2 ± 5.5**	42.0 ± 6.4**
Week 3	24.1 ± 2.1	40.5 ± 5.6	43.6 ± 6.2	33.4 ± 3.0	40.4 ± 1.9	100.3 ± 18.0**
Month 3	34.7 ± 3.8	34.3 ± 3.9	37.3 ± 3.8	39.2 ± 3.2	37.6 ± 5.2	74.4 ± 17.0

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test; pairwise comparisons between the untreated control and other groups are not presented.
** $P \leq 0.01$
[a] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE F2
Hematology Data for Mice in the 3-Month Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Male						
n	10	9	9	10	5	1
Hematocrit (%)	50.0 ± 0.7	51.1 ± 0.7	51.0 ± 1.0	50.0 ± 0.9	49.9 ± 0.8	55.5
Hemoglobin (g/dL)	16.5 ± 0.2	16.6 ± 0.2	16.7 ± 0.2	16.2 ± 0.3	16.0 ± 0.3	16.9
Erythrocytes (10^6/μL)	10.71 ± 0.17	10.87 ± 0.15	10.95 ± 0.21	10.83 ± 0.24	10.84 ± 0.19	12.15
Reticulocytes (10^6/μL)	0.08 ± 0.01	0.10 ± 0.01	0.07 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.06
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00
Mean cell volume (fL)	46.8 ± 0.2	46.9 ± 0.1	46.7 ± 0.2	46.0 ± 0.2**	46.2 ± 0.4*	46.0
Mean cell hemoglobin (pg)	15.4 ± 0.1	15.2 ± 0.1	15.3 ± 0.1	15.0 ± 0.1	14.8 ± 0.1**	13.9
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.1	32.4 ± 0.2	32.8 ± 0.2	32.6 ± 0.2	32.1 ± 0.2	30.5
Platelets (10^3/μL)	684.5 ± 26.8	730.6 ± 37.0	681.8 ± 34.8	666.0 ± 18.9	700.2 ± 15.2	837.0
Leukocytes (10^3/μL)	5.62 ± 0.53	5.12 ± 0.76	3.68 ± 0.64	4.28 ± 0.60	2.22 ± 0.12*	1.30
Segmented neutrophils (10^3/μL)	1.27 ± 0.28	0.89 ± 0.16	0.92 ± 0.15	1.12 ± 0.32	0.53 ± 0.10	0.23
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00
Lymphocytes (10^3/μL)	4.30 ± 0.48	4.11 ± 0.67	2.72 ± 0.52	3.12 ± 0.49	1.68 ± 0.13**	1.07
Monocytes (10^3/μL)	0.00 ± 0.00	0.02 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000
Eosinophils (10^3/μL)	0.06 ± 0.02	0.09 ± 0.04	0.03 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.00
Female						
n	10	10	10	10	10	10
Hematocrit (%)	48.3 ± 0.5	47.7 ± 0.4	47.3 ± 0.6	48.5 ± 0.3	48.1 ± 0.4	48.4 ± 0.6
Hemoglobin (g/dL)	16.1 ± 0.1	15.9 ± 0.1	15.8 ± 0.2	16.1 ± 0.1	15.6 ± 0.1	15.5 ± 0.2
Erythrocytes (10^6/μL)	10.13 ± 0.11	10.0 ± 0.1	9.97 ± 0.12	10.31 ± 0.06*	10.31 ± 0.09*	10.50 ± 0.13**
Reticulocytes (10^6/μL)	0.08 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.10 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.7 ± 0.2	47.7 ± 0.2	47.2 ± 0.1*	47.3 ± 0.2	46.8 ± 0.1**	46.1 ± 0.2**
Mean cell hemoglobin (pg)	15.9 ± 0.1	15.8 ± 0.1	15.8 ± 0.1	15.6 ± 0.1	15.1 ± 0.1**	14.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.3 ± 0.1	33.3 ± 0.2	33.4 ± 0.2	33.1 ± 0.1	32.4 ± 0.2*	31.9 ± 0.2**
Platelets (10^3/μL)	687.8 ± 33.2	703.0 ± 15.5	728.6 ± 24.5	682.5 ± 36.4	737.7 ± 38.2	705.6 ± 31.9
Leukocytes (10^3/μL)	4.14 ± 0.31	4.06 ± 0.27	3.95 ± 0.20	4.74 ± 0.48	4.00 ± 0.44	3.53 ± 0.37
Segmented neutrophils (10^3/μL)	0.64 ± 0.10	0.58 ± 0.05	0.54 ± 0.08	0.68 ± 0.15	0.61 ± 0.13	0.45 ± 0.07
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	3.43 ± 0.24	3.36 ± 0.26	3.31 ± 0.16	3.95 ± 0.36	3.32 ± 0.37	2.99 ± 0.31
Monocytes (10^3/μL)	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.06 ± 0.02	0.10 ± 0.02	0.09 ± 0.02	0.09 ± 0.02	0.06 ± 0.01	0.07 ± 0.02

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test; pairwise comparisons between the untreated control and other groups are not presented.
** $P \leq 0.01$
[a] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.

APPENDIX G
HIPPURIC ACID – BIOMARKER OF EXPOSURE

TABLE G1
Urinary Biomarker Data for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
n	5	5	5	5	5	5
Male						
Volume (mL/24 hours)	9.7 ± 0.4	7.2 ± 0.5	7.7 ± 0.5	6.0 ± 0.5	5.3 ± 0.8	3.2 ± 0.2**
Creatinine (mg/dL)	141 ± 8	178 ± 10	161 ± 11	175 ± 22	168 ± 22	115 ± 13*
Hippuric acid (mg/mL)	1.59 ± 0.08	1.70 ± 0.08	8.46 ± 0.83**	14.2 ± 2.1**	21.4 ± 2.5**	53.1 ± 2.4**
Hippuric acid/ creatinine ratio	1.14 ± 0.05	0.966 ± 0.057	5.23 ± 0.23	8.11 ± 0.71	12.9 ± 0.9	48.5 ± 5.4
Total hippuric acid excreted (mg)	15.4 ± 0.6	12.2 ± 1.0	63.6 ± 3.4	81.2 ± 8.1	107 ± 8.6	169 ± 16
Female						
Volume (mL/24 hours)	8.2 ± 1.7	8.4 ± 1.7	4.2 ± 0.6*	4.6 ± 0.1*	4.1 ± 0.4**	3.2 ± 0.3**
Creatinine (mg/dL)	85.7 ± 9.7	81.4 ± 11.8	141 ± 13*	130 ± 7*	111 ± 8	90.0 ± 3.5
Hippuric acid (mg/mL)	1.49 ± 0.22	1.19 ± 0.14	11.1 ± 0.6**	15.5 ± 1.5**	29.3 ± 2.5**	45.0 ± 2.3**
Hippuric acid/ creatinine ratio	1.70 ± 0.10	1.50 ± 0.09	7.97 ± 0.36	11.9 ± 0.9	26.6 ± 1.84	50.1 ± 2.2
Total hippuric acid excreted (mg)	10.8 ± 0.7	9.14 ± 0.76	45.5 ± 4.5	70.1 ± 5.6	117 ± 10	142 ± 7

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test; pairwise comparisons between the untreated control and other groups are not presented.
** ($P \leq 0.01$)
[a] Data are presented as mean ± standard error.

TABLE G2
Urinary Biomarker Data for Rats at 2 Weeks and 3, 12, and 18 Months in the 2-Year Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Male					
n					
Week 2	9	10	10	10	10
Month 3	10	10	10	10	10
Month 12	10	10	10	10	10
Month 18	10	10	10	10	10
Volume (mL/24 hours)					
Week 2	5.8 ± 0.4	4.8 ± 0.6	6.9 ± 0.5*	4.8 ± 0.4	5.1 ± 0.3
Month 3	7.6 ± 0.5	8.2 ± 0.4	9.0 ± 0.5	7.2 ± 0.4	6.8 ± 0.6*
Month 12	6.0 ± 0.6	5.8 ± 0.5	5.9 ± 0.5	5.4 ± 0.5	5.5 ± 0.3
Month 18	6.8 ± 0.5	5.4 ± 0.5	6.8 ± 0.5	6.1 ± 0.9	6.7 ± 0.5[b]
Creatinine (mg/dL)					
Week 2	94.2 ± 4.8	107 ± 4	88.4 ± 3.7**	100 ± 5	96.7 ± 4.7
Month 3	182 ± 11	179 ± 8	154 ± 6	174 ± 7	180 ± 9
Month 12	214 ± 15	240 ± 16	216 ± 13	199 ± 14	213 ± 10
Month 18	182 ± 10	197 ± 6	190 ± 12	175 ± 12	187 ± 17
Hippuric acid (mg/mL)					
Week 2	1.88 ± 0.25	2.41 ± 0.11[b]	4.31 ± 0.16**	8.13 ± 0.37**	12.5 ± 0.47**
Month 3	1.64 ± 0.16	1.88 ± 0.11	3.36 ± 0.18**	5.53 ± 0.38**	9.28 ± 0.54**
Month 12	1.93 ± 0.14	2.00 ± 0.13	3.39 ± 0.26**	4.17 ± 0.35**	9.04 ± 0.74**
Month 18	1.86 ± 0.12	2.00 ± 0.16	3.08 ± 2.26**	4.46 ± 0.53**	8.22 ± 1.10**
Hippuric acid/creatinine ratio					
Week 2	2.01 ± 0.25	2.24 ± 0.09[b]	4.90 ± 0.14**	8.18 ± 0.42**	13.2 ± 0.86**
Month 3	0.92 ± 0.09	1.05 ± 0.05	2.20 ± 0.10**	3.18 ± 0.20**	5.25 ± 0.37**
Month 12	0.90 ± 0.03	0.85 ± 0.06	1.59 ± 0.08**	2.10 ± 0.14**	4.26 ± 0.33**
Month 18	1.02 ± 0.02	1.01 ± 0.06	1.61 ± 0.09**	2.50 ± 0.21**	4.36 ± 0.35**
Total hippuric acid excreted (mg)					
Week 2	10.9 ± 1.7	10.0 ± 1.6	29.5 ± 1.8**	38.2 ± 2.7**	63.6 ± 3.7**
Month 3	12.3 ± 1.3	15.2 ± 0.9	30.1 ± 2.1**	40.3 ± 3.8**	61.7 ± 4.7**
Month 12	11.3 ± 1.0	11.3 ± 0.9	19.3 ± 1.3**	22.8 ± 3.0**	49.8 ± 4.9**
Month 18	12.1 ± 0.5	10.6 ± 1.0	20.1 ± 1.5**	24.7 ± 3.5**	47.5 ± 3.9**[b]

TABLE G2
Urinary Biomarker Data for Rats at 2 Weeks and 3, 12, and 18 Months in the 2-Year Feed Study of *trans*-Cinnamaldehyde

	Untreated Control	Vehicle Control	1,000 ppm	2,100 ppm	4,100 ppm
Female					
n					
Week 2	10	10	9	10	10
Month 3	10	10	10	10	10
Month 12	10	10	10	10	10
Month 18	10	10	10	10	10
Volume (mL/24 hours)					
Week 2	6.2 ± 0.7	5.0 ± 0.5	4.4 ± 0.6	5.3 ± 0.6	5.1 ± 0.4
Month 3	6.3 ± 1.3	6.3 ± 0.4	5.4 ± 0.5	6.7 ± 0.4	5.7 ± 0.5
Month 12	4.2 ± 0.4	4.5 ± 0.3	5.4 ± 0.5	4.6 ± 0.6	5.6 ± 0.6
Month 18	7.8 ± 0.8	6.5 ± 0.4	7.3 ± 0.7	7.9 ± 1.6	7.4 ± 0.5
Creatinine (mg/dL)					
Week 2	71.9 ± 5.9	74.9 ± 4.5	93 ± 16	71.8 ± 4.9	72.0 ± 4.5
Month 3	128 ± 14	117 ± 6	134 ± 9	118 ± 7	127 ± 8
Month 12	172 ± 10	178 ± 12	132 ± 7*	152 ± 12	139 ± 13*
Month 18	119 ± 11	131 ± 10	130 ± 11	140 ± 17	129 ± 8
Hippuric acid (mg/mL)					
Week 2	1.71 ± 0.16	1.83 ± 0.12	4.70 ± 0.57**	5.66 ± 0.41**	10.1 ± 0.6**
Month 3	1.62 ± 0.20	1.35 ± 0.07	4.02 ± 0.32**	5.04 ± 0.42**	8.59 ± 0.48**
Month 12	2.01 ± 0.13	1.88 ± 0.13	2.94 ± 0.28**	5.32 ± 0.45**	8.86 ± 0.80**
Month 18	1.61 ± 0.17	1.66 ± 0.11	3.44 ± 0.30**	5.72 ± 0.68**	8.58 ± 0.52**
Hippuric acid/creatinine ratio					
Week 2	2.40 ± 0.12	2.48 ± 0.16	5.27 ± 0.21**	7.89 ± 0.27**	14.3 ± 0.8**
Month 3	1.24 ± 0.10	1.17 ± 0.05	3.05 ± 0.19**	4.35 ± 0.33**	6.84 ± 0.32**
Month 12	1.18 ± 0.06	1.07 ± 0.07	2.21 ± 0.11**	3.54 ± 0.19**	6.50 ± 0.43**
Month 18	1.36 ± 0.07	1.29 ± 0.06	2.68 ± 0.11**	4.17 ± 0.18**	6.80 ± 0.48**
Total hippuric acid excreted (mg)					
Week 2	9.86 ± 0.70	9.03 ± 1.07	18.2 ± 1.7**	28.7 ± 2.6**	50.7 ± 3.0**
Month 3	8.33 ± 0.77	8.44 ± 0.59	21.0 ± 1.8**	33.4 ± 2.7**	47.5 ± 3.2**
Month 12	8.21 ± 0.63	8.18 ± 0.56	15.6 ± 1.5**	25.1 ± 3.0**	46.6 ± 4.7**
Month 18	11.8 ± 0.9	10.59 ± 0.72	23.7 ± 1.0**	37.8 ± 2.7**	63.3 ± 5.7**[b]

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test; pairwise comparisons between the untreated control and other groups are not presented.
** ($P \leq 0.01$)
[a] Data are presented as mean ± standard error.
[b] n=9

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

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	364 ± 6	371 ± 6	349 ± 7**	307 ± 4**	256 ± 2**	135 ± 5**
Heart						
Absolute	1.089 ± 0.032	1.045 ± 0.027	1.024 ± 0.024	1.045 ± 0.068	0.836 ± 0.014**	0.518 ± 0.014**
Relative	2.991 ± 0.069	2.818 ± 0.057	2.936 ± 0.053	3.397 ± 0.204**	3.267 ± 0.045**	3.855 ± 0.086**
R. Kidney						
Absolute	1.131 ± 0.024	1.154 ± 0.037	1.141 ± 0.028	1.051 ± 0.024**	0.892 ± 0.014**	0.554 ± 0.019**
Relative	3.110 ± 0.058	3.107 ± 0.061	3.272 ± 0.058	3.423 ± 0.051**	3.488 ± 0.051**	4.113 ± 0.091**
Liver						
Absolute	13.675 ± 0.424	13.858 ± 0.392	12.863 ± 0.302*	11.537 ± 0.211**	9.445 ± 0.266**	4.984 ± 0.215**
Relative	37.571 ± 1.006	37.339 ± 0.645	36.849 ± 0.270	37.611 ± 0.631	36.917 ± 0.932	36.876 ± 0.694
Lung						
Absolute	1.906 ± 0.071	1.972 ± 0.107	1.935 ± 0.106	1.692 ± 0.054*	1.534 ± 0.054**	0.920 ± 0.029**[b]
Relative	5.234 ± 0.177	5.317 ± 0.267	5.517 ± 0.216	5.506 ± 0.126	5.999 ± 0.214*	6.711 ± 0.075**[b]
R. Testis						
Absolute	1.519 ± 0.022	1.523 ± 0.021	1.510 ± 0.017	1.336 ± 0.131	1.465 ± 0.010	1.047 ± 0.089**
Relative	4.179 ± 0.068	4.111 ± 0.043	4.337 ± 0.072	4.362 ± 0.427	5.732 ± 0.059**	7.667 ± 0.530**
Thymus						
Absolute	0.291 ± 0.010	0.330 ± 0.018	0.292 ± 0.013*	0.237 ± 0.008**	0.202 ± 0.007**	0.080 ± 0.007**
Relative	0.800 ± 0.025	0.888 ± 0.040	0.836 ± 0.025	0.774 ± 0.028*	0.791 ± 0.030*	0.585 ± 0.038**
Female						
Necropsy body wt	200 ± 4	196 ± 2	190 ± 3	183 ± 3*	157 ± 5**	121 ± 7**
Heart						
Absolute	0.702 ± 0.018	0.664 ± 0.016	0.680 ± 0.017	0.630 ± 0.020	0.566 ± 0.016**	0.469 ± 0.014**
Relative	3.517 ± 0.069	3.386 ± 0.073	3.580 ± 0.064	3.430 ± 0.081	3.608 ± 0.092	3.951 ± 0.146**
R. Kidney						
Absolute	0.635 ± 0.023	0.648 ± 0.010	0.640 ± 0.019	0.616 ± 0.018	0.564 ± 0.012**	0.502 ± 0.018**
Relative	3.179 ± 0.099	3.308 ± 0.050	3.368 ± 0.080	3.357 ± 0.081	3.614 ± 0.133	4.220 ± 0.142**
Liver						
Absolute	6.742 ± 0.194	6.306 ± 0.144	6.074 ± 0.137	6.082 ± 0.106	5.315 ± 0.147**	4.570 ± 0.295**
Relative	33.757 ± 0.689	32.175 ± 0.694	31.960 ± 0.489	33.184 ± 0.465	33.830 ± 0.296*	37.713 ± 0.616**
Lung						
Absolute	1.131 ± 0.042	1.122 ± 0.032	1.220 ± 0.051	1.084 ± 0.030	0.998 ± 0.032*	0.803 ± 0.032**
Relative	5.662 ± 0.178	5.724 ± 0.157	6.429 ± 0.273	5.917 ± 0.150	6.395 ± 0.276*	6.736 ± 0.216**
Thymus						
Absolute	0.242 ± 0.006	0.236 ± 0.007	0.226 ± 0.005	0.229 ± 0.006	0.198 ± 0.007**	0.139 ± 0.014**
Relative	1.217 ± 0.035	1.203 ± 0.035	1.188 ± 0.022	1.248 ± 0.026	1.258 ± 0.019	1.123 ± 0.074

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test; pairwise comparisons between the untreated control and other groups are not presented.
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Feed Study of *trans*-Cinnamaldehyde[a]

	Untreated Control	Vehicle Control	4,100 ppm	8,200 ppm	16,500 ppm	33,000 ppm
Male						
n	10	9	9	10	5	1
Necropsy body wt	30.6 ± 1.1	31.2 ± 1.0	27.4 ± 0.7**	26.5 ± 0.7**	24.5 ± 0.6**	17.9
Heart						
Absolute	0.154 ± 0.005	0.154 ± 0.005	0.141 ± 0.004	0.158 ± 0.009	0.148 ± 0.006	0.113
Relative	5.050 ± 0.158	4.971 ± 0.161	5.164 ± 0.206	5.994 ± 0.375*	6.058 ± 0.394*	6.313
R. Kidney						
Absolute	0.271 ± 0.008	0.266 ± 0.006	0.251 ± 0.008	0.245 ± 0.008*	0.216 ± 0.007**	0.151
Relative	8.876 ± 0.168	8.555 ± 0.197	9.182 ± 0.127	9.261 ± 0.217*	8.826 ± 0.249	8.436
Liver						
Absolute	1.338 ± 0.039	1.385 ± 0.046	1.156 ± 0.032**	1.238 ± 0.038*	1.221 ± 0.027*	0.933
Relative	43.832 ± 0.737	44.450 ± 0.843	42.294 ± 0.830	46.747 ± 0.760*	49.794 ± 0.620**	52.123
Lung						
Absolute	0.292 ± 0.014	0.269 ± 0.013	0.280 ± 0.006	0.283 ± 0.008	0.255 ± 0.013	0.239
Relative	9.676 ± 0.605	8.682 ± 0.539	10.285 ± 0.411*	10.729 ± 0.300**	10.423 ± 0.531*	13.352
R. Testis						
Absolute	0.113 ± 0.003	0.113 ± 0.002	0.111 ± 0.003	0.113 ± 0.002	0.105 ± 0.004	0.084
Relative	3.725 ± 0.106	3.652 ± 0.113	4.061 ± 0.119*	4.268 ± 0.110**	4.298 ± 0.158**	4.693
Thymus						
Absolute	0.040 ± 0.002	0.040 ± 0.003	0.036 ± 0.001	0.038 ± 0.002	0.040 ± 0.004	0.027
Relative	1.311 ± 0.062	1.287 ± 0.068	1.312 ± 0.070	1.437 ± 0.073	1.622 ± 0.132*	1.508
Female						
n	10	10	10	10	10	9
Necropsy body wt	27.8 ± 0.5	28.5 ± 0.6	28.1 ± 0.8	25.2 ± 0.7**	21.7 ± 0.2**	18.0 ± 0.2**
Heart						
Absolute	0.133 ± 0.004	0.127 ± 0.003	0.138 ± 0.005	0.132 ± 0.008	0.117 ± 0.003	0.101 ± 0.003**
Relative	4.796 ± 0.141	4.488 ± 0.185	4.933 ± 0.239	5.245 ± 0.258*	5.390 ± 0.121**	5.618 ± 0.155**
R. Kidney						
Absolute	0.177 ± 0.004	0.168 ± 0.003	0.167 ± 0.004	0.170 ± 0.006	0.151 ± 0.002**	0.125 ± 0.003**
Relative	6.371 ± 0.135	5.908 ± 0.106	5.961 ± 0.123	6.778 ± 0.188**	6.937 ± 0.082**	6.954 ± 0.166**
Liver						
Absolute	1.198 ± 0.019	1.223 ± 0.022	1.315 ± 0.024	1.170 ± 0.027	1.015 ± 0.026**	0.839 ± 0.025**
Relative	43.169 ± 0.607	42.937 ± 0.822	46.915 ± 0.973*	46.587 ± 0.623*	46.740 ± 1.043*	46.719 ± 1.048*
Lung						
Absolute	0.251 ± 0.016	0.231 ± 0.011	0.235 ± 0.016	0.264 ± 0.016	0.225 ± 0.015	0.191 ± 0.010
Relative	9.062 ± 0.606	8.107 ± 0.352	8.377 ± 0.590	10.514 ± 0.568**	10.359 ± 0.644**	10.625 ± 0.491**
Thymus						
Absolute	0.052 ± 0.002	0.056 ± 0.003	0.047 ± 0.002*	0.046 ± 0.002*	0.048 ± 0.002	0.055 ± 0.004
Relative	1.888 ± 0.057	1.973 ± 0.116	1.662 ± 0.081	1.857 ± 0.099	2.227 ± 0.098	3.040 ± 0.180**

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test; pairwise comparisons between the untreated control and other groups are not presented.
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization of *trans*-Cinnamaldehyde

trans-Cinnamaldehyde was obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI), in two lots. Lot 10120 TF was used in the 3-month studies, and lot 13831AR was used in the 2-year studies. The chemical was microencapsulated by the analytical chemistry laboratory, Midwest Research Institute (MRI, Kansas City, MO), and the loaded microcapsules were assigned separate lot numbers (3-month studies: DB 1-23-95; 2-year studies: 042497MC). Identity, purity, moisture content, and stability analyses of the neat and microencapsulated *trans*-cinnamaldehyde were conducted by the analytical chemistry laboratory. Reports on analyses performed in support of the *trans*-cinnamaldehyde studies are on file at the National Institute of Environmental Health Sciences.

Analyses of Neat Chemical

Both lots of the chemical, a pale yellow liquid, were identified as *trans*-cinnamaldehyde by the analytical chemistry laboratory using infrared and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*, 1966; *Aldrich*, 1985, 1993) and with the structure of *trans*-cinnamaldehyde. The infrared and NMR spectra for lot 13831AR are presented in Figures I1 and I2.

The purity of *trans*-cinnamaldehyde was determined by the analytical chemistry laboratory using free acid titration and high-performance liquid chromatography (HPLC) (lot 10120 TF) or free acid titration, thin-layer chromatography (TLC), and gas chromatography (GC) (lot 13831AR). The moisture content of lot 13831AR was determined using Karl Fischer titration. To measure the concentration of free acid, lot 10120 TF was titrated with a standardized sodium hydroxide solution using a Metrohm potentiograph equipped with a dosimat; lot 13831AR was dissolved in neutralized methanol and titrated with standardized 1 N sodium hydroxide to the phenolphthalein endpoint. HPLC (Varian, Inc., Palo Alto, CA) was performed with a Brownlee RP-18 Spheri-5 column (100 mm × 4.6 mm, 5-µm particle size; Perkin-Elmer, Norwalk, CT) and a mobile phase of methanol:water (40:60) with 5 mM tetrabutylammonium hydroxide adjusted to pH 7.3 with phosphoric acid. The flow rate was 1 mL/minute; ultraviolet detection at 254 nm was used. TLC was performed with 0.25-mm Silica Gel 60 F-254 TLC plates with a hexane:ethyl acetate (60:40) solvent system. The plates were examined with ultraviolet light at 254 nm using a reagent spray of 1,4-phenylenediamine in methanol solution with vanillin as a reference standard. GC (Varian, Inc.) was performed on samples from each of the two shipments of lot 13831AR received (batches 1 and 2); the following system was used: flame ionization detection (FID); DB WAX column (30 m × 0.53 mm, 1-µm film thickness; Agilent Technologies, Palo Alto, CA); helium carrier at 10 mL/minute; oven temperature program of 60° C for 6 minutes, then 10° C/minute to 200° C.

For lot 10120 TF, free acid titration indicated 0.38% ± 0.02% free acid, present as cinnamic acid. HPLC indicated a major peak and four impurity peaks with a total area of 5.2% relative to the major peak area. The overall purity of lot 10120 TF was determined to be approximately 95%.

For lot 13831AR, Karl Fischer titration indicated 0.04% ± 0.03% water. Free acid titration indicated 0.56% ± 0.01% free acid, present as cinnamic acid. TLC indicated one major spot and one minor spot. GC indicated one major peak and two impurities with a combined area of 1.07% (batch 1) relative to the major peak area. The overall purity was determined to be approximately 99%. Homogeneity analyses of batches 1 and 2 were performed by the analytical chemistry laboratory using GC as described for the purity analyses. Homogeneity was confirmed; both samples were consistent with a *trans*-cinnamaldehyde standard (Aldrich Chemical Company, Inc.).

Stability analyses of lot M5016 of neat *trans*-cinnamaldehyde (not used in the current studies) were performed by the analytical chemistry laboratory using GC (Varian, Inc.) with FID, a 10% Carbowax 20M-TPA on 80/100-mesh Chromosorb W(AW) column (1.8 m × 4 mm), and nitrogen carrier gas at a flow rate of 70 mL/minute. The oven

temperature was isothermal at 200° C. Samples stored under a nitrogen head space in amber glass vials, sealed with aluminum caps and Teflon®-lined septa were stable for at least 2 weeks at temperatures up to 60° C.

Microcapsule Formulation and Analyses

Microcapsules loaded with neat *trans*-cinnamaldehyde and placebos (empty microcapsules) were prepared by the analytical chemistry laboratory with a proprietary process using food-grade, modified corn starch (CAPSUL®) and sucrose to produce dry microspheres; the outer surfaces of the microcapsules were coated with food-grade, hydrophobic, modified corn starch. Following microencapsulation, the analytical chemistry laboratory tested lot 042497MC of the microcapsules for conformance to specifications. The microcapsules were examined microscopically for appearance, and particle sizes were profiled. Particles were smooth, shiny, translucent or opaque white spheres, heavily coated with small, colorless particles. Only occasional particle fragments and no leaking capsules or foreign particles were observed. For particle size profiling, microcapsules were passed through U.S. standard sieves (numbers 30, 40, 60, 80, 100, and 120); 98.6% of the microcapsules were retained by the sieves.

The chemical loads of freshly prepared microcapsules (both lots) and the purity of lot 042497MC were determined by the analytical chemistry laboratory with HPLC as described for the purity analyses; propiophenone was added as an internal standard. The chemical load for both lots of microcapsules was determined to be 30% to 34%. Lot DB 1-23-95 contained 1.58% cinnamic acid and no cinnamyl alcohol. Lot 042497MC contained approximately 0.4% cinnamic acid; one additional impurity peak with an area of 0.05% of the total peak area was identified. The study laboratory confirmed the chemical load of lot 042497MC to be 33% using HPLC with a Prodigy ODS (3) column (150 mm × 4.6 mm, 5-µm particle size; Phenomenex, Torrance, CA) and a mobile phase of methanol:water (50:50, isocratic) with 5 mM tetrabutylammonium hydroxide adjusted to pH 7.3 with phosphoric acid. The flow rate was 1 mL/minute, and propiophenone was added as an internal standard; ultraviolet detection at 254 nm was used.

Microcapsules were stored in amber glass bottles at approximately 5° C, protected from light. Stability was monitored by the analytical chemistry laboratory for the 3-month study, and stability was monitored by the study laboratory for the 2-year study using HPLC as described for the microcapsule load determinations. From July 1998 through the end of the studies, slight decreases (1% to 2%) in the *trans*-cinnamaldehyde load and increases in cinnamic acid concentrations in the microcapsules were observed.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared at least every 3 weeks by mixing microencapsulated *trans*-cinnamaldehyde with nonirradiated NTP-2000 feed during the 3-month studies and with irradiated NTP-2000 feed during the 2-year studies (Table I1). Placebo and/or loaded microcapsules were combined with feed to a concentration of 10% (3-month studies) or 1.25% (2-year studies) in the diet. A premix was prepared by hand and then blended with additional feed in a Patterson-Kelly twin-shell blender for 15 minutes, without the use of the intensifier bar. Formulations were stored in plastic buckets at room temperature (3-month studies) or at approximately 5° C (2-year studies) for up to 5 weeks.

Homogeneity and stability studies of a 0.3% dose formulation prepared with nonirradiated feed and an approximately 0.447% dose formulation prepared with irradiated feed were conducted by the analytical chemistry laboratory using HPLC by methods similar to those described for the purity analyses. Homogeneity was confirmed; stability was confirmed for up to 42 days for dose formulations stored in sealed containers in the dark at temperatures up to approximately 25° C or for 9 days under simulated animal room conditions, open to air and light at room temperature. The study laboratory also analyzed the homogeneity of the 1,000 and 4,100 ppm dose formulations and the stability under simulated and actual animal room conditions of the 1,000, 2,100, and 4,100 ppm dose formulations for the 2-year studies. Homogeneity was confirmed; dose formulations contaminated

with urine and feces showed some losses of the chemical load, as did dose formulations collected from the feeders in the female mouse cages.

Periodic analyses of the dose formulations of *trans*-cinnamaldehyde used during the 3-month studies were conducted by the analytical chemistry laboratory using the HPLC system described for the purity analyses. The dose formulations were analyzed at the beginning, midpoint, and end of the studies; animal room samples of these dose formulations were also analyzed. Original acceptance criteria were based on the concentration of loaded microcapsules in the feed. Table I2 provides analysis results in both ppm and percent loaded microcapsules for clarity. Based on the original criteria, all formulations were within 10% of the target concentration. Periodic analyses of the dose formulations used during the 2-year studies were conducted by the study laboratory using HPLC by the system described for the microcapsule load analyses. During the 2-year studies, the dose formulations were analyzed approximately every 9 to 12 weeks; animal room samples of these dose formulations were also analyzed. Original acceptance criteria were based on the concentration of loaded microcapsules in the feed. Table I3 provides analysis results in both ppm and percent loaded microcapsules for clarity. Based on the original criteria, all formulations were within 10% of the target concentration. During the 3-month and 2-year studies, problems with animal room samples were encountered due to the animals' ability to eat around the microcapsules (causing high animal room sample analyses results) and due to contamination of the feed with urine and feces which softened the microcapsules (causing low results). Both problems were more prevalent in the 3-month studies because the animals were younger and smaller and because of the higher concentrations of cinnamaldehyde in the feed.

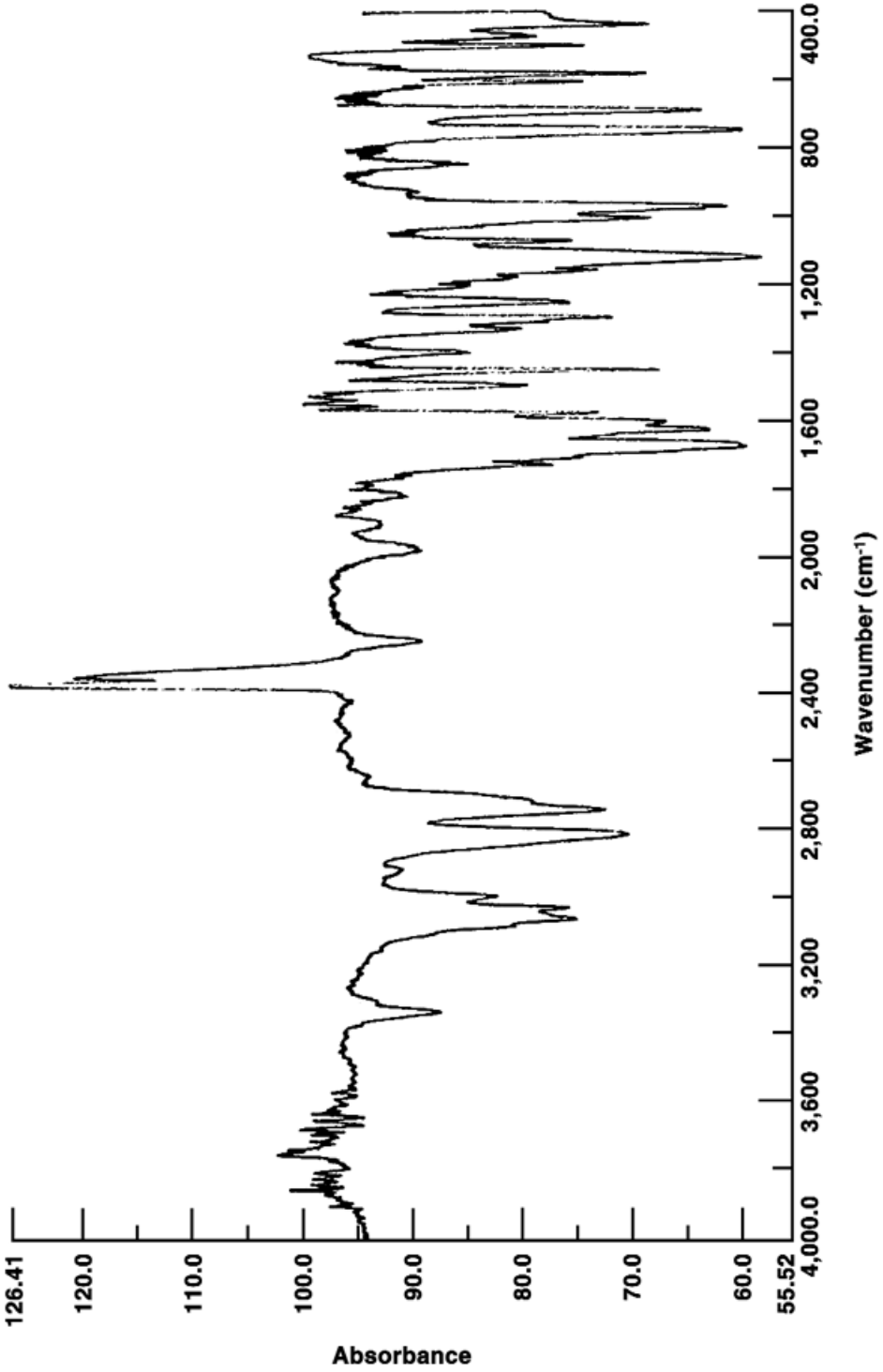

FIGURE I1
Infrared Absorption Spectrum of *trans*-Cinnamaldehyde

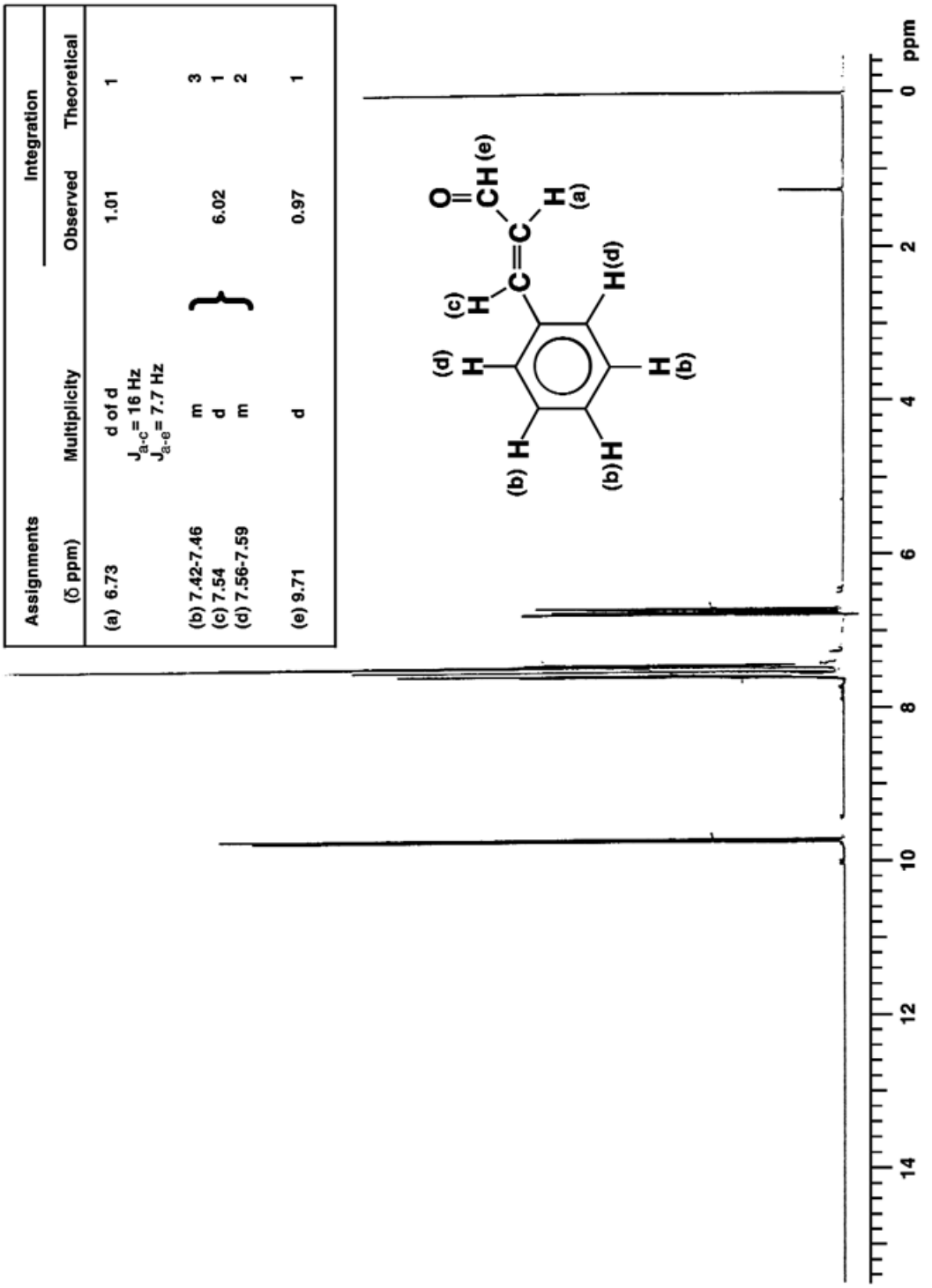

FIGURE I2
Nuclear Magnetic Resonance Spectrum of *trans*-Cinnamaldehyde

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of *trans*-Cinnamaldehyde

3-Month Studies	2-Year Studies
Preparation	
A premix of microencapsulated *trans*-cinnamaldehyde and feed was prepared by hand and then blended with additional feed in a Patterson-Kelly twin-shell blender for approximately 15 minutes, without the use of the intensifier bar. Dose formulations were prepared at least every 3 weeks.	Same as 3-month studies. Dose formulations were prepared every 3 weeks.
Chemical Lot Number	
Neat: 10120 TF Microcapsules: DB 1-23-95	Neat: 13831AR Microcapsules: 042497MC
Maximum Storage Time	
35 days	35 days
Storage Conditions	
Stored in sealed plastic buckets with plastic liners at room temperature	Stored in sealed plastic buckets at approximately 5° C
Study Laboratory	
Battelle Columbus Operations (Columbus, OH)	Battelle Columbus Operations (Columbus, OH)

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Feed Studies of *trans*-Cinnamaldehyde[a]

Date Prepared	Date Analyzed	Target Concentration (ppm)	Target Concentration microcaps[c]	Determined Concentration[b] (ppm)	Determined Concentration microcaps[c]	Difference from Target (%) (ppm)	Difference from Target (%) microcaps
Rats							
April 24, 1995	April 26, 1995	4,100	1.25	4,092	1.24	0	–1
		4,100	1.25	4,092	1.24	0	–1
		4,100	1.25	4,587	1.39	+12	+11
		8,200	2.5	8,316	2.52	+1	+1
		8,200	2.5	8,613	2.61	+5	+4
		8,200	2.5	8,316	2.52	+1	+1
		16,500	5	16,731	5.07	+1	+1
		16,500	5	16,731	5.07	+1	+1
		16,500	5	16,764	5.08	+2	+2
		33,000	10	31,911	9.67	–3	–3
		33,000	10	31,878	9.66	–3	–3
		33,000	10	31,812	9.64	–4	–4
	May 23-26, 1995[d]	4,100	1.25	3,993	1.21	–3	–3
		4,100	1.25	3,597	1.09	–12	–13
		8,200	2.5	5,940	1.80	–28	–28
		8,200	2.5	6,765	2.05	–17	–18
		16,500	5	12,705	3.85	–23	–23
		16,500	5	13,926	4.22	–16	–16
		16,500	5	13,266	4.02	–20	–20
		33,000	10	21,153	6.41	–36	–36
		33,000	10	21,417	6.49	–35	–35
		33,000	10	21,582	6.54	–35	–35
May 30, 1995	May 31-June 1, 1995	4,100	1.25	3,993	1.21	–3	–3
		4,100	1.25	3,927	1.19	–4	–5
		4,100	1.25	3,828	1.16	–7	–7
		8,200	2.5	7,986	2.42	–3	–3
		8,200	2.5	7,920	2.40	–3	–4
		8,200	2.5	7,854	2.38	–4	–5
		16,500	5	16,467	4.99	0	0
		16,500	5	16,665	5.05	+1	+1
		16,500	5	16,566	5.02	0	0
		33,000	10	33,990	10.3	+3	+3
		33,000	10	34,320	10.4	+4	+4
		33,000	10	34,320	10.4	+4	+4
	July 3-5, 1995[d]	4,100	1.25	4,100	1.25	0	0
		4,100	1.25	4,257	1.29	+4	+3
		8,200	2.5	7,293	2.21	–11	–12
		8,200	2.5	7,722	2.34	–6	–6
		8,200	2.5	7,128	2.16	–13	–14
		16,500	5	15,180	4.60	–8	–8
		16,500	5	13,530	4.10	–18	–18
		16,500	5	13,266	4.02	–20	–20
		33,000	10	23,529	7.13	–29	–29
		33,000	10	26,136	7.92	–21	–21
		33,000	10	23,661	7.17	–28	–28

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Feed Studies of *trans*-Cinnamaldehyde

Date Prepared	Date Analyzed	Target Concentration		Determined Concentration		Difference from Target (%)	
		(ppm)	microcaps	(ppm)	microcaps	(ppm)	microcaps
Rats (continued)							
July 10, 1995	July 11-12, 1995	4,100	1.25	3,729	1.13	–9	–10
		4,100	1.25	3,762	1.14	–8	–9
		8,200	2.5	7,689	2.33	–6	–7
		8,200	2.5	7,524	2.28	–8	–9
		16,500	5	15,609	4.73	–5	–5
		16,500	5	15,444	4.68	–6	–6
		33,000	10	30,591	9.27	–7	–7
		33,000	10	31,020	9.40	–6	–6
	August 8-9, 1995[d]	4,100	1.25	4,389	1.33	+7	+6
		4,100	1.25	4,356	1.32	+6	+6
		8,200	2.5	9,273	2.81	+13	+12
		8,200	2.5	8,613	2.61	+5	+4
		16,500	5	19,437	5.89	+18	+18
		16,500	5	20,196	6.12	+22	+22
		33,000	10	25,839	7.83	–22	–22
		33,000	10	29,634	8.98	–10	–10
Mice							
April 24, 1995	April 26, 1995	4,100	1.25	4,092	1.24	0	–1
		4,100	1.25	4,092	1.24	0	–1
		4,100	1.25	4,587	1.39	+12	+11
		8,200	2.5	8,316	2.52	+1	+1
		8,200	2.5	8,613	2.61	+5	+4
		8,200	2.5	8,316	2.52	+1	+1
		16,500	5	16,731	5.07	+1	+1
		16,500	5	16,731	5.07	+1	+1
		16,500	5	16,764	5.08	+2	+2
		33,000	10	31,911	9.67	–3	–3
		33,000	10	31,878	9.66	–3	–3
		33,000	10	31,812	9.64	–4	–4
	May 23-26, 1995[d]	16,500	5	13,068	3.96	–21	–21
		16,500	5	2,211	0.67	–87	–87
		33,000	10	28,347	8.59	–14	–14
		33,000	10	18,744	5.68	–43	–43
		33,000	10	30,756	9.32	–7	–7

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Feed Studies of *trans*-Cinnamaldehyde

Date Prepared	Date Analyzed	Target Concentration		Determined Concentration		Difference from Target (%)	
		(ppm)	microcaps	(ppm)	microcaps	(ppm)	microcaps
Mice (continued)							
May 30, 1995	May 31-June 1, 1995	4,100	1.25	3,993	1.21	–3	–3
		4,100	1.25	3,927	1.19	–4	–5
		4,100	1.25	3,828	1.16	–7	–7
		8,200	2.5	7,986	2.42	–3	–3
		8,200	2.5	7,920	2.40	–3	–4
		8,200	2.5	7,854	2.38	–4	–5
		16,500	5	16,467	4.99	0	0
		16,500	5	16,665	5.05	+1	+1
		16,500	5	16,566	5.02	0	0
		33,000	10	33,990	10.3	+3	+3
		33,000	10	34,320	10.4	+4	+4
		33,000	10	34,320	10.4	+4	+4
	July 3-5, 1995[d]	4,100	1.25	1,353	0.41	–67	–67
		4,100	1.25	3,300	1.00	–20	–20
		4,100	1.25	2,178	0.66	–47	–47
		8,200	2.5	6,501	1.97	–21	–21
		8,200	2.5	4,752	1.44	–42	–42
		8,200	2.5	4,653	1.41	–43	–44
		16,500	5	16,896	5.12	+2	+2
		16,500	5	15,675	4.75	–5	–5
		16,500	5	10,956	3.32	–34	–34
		33,000	10	36,300	11.0	+10	+10
July 10, 1995	July 11-12, 1995	4,100	1.25	3,729	1.13	–9	–10
		4,100	1.25	3,762	1.14	–8	–9
		8,200	2.5	7,689	2.33	–6	–7
		8,200	2.5	7,524	2.28	–8	–9
		16,500	5	15,609	4.73	–5	–5
		16,500	5	15,444	4.68	–6	–6
		33,000	10	30,591	9.27	–7	–7
		33,000	10	31,020	9.40	–6	–6
	August 8-9, 1995[d]	4,100	1.25	2,013	0.61	–51	–51
		4,100	1.25	1,848	0.56	–55	–55
		8,200	2.5	4,818	1.46	–41	–42
		8,200	2.5	3,861	1.17	–53	–53
		16,500	5	11,253	3.41	–32	–32
		16,500	5	17,424	5.28	+6	+6
		33,000	10	38,280	11.6	+16	+16

[a] Analyses were performed by Midwest Research Institute (Kansas City, MO).
[b] Results of triplicate analyses
[c] Percentage of loaded microcapsules in the feed
[d] Animal room samples

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *trans*-Cinnamaldehyde

Date Prepared	Date Analyzed	Target Concentration		Determined Concentration[a]		Difference from Target (%)	
		(ppm)	microcaps[b]	(ppm)	microcaps[b]	(ppm)	microcaps
Rats							
August 26, 1997	August 26-27, 1997	1,000	0.312	1,034	0.3134	+3	0
		2,100	0.625	2,087	0.6323	–1	+1
		4,100	1.25	4,066	1.232	–1	–1
	September 23-24, 1997[c]	1,000	0.312	1,069	0.3238	+7	+4
		2,100	0.625	2,120	0.6425	+1	+3
		4,100	1.25	4,528	1.372	+10	+10
September 9, 1997	September 13, 1997	1,000	0.312	1,028	0.3114	+3	0
		2,100	0.625	2,032	0.6157	–3	–1
		4,100	1.25	4,125	1.250	+1	0
November 11, 1997	November 12, 1997	1,000	0.312	1,055	0.3197	+6	+2
		2,100	0.625	2,117	0.6414	+1	+3
		4,100	1.25	4,534	1.374	+11	+10
February 3, 1998	February 9, 1998	1,000	0.312	1,038	0.3145	+4	+1
		2,100	0.625	2,066	0.6260	–2	0
		4,100	1.25	4,214	1.277	+3	+2
April 7, 1998	April 8-9, 1998	1,000	0.312	1,071	0.3244	+7	+4
		2,100	0.625	2,151	0.6518	+2	+4
		4,100	1.25	4,376	1.326	+7	+6
	May 7, 1998[c]	1,000	0.312	958	0.2903	–4	–7
		2,100	0.625	2,030	0.6153	–3	–2
		4,100	1.25	4,254	1.289	+4	+3
June 30, 1998	July 1-2, 1998	1,000	0.312	1,028	0.3114	+3	0
		2,100	0.625	2,071	0.6276	–1	0
		4,100	1.25	4,112	1.246	0	0
September 1, 1998	September 2-3, 1998	1,000	0.312	987	0.2992	–1	–4
		2,100	0.625	1,981	0.6002	–6	–4
		4,100	1.25	4,138	1.254	+1	0
November 24, 1998	November 24-25, 1998	1,000	0.312	1,058	0.3207	+6	+3
		2,100	0.625	2,132	0.6461	+2	+3
		4,100	1.25	4,274	1.295	+4	+4
	January 6-7, 1999[c]	1,000	0.312	1,056	0.3199	+6	+3
		2,100	0.625	2,190	0.6637	+4	+6
		4,100	1.25	4,247	1.287	+4	+3

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *trans*-Cinnamaldehyde

Date Prepared	Date Analyzed	Target Concentration (ppm)	Target Concentration microcaps	Determined Concentration (ppm)	Determined Concentration microcaps	Difference from Target (%) (ppm)	Difference from Target (%) microcaps
Rats (continued)							
January 26, 1999	January 26-27, 1999	1,000	0.312	1,264[d]	0.3830[d]	+26	+23
		1,000	0.312	1,198[d,e]	0.3631[d,e]	+20	+16
		2,100	0.625	2,203	0.6676	+5	+7
		4,100	1.25	4,363	1.322	+6	+6
January 28, 1999	January 28, 1999	1,000	0.312	1,126[e]	0.3411[e]	+13	+9
April 20, 1999	April 21, 1999	1,000	0.312	1,127	0.3415	+13	+9
		2,100	0.625	2,175	0.6592	+4	+5
		4,100	1.25	4,102	1.243	0	–1
June 23, 1999	June 23, 1999	1,000	0.312	1,058	0.3207	+6	+3
		2,100	0.625	2,073	0.6282	–1	+1
		4,100	1.25	4,095	1.241	0	–1
	July 21-22, 1999[c]	1,000	0.312	928	0.2813	–7	–10
		2,100	0.625	2,108[f]	0.6389 ± 0.0568[f]	0	+2
		4,100	1.25	4,323	1.310	+5	+5
Mice							
September 9, 1997	September 13, 1997	1,000	0.312	1,028	0.3114	+3	0
		2,100	0.625	2,032	0.6157	–3	–1
		4,100	1.25	4,125	1.250	+1	0
	October 16, 1997[c]	1,000	0.312	610	0.1847	–39	–41
		2,100	0.625	1,753	0.5311	–17	–15
		4,100	1.25	3,236	0.9805	–21	–22
November 11, 1997	November 12, 1997	1,000	0.312	1,055	0.3197	+6	+2
		2,100	0.625	2,117	0.6414	+1	+3
		4,100	1.25	4,534	1.374	+11	+10
February 3, 1998	February 9, 1998	1,000	0.312	1,038	0.3145	+4	+1
		2,100	0.625	2,066	0.6260	–2	0
		4,100	1.25	4,214	1.277	+3	+2
April 7, 1998	April 8-9, 1998	1,000	0.312	1,071	0.3244	+7	+4
		2,100	0.625	2,151	0.6518	+2	+4
		4,100	1.25	4,376	1.326	+7	+6
	May 7, 1998[c]	1,000	0.312	1,027	0.3111	+3	0
		2,100	0.625	2,018	0.6114	–4	–2
		4,100	1.25	4,148	1.257	+1	+1

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *trans*-Cinnamaldehyde

Date Prepared	Date Analyzed	Target Concentration (ppm)	Target Concentration microcaps	Determined Concentration (ppm)	Determined Concentration microcaps	Difference from Target (%) (ppm)	Difference from Target (%) microcaps
Mice (continued)							
June 30, 1998	July 1-2, 1998	1,000	0.312	1,028	0.3114	+3	0
		2,100	0.625	2,071	0.6276	–1	0
		4,100	1.25	4,112	1.246	0	0
September 1, 1998	September 2-3, 1998	1,000	0.312	987	0.2992	–1	–4
		2,100	0.625	1,981	0.6002	–6	–4
		4,100	1.25	4,138	1.254	+1	0
November 24, 1998	November 24-25, 1998	1,000	0.312	1,058	0.3207	+6	+3
		2,100	0.625	2,132	0.6461	+2	+3
		4,100	1.25	4,274	1.295	+4	+4
	January 6-7, 1999[c]	1,000	0.312	1,072	0.3247	+7	+4
		2,100	0.625	1,932	0.5854	–8	–6
		4,100	1.25	3,894	1.180	–5	–6
January 26, 1999	January 26-27, 1999	1,000	0.312	1,264[d]	0.3830[d]	+26	+23
		1,000	0.312	1,198[d,e]	0.3631[d,e]	+20	+16
		2,100	0.625	2,203	0.6676	+5	+7
		4,100	1.25	4,363	1.322	+6	+6
January 28, 1999	January 28, 1999	1,000	0.312	1,126[e]	0.3411[e]	+13	+9
April 20, 1999	April 21, 1999	1,000	0.312	1,127	0.3415	+13	+9
		2,100	0.625	2,175	0.6592	+4	+5
		4,100	1.25	4,102	1.243	0	–1
June 23, 1999	June 23, 1999	1,000	0.312	1,058	0.3207	+6	+3
		2,100	0.625	2,073	0.6282	–1	+1
		4,100	1.25	4,095	1.241	0	–1
	July 28-29, 1999[c]	1,000	0.312	888	0.2690	–11	–14
		2,100	0.625	2,045	0.6197	–3	–1
		4,100	1.25	4,039	1.224	–1	–2
August 24, 1999	August 25-26, 1999	1,000	0.312	1,066	0.3231	+7	+4
		2,100	0.625	2,073	0.6281	–1	0
		4,100	1.25	4,184	1.268	+2	+1

[a] Results of duplicate analyses
[b] Percentage of loaded microcapsules in the feed
[c] Animal room samples
[d] Remixed; not used in study
[e] Results of remix
[f] Average of two sets of duplicate analyses. Additional samples were analyzed because the expected/observed ratio for the initial set of two aliquots indicated poor reproducibility. Application of the Q-test indicated that none of the values could be discarded.

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF *trans*-CINNAMALDEHYDE

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Week	Untreated Control		Vehicle Control		1,000 ppm			2,100 ppm			4,100 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
1	17.2	98	17.3	97	16.6	98	175	15.5	98	328	12.6	98	530
2	17.3	134	17.6	134	16.9	132	131	16.2	129	259	15.4	122	523
6	19.7	253	20.0	255	19.7	252	81	19.5	244	165	18.7	237	326
10	16.7	307	16.2	308	16.4	304	56	16.4	294	115	16.3	284	237
14	17.4	343	17.7	350	17.2	342	52	16.5	329	104	16.9	320	218
18	17.0	374	17.0	378	15.9	368	45	16.0	358	92	15.0	345	180
22	18.2	393	18.3	397	17.6	382	48	17.6	375	97	17.1	361	195
26	18.9	404	20.2	410	19.3	397	50	18.0	387	96	18.2	373	201
30	19.6	421	19.1	424	18.5	413	46	19.4	404	99	17.4	388	185
34	19.2	439	19.3	444	18.4	430	44	18.8	420	92	18.5	404	189
38	19.4	445	19.1	448	19.2	438	45	18.3	429	88	18.4	411	185
42	18.1	458	18.1	463	17.4	449	40	18.3	440	86	16.3	421	160
46	18.5	466	18.7	468	18.2	456	41	18.5	446	85	18.0	427	174
50	18.4	468	19.8	475	18.7	462	42	18.4	453	84	17.7	433	168
54	18.0	474	17.9	484	17.3	468	38	17.8	458	80	17.1	438	161
58	16.8	478	17.1	482	15.8	468	35	16.2	463	72	15.6	441	146
62	16.0	472	16.9	476	16.4	466	36	16.6	457	75	16.0	438	151
66	18.0	479	18.5	489	18.3	471	40	17.6	461	79	17.3	445	160
70	17.1	478	17.0	480	16.9	472	37	17.2	464	77	15.6	442	145
74	17.9	483	17.8	485	18.4	475	40	17.9	468	79	17.9	445	161
78	18.1	482	18.2	486	18.4	476	40	18.0	469	79	17.4	444	161
82	17.7	485	17.3	491	16.4	476	36	17.0	470	75	16.1	448	149
86	17.8	478	16.9	487	16.6	474	36	17.3	467	76	16.6	445	154
90	17.4	480	17.7	492	17.0	475	37	16.6	460	74	15.9	440	149
94	17.3	477	16.6	485	16.3	475	35	16.3	461	73	14.8	444	138
98	15.8	480	17.0	488	14.8	466	33	14.9	451	68	15.6	439	147
102	16.0	470	17.5	487	16.2	467	36	15.0	443	70	15.7	435	149
Mean for weeks													
1-13	17.7	198	17.8	199	17.4	196	111	16.9	191	217	15.8	185	404
14-52	18.5	421	18.7	426	18.0	414	45	18.0	404	92	17.4	388	185
53-102	17.2	478	17.4	486	16.8	472	37	16.8	461	75	16.3	442	152

[a] Grams of feed consumed per animal per day
[b] Milligrams of *trans*-cinnamaldehyde consumed per kilogram body weight per day

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Week	Untreated Control		Vehicle Control		1,000 ppm			2,100 ppm			4,100 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
1	12.9	92	12.9	94	12.8	91	144	12.5	93	278	10.8	94	473
2	12.4	113	12.3	113	12.4	113	113	12.5	113	229	12.1	110	453
6	12.1	162	12.4	163	12.2	160	79	11.8	160	153	11.5	156	305
10	10.8	181	10.6	182	10.7	179	62	9.8	175	116	10.2	173	244
14	10.3	191	10.3	191	11.2	194	60	10.6	187	117	10.5	185	235
18	10.9	201	10.9	201	10.8	201	55	10.7	198	111	10.4	191	225
22	11.0	209	11.5	212	11.8	212	57	10.6	204	107	10.6	200	219
26	11.1	211	11.5	214	12.0	214	58	11.3	207	112	10.8	201	221
30	12.0	220	12.9	221	11.9	222	55	11.8	215	113	11.5	207	229
34	12.2	230	12.3	234	12.5	232	56	11.5	225	106	11.4	218	216
38	11.7	236	12.0	238	12.2	239	53	11.8	229	107	11.4	222	212
42	11.4	243	11.7	247	11.7	246	49	11.6	239	100	10.8	228	196
46	12.1	250	12.4	255	12.6	255	51	11.9	246	100	11.3	236	197
50	12.7	261	11.4	262	12.5	264	49	12.1	253	99	12.0	243	204
54	12.3	271	12.2	274	11.8	274	44	12.1	264	95	11.8	252	192
58	11.6	278	12.1	283	11.4	280	42	12.1	269	92	11.3	258	180
62	11.6	286	11.4	289	12.0	288	43	11.3	276	84	11.3	266	175
66	11.8	292	11.4	294	12.4	293	44	11.8	283	86	11.6	271	178
70	11.9	297	12.0	299	12.7	299	44	12.6	288	90	12.0	277	179
74	12.6	308	13.1	310	13.3	310	44	12.5	298	86	12.2	286	177
78	12.6	309	12.7	316	12.6	312	42	12.3	298	85	11.4	286	165
82	12.7	315	13.1	320	13.0	318	42	13.4	308	89	12.2	291	173
86	13.2	321	13.0	324	13.4	321	43	12.8	313	84	12.1	295	169
90	13.0	328	12.4	331	12.5	325	40	12.2	315	80	12.0	301	165
94	12.4	325	13.2	336	12.8	327	40	13.2	326	83	12.5	310	166
98	12.9	331	12.3	338	12.6	329	40	11.9	330	75	11.4	310	151
102	11.9	329	12.7	344	13.4	332	42	13.6	337	83	11.8	309	157
Mean for weeks													
1-13	12.1	137	12.0	138	12.0	136	99	11.7	135	194	11.2	133	369
14-52	11.5	225	11.7	227	11.9	228	54	11.4	220	107	11.1	213	215
53-102	12.4	307	12.4	312	12.6	308	42	12.4	300	86	11.8	285	171

[a] Grams of feed consumed per animal per day
[b] Milligrams of *trans*-cinnamaldehyde consumed per kilogram body weight per day

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Week	Untreated Control		Vehicle Control		1,000 ppm			2,100 ppm			4,100 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
2	4.5	22.2	4.4	22.8	4.4	22.4	203	4.3	22.0	405	4.3	22.0	811
6	4.5	25.6	4.5	25.8	4.4	25.9	175	4.5	25.3	370	4.5	24.5	753
9	4.7	29.3	4.8	29.9	4.6	29.2	163	4.8	28.3	349	4.8	27.5	726
13	4.3	31.8	4.5	32.3	4.4	31.5	143	4.4	30.3	298	4.4	29.0	621
18	4.5	34.8	4.5	35.4	4.3	34.5	129	4.7	32.4	300	4.5	31.8	583
22	4.5	36.8	4.6	36.9	4.5	36.7	127	4.7	34.4	280	4.7	33.2	579
26	4.5	38.9	4.5	39.1	4.5	39.0	119	4.4	36.4	250	4.4	35.7	511
30	4.2	40.2	4.3	40.6	4.1	40.5	105	4.2	38.2	229	4.3	36.8	476
34	4.5	42.0	4.5	42.5	4.4	42.4	106	4.4	39.9	226	4.2	38.1	459
38	4.8	42.2	4.9	42.6	4.8	42.2	116	4.7	40.1	245	4.7	38.1	508
42	4.5	42.2	4.6	43.0	4.5	42.6	108	4.3	40.0	224	4.3	38.1	465
46	4.8	43.0	4.9	43.7	4.8	43.2	115	4.8	40.7	244	4.6	38.6	497
50	4.5	44.2	4.7	45.4	4.5	44.6	103	4.6	42.4	226	4.5	40.3	463
54	4.6	45.3	4.7	46.0	4.6	45.3	104	4.6	43.1	218	4.4	41.0	447
58	4.6	45.5	4.6	46.5	4.5	45.9	101	4.6	43.2	218	4.3	40.9	438
62	4.5	44.5	4.7	46.1	4.4	45.1	100	4.5	42.1	219	4.4	40.1	457
66	4.6	43.6	4.7	45.1	4.6	44.0	107	4.6	41.1	230	4.5	39.0	472
70	4.7	43.5	4.8	44.8	4.7	43.8	111	4.6	40.5	236	4.3	38.2	466
74	4.7	43.1	4.7	43.8	4.4	42.4	106	4.4	39.0	231	4.3	36.3	483
78	4.3	39.6	4.6	40.5	4.0	38.3	109	4.3	35.0	250	4.3	32.8	543
82	4.8	38.3	4.9	38.9	4.7	36.8	132	4.9	33.6	300	4.7	32.0	609
86	4.9	37.4	4.9	37.9	4.8	35.6	138	4.9	32.6	308	4.8	31.6	626
90	4.9	34.7	4.8	35.4	4.9	33.4	150	5.1	32.1	328	4.6	32.3	587
94	4.2	34.6	4.5	35.9	4.3	33.7	131	4.3	32.6	275	4.1	32.1	528
98	4.5	34.6	4.6	36.0	4.4	33.2	136	4.3	32.2	277	4.3	32.0	551
102	4.5	34.8	4.6	35.6	4.3	33.1	134	4.5	32.3	287	4.3	32.1	551
Mean for weeks													
1-13	4.5	27.2	4.5	27.7	4.4	27.2	171	4.5	26.5	356	4.5	25.7	728
14-52	4.6	40.5	4.6	41.0	4.5	40.6	114	4.5	38.3	247	4.5	36.7	505
53-102	4.6	40.0	4.7	41.0	4.5	39.3	120	4.6	36.9	260	4.4	35.4	520

[a] Grams of feed consumed per animal per day
[b] Milligrams of *trans*-cinnamaldehyde consumed per kilogram body weight per day

TABLE J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of *trans*-Cinnamaldehyde

Week	Untreated Control		Vehicle Control		1,000 ppm			2,100 ppm			4,100 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
1	3.5	17.9	3.3	17.9	3.1	17.6	179	3.2	17.9	373	3.1	17.9	728
2	3.6	18.8	3.5	18.8	3.6	18.4	202	3.5	18.5	388	3.3	18.5	745
6	3.9	22.0	3.2	20.6	3.9	21.5	186	3.5	20.5	351	3.9	21.1	761
9	4.1	24.7	4.1	24.6	4.2	24.4	176	4.1	23.9	353	4.0	23.8	699
13	4.3	28.0	4.1	27.4	4.3	27.1	163	4.2	26.5	330	4.3	25.7	687
18	4.2	31.5	4.6	31.5	4.5	31.1	148	4.6	29.7	318	4.3	28.6	619
22	4.7	34.1	4.3	33.8	4.7	33.4	145	4.8	32.5	304	4.9	30.5	664
26	4.7	35.8	4.5	36.5	4.7	36.1	135	4.8	35.5	276	4.9	33.1	610
30	4.2	36.8	4.2	36.2	3.9	36.3	112	4.2	35.3	243	4.1	33.7	507
34	4.5	39.6	4.6	39.5	4.6	38.9	123	4.8	38.4	257	4.5	35.9	521
38	4.4	39.9	4.3	40.0	4.3	38.8	114	4.3	38.3	231	4.5	36.3	514
42	4.3	40.8	4.5	40.8	4.4	39.7	115	4.4	38.9	235	4.6	36.7	511
46	4.9	41.6	4.8	41.8	4.5	40.4	116	4.6	39.2	244	4.7	37.0	525
50	4.6	42.8	4.4	43.2	4.3	41.7	107	4.2	40.1	215	4.3	38.5	457
54	4.6	43.7	4.8	44.2	4.7	43.2	113	4.8	41.8	237	5.0	39.5	523
58	4.4	44.7	4.4	45.2	4.4	44.1	103	4.4	42.7	213	4.0	38.8	429
62	4.4	44.9	4.5	45.4	4.6	44.0	109	4.6	41.9	224	5.0	38.3	534
66	4.4	44.2	4.3	43.4	4.3	43.2	104	4.5	40.9	229	4.6	37.8	500
70	4.7	45.2	4.5	44.8	4.8	43.3	115	4.2	40.7	215	4.6	38.3	492
74	5.0	45.3	5.0	46.0	4.9	43.9	116	4.9	40.9	247	4.8	37.7	520
78	4.2	42.7	3.8	42.7	4.3	41.2	106	4.2	37.1	235	4.4	34.8	519
82	4.3	40.8	4.3	40.2	4.4	39.9	115	4.6	34.8	275	5.1	33.3	636
86	4.7	39.6	4.6	40.0	4.6	39.6	119	5.0	34.1	304	5.2	33.1	653
90	4.8	37.8	4.9	39.2	5.0	38.3	133	4.9	34.1	294	4.9	33.3	607
94	4.4	38.8	4.1	39.0	4.5	37.7	123	5.0	34.7	295	4.3	33.5	527
98	4.9	40.2	5.0	40.9	4.7	39.2	124	5.0	35.5	291	4.5	33.6	550
102	4.7	39.6	4.8	40.4	4.7	39.0	125	4.7	35.0	278	4.7	34.2	567
Mean for weeks													
1-13	3.9	22.3	3.6	21.9	3.8	21.8	181	3.7	21.5	359	3.7	21.4	724
14-52	4.5	38.1	4.5	38.1	4.5	37.4	124	4.5	36.4	258	4.5	34.5	548
53-102	4.6	42.1	4.5	42.4	4.6	41.3	116	4.7	38.0	257	4.7	35.9	543

[a] Grams of feed consumed per animal per day
[b] Milligrams of *trans*-cinnamaldehyde consumed per kilogram body weight per day

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

TABLE K1
Ingredients of NTP-2000 Rat and Mouse Ration

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

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

TABLE K2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

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

[a] Per kg of finished product

TABLE K3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.6 ± 0.38	12.9 – 14.5	26
Crude fat (% by weight)	8.1 ± 0.26	7.6 – 8.6	26
Crude fiber (% by weight)	9.2 ± 0.70	8.2 – 11.1	26
Ash (% by weight)	5.2 ± 0.24	4.6 – 5.6	26
Amino Acids (% of total diet)			
Arginine	0.731 ± 0.050	0.670 – 0.800	8
Cystine	0.224 ± 0.012	0.210 – 0.240	8
Glycine	0.684 ± 0.041	0.620 – 0.740	8
Histidine	0.333 ± 0.018	0.310 – 0.350	8
Isoleucine	0.524 ± 0.046	0.430 – 0.590	8
Leucine	1.061 ± 0.061	0.960 – 1.130	8
Lysine	0.708 ± 0.056	0.620 – 0.790	8
Methionine	0.401 ± 0.035	0.350 – 0.460	8
Phenylalanine	0.598 ± 0.036	0.540 – 0.640	8
Threonine	0.501 ± 0.051	0.430 – 0.590	8
Tryptophan	0.126 ± 0.014	0.110 – 0.150	8
Tyrosine	0.390 ± 0.056	0.280 – 0.460	8
Valine	0.640 ± 0.049	0.550 – 0.690	8
Essential Fatty Acids (% of total diet)			
Linoleic	3.97 ± 0.284	3.59 – 4.54	8
Linolenic	0.30 ± 0.042	0.21 – 0.35	8
Vitamins			
Vitamin A (IU/kg)	5,786 ± 1,381	3,950 – 8,710	26
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	82.2 ± 14.08	62.2 – 107.0	8
Thiamine (ppm)	8.8 ± 1.71	6.3 – 15.7	26
Riboflavin (ppm)	5.6 ± 1.12	4.20 – 7.70	8
Niacin (ppm)	74.3 ± 5.94	66.4 – 85.8	8
Pantothenic acid (ppm)	22.5 ± 3.96	17.4 – 29.1	8
Pyridoxine (ppm)	9.04 ± 2.37	6.4 – 12.4	8
Folic acid (ppm)	1.64 ± 0.38	1.26 – 2.32	8
Biotin (ppm)	0.333 ± 0.15	0.225 – 0.704	8
Vitamin B_{12} (ppb)	68.7 ± 63.0	18.3 – 174.0	8
Choline (ppm)	3,155 ± 325	2,700 – 3,790	8
Minerals			
Calcium (%)	1.015 ± 0.068	0.908 – 1.240	26
Phosphorus (%)	0.563 ± 0.032	0.487 – 0.628	26
Potassium (%)	0.659 ± 0.022	0.627 – 0.691	8
Chloride (%)	0.357 ± 0.027	0.300 – 0.392	8
Sodium (%)	0.189 ± 0.019	0.160 – 0.212	8
Magnesium (%)	0.199 ± 0.009	0.185 – 0.213	8
Sulfur (%)	0.178 ± 0.021	0.153 – 0.209	8
Iron (ppm)	160 ± 14.7	135 – 177	8
Manganese (ppm)	50.3 ± 4.82	42.1 – 56.0	8
Zinc (ppm)	50.7 ± 6.59	43.3 – 61.1	8
Copper (ppm)	6.29 ± 0.828	5.08 – 7.59	8
Iodine (ppm)	0.461 ± 0.187	0.233 – 0.843	8
Chromium (ppm)	0.542 ± 0.128	0.330 – 0.707	7
Cobalt (ppm)	0.23 ± 0.049	0.20 – 0.30	7

[a] From formulation

TABLE K4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.20 ± 0.142	0.10 – 0.62	26
Cadmium (ppm)	0.04 ± 0.006	0.04 – 0.07	26
Lead (ppm)	0.08 ± 0.043	0.05 – 0.28	26
Mercury (ppm)	<0.02		26
Selenium (ppm)	0.20 ± 0.039	0.14 – 0.29	26
Aflatoxins (ppb)	<5.00		26
Nitrate nitrogen (ppm)[c]	14.4 ± 7.85	9.04 – 43.2	26
Nitrite nitrogen (ppm)[c]	<0.61		26
BHA (ppm)[d]	1.1 ± 0.47	1.0 – 3.4	26
BHT (ppm)[d]	<1.0		26
Aerobic plate count (CFU/g)	<10		26
Coliform (MPN/g)	0.1 ± 0.6	0 – 3	26
Escherichia coli (MPN/g)	<10		26
Salmonella (MPN/g)	Negative		26
Total nitrosoamines (ppb)[e]	5.3 ± 1.77	2.4 – 9.3	26
N-Nitrosodimethylamine (ppb)[e]	2.2 ± 0.66	1.2 – 3.5	26
N-Nitrosopyrrolidine (ppb)[e]	3.1 ± 1.4	1.0 – 6.0	26
Pesticides (ppm)			
α-BHC	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.10		26
Estimated PCBs	<0.20		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.10		26
Methyl chlorpyrifos	0.104 ± 0.099	0.020 – 0.401	26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion	0.279 ± 0.465	0.020 – 2.430	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

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

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

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

Method and Test	Time of Analysis
RATS	
3-Month Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	5 weeks, study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	5 weeks, study termination
Sendai	5 weeks, study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	5 weeks, study termination
KRV (Kilham rat virus)	5 weeks, study termination
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
RCV/SDA	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	1, 6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE	
3-Month Study	
ELISA	
Ectromelia virus	5 weeks, study termination
EDIM (epizootic diarrhea of infant mice)	5 weeks, study termination
GDVII (mouse encephalomyelitis virus)	5 weeks, study termination
LCM (lymphocytic choriomeningitis virus)	5 weeks, study termination
Mouse adenoma virus-FL	5 weeks, study termination
MHV (mouse hepatitis virus)	5 weeks, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	5 weeks, study termination
Reovirus 3	5 weeks, study termination
Sendai	5 weeks, study termination
Immunofluorescence Assay	
MCMV (mouse cytomegalovirus)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	5 weeks, study termination
MVM (minute virus of mice)	5 weeks, study termination
Polyoma virus	5 weeks, study termination
2-Year Study	
ELISA	
Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM	1, 6, 12, and 18 months, study termination
GDVII	1, 6, 12, and 18 months, study termination
LCM	1, 6, 12, and 18 months, study termination
Mouse adenoma virus-FL	1, 6, 12, and 18 months, study termination
MHV	1, 6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	1, 6, 12, and 18 months, study termination
MCMV	Study termination

RESULTS

All test results were negative.

National Toxicology Program Technical Reports

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Chemical	TR No.
Acetaminophen	394
Acetonitrile	447
Acrylonitrile	506
Agar	230
Allyl Glycidyl Ether	376
Allyl Isothiocyanate	234
Allyl Isovalerate	253
1-Amino-2,4-Dibromoanthraquinone	383
2-Amino-4-Nitrophenol	339
2-Amino-5-Nitrophenol	334
11-Aminoundecanoic Acid	216
dl-Amphetamine Sulfate	387
Ampicillin Trihydrate	318
Asbestos, Amosite (Hamsters)	249
Asbestos, Amosite (Rats)	279
Asbestos, Chrysotile (Hamsters)	246
Asbestos, Chrysotile (Rats)	295
Asbestos, Crocidolite	280
Asbestos, Tremolite	277
L-Ascorbic Acid	247
AZT and AZT/α-Interferon A/D	469
Barium Chloride Dihydrate	432
Benzaldehyde	378
Benzene	289
Benzethonium Chloride	438
Benzofuran	370
Benzyl Acetate (Gavage)	250
Benzyl Acetate (Feed)	431
Benzyl Alcohol	343
o-Benzyl-*p*-Chlorophenol (Gavage)	424
o-Benzyl-*p*-Chlorophenol (Mouse Skin)	444
2-Biphenylamine Hydrochloride	233
2,2-Bis(Bromomethyl)-1,3-Propanediol	452
Bis(2-Chloro-1-Methylethyl) Ether	239
Bisphenol A	215
Boric Acid	324
Bromodichloromethane	321
Bromoethane	363
1,3-Butadiene	288
1,3-Butadiene	434
t-Butyl Alcohol	436
Butyl Benzyl Phthalate	213
Butyl Benzyl Phthalate	458
n-Butyl Chloride	312
t-Butylhydroquinone	459
γ-Butyrolactone	406
Caprolactam	214
d-Carvone	381
Chloral Hydrate	502
Chloral Hydrate	503
Chlorinated and Chloraminated Water	392
Chlorendic Acid	304
Chlorinated Paraffins: C_{23}, 43% Chlorine	305
Chlorinated Paraffins: C_{12}, 60% Chlorine	308
Chlorinated Trisodium Phosphate	294
2-Chloroacetophenone	379
p-Chloroaniline Hydrochloride	351
Chlorobenzene	261
Chlorodibromomethane	282
Chloroethane	346
2-Chloroethanol	275
3-Chloro-2-Methylpropene	300
Chloroprene	467
1-Chloro-2-Propanol	477
Chlorpheniramine Maleate	317
C.I. Acid Orange 3	335
C.I. Acid Orange 10	211
C.I. Acid Red 14	220
C.I. Acid Red 114	405
C.I. Basic Red 9 Monohydrochloride	285
C.I. Direct Blue 15	397
C.I. Direct Blue 218	430
C.I. Disperse Blue 1	299
C.I. Disperse Yellow 3	222
C.I. Pigment Red 3	407
C.I. Pigment Red 23	411
C.I. Solvent Yellow 14	226
trans-Cinnamaldehyde	514
Citral	505
Cobalt Sulfate Heptahydrate	471
Coconut Oil Acid Diethanolamine Condensate	479
Codeine	455
Comparative Initiation/Promotion Studies (Mouse Skin)	441
Corn Oil, Safflower Oil, and Tricaprylin	426
Coumarin	422
CS2	377
Cytembena	207
D&C Red No. 9	225
D&C Yellow No. 11	463
Decabromodiphenyl Oxide	309
Diallyl Phthalate (Mice)	242
Diallyl Phthalate (Rats)	284
4,4′-Diamino-2,2′-Stilbenedisulfonic Acid, Disodium Salt	412
2,4-Diaminophenol Dihydrochloride	401
1,2-Dibromo-3-Chloropropane	206
1,2-Dibromoethane	210
2,3-Dibromo-1-Propanol	400
1,2-Dichlorobenzene (*o*-Dichlorobenzene)	255
1,4-Dichlorobenzene (*p*-Dichlorobenzene)	319
p,p′-Dichlorodiphenyl sulfone	501
2,4-Dichlorophenol	353
2,6-Dichloro-*p*-Phenylenediamine	219
1,2-Dichloropropane	263
1,3-Dichloropropene (Telone II)	269
Dichlorvos	342
Dietary Restriction	460
Diethanolamine	478
Di(2-Ethylhexyl) Adipate	212
Di(2-Ethylhexyl) Phthalate	217
Diethyl Phthalate	429
Diglycidyl Resorcinol Ether	257
3,4-Dihydrocoumarin	423
1,2-Dihydro-2,2,4-Trimethylquinoline (Monomer)	456
Dimethoxane	354
3,3′-Dimethoxybenzidine Dihydrochloride	372
N,N-Dimethylaniline	360
3,3′-Dimethylbenzidine Dihydrochloride	390
Dimethyl Hydrogen Phosphite	287
Dimethyl Methylphosphonate	323
Dimethyl Morpholinophosphoramidate	298
Dimethylvinyl Chloride	316
Diphenhydramine Hydrochloride	355
5,5-Diphenylhydantoin	404
Emodin	493
Ephedrine Sulfate	307
Epinephrine Hydrochloride	380
1,2-Epoxybutane	329
Erythromycin Stearate	338

Chemical	TR No.
Ethyl Acrylate	259
Ethylbenzene	466
Ethylene Glycol	413
Ethylene Glycol Monobutyl Ether	484
Ethylene Oxide	326
Ethylene Thiourea	388
Eugenol	223
FD&C Yellow No. 6	208
Fumonisin B_1	496
Furan	402
Furfural	382
Furfuryl Alcohol	482
Furosemide	356
Gallium Arsenide	492
Geranyl Acetate	252
Glutaraldehyde	490
Glycidol	374
Guar Gum	229
Gum Arabic	227
HC Blue 1	271
HC Blue 2	293
HC Red 3	281
HC Yellow 4	419
Hexachlorocyclopentadiene	437
Hexachloroethane	361
2,4-Hexadienal	509
4-Hexylresorcinol	330
Hydrochlorothiazide	357
Hydroquinone	366
8-Hydroxyquinoline	276
Indium Phosphide	499
Iodinated Glycerol	340
Isobutene	487
Isobutyl Nitrite	448
Isobutyraldehyde	472
Isophorone	291
Isoprene	486
Lauric Acid Diethanolamine Condensate	480
d-Limonene	347
Locust Bean Gum	221
60-Hz Magnetic Fields	488
Magnetic Field Promotion	489
Malonaldehyde, Sodium Salt	331
Manganese Sulfate Monohydrate	428
D-Mannitol	236
Marine Diesel Fuel and JP-5 Navy Fuel	310
Melamine	245
2-Mercaptobenzothiazole	332
Mercuric Chloride	408
Methacrylonitrile	497
8-Methoxypsoralen	359
α-Methylbenzyl Alcohol	369
Methyl Bromide	385
Methyl Carbamate	328
Methyldopa Sesquihydrate	348
Methylene Chloride	306
4,4′-Methylenedianiline Dihydrochloride	248
Methyleugenol	491
Methyl Methacrylate	314
N-Methylolacrylamide	352
Methylphenidate Hydrochloride	439
Mirex	313
Molybdenum Trioxide	462
Monochloroacetic Acid	396
Monuron	266
Nalidixic Acid	368
Naphthalene (Mice)	410
Naphthalene (Rats)	500
Nickel (II) Oxide	451
Nickel Sulfate Hexahydrate	454
Nickel Subsulfide	453
p-Nitroaniline	418
o-Nitroanisole	416
p-Nitrobenzoic Acid	442
Nitrofurantoin	341
Nitrofurazone	337
Nitromethane	461
p-Nitrophenol	417
o-Nitrotoluene	504
p-Nitrotoluene	498
Ochratoxin A	358
Oleic Acid Diethanolamine Condensate	481
Oxazepam (Mice)	443
Oxazepam (Rats)	468
Oxymetholone	485
Oxytetracycline Hydrochloride	315
Ozone and Ozone/NNK	440
Penicillin VK	336
Pentachloroanisole	414
Pentachloroethane	232
Pentachloronitrobenzene	325
Pentachlorophenol, Purified	483
Pentachlorophenol, Technical Grade	349
Pentaerythritol Tetranitrate	365
Phenolphthalein	465
Phenylbutazone	367
Phenylephrine Hydrochloride	322
N-Phenyl-2-Naphthylamine	333
o-Phenylphenol	301
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Gavage)	244
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Feed)	398
Polysorbate 80 (Glycol)	415
Polyvinyl Alcohol	474
Primidone	476
Probenecid	395
Promethazine Hydrochloride	425
Propylene	272
Propylene Glycol Mono-*t*-butyl Ether	515
1,2-Propylene Oxide	267
Propyl Gallate	240
Pyridine	470
Quercetin	409
Riddelliine	508
Resorcinol	403
Rhodamine 6G	364
Rotenone	320
Roxarsone	345
Salicylazosulfapyridine	457
Scopolamine Hydrobromide Trihydrate	445
Sodium Azide	389
Sodium Fluoride	393
Sodium Nitrite	495
Sodium Xylenesulfonate	464
Stannous Chloride	231
Succinic Anhydride	373
Talc	421
Tara Gum	224
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Dermal)	201
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Gavage)	209
1,1,1,2-Tetrachloroethane	237
Tetrachloroethylene	311
Tetracycline Hydrochloride	344
Tetrafluoroethylene	450
1-Trans-Delta^9-Tetrahydrocannabinol	446
Tetrahydrofuran	475
Tetrakis(Hydroxymethyl)Phosphonium Sulfate	296
Tetrakis(Hydroxymethyl)Phosphonium Chloride	296
Tetranitromethane	386
Theophylline	473
4,4-Thiobis(6-*t*-Butyl-*m*-Cresol)	435
Titanocene Dichloride	399
Toluene	371

Chemical	TR No.	Chemical	TR No.
2,4- & 2,6-Toluene Diisocyanate	251	Turmeric Oleoresin (Curcumin)	427
Triamterene	420	Vanadium Pentoxide	507
Tribromomethane	350	4-Vinylcyclohexene	303
Trichloroethylene	243	4-Vinyl-1-Cyclohexene Diepoxide	362
Trichloroethylene	273	Vinylidene Chloride	228
1,2,3-Trichloropropane	384	Vinyl Toluene	375
Tricresyl Phosphate	433	Xylenes (Mixed)	327
Triethanolamine	449	2,6-Xylidine	278
Tris(2-Chloroethyl) Phosphate	391	Zearalenone	235
Tris(2-Ethylhexyl) Phosphate	274	Ziram	238

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