NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF CITRAL (MICROENCAPSULATED)

(CAS NO. 5392-40-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

January 2003

NTP TR 505

NIH Publication No. 03-4439

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 basis 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 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 NTP Technical Reports printed since 1982 appears on the inside back cover.

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SUMMARY

Background

Citral is used as a lemon flavoring in foods, drinks, and candies and as a lemon fragrance. We studied the effects of citral on male and female rats and mice to identify potential toxic or cancer-related hazards to humans.

Methods

Because citral 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 to rats were 1,000, 2,000, or 4,000 parts per million (ppm) citral (equivalent to 0.1%, 0.2%, or 0.4%). Doses of 500 ppm, 1,000 ppm, or 2,000 ppm were given to mice. Control animals received empty starch microcapsules in their feed. Tissues from more than 40 sites were examined for every animal.

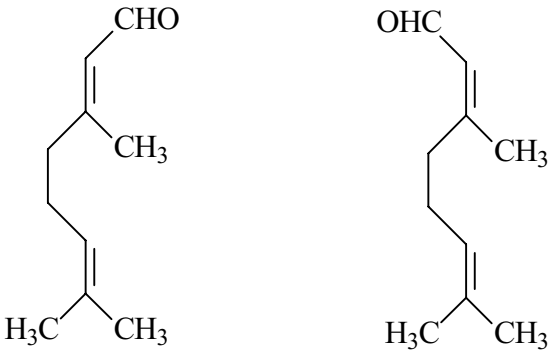
Results

Rats receiving 4,000 ppm citral and mice receiving 1,000 or 2,000 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 given citral compared with the rats that were not. Female mice receiving 2,000 ppm citral had higher numbers of malignant lymphomas than did their controls.

Conclusions

We conclude that citral did not cause cancer in male or female rats or in male mice. An increase in lymphomas in female mice may have been related to eating citral.

ABSTRACT



Geranial Neral

CITRAL

CAS No. 5392-40-5

Chemical Formula: $C_{10}H_{16}O$ Molecular Weight: 152.23

Synonyms: **Geranial**–*E*-3,7-dimethyl-2,6-octadienal; citral A
Neral–*Z*-3,7-dimethyl-2,6-octadienal; citral B
Trade names: Citral, Lemsyn GB

Citral is used primarily as lemon flavoring in foods, beverages, and candies. It is also used as a lemon fragrance in detergents, perfumes, and other toiletries. Citral was nominated by the National Cancer Institute for study because of its widespread use in foods, beverages, cosmetics, and other consumer products and its structure as a representative β-substituted vinyl aldehyde. Male and female F344/N rats and B6C3F$_1$ mice were exposed to microencapsulated citral (greater than 96% pure) in feed for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, mouse bone marrow cells, and mouse peripheral blood erythrocytes.

14-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were fed diets containing starch microcapsules with a load of 31.3% citral. The concentration of citral in the diet was 3,900, 7,800, 15,600, or 31,300 ppm microencapsulated citral (equivalent to average daily doses of approximately 345, 820, 1,785, and 1,585 mg citral/kg body weight to males and 335, 675, 1,330, and 2,125 mg/kg to females) for 14 weeks. Additional groups of 10 male and 10 female rats received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). In the second week of the study, all rats in the 31,300 ppm groups were killed moribund.

Mean body weights of exposed males and females that survived to the end of the study were generally significantly less than those of the vehicle controls. Feed consumption by 15,600 and 31,300 ppm males and females was less than that by the vehicle controls during the first week of the study. Males and females in the 31,300 ppm groups exhibited listlessness, hunched posture, absent or slow paw reflex, and dull eyes. Exposure of rats to citral may have been associated with forestomach epithelial hyperplasia and hyperkeratosis, bone marrow atrophy and hemorrhage, and nephrotoxicity.

14-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were fed diets containing 3,900, 7,800, 15,600, or 31,300 ppm microencapsulated citral (equivalent to average daily doses of approximately 745, 1,840, 3,915, and 8,110 mg/kg to males and 790, 1,820, 3,870, and 7,550 mg/kg to females) for 14 weeks. Additional groups of 10 male and 10 female mice received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). In the second week of the study, four males in the 31,300 ppm group were killed moribund. Mean body weights of all exposed groups of males and females were significantly less than those of the vehicle controls. Feed consumption by females exposed to 7,800 ppm or greater was less than that by the vehicle controls during the first week of the study. By the end of the study, feed consumption by all exposed groups was greater than that by the vehicle controls. Mice in the 15,600 and 31,300 ppm groups were generally thin and lethargic; a few males in the 7,800 ppm group were also thin. The incidences of ovarian atrophy were significantly increased in females exposed to 15,600 or 31,300 ppm.

2-Year Study in Rats

Groups of 50 male and 50 female F344/N rats were fed diets containing 1,000, 2,000, or 4,000 ppm microencapsulated citral 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, 2,000, and 4,000 ppm delivered average daily doses of approximately 50, 100, and 210 mg/kg to males and females. Survival of all exposed groups of males was significantly greater than that of the vehicle control group. Mean body weights of rats exposed to 4,000 ppm were generally less than those of the vehicle controls from week 49 (males) or 25 (females) to the end of the study. Feed consumption by exposed groups was similar to that by the vehicle controls. No neoplasms or nonneoplastic lesions were attributed to exposure to citral.

2-Year Study in Mice

Groups of 50 male and 50 female B6C3F$_1$ mice were fed diets containing 500, 1,000, or 2,000 ppm microencapsulated citral 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 500, 1,000, and 2,000 ppm delivered average daily doses of approximately 60, 120, and 260 mg/kg to males and females. Survival of exposed males and females was similar to that of the vehicle control groups. Mean body weights of mice exposed to 1,000 or 2,000 ppm were generally less than those of the vehicle controls throughout the study, and mean body weights of 500 ppm females were less from week 30 to the end of the study. Feed consumption by the exposed groups was similar to that by the vehicle controls.

The incidences of malignant lymphoma occurred with a positive trend in female mice, and the incidence in 2,000 ppm females was significantly greater than that in the vehicle control group. Tissues most commonly affected by malignant lymphoma were the spleen, mesenteric lymph node, thymus, and, to a lesser extent, the ovary.

Genetic Toxicology

Citral was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without induced rat or hamster liver S9 enzymes. In cytogenetic tests with cultured Chinese hamster ovary cells, citral induced sister chromatid exchanges with and without S9, but chromosomal aberrations were not significantly increased after exposure to citral, with or without S9. Negative results were obtained in an *in vivo* bone marrow micronucleus test in male B6C3F$_1$ mice treated by intraperitoneal injection with 250 to 750 mg/kg daily for 3 days. Likewise, no increases in the frequencies of

micronucleated erythrocytes were observed in peripheral blood samples collected from male and female mice within 24 hours of the final exposure in the 14-week study.

In conclusion, citral gave negative results in *in vitro* and *in vivo* tests for genotoxicity, with the exception of the *in vitro* mammalian cell test for sister chromatid exchange induction.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of citral in male or female F344/N rats exposed to 1,000, 2,000, or 4,000 ppm. There was *no evidence of carcinogenic activity* of citral in male B6C3F$_1$ mice exposed to 500, 1,000, or 2,000 ppm. There was *equivocal evidence of carcinogenic activity* in female B6C3F$_1$ mice based on increased incidences of malignant lymphoma.

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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 public discussion on this Technical Report appears on page 11.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in feed	Vehicle control, 1,000, 2,000, or 4,000 ppm	Vehicle control, 1,000, 2,000, or 4,000 ppm	Vehicle control, 500, 1,000, or 2,000 ppm	Vehicle control, 500, 1,000, or 2,000 ppm
Body weights	4,000 ppm group less than the vehicle control group	4,000 ppm group less than the vehicle control group	1,000 and 2,000 ppm groups less than the vehicle control group	Exposed groups less than the vehicle control group
Survival rates	22/50, 32/50, 35/50, 34/50	40/50, 36/50, 36/50, 36/50	43/50, 40/50, 42/50, 40/50	41/49, 45/50, 43/50, 40/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None
Equivocal findings	None	None	None	Malignant Lymphoma: (3/49, 5/50, 9/50, 12/50)
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges				
Chinese hamster ovary cells *in vitro:*	Positive with and without S9			
Chromosomal aberrations				
Chinese hamster ovary cells *in vitro:*	Negative with and without S9			
Micronucleated erythrocytes				
Mouse bone marrow *in vivo:*	Negative			
Mouse peripheral blood *in vivo:*	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on citral on May 3, 2001, 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 May 3, 2001, the draft of the Technical Report on the toxicology and carcinogenesis studies of citral 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. N.B. Ress, NIEHS, introduced the toxicology and carcinogenesis studies of citral by describing the properties and uses of the chemical, the study rationale, the protocol, the microencapsulation of citral in the feed, and the lesions observed in rats and mice. The proposed conclusions were *no evidence of carcinogenic activity* of citral in male or female F344/N rats, *no evidence of carcinogenic activity* in male $B6C3F_1$ mice, and *some evidence of carcinogenic activity* in female $B6C3F_1$ mice.

Dr. Davis, the first principal reviewer, said that lymphomas are a fairly common neoplasm, and a conclusion of equivocal evidence would be more appropriate for the female mouse study.

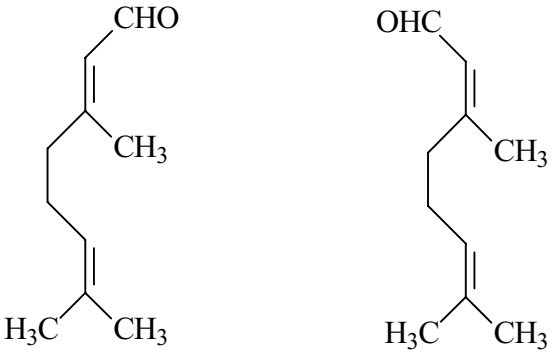
Dr. Piegorsch, the second principal reviewer, suggested the use of formal statistical comparisons with historical data. Dr. J.K. Haseman, NIEHS, said that due to differences in laboratory conditions and other factors among studies, formal comparisons might not be warranted, but the historical data should be used for informal comparisons.

Dr. Thrall, the third principal reviewer, questioned whether hematologic changes should be attributed to reduced feed consumption rather than dehydration, as was urea nitrogen concentration, and felt that both might be related to nephropathy.

Ms. J. Cocchiara, representing the Research Institute for Fragrance Materials, inquired if the ability of citral to change retinal to retinoic acid could have added nutritional stress to the study animals and contributed to decreases in body weight. Dr. Ress believed the main cause of lowered body weights was the toxicity of citral.

Dr. Davis moved that the conclusion be accepted as written, with the exception that the conclusion for female mice be changed to *equivocal evidence of carcinogenic activity*. The vote on the motion was four yes and four no; Dr. Hecht, as chair, broke the tie, and the motion was approved.

INTRODUCTION



Geranial Neral

CITRAL

CAS No. 5392-40-5

Chemical Formula: $C_{10}H_{16}O$ Molecular Weight: 152.23

Synonyms: **Geranial**–*E*-3,7-dimethyl-2,6-octadienal; citral A
Neral–*Z*-3,7-dimethyl-2,6-octadienal; citral B
Trade names: Citral, Lemsyn GB

Chemical and Physical Properties

Citral is a mixture of two geometric isomers: geranial (*E*-3,7-dimethyl-2,6-octadienal) and neral (*Z*-3,7-dimethyl-2,6-octadienal). The geranial-to-neral ratio is usually 2:1 (Steltenkamp *et al*., 1980). It is a light, oily liquid with a strong, lemony odor and a characteristic bittersweet taste (*Fenaroli's*, 1975; HSDB, 1999). Citral has a boiling point of 226° to 228° C, a melting point below −10° C, a vapor pressure of 5 mm Hg at 91° to 95° C, and a specific gravity of 0.891 to 0.897 at 15° C. Citral is miscible with ether, benzyl benzoate, propylene glycol, diethyl phthalate, and glycerol. The solubility of citral in water is 1.34 g/L at 37° C (HSDB, 1999).

Production, Use, and Human Exposure

Citral is on the United States Environmental Protection Agency's (2001) list of high production volume chemicals, which means that it is produced in quantities over 1 million pounds per year. Citral has been a high production chemical for the last three reporting periods (1986, 1990, and 1994) (John Walker, Interagency Testing Committee, personal communication). It is synthesized from isoprene, by dehydrogenation of a geraniol-nerol mixture obtained from β-pinene, or by oxidation of geraniol, nerol, or linalool by chromic acid (HSDB, 1999). Citral is the principal constituent (75%-85%) of lemon grass oil (*Cymbopogon flexuosus*)

and often is isolated by fractional distillation (Opdyke, 1979).

Citral has been identified in litsea [*Litsea citrata* (90%) and *L. cubeba blume* (70%)], a small tree that grows in Eastern Asia and is cultivated, to a minor extent, in Taiwan and Japan. Oil of *L. cubeba* is a pale yellow, mobile oil with an intense lemon-like, fresh, sweet odor. Citral also has been identified in the spice bush [*Lindera citriodora* (65%)], myrtle trees [*Buckhousia citriodora* (95%-97%) and *Calyptranthes parriculata* (62%)], the lemon-scented tea tree [*Leptospermum liversidgei* var. A leaves (70%-80%)], and African basil [*Osimum gratissimum* (97%)] (Opdyke, 1979). Citral has been identified in lemons (2%-5%), limes (6%-9%), grapefruit oil and juice, orange oil and juice, tomatoes, celery, apricot oil, verbena oil, and black currants. In addition, citral has been isolated from sassafras plants (roots and leaves) and from the soil where sassafras grows (*Fenaroli's*, 1975).

Citral is used as a flavoring agent in chewing gum (~170 ppm), baked goods (~43 ppm), candy (~41 ppm), ice cream (~23 ppm), and beverages (~9 ppm) (Opdyke, 1979). It is also used as a fragrance in soaps (0.02%-0.2%), detergents (0.002%-0.02%), creams and lotions (0.005%-0.02%), and perfumes (0.2%-0.8%) (Opdyke, 1979). In addition, citral is used as a chemical intermediate in the synthesis of vitamin A, ionone, and methylionone (*Merck Index*, 1989). The Acceptable Daily Intake is 5 mg citral/kg body weight as listed by the Council of Europe (1973).

The National Occupational Exposure Survey (1981-1983) estimated that at least 65,000 people in the United States are regularly exposed to citral in the workplace each year (NIOSH, 1990). Citral is approved by the Food and Drug Administration for use in foods as a flavoring substance and adjuvant (21 CFR §§ 182.60, 582.60). It was given Generally Recognized As Safe (GRAS) status in the United States (*Fenaroli's*, 1975).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals and Systems

In a study to determine the disposition of citral, male Fischer 344 rats were orally, dermally, or intravenously exposed to [^{14}C]-citral (Diliberto *et al.*, 1988). In the 72 hours after oral exposure to 5, 50, or 500 mg citral/kg body weight, excretion occurred mainly in the urine (48%-63%), followed by exhalation as $^{14}CO_2$ (10%-17%), excretion in the feces (12%-13%), and exhalation as [^{14}C]-citral (less than 1%). The excretion profile did not change with dose. Following dermal exposure to 5 or 50 mg/kg, less than 50% of the administered dose was available for absorption due to evaporation of the citral and adsorption on the metal cap used to prevent grooming of the dose site. The amount that was absorbed was excreted primarily in the urine. Intravenous administration of 5 mg/kg resulted in rapid urinary excretion; after 72 hours, 58% had been excreted in the urine, 8% as $^{14}CO_2$, and 7% in the feces; 6% remained in the carcass, and less than 1% was exhaled as unmetabolized citral. Based on the difference between fecal excretion after oral and intravenous administration, it was estimated that 91% to 95% of the citral was absorbed orally. The whole-body half-life for [^{14}C]-citral-derived radioactivity was estimated to be 8 hours after intravenous administration. In addition, 75% of the citral-derived radioactivity was eliminated from the blood within 2 minutes, with 20% of the radioactivity not being parent citral. Five minutes after intravenous exposure, only metabolites were detected in the blood. After a single intravenous dose of 5 mg/kg, 20% of the total dose was excreted in the bile within an hour, with another 7% appearing after 4.5 hours. Pretreatment with 5 mg/kg for 10 days increased the excretion of the radiolabeled compound in the bile to 34% of the total dose but did not change the elimination pattern. All three exposure routes resulted in a widespread tissue distribution, with no evidence of a major depot.

Urinary metabolites were identified in male Fischer rats after a single oral exposure of 500 mg citral/kg body weight as 3-hydroxy-3,7-dimethyl-6-octenedioic acid; 3,8-dihydroxy-3,7-dimethyl-6-octenoic acid; 3,9-dihydroxy-3,7-dimethyl-6-octenoic acid; *E*-3,7-dimethyl-2,6-octadienedioic acid; 3,7-dimethyl-6-octenedioic acid; *Z*-3,7-dimethyl-2,6-octadienedioic acid; and *E*-3,7-dimethyl-2,6-octadienoic acid (Figure 1); (Diliberto *et al*., 1990). The proposed metabolism involves reduction or hydration of the 2,3-double bond, oxidation of the aldehyde function, and allylic oxidation at the C-8 and possibly the C-9 position. Although citral contains double bonds that are potential sites for oxidation, none of the urinary metabolites were produced from epoxides. In addition, none of the metabolites were

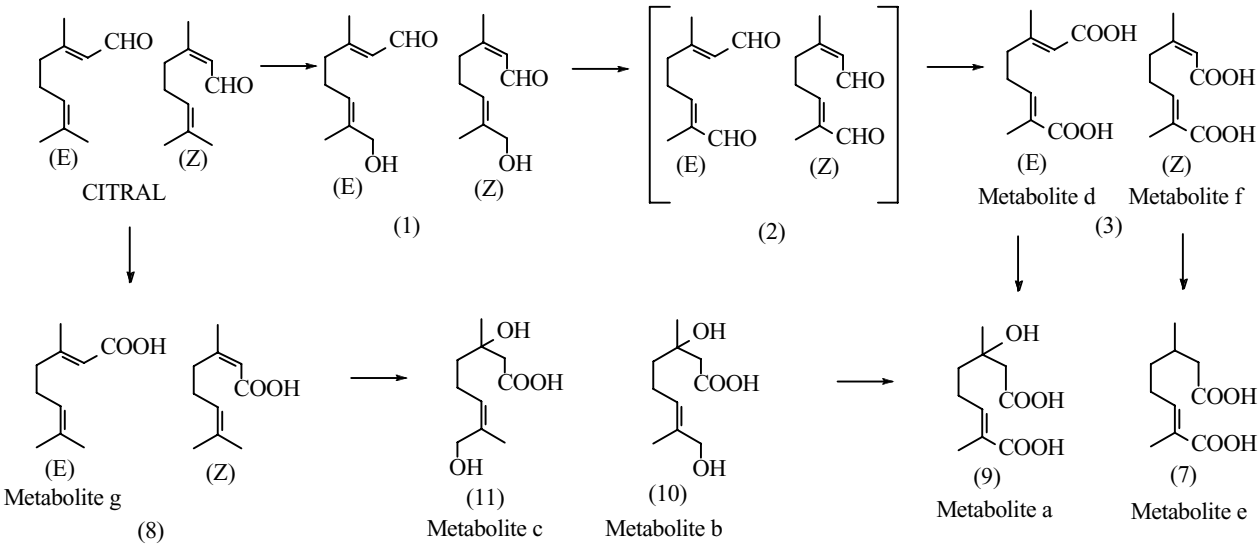


FIGURE 1
Proposed Metabolism of Citral. 9: 3-hydroxy-3,7-dimethyl-6-octenedioic acid; 10: 3,8-dihydroxy-3,7-dimethyl-6-octenoic acid; 11: 3,9-dihydroxy-3,7-dimethyl-6-octenoic acid; (E-3): *E*-3,7-dimethyl-2,6-octadienedioic acid; 7: 3,7-dimethyl-6-octenedioic acid; (Z-3): *Z*-3,7-dimethyl-2,6-octadienedioic acid; (E-8): *E*-3,7-dimethyl-2,6-octadienoic acid (Diliberto *et al*., 1990).
Note: Structures 4, 5, and 6 are synthetic intermediates prepared as part of the structure identification.

derived from reaction of nucleophiles with the α,β-unsaturated aldehyde.

Oral exposure of male Wistar rats and male LACA mice to 5, 770, or 960 mg [^{14}C]-citral/kg body weight resulted in rapid absorption by both species (Phillips *et al*., 1976). In rats, most of the radioactivity was excreted within 72 hours; in mice, citral was excreted less rapidly (120 hours). Twenty-four hours after administration of citral, radiolabel was found mainly in the gastrointestinal tract, liver, and kidney of rats. In mice, a more general distribution of radioactivity throughout the organs was observed, with some accumulation of radioactivity in the liver, kidney, and gastrointestinal tract. In rats and mice, the major route of excretion was the urine (47%-61%), although radiolabel was excreted in the feces (9%-17%) and via the lungs as CO_2 (7%-20%). The rapid excretion of CO_2 suggests that citral was oxidized rapidly and directly decarboxylated (Phillips *et al*., 1976).

Exposure to citral resulted in increases in hepatic biphenyl-4-hydroxylase, glucuronyl transferase, 4-nitrobenzoate reductase, and CYP4A1 activities in rats (Roffey *et al*., 1990). Citral is also a weak inhibitor of glutathione *S*-transferase and CYP2B1 (van Iersel *et al*., 1996; De-Oliveira *et al*., 1997). Citral has been shown to inhibit retinoic acid formation from retinol in the epidermis of mice *in vivo* (Connor and Smit, 1987).

Humans
No reports were found in the literature on the absorption, distribution, metabolism, or excretion of citral by humans.

TOXICITY
Experimental Animals
Reported LD_{50} values for citral vary considerably. The oral LD_{50} of unpurified citral in Osborne-Mendel rats was reported to be 4,960 mg citral/kg body weight (Jenner *et al.*, 1964). Comparatively, the LD_{50} in an unspecified rat strain exposed to citral *per os* was 500 mg/kg (RTECS, 1999). In a study by Toaff *et al.* (1979), female Wistar rats exposed to 300 mg/kg per day for 6 days exhibited no apparent toxic effects. In Wistar rats, dermal exposures to 460 mg/kg per day for 60 or

100 days did not produce any toxic effects (Toaff *et al*., 1979). The dermal LD_{50} was reported to be 2,250 mg/kg in rabbits (RTECS, 1999).

Citral has been shown to be a sensitizing agent in multiple species. Citral was found to be severely irritating to albino Angora rabbits and male Hartley guinea pigs treated dermally with 100 mg for 24 hours (Motoyoshi *et al*., 1979). Citral at concentrations ranging from 0.2% to 5% was moderately sensitizing to albino Hartley guinea pigs (Brulos *et al*., 1977; Basketter and Scholes, 1992) and at concentrations ranging from 5% to 25% in the local lymph node assay (Basketter and Scholes, 1992). Citral-induced skin irritation has been shown to be related to increased activities of mouse epidermal ornithine decarboxylase and *S*-adenosylmethionine decarboxylase, the rate-limiting enzymes involved in polyamine biosynthesis (Oguro *et al*., 1991).

Peroxisome proliferation and microsomal P450 levels were increased in male Wistar albino rats given 1,500 mg/kg citral by gavage daily for 5 days (Roffey *et al*., 1990). In addition, an increase in liver weight was observed and attributed to both hyperplasia and hypertrophy. The hyperplasia was caused by an increase in DNA synthesis, and hypertrophy was characterized by proliferation of smooth endoplasmic reticulum, peroxisomes, and mitochondria.

Male Wistar and Long-Evans rats were exposed to 2,400 mg/kg per day for 3 or 10 days by gastric intubation (Jackson *et al*., 1987). Feed consumption by each strain of exposed rats was less than that by the controls through day 6 but returned to control values by day 10. Hepatomegaly was observed on days 3 and 10 in both strains. Additionally, an increase in total liver DNA accompanied by liver enlargement was observed on day 3 in Long-Evans rats, but not in Wistar rats. Also, hepatomegaly was accompanied by altered distribution of lipid and glycogen in the liver on day 10. Citral treatment did not cause an increase in microsomal P450 activity in either strain, as measured by 7-ethoxyresorufin-O-deethylase and benzphetamine-n-demethylase activities. The peroxisomal marker, cyanide-insensitive palmitoyl CoA-oxidation, was significantly elevated in both strains.

A 14-day feed study with citral in microcapsules was performed with male and female F344/N rats and $B6C3F_1$ mice at concentrations of 0%, 0.63%, 1.25%, 2.5%, 5%, or 10% (approximately 394, 4,750, 9,500, 19,000, and 38,000 ppm) (Dieter *et al*., 1993). The chemical load of citral in the microcapsules was 38%. These exposure concentrations were equivalent to average daily doses of 0, 142, 285, 570, 1,140, or 2,280 mg/kg for rats and 0, 534, 1,068, 2,137, 4,275, or 8,550 mg/kg for mice. Significant decreases in body weight gain, when compared to the vehicle controls, were observed in rats exposed to 1,140 or 2,280 mg/kg citral and in mice exposed to 8,550 mg/kg. In addition, decreases in absolute liver, kidney, and spleen weights were observed in rats in the 2,280 mg/kg groups. Minimal to mild hyperplasia and/or squamous metaplasia of the respiratory epithelium in the anterior portion of the nasal passages occurred in rats fed 1,140 or 2,280 mg/kg.

In the same study, male and female F344/N rats and $B6C3F_1$ mice were given citral by gavage at doses of 0, 570, 1,140, or 2,280 mg/kg for rats and 0, 534, 1,068, or 2,137 mg/kg for mice (Dieter *et al*., 1993). All mice in the 2,137 mg/kg groups died or were killed moribund, and two male mice in the 1,068 mg/kg group died. Dose-dependent increases in liver weights were observed in male and female mice. Inflammation and hyperplasia of the forestomach were observed in mice in the 1,068 mg/kg groups. Cytoplasmic vacuolization of hepatocytes was observed in female mice in the 1,068 and 2,137 mg/kg groups and male mice in the 2,137 mg/kg group. In mice administered 2,137 mg/kg, necrosis, ulceration, and acute inflammation of the forestomach were observed. Citral at gavage doses up to 2,280 mg/kg did not cause toxicity in rats, except for minimal hyperplasia of the squamous epithelium of the forestomach in high-dose rats.

In a 13-week feed study, male and female Osborne-Mendel rats were exposed to diets containing 1,000, 2,500, or 10,000 ppm citral (Hagan *et al*., 1967). No chemical-related effects on body weights, organ weights, clinical pathology, or histopathology were observed. However, due to the volatility of citral in the dosed feed (58% was lost over a 7-day period), the actual exposure concentrations were considerably less than the target concentrations.

Citral has been shown to induce benign and atypical prostatic hyperplasia in rats in a number of studies. Male Wistar rats exposed dermally to 150 mg/kg per day, 5 days per week, for 10, 20, 30, 60, or 90 days developed hyperplastic lesions after 10 days; the lesions became more prominent after 30 days (Servadio *et al*., 1986). Similar results were seen in Wistar rats dermally exposed to a total dose of 185 mg/kg (Engelstein *et al*., 1996) or to 1 mg/kg per day for 30 days (Kessler *et al*., 1998). Citral also has been shown to induce benign and

atypical prostastic hyperplasia in Wistar and Sprague-Dawley rats, but not in Fischer 344 or ACI/Ztm rats (Scolnik *et al*., 1994).

The mechanism by which citral induces benign prostatic hyperplasia is unknown; however, it has been suggested that interaction of citral with serum testosterone (Engelstein *et al*., 1996) and/or estrogen (Geldof *et al*., 1992) may play a role in this disease. The interaction between citral and serum testosterone in the induction of hyperplastic changes in the ventral prostate was investigated in intact and orchiectomized Wistar rats with and without testosterone implants (Engelstein *et al*., 1996). In orchiectomized rats, citral did not promote prostatic acinar proliferation. However, following supplementation with testosterone, severe atypical hyperplastic changes in the prostate were observed. In intact rats, atypical changes in the ventral prostate were observed in citral-treated rats with and without testosterone implants, however, the most severe changes were observed in rats with high serum testosterone levels.

Geldof and coworkers (1992) showed that application of citral directly to the vagina of ovariectomized female Copenhagen rats significantly increased proliferation of the vaginal epithelium. In addition, citral inhibited estrogen binding to estrogen receptors but did not inhibit binding of testosterone to androgen receptors *in vitro.* In the same study, male Copenhagen rats were treated dermally with 62 mg citral for 4 months. Marked hyperplasia of the glandular epithelium and interglandular stroma was observed in the prostate, but despite evidence of hyperplasia, no effect on prostate weight was observed. The authors suggested that citral may induce prostatic hyperplasia through an estrogenic pathway, either dependently or independently of androgen receptor pathways.

Citral also induced hyperplasia of the sebaceous gland in male rats (strain unspecified) dermally exposed to approximately 185 mg/kg per day for 90 days (Abramovici *et al*., 1982; Sandbank *et al*., 1988). The hyperplasia was marked by an increase in the number of partially differentiated cells of the sebaceous gland.

Humans

Fifty male volunteers were dermally exposed to 32% citral in acetone for 48 hours (Motoyoshi *et al*., 1979). Positive skin reactions were scored based on the presence of erythema, edema, papules, and bullous reaction. Patch test results indicated that over 70% of the test subjects showed severe irritation after exposure to citral.

Rothenborg *et al.* (1977) investigated an outbreak of hand eczema associated with the use of lemon-scented detergent. Patch tests with citral, performed at varying temperatures, showed that lemon-scented detergent was a primary irritant if applied in association with heat (43° C) but was not irritating at a temperature of 23° C. Hand dermatitis and allergic contact sensitivity of the skin to lemon, lime, and orange were observed in a bartender. Patch tests were positive for geraniol and citral, but not for *d*-limonene (Cardullo *et al*., 1989).

A review article by Opdyke (1979) mentioned unpublished data from the Research Institute for Fragrance Materials (RIFM), which indicated that an 8% concentration of citral was mildly irritating after 21 days in a closed-patch test. Comparatively, no irritation was found at concentrations of 1% to 8% over a 48-hour period. However, a repeated-insult patch test procedure with 4% citral resulted in skin sensitization. The sensitization was found to depend on the concentration (as low as 0.1%) as well as the number of exposures (e.g., 15 at 0.1%). The RIFM also published results from a patch test at concentrations below 0.5%. Consumer products containing citral at this concentration did not cause hypersensitivity or allergic reaction in more than 12,500 patch tests (Steltenkamp *et al*., 1980).

Reproductive and Developmental Toxicity

Experimental Animals

Wistar rats were given citral by gavage on gestation days 6 to 15 at doses of 60, 125, 250, 500, or 1,000 mg/kg (Nogueira *et al*., 1995). This treatment regime was maternally toxic at all doses based on significant decreases in body and uterine weights. On gestation day 21, increases in the percentage of resorptions per implantation were observed in the 60 and 125 mg/kg groups. Doses greater than 125 mg/kg resulted in a dose-dependent reduction in the ratio of pregnant animals to mated animals. At doses greater than 60 mg/kg, growth retardation as well as increases in the incidences of minor skeletal abnormalities were observed. At doses greater than 125 mg/kg, increased fetal spleen weights were observed.

Twenty-eight virgin female Wistar rats were exposed to 300 mg citral/kg by intraperitoneal injection on day 1 of proestrus for six cycles (Toaff *et al.*, 1979). Nineteen rats were treated dermally with 460 mg/kg in 70% ethanol for 60 days and 17 rats were treated with the

same concentration for 100 days. On the first day of proestrus, some of the animals were euthanized; the remaining females were housed with fertile males and transferred to separate cages once spermatozoa were detected in vaginal smears. Twenty-one days after parturition, all dams and pups were euthanized. No maternally toxic effects were observed in any treatment group. Citral treatment (both routes of exposure) resulted in a decrease in the number of implantations and litter size. Additionally, both treatment regimes markedly reduced the number of primordial-primary and intermediate follicles. This effect was more pronounced in animals that received 460 mg/kg dermally for 100 days. Reduced follicular numbers were associated with an increase in the numbers of follicles with Type III atresia (characterized as degenerative changes in oocytes, but not in the surrounding follicular cells). Citral treatment did not alter the histologic appearance or number of corpora lutea per section. The authors suggested that the pattern of citral-induced follicular degeneration was not similar to that observed with alkylating agents or X-irradiation in which both the oocytes and the follicular cells are damaged. The authors also suggested that the increased incidence of Type III atresia, and not Type I or II, indicates that citral does not disturb the endocrine status of the animal. However, hormone determinations were not performed.

Pregnant Sprague-Dawley rats were exposed to citral by inhalation at concentrations of 0, 10, or 34 ppm as a vapor or 68 ppm as an aerosol/vapor mixture 6 hours per day on gestation days 6 through 15 (Gaworski *et al*., 1992). Clinical signs of toxicity and significant reductions in maternal body weight were observed in the 68 ppm group. No citral-related effects on the number of corpora lutea, implantations, resorptions, fetal viability, litter size, sex ratio, or fetal body weight were observed. A slight increase in the incidence of hypoplastic bones (lumbar and pubic) was observed in fetuses in the 68 ppm group.

Injection of 0.1 to 100 mM citral into the suprablastodermal space of 3-day-old chick embryos resulted in dose-dependent embryotoxicity. Malformations of the limbs, head, body, and tail were reported. Limb malformations included micromelia, phocomelia, and oligodactyly (30%). Malformations of the head included exencephalia, anophthalmia, microphthalmia, and crossed beak (14.6%) (Abramovici, 1972). In a subsequent study using the same experimental design, citral interfered with myofibrilogenesis of striated muscles (Abramovici *et al*., 1973).

In a study to reduce the teratogenic effects of retinoic acid (a vitamin A metabolite), stage 9.5 to 10.5 *Xenopus* embryos were first treated with retinol, the metabolic precursor to retinoic acid (Schuh *et al*., 1993) and then exposed to citral, which partially blocks the conversion of retinol to retinoic acid. Citral significantly reduced, but was unable to completely void, all of the teratogenic effects of retinol in *Xenopus* embryos. In addition, a 62% decrease in endogenous retinoic acid was observed in gastrula-stage embryos treated with citral (not pre-exposed to retinol), suggesting that citral interfered with the metabolic conversion of retinol to retinoic acid. In contrast, the "protective" effect of citral observed in gastrulation was not extended to tadpole development. Head abnormalities, alterations in gut development, changes in pigmentation levels, microphthalmia, and heart defects were observed in embryos treated with citral (data not presented). The authors postulated that inhibition of retinoic acid production by citral at sufficient concentrations or at specific times may cause developmental effects.

Humans

No reproductive or developmental toxicity studies of citral in humans were found in the literature.

CARCINOGENICITY

Experimental Animals

Citral inhibited skin tumorigenesis in an initiation and promotion experiment in female hairless *skh/hr1* mice (Connor, 1991). Tetradecanoylphorbol-13-acetate (TPA) was applied twice weekly for 20 weeks to the skin of mice initiated with dimethylbenzanthracene. Prior to application of TPA, some groups were exposed to citral. Citral treatment had a dose-dependent inhibitory effect on tumor formation. It was suggested that citral inhibits tumor formation in the mouse epidermis through interference with the conversion of retinol to retinoic acid, a vitamin A precurser that has been associated with tumor promotion.

Humans

No epidemiological studies in humans were found in the literature.

GENETIC TOXICOLOGY

Citral has been tested by several laboratories for induction of gene mutations in numerous strains of *Salmonella typhimurium,* with and without exogenous

metabolic activation (S9), and all results were negative (Lutz *et al*., 1982; Ishidate *et al.*, 1984; Zeiger *et al*., 1987; Gomes-Carneiro *et al*., 1998). The testing laboratories used either plate incorporation or preincubation protocols, and all studies employed concentrations of citral that extended to toxic levels or to the maximum concentration defined in the assay protocol.

In addition to the extensive testing in *S. typhimurium*, citral was tested in two *in vitro* mammalian cell assays. The first, a test for induction of chromosomal aberrations conducted in the absence of S9 in cultured Chinese hamster fibroblasts, gave negative results over a range of concentrations up to 0.03 mg/mL (Ishidate *et al*., 1984). The second mammalian cell test was a recently developed DNA damage assay that measures induction of *p53* tumor suppressor protein in mouse fibroblasts (NCTC 929 cell line) *in vitro* (Duerksen-Hughes *et al*., 1999). In this assay, increased concentrations of *p53* are considered to indicate induced DNA damage. Results with citral in this assay were strongly positive, with significant (P=0.0001) dose-related increases in *p53* induction noted at citral concentrations of 10, 15, 20, 25, and 30 µg/mL after 17 hours of incubation.

Study Rationale

The National Cancer Institute nominated citral for carcinogenicity studies based on its widespread use as a flavor and fragrance ingredient and its structural considerations as a representative β-substituted vinyl aldehyde. The 14-week and 2-year studies were performed in male and female F344/N rats and B6C3F$_1$ mice to evaluate the toxicity and carcinogenicity of citral.

Because the oral route is the most likely route of human exposure through consumption of foods, 14-day gavage and feed studies using microencapsulated citral were conducted (Kuhn *et al*., 1991; Dieter *et al*., 1993). Based on the results of those 14-day studies, the current 14-week toxicity and 2-year carcinogenicity studies were performed using microencapsulated citral in feed.

MATERIALS AND METHODS

Procurement and Characterization of Citral

Citral was obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI) in two lots. Lot 06930PG was used during the 14-week studies, and lot 04402AQ was used during the 2-year studies. The manufacturer indicated a purity of 96.5% for each lot. The chemical was microencapsulated by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and the loaded microcapsules were assigned separate lot numbers. Lot 20295 was prepared for use in the 14-week studies, and lot MRI 020196MC was prepared for use in the 2-year studies. Identity, purity, moisture content, and stability analyses of the neat chemical and the loaded microcapsules were conducted by the analytical chemistry laboratory and the study laboratory. Reports on analyses performed in support of the citral studies are on file at the National Institute of Environmental Health Sciences.

Analyses of Neat Chemical

The chemical, a colorless liquid, was identified as citral by the analytical laboratory using infrared, ultraviolet/visible (lot 04402AQ), and nuclear magnetic resnance spectroscopy and gas chromatography/mass spectrometry (GC/MS) (lot 04402AQ). The purity of lot 06930PG was determined by the analytical chemistry laboratory using GC. The purity of lot 04402AQ was determined by the analytical chemistry laboratory using functional group titration, thin-layer chromatography (TLC), and GC. Moisture content was determined using Karl Fischer titration.

For lot 06930PG, GC indicated two major peaks and seven impurities with a combined area of 2.4% relative to the combined major peak area. The isomer ratio was approximately 2:1 geranial:neral. For lot 04402AQ, Karl Fischer titration indicated 0.12% ± 0.05% water. Functional group titration indicated 92.2% ± 0.4% aldehydes. TLC indicated a major spot, a minor spot, and two trace impurities. GC analyses resolved two major peaks and 20 impurities with areas 0.72% or less of the major peak area and a combined area of 5.78% relative to the combined major peak area; geranial and neral were identified on the basis of the elution order indicated by a literature reference (*Food Chemicals Codex*, 1981). The overall purity of lot 04402AQ was determined to be approximately 94%, with an isomer composition of approximately 63% geranial and 37% neral.

Accelerated stability studies of the neat chemical were performed by the analytical chemistry laboratory using GC. These studies indicated no degradation after storage for 2 weeks at temperatures up to 60° C when stored protected from light.

Microcapsule Formulation and Analyses

Microcapsules loaded with neat citral and placebos (empty microcapsules) were prepared in several batches at the analytical chemistry laboratory by a proprietary process using food-grade sugar and starch to produce dry microspheres. The batches were homogenized and passed through 40- over 140-mesh sieves and were stored in amber glass bottles at room temperature before shipping to the study laboratory.

Lot MRI 020196MC microcapsules were examined microscopically for appearance, and particle sizes were profiled. Particles were clear or translucent white spheres approximately 50 to 100 µm in diameter. Less than 3% were agglomerated. The surfaces were smooth and shiny. About 25% had a few adherent, small particles, and 50% had a heavy coating of smaller particles. Only two or three broken microcapsules and no leaking microcapsules were observed. Microcapsules were passed through U.S. standard sieves (Nos. 30, 40, 60, 80, and 120). Greater than 99% of the microcapsules were retained by sieves with pores ranging from less than 125 to 250 µm.

The chemical load of the microcapsules was determined by the analytical chemistry laboratory using GC. The chemical load was determined to be 31.3% for lot 20295 and 31.9% for lot MRI 020196MC. An impurity profile analysis of lot MRI 020196MC was performed by the analytical chemistry laboratory using GC; 15 impurities with areas of 0.1% or greater relative to the combined peak area were detected. The identity of the microencapsulated citral (lot MRI 020196MC) was confirmed

by the study laboratory using GC/MS; a chemical load of 32.3% was determined by the study laboratory using high-performance liquid chromatography (HPLC), which confirms the 31.9% from the analytical chemistry laboratory.

A 1-year shelf-life study conducted by the analytical chemistry laboratory using GC indicated that lot CIT-4B of microcapsules (not used in the current studies) retained approximately 94% of its chemical load when stored for up to 6 months at room temperature, protected from light; microcapsules stored at room temperature for 6 months and then at approximately 5° C for 6 months retained 95.8% of the zero-time chemical load. No change in the ratio of the isomers geranial and neral was noted at either time point. Microcapsules stored at room temperature, open to air and light for up to 28 days, showed no changes in chemical retention after 6 months of storage at room temperature, after 6 months at room temperature plus 6 months at 5° C, or after seven freeze-thaw cycles. Slight increases were observed in the concentrations of total impurities in samples stored for 6 months (1.30%) or 12 months (1.57%) compared to freshly prepared microcapsules (1.15%). The microcapsules were stored in amber glass bottles, protected from light, at approximately 5° C. The stability of the microcapsules was monitored by the analytical chemistry laboratory using GC for the 14-week studies and by the study laboratory using HPLC for the 2-year studies; no loss of citral from the microcapsules was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared with nonirradiated NTP-2000 feed every 2 to 4 weeks during the 14-week studies and with irradiated NTP-2000 feed approximately every 4 weeks during the 2-year studies (Table H2). Placebo and/or loaded microcapsules were combined with feed to a concentration of 10% microcapsules for the 14-week studies and 1.25% microcapsules for the 2-year studies. Dose formulations were stored in polyethylene bags inside sealed plastic buckets at room temperature (14-week studies) or at approximately 5° C (2-year studies) for up to 35 days.

Homogeneity and stability studies of an 830 ppm dose formulation and homogeneity studies of the 4,000 and 31,300 ppm dose formulations were performed by the analytical chemistry laboratory using GC. Homogeneity was confirmed. The study laboratory conducted homogeneity studies of the 500 and 4,000 ppm dose formulations and stability studies of the 500 ppm dose formulation for the 2-year studies using GC. Homogeneity was confirmed. Storage stability was demonstrated at approximately 89% of the day 0 concentration for samples stored at room temperature and was greater than 96% of the day 0 concentration for samples stored at –20° C or 5° C.

Periodic analyses of the dose formulations of citral used during the 14-week studies were conducted by the analytical chemistry laboratory using GC. The dose formulations were analyzed at the beginning, midpoint, and end of the studies; animal room samples of these dose formulations were also analyzed (Table H3). All 29 dose formulations analyzed were within 10% of the target concentrations. Of the animal room samples, 7 of 21 for rats and 4 of 29 for mice were within 10% of the target concentrations. Periodic analyses of the dose formulations used during the 2-year studies were conducted by the study laboratory using GC. During the 2-year studies, the dose formulations were analyzed approximately every 9 to 12 weeks; animal room samples were also analyzed (Table H4). All 36 and 33 dose formulations analyzed for rats and mice, respectively, were within 10% of the target concentrations. Of the animal room samples, 8 of 12 for rats and 6 of 12 for mice were within 10% of the target concentrations. In the 14-week and 2-year studies, loss of citral in the animal room samples was attributed to contamination with urine and feces, which softened the microcapsules. This was observed early in each study and continued longer with mice than with rats. Also, in the 14-week studies, high concentrations of citral in the animal room samples were attributed to the animals' ability to avoid microcapsules mixed with the feed.

During a 3-week period, at approximately 19 months into the 2-year studies, vehicle control animals inadvertently received feed containing some loaded microcapsules at a concentration of approximately 650 ppm citral. Vehicle control male and female rats received approximately 24 and 27 mg/kg per day, respectively. Male and female control mice received approximately 67 and 58 mg/kg per day, respectively. Because this exposure occurred for a short period of time late in the study, it is unlikely this impacted the results.

14-Week Studies

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to citral 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 4 weeks old. Rats were quarantined for 11 (males) or 12 (females) days and mice were quarantined for 13 (males) or 14 (females) days; rats and mice were approximately 6 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 5 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 K).

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 3,900, 7,800, 15,600, or 31,300 ppm microencapsulated citral 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. Clinical findings were recorded weekly for rats and mice. Feed consumption was recorded once weekly (rats and male mice) or twice weekly (female mice). The animals were weighed initially, weekly thereafter, and at the end of the studies. 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 4 and 22. Using the same method, blood was collected 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 volume, 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. The hematology and clinical chemistry parameters measured are listed in Table 1.

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. A complete histopathologic examination was performed on all core study untreated control and vehicle control rats and mice, 15,600 ppm rats, and 31,300 ppm rats and 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 500 (mice), 1,000, 2,000, or 4,000 (rats) ppm microencapsulated citral for 104 to 105 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 and mice were quarantined for 13 to 15 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 K).

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 J.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded initially (body weights only), on day 8, day 33 (rats), day 36 (mice), 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 adrenal gland of rats, the prostate gland and thyroid gland of male rats, the clitoral gland, mammary gland, and uterus of female rats, the bone marrow, lung, oral mucosa, spleen, and stomach of male and female mice, the prostate gland of male mice, and the mesenteric lymph node, ovary, pancreatic islets, and thymus of female mice.

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

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

14-Week 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: 11 (males) or 12 (females) days Mice: 13 (males) or 14 (females) days	Rats: 14 (males) or 15 (females) days Mice: 13 (males) or 14 (females) days
Average Age When Studies Began 6 weeks	6 weeks
Date of First Exposure Rats: June 5 (males) or June 6 (females), 1995 Mice: June 7 (males) or June 8 (females), 1995	Rats: June 6 (males) or June 7 (females), 1996 Mice: June 19 (males) or June 20 (females), 1996
Duration of Exposure 14 weeks	104-105 weeks
Date of Last Exposure and Necropsy Rats: September 5 (males) or September 6 (females), 1995 Mice: September 7 (males) or September 8 (females), 1995	Rats: June 1-5 (males) or June 8-10 (females), 1998 Mice: June 15-19 (males) or June 22-24 (females), 1998
Average Age at Necropsy 19 weeks (rats and male mice) or 20 weeks (female mice)	110 or 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 14-week 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	Rats: Tail tattoo Mice: Tail tattoo and eartag

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

14-Week Studies	2-Year Studies
Diet Nonirradiated NTP-2000 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 14-week 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 14-week studies
Cages Polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice weekly (rats and female mice) or once weekly (male mice)	Same as 14-week 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 14-week studies; irradiated beginning September 1, 1996
Cage Filters Dupont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks	Same as 14-week studies
Racks Stainless steel (Lab Products, Inc., Maywood, NJ), changed and rotated every 2 weeks	Same as 14-week studies
Animal Room Environment Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour
Exposure Concentrations 0, 3,900, 7,800, 15,600, or 31,300 ppm, microencapsulated in feed	0, 500 (mice), 1,000, 2,000, or 4,000 (rats) 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 weekly. Feed consumption was recorded weekly (rats and male mice) or twice weekly (female mice).	Observed twice daily; animals were weighed and clinical findings were recorded initially (body weights only), on day 8, day 33 (rats), day 36 (mice), 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 14-week studies
Necropsy Necropsies were performed on all core study animals. Organs weighed were the heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all rats and mice.

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

14-Week Studies	2-Year Studies
Clinical Pathology Blood was collected from the retroorbital sinus of clinical pathology study rats on days 4 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, bile acids	None
Histopathology Complete histopathology was performed on untreated controls, vehicle controls, and core study rats and mice exposed to 15,600 (rats) or 31,300 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 only), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung and mainstem bronchi, 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 bone marrow of rats, the kidney of male rats, the forestomach of rats and mice, and the ovary of female mice were examined to a no-effect level.	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 only), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung and mainstem bronchi, 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.

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, A4, B1, B4, C1, C4, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with the vehicle controls, pairwise comparisons between the two control groups, 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 and clinical chemistry 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).

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. Until recently, the NTP historical control database consisted of animals fed NIH-07 diet. In 1995, the NTP changed the diet fed to animals used in toxicity and carcinogenesis studies conducted by the NTP. This new diet (NTP-2000) contains less protein and more fiber and fat than the NIH-07 diet previously used (Rao, 1996, 1997). This dietary change was instituted primarily to increase longevity and decrease the incidence and/or severity of some spontaneous neoplasms and nonneoplastic lesions in the rats and mice used in NTP studies. These studies of citral are among the first in which the animals on study were fed the NTP-2000 diet. Because the incidence of some neoplastic and nonneoplastic lesions may be affected by the dietary change, use of the existing historical control database (NIH-07 diet) may not be appropriate for all neoplasm types.

The concurrent database included 11 (10 for male rats) studies by various routes in which the NTP-2000 diet was used. Based on the extensive NTP historical database using the NIH-07 diet, incidences of the vast majority of spontaneous neoplasms are not significantly different between control groups regardless of the route of administration. There is no reason to expect this to be different with the NTP-2000 diet. For example, control animals from dosed feed and dosed water studies are treated no differently and no differences in incidences of

neoplasms are expected. However, the incidences of a few endpoints may differ with divergent routes of administration. In this study, starch microcapsules were used to deliver citral resulting in a relatively unique vehicle control group for NTP studies. A concurrent untreated control group was also included in this study; only minor differences in incidences between the vehicle and untreated control groups were observed. Therefore, it was concluded that judicious use of NTP historical controls for comparison was warranted.

Quality Assurance Methods

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, 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 citral 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, micronucleated erythrocytes in mouse bone marrow, and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity 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

14-WEEK STUDIES

In the second week of the study, all rats in the 31,300 ppm groups were killed moribund (Table 2). Final mean body weights and body weight gains of males and females that survived to the end of the study were generally significantly less than those of the vehicle controls. Feed consumption by 15,600 and 31,300 ppm males and females was less than that by the vehicle controls during the first week of the study, possibly due to poor palatability. Dietary concentrations of 3,900, 7,800, 15,600, and 31,300 ppm resulted in average daily doses of approximately 345, 820, 1,785, and 1,585 mg citral/kg body weight to males and 335, 675, 1,330, and 2,125 mg/kg to females. Males and females in the 31,300 ppm groups exhibited listlessness, hunched posture, absent or slow paw reflex, and dull eyes.

There were several transient treatment-related hematological and serum biochemical effects (Tables 3 and F1). On day 4, increases in hematocrit values, hemoglobin concentrations, and erythrocyte and platelet counts relative to the vehicle controls were observed in male and female rats exposed to 7,800 ppm or greater. In addition, decreases in mean cell volumes and mean cell hemoglobin values, as well as decreases in reticulocyte and

TABLE 2
Survival, Body Weights, and Feed Consumption of Rats in the 14-Week Feed Study of Citral

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Vehicle Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 14
Male							
Vehicle Control	10/10	81 ± 2	336 ± 6	255 ± 6		15.4	18.7
3,900	10/10	80 ± 2	318 ± 6*	238 ± 5**	95	15.9	19.9
7,800	10/10	84 ± 3	292 ± 4**	208 ± 3**	87	15.1	20.1
15,600	10/10	84 ± 2	247 ± 4**	163 ± 4**	73	8.4	15.6
31,300	0/10[d]	80 ± 2	—	—	—	4.0	—
Female							
Vehicle Control	10/10	82 ± 3	190 ± 4	108 ± 4		12.8	10.7
3,900	10/10	79 ± 3	180 ± 4*	101 ± 4	95	11.6	9.6
7,800	10/10	84 ± 3	181 ± 2*	97 ± 2*	96	11.8	10.8
15,600	10/10	84 ± 3	166 ± 2**	82 ± 2**	88	6.5	10.2
31,300	0/10[d]	84 ± 2	—	—	—	4.7	—

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. No final mean body weights were calculated for groups with 100% mortality.
[c] Feed consumption is expressed as grams per animal per day.
[d] Week of death: 2

TABLE 3
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral[a]

	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male					
n					
Day 4	10	10	10	10	10
Day 22	10	10	10	8	0
Week 14	10	10	10	10	0
Hematology					
Hematocrit (%)					
Day 4	38.9 ± 0.6	40.1 ± 0.4	42.4 ± 0.5**	44.7 ± 0.5**	45.8 ± 0.7**
Day 22	44.3 ± 0.4	44.1 ± 0.8	43.8 ± 0.4	51.1 ± 2.7	
Week 14	44.7 ± 0.5	44.9 ± 0.8	44.6 ± 0.5	45.4 ± 0.5	
Hemoglobin (g/dL)					
Day 4	12.4 ± 0.2	12.8 ± 0.1	13.6 ± 0.2**	14.2 ± 0.2**	14.6 ± 0.2**
Day 22	14.5 ± 0.2	14.2 ± 0.3	14.3 ± 0.1	16.2 ± 0.8	
Week 14	15.0 ± 0.1	15.2 ± 0.2	15.2 ± 0.1	15.3 ± 0.1	
Erythrocytes (10^6/μL)					
Day 4	6.41 ± 0.10	6.65 ± 0.07	7.18 ± 0.12**	7.60 ± 0.06**	7.72 ± 0.13**
Day 22	7.25 ± 0.07	7.18 ± 0.14	7.21 ± 0.08	8.60 ± 0.48	
Week 14	8.45 ± 0.11	8.39 ± 0.15	8.35 ± 0.08	8.39 ± 0.09	
Reticulocytes (10^5/μL)					
Day 4	4.25 ± 0.27	2.93 ± 0.43*	1.84 ± 0.22**	2.12 ± 0.14**	2.01 ± 0.26**
Day 22	2.09 ± 0.26	1.66 ± 0.23	2.42 ± 0.29	1.72 ± 0.39	
Week 14	1.15 ± 0.15	1.25 ± 0.11	1.06 ± 0.15	1.18 ± 0.10	
Mean cell volume (fL)					
Day 4	60.8 ± 0.2	60.4 ± 0.4	59.2 ± 0.5**	58.8 ± 0.4**	59.5 ± 0.4**
Day 22	61.3 ± 0.2	61.3 ± 0.2	61.0 ± 0.3	59.5 ± 0.4**	
Week 14	52.9 ± 0.1	53.5 ± 0.2*	53.6 ± 0.2**	54.3 ± 0.2**	
Mean cell hemoglobin (pg)					
Day 4	19.4 ± 0.1	19.2 ± 0.2	18.9 ± 0.2	18.6 ± 0.1**	18.9 ± 0.1**
Day 22	20.0 ± 0.2	19.8 ± 0.2	19.8 ± 0.2	18.9 ± 0.2**	
Week 14	17.8 ± 0.2	18.1 ± 0.1	18.2 ± 0.1	18.2 ± 0.1	
Platelets (10^3/μL)					
Day 4	871.2 ± 18.0	877.8 ± 46.9	990.6 ± 25.3**	1,054.3 ± 16.6**	1,137.5 ± 43.4**
Day 22	844.1 ± 16.9	852.8 ± 28.0	881.5 ± 15.0	822.4 ± 26.0	
Week 14	698.6 ± 8.0	708.0 ± 18.3	707.7 ± 10.3	707.8 ± 8.1	
Clinical Chemistry					
Albumin (g/dL)					
Day 4	3.7 ± 0.0	4.0 ± 0.0**	3.9 ± 0.0**	4.1 ± 0.0**	4.2 ± 0.0**
Day 22	4.5 ± 0.1	4.6 ± 0.0	4.6 ± 0.0	4.9 ± 0.1**	
Week 14	4.7 ± 0.1	4.8 ± 0.1	5.0 ± 0.1**	4.8 ± 0.1	
Total protein (g/dL)					
Day 4	4.9 ± 0.1	5.1 ± 0.0	5.0 ± 0.1	5.2 ± 0.1**	5.2 ± 0.0**
Day 22	6.1 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.4 ± 0.2	
Week 14	6.5 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	6.3 ± 0.1	
Urea nitrogen (mg/dL)					
Day 4	9.4 ± 0.9	12.6 ± 0.3**	14.1 ± 0.5**	13.5 ± 0.7**	22.8 ± 1.7**
Day 22	11.1 ± 0.4	12.4 ± 0.4*	13.3 ± 0.3**	19.3 ± 1.5**	
Week 14	15.9 ± 0.5	16.3 ± 0.8	15.9 ± 0.5	18.2 ± 0.6*	

TABLE 3
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral

	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male (continued)					
n					
Day 4	10	10	10	10	10
Day 22	10	10	10	8	0
Week 14	10	10	10	10	0
Clinical Chemistry (continued)					
Alkaline phosphatase (IU/L)					
Day 4	2,172 ± 80	2,198 ± 35	2,026 ± 58	1,735 ± 39**	1,362 ± 40**
Day 22	1,361 ± 33	1,328 ± 31	1,479 ± 31	1,163 ± 143	
Week 14	574 ± 12	551 ± 14	607 ± 20	619 ± 25	
Bile acids (µmol/L)					
Day 4	33.9 ± 2.7	43.7 ± 3.8	36.8 ± 4.3	54.6 ± 10.2	38.6 ± 3.4[b]
Day 22	28.8 ± 3.5	31.8 ± 2.1	33.8 ± 2.9	28.6 ± 4.9	
Week 14	27.1 ± 2.9	25.1 ± 2.2	27.6 ± 2.1	30.9 ± 1.6	
Female					
Hematology					
n					
Day 4	9	9	10	10	10
Day 22	10	10	10	10	0
Week 14	10	10	10	10	0
Hematocrit (%)					
Day 4	41.6 ± 0.9	43.4 ± 1.0	46.3 ± 0.9**	48.2 ± 0.8**	47.3 ± 0.7**
Day 22	46.4 ± 0.6	46.1 ± 0.9	44.9 ± 0.5	44.8 ± 0.4	
Week 14	43.2 ± 0.3	44.7 ± 0.5	43.1 ± 0.4	44.0 ± 0.3	
Hemoglobin (g/dL)					
Day 4	13.2 ± 0.3	13.6 ± 0.4	14.8 ± 0.3**	15.2 ± 0.2**	15.0 ± 0.2**
Day 22	15.3 ± 0.2	15.2 ± 0.3	15.1 ± 0.1	15.0 ± 0.2	
Week 14	14.8 ± 0.1	15.2 ± 0.1	14.9 ± 0.1	15.1 ± 0.1	
Erythrocytes (10^6/µL)					
Day 4	6.79 ± 0.17	7.09 ± 0.18	7.81 ± 0.16**	8.10 ± 0.15**	7.89 ± 0.08**
Day 22	7.73 ± 0.12	7.64 ± 0.16	7.61 ± 0.1	7.84 ± 0.09	
Week 14	7.61 ± 0.06	7.87 ± 0.06*	7.59 ± 0.06	7.89 ± 0.1*	
Reticulocytes (10^5/µL)					
Day 4	3.16 ± 0.40	3.23 ± 0.32	2.01 ± 0.15*	1.98 ± 0.21*	2.09 ± 0.11*
Day 22	1.36 ± 0.14	1.30 ± 0.13	1.19 ± 0.08	1.41 ± 0.13	
Week 14	1.10 ± 0.12	0.98 ± 0.11	0.86 ± 0.11	0.90 ± 0.11	
Mean cell volume (fL)					
Day 4	61.2 ± 0.4	61.3 ± 0.4	59.4 ± 0.3**	59.7 ± 0.4*	59.9 ± 0.4*
Day 22	60.1 ± 0.3	60.5 ± 0.3	59.0 ± 0.4	57.2 ± 0.2**	
Week 14	57.0 ± 0.3	56.7 ± 0.2	56.8 ± 0.1	56.1 ± 0.2*	

TABLE 3
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral

	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Female (continued)					
Hematology (continued)					
n					
Day 4	9	9	10	10	10
Day 22	10	10	10	10	0
Week 14	10	10	10	10	0
Mean cell hemoglobin (pg)					
Day 4	19.4 ± 0.1	19.2 ± 0.1	19.0 ± 0.1	18.8 ± 0.2	19.0 ± 0.1
Day 22	19.8 ± 0.1	19.9 ± 0.1	19.8 ± 0.1	19.1 ± 0.1**	
Week 14	19.5 ± 0.1	19.3 ± 0.1	19.7 ± 0.1	19.3 ± 0.1	
Platelets (10^3/µL)					
Day 4	759.2 ± 45.3	798.8 ± 29.8	899.0 ± 31.7**	990.4 ± 31.0**	1,067.9 ± 22.8**
Day 22	758.5 ± 17.3	737.7 ± 20.6	821.1 ± 23.2	789.4 ± 19.8	
Week 14	636.7 ± 13.8	660.4 ± 11.9	618.2 ± 12.2	676.2 ± 13.9	
Clinical Chemistry					
n					
Day 4	10	10	10	10	10
Day 22	10	10	10	10	0
Week 14	10	10	10	10	0
Albumin (g/dL)					
Day 4	4.1 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.3 ± 0.0
Day 22	4.5 ± 0.0	4.7 ± 0.1	4.7 ± 0.0	4.8 ± 0.1**	
Week 14	5.0 ± 0.1	5.1 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	
Total protein (g/dL)					
Day 4	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.2 ± 0.0
Day 22	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.0	6.1 ± 0.1	
Week 14	6.5 ± 0.1	6.5 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	
Urea nitrogen (mg/dL)					
Day 4	7.6 ± 0.4	10.9 ± 0.5**	11.2 ± 0.4**	13.6 ± 1.2**	26.7 ± 2.4**
Day 22	13.4 ± 0.2	13.2 ± 0.5	13.6 ± 0.5	14.8 ± 0.4*	
Week 14	15.2 ± 0.6	15.6 ± 0.5	15.6 ± 0.5	16.6 ± 0.7	
Alkaline phosphatase (IU/L)					
Day 4	1,768 ± 54	1,816 ± 66	1,725 ± 29	1,473 ± 46**	1,031 ± 41**
Day 22	902 ± 22	966 ± 31	1,110 ± 16**	1,107 ± 14**	
Week 14	544 ± 16	534 ± 18	651 ± 18**	626 ± 20**	
Bile acids (µmol/L)					
Day 4	35.8 ± 4.3	34.5 ± 5.0	47.2 ± 5.0	57.2 ± 3.5**[b]	53.5 ± 7.1*
Day 22	29.6 ± 3.7	20.9 ± 3.1	34.9 ± 1.7	52.1 ± 2.4**	
Week 14	41.4 ± 5.7	30.6 ± 4.0	35.2 ± 2.9	41.8 ± 4.7	

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

nucleated erythrocyte counts were observed at exposure concentrations greater than 7,800 ppm. In general, these effects were transient and were not observed after day 22. The changes in the erythron and platelet counts were consistent with physiologic responses related to decreased feed and water consumption (Table 2).

Clinical chemistry data also demonstrated transient treatment-related changes that would be consistent with decreased feed and possibly water consumption. On day 4, albumin and total protein in males and urea nitrogen concentrations in males and females were increased in various exposed groups, but most consistently in the 15,600 and 31,300 ppm groups. Additionally, decreases in serum alkaline phosphatase activity occurred on day 4 in males and females exposed to 15,600 or 31,300 ppm. These changes were of minimal to mild severity, generally occurred in an exposure concentration-related manner, and were more apparent in males than in females. The alterations in albumin, total protein, and urea nitrogen concentrations may be related to possible dehydration or to decreased glomerular filtration rates due to renal damage. On days 4 and 22, urea nitrogen concentrations in all exposed groups of males were significantly increased compared to the vehicle control group. At week 14, the urea nitrogen concentration in 15,600 ppm males remained minimally increased relative to the vehicle controls. The decreases in alkaline phosphatase activity may reflect a loss of circulating intestinal isoenzyme fraction related to decreased feed consumption. The effects on day 4 were transient and generally improved by day 22.

Bile acid concentration and alkaline phosphatase activity were increased in 15,600 and 31,300 ppm females. Bile acid concentrations were increased on days 4 and 22 and were accompanied by increased alkaline phosphatase activity on day 22. By week 14, bile acid concentrations in exposed females were similar to that in the vehicle controls, but alkaline phosphatase activity remained minimally increased. In general, increases in bile acid concentration and alkaline phosphatase activity are considered indicators of bile stasis and would suggest that a cholestatic event may have occurred. However, alterations were of minimal severity, the change in bile acid concentration was transient, and there was no histopathologic evidence of cholestasis, all suggesting that these changes were not biologically significant.

Minor changes in organ weights appeared to be related to changes in body weight and were not considered biologically relevant or toxicologically significant (Table G1).

No gross lesions were observed that could be attributed to exposure to citral. Microscopically, exposure of rats to citral was associated with forestomach epithelial hyperplasia and hyperkeratosis, bone marrow hemorrhage and atrophy, and nephrotoxicity (Table 4).

Forestomach epithelial hyperplasia and hyperkeratosis, characterized by thickening of the stratified squamous epithelium and of the cornified superficial layer of the mucosa, were observed in 31,300 ppm males and females, with a somewhat greater effect in females. These changes typically were not accompanied by inflammation.

The incidences of bone marrow atrophy were significantly increased in 15,600 and 31,300 ppm males and females. In the groups receiving 31,300 ppm, atrophy was of mild severity and was characterized by decreased myelopoietic cells with a relative increase in the adipose cells in the marrow spaces. Hemorrhage was also present in all males and nine females exposed to 31,300 ppm and was attributed to loss of vascular sinus integrity and extravasation of erythrocytes throughout the marrow spaces. Minimal atrophy, without accompanying hemorrhage, was considered a borderline lesion in the 15,600 ppm groups. It was not clear if the bone marrow lesions were a direct effect of citral toxicity or due to inanition in rats in the 31,300 ppm groups.

Nephropathy was present in the kidneys of 3,900, 7,800, and 15,600 ppm males; the incidences were significantly increased in the 7,800 and 15,600 ppm groups. Nephropathy was generally a minimal to mild change characterized by foci of regenerative epithelium, occasional eosinophilic casts, peritubular mononuclear infiltrates, and dilated tubules. Granular casts were few and scattered within the outer strip of the outer medulla. They were characterized by dilated tubules filled with granular eosinophilic material presumed to be proteinacious material and cellular debris. The presence of granular casts and exacerbation of spontaneous nephropathy is suggestive of an α2u globulin nephropathy. The protein, α2u globulin, is produced by male rats under the influence of testosterone; therefore, production begins with sexual maturity and starts declining later in life. Some is filtered through the glomerulus with a portion being lost in the urine and a portion reabsorbed via the cytoplasm of the proximal renal tubular epithelium.

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 14-Week Feed Study of Citral

	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male					
Stomach, Forestomach[a]	10	0	0	10	10
Hyperkeratosis[b]	0	0	0	0	2 (1.0)[c]
Epithelium, Hyperplasia	0	0	0	0	2 (2.0)
Bone Marrow	10	0	10	10	10
Atrophy	0	0	0	7** (1.0)	10** (1.9)
Hemorrhage	0	0	0	0	10** (1.9)
Kidney	10	10	10	10	10
Nephropathy	0	3 (1.0)	10** (1.0)	8** (1.0)	0
Renal Tubule, Casts Granular	0	3 (1.0)	10** (1.2)	10** (1.5)	0
Thymus	10	0	0	10	10
Atrophy	0	0	0	0	5* (2.8)
Testes	10	0	0	10	10
Aspermia	0	0	0	0	10** (4.0)
Female					
Stomach, Forestomach	10	0	0	10	10
Hyperkeratosis	0	0	0	0	4* (1.5)
Epithelium, Hyperplasia	0	0	0	0	4* (1.3)
Bone Marrow	10	0	10	10	10
Atrophy	0	0	0	8** (1.0)	4* (1.5)
Hemorrhage	0	0	0	0	9** (2.1)
Thymus	10	0	0	10	10
Atrophy	0	0	0	0	4* (2.8)

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

With chemicals that induce α2u globulin, the amount of hyaline droplets within the proximal renal tubule epithelium is increased and can be detected microscopically. There was no apparent increase in the amount of hyaline droplets in this study as determined by H&E and Mallory Heidenhain stains. Therefore, it was considered unlikely that renal lesions were mediated by α2u globulin.

Thymic atrophy was observed in 31,300 ppm males and females. Aspermia was observed in the testes of all 31,300 ppm males. These lesions only occurred in the 31,300 ppm groups and were not considered to be directly related to exposure.

Exposure Concentration Selection Rationale: Based on the lack of recovery from an initial 13% decrease in body weight of male rats and lower final mean body weights of female rats exposed to 7,800 ppm or greater, exposure concentrations selected for the 2-year feed study in rats were 1,000, 2,000, and 4,000 ppm.

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 all exposed groups of males was significantly greater than that of the vehicle control group; survival of exposed groups of females was similar to that of the vehicle control group.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of rats exposed to 4,000 ppm were generally less than those of the vehicle controls from week 49 (males) or 25 (females) to the end of the study (Tables 6 and 7; Figure 3). Feed consumption by exposed groups was similar to that by vehicle controls (Tables I1 and I2). Dietary concentrations of 1,000, 2,000, and 4,000 ppm delivered average daily doses of approximately 50, 100, and 210 mg citral/kg body weight to males and females. There were no clinical findings attributed to citral exposure.

TABLE 5
Survival of Rats in the 2-Year Feed Study of Citral

	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	22	15	11	10
Natural deaths	6	3	4	6
Animals surviving to study termination	22	32	35	34
Percent probability of survival at end of study[a]	44	64	70	68
Mean survival (days)[b]	675	701	712	698
Survival analysis[c]	P=0.022N	P=0.032N	P=0.005N	P=0.020N
Female				
Animals initially in study	50	50	50	50
Moribund	10	11	11	12
Natural deaths	0	3	3	2
Animals surviving to study termination	40	36	36	36
Percent probability of survival at end of study	80	72	72	72
Mean survival (days)	707	705	701	693
Survival analysis	P=0.437	P=0.441	P=0.441	P=0.413

[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. 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**.

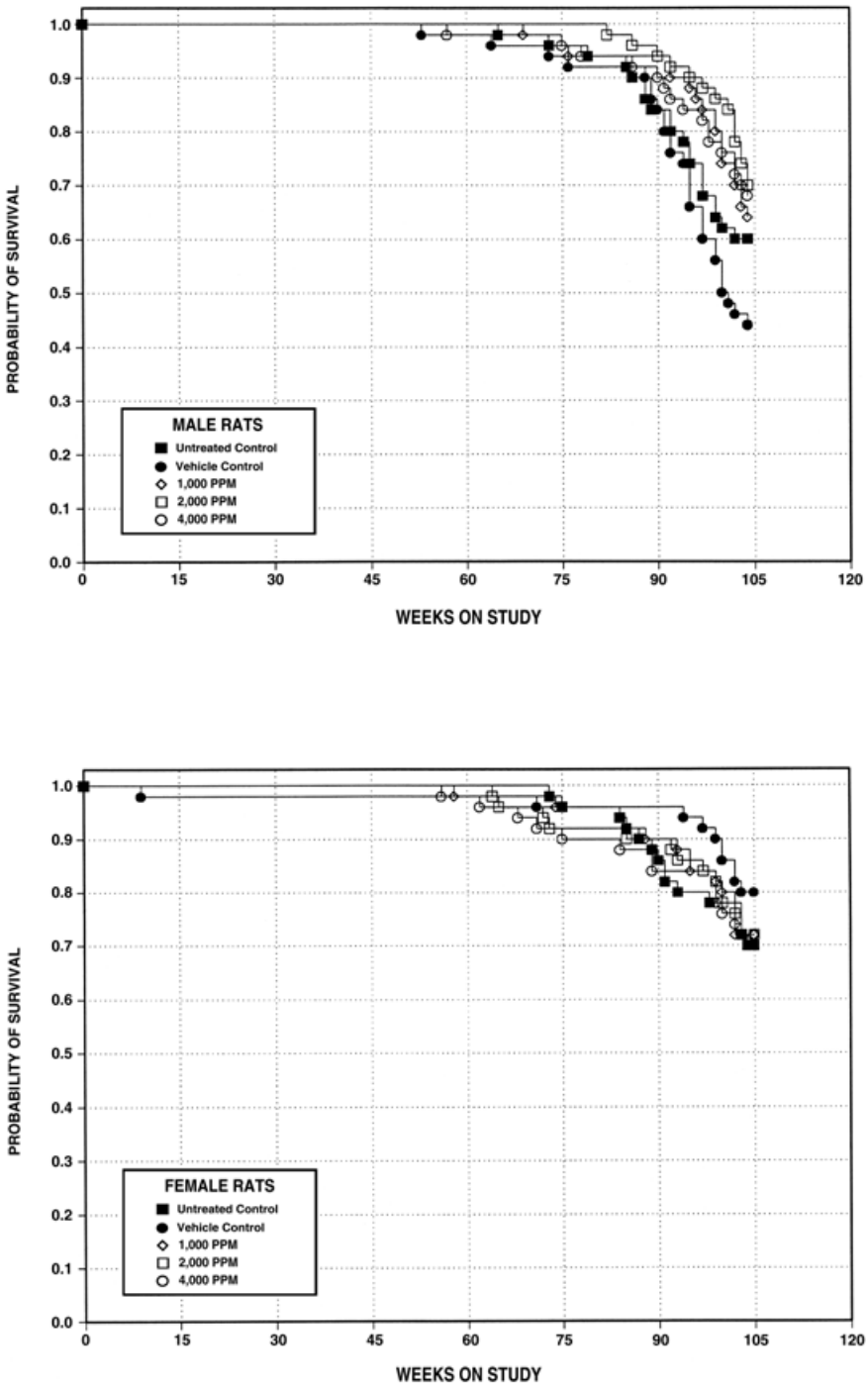


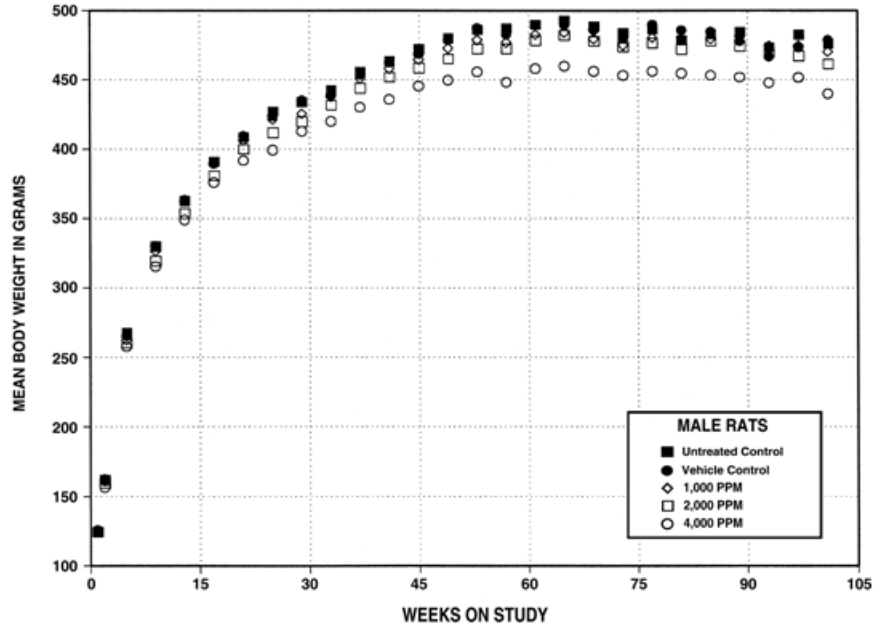
FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Citral in Feed for 2 Years

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

Weeks on Study	Vehicle Control		1,000 ppm			2,000 ppm			4,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	126	50	126	100	50	125	99	50	126	100	50
2	161	50	163	101	50	160	99	50	157	97	50
5	266	50	262	99	50	260	98	50	258	97	50
9	330	50	327	99	50	319	97	50	315	96	50
13	363	50	362	100	50	354	97	50	349	96	50
17	390	50	390	100	50	381	98	50	376	97	50
21	410	50	406	99	50	400	98	50	392	96	50
25	424	50	421	99	50	412	97	50	399	94	50
29	435	50	426	98	50	420	97	50	413	95	50
33	439	50	438	100	50	432	98	50	420	96	50
37	453	50	451	99	50	444	98	50	430	95	50
41	462	50	458	99	50	452	98	50	436	94	50
45	469	50	464	99	50	458	98	50	445	95	50
49	479	50	473	99	50	465	97	50	450	94	50
53	487	49	479	98	50	472	97	50	456	94	50
57	483	49	477	99	50	472	98	50	448	93	50
61	490	49	483	99	50	478	98	50	458	94	49
65	490	48	484	99	50	482	98	50	460	94	49
69	486	48	479	99	49	478	98	50	456	94	49
73	480	48	475	99	48	474	99	50	453	95	49
77	490	46	480	98	47	476	97	50	456	93	48
81	486	46	480	99	47	472	97	50	455	94	47
85	485	46	479	99	47	478	99	49	453	94	47
89	478	44	481	101	47	474	99	48	452	95	46
93	466	38	475	102	45	469	101	46	448	96	43
97	473	31	475	100	42	467	99	44	452	95	41
101	479	25	470	98	37	461	96	42	440	92	38
Mean for weeks											
1-13	249		248	100		244	98		241	97	
14-52	440		436	99		429	98		418	95	
53-101	483		478	99		473	98		453	94	

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

Weeks on Study	Vehicle Control		1,000 ppm			2,000 ppm			4,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	106	50	107	101	50	107	101	50	108	102	50
2	125	50	124	99	50	124	100	50	122	98	50
5	166	50	162	98	50	162	98	50	159	96	50
9	187	50	186	99	50	185	99	50	178	95	50
13	201	49	196	98	50	198	99	50	190	95	50
17	208	49	203	98	50	204	98	50	198	95	50
21	213	49	210	98	50	212	99	50	203	95	50
25	219	49	214	98	50	215	98	50	207	94	50
29	226	49	223	99	50	224	99	50	211	93	50
33	230	49	226	98	50	226	98	50	216	94	50
37	238	49	232	98	50	232	98	50	221	93	50
41	242	49	237	98	50	235	97	50	222	92	50
45	253	49	245	97	50	244	97	50	229	91	50
49	259	49	252	97	50	252	97	50	235	91	50
53	270	49	260	96	50	257	96	50	236	87	50
57	276	49	268	97	50	264	96	50	240	87	49
61	286	49	275	96	49	274	96	50	246	86	49
65	290	49	283	97	49	282	97	48	253	87	48
69	302	49	291	97	49	291	96	48	263	87	47
73	309	48	298	96	49	296	96	47	266	86	46
77	318	48	307	97	48	305	96	46	275	87	45
81	327	48	313	96	48	311	95	46	282	86	45
85	332	48	319	96	47	318	96	46	286	86	44
89	334	48	324	97	45	322	96	45	291	87	42
93	332	48	324	98	44	322	97	43	291	88	42
97	331	47	322	97	42	323	97	42	289	87	42
101	335	43	326	97	40	323	96	39	298	89	38
Mean for weeks											
1-13	157		155	99		155	99		151	96	
14-52	232		227	98		227	98		216	93	
53-101	311		301	97		299	96		270	87	



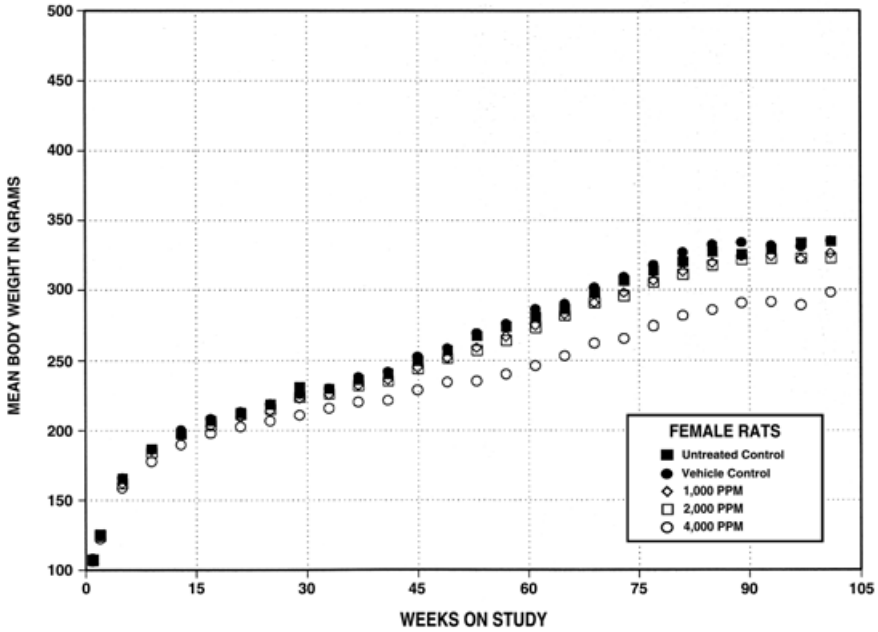


FIGURE 3
Growth Curves for Male and Female Rats Exposed to Citral in Feed for 2 Years

Untreated Controls Versus Vehicle Controls

In males, the incidences of heart thrombosis (untreated control: 0/50; vehicle control, 6/50) and liver angiectasis (0/50, 5/50) were significantly greater in the vehicle control group compared to those in the untreated control group (Table A4). In females, the incidences of clitoral gland hyperplasia (7/49, 17/49), cardiomyopathy (41/50, 48/50), liver basophilic focus (42/50, 48/50), mandibular lymph node hyperplasia (6/50, 17/50), and ovarian cyst (3/50, 11/50), were significantly greater in the vehicle control group compared to those in the untreated control group (Table B4). The incidence of uterine stromal polyp (14/50, 5/50; Table B1) was significantly less in vehicle control females compared to the untreated controls and was less than the historical control range in controls (all routes) given NTP-2000 diet [115/659 (17.7% ± 5.6%; range 12%-31%]. The reason for these differences is unknown, but the differences are likely due to individual animal variation.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms and/or nonneoplastic lesions of the kidney, adrenal cortex, clitoral gland, and mammary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats.

Mononuclear Cell Leukemia: The incidence of mononuclear cell leukemia was significantly increased in 1,000 ppm females compared to that in the vehicle controls (vehicle control, 10/50; 1,000 ppm, 22/50; 2,000 ppm, 14/50; 4,000 ppm, 15/50; Table B3). The increased incidence in 1,000 ppm females was not considered to be treatment related because there was no obvious exposure concentration-related response and the incidence in the vehicle control group was low.

Kidney: There were exposure concentration-related increases in the incidences of kidney mineralization in males (42/50, 45/50, 48/50, 50/50; Table A4). The lesion was characterized by the presence of minute to focally extensive mineralization of stromal tissue between collecting ducts. The severity of this lesion was increased in 2,000 and 4,000 ppm males (1.0, 1.0, 1.4, 2.4). Because the vehicle control incidence of renal mineralization was 84%, the increased incidences observed in the exposed groups are believed to reflect an exacerbation of this spontaneously occurring lesion. These renal changes are considered to have minimal toxicologic significance. A reexamination of kidneys from the 14-week study did not reveal a treatment-related increase in the incidence of renal mineralization.

Adrenal Cortex: A significantly increased incidence of adrenal cortical angiectasis occurred in 4,000 ppm females (1/50, 1/50, 3/50, 10/50; Table B4); this change was considered to be within the normal range of histopathologic changes observed in aged rats and was not considered to be a toxicologically significant effect of exposure.

Clitoral Gland: There was a significant decrease in the incidence of clitoral gland adenoma or carcinoma (combined) in 4,000 ppm females (7/49, 3/49, 4/50, 1/49, Table B3), and the incidences occurred with a negative trend. The incidences were within the historical control range in controls (all routes) given NTP-2000 diet [84/636 (12.8% ± 7.4%), range 2%-24%]. Incidences of hyperplasia in the 1,000 and 4,000 ppm groups were significantly decreased (17/49, 8/49, 15/50, 4/49; Table B4).

Mammary Gland: There was a negative trend in the incidence of mammary gland fibroadenoma and a statistically significant decrease in the incidence in 4,000 ppm females compared to that in the vehicle controls (27/50, 22/50, 18/50, 16/50; Table B3). The incidence in the vehicle control group was at the upper end of the historical control range in controls given NTP-2000 diet [284/659 (41.1% ± 10.1%), range 28%-56%].

MICE

14-WEEK STUDY

In the second week of the study, four males in the 31,300 ppm group were killed moribund (Table 8). Animals exposed to 31,300 ppm lost weight during the study. Final mean body weights and body weight gains were significantly decreased in all exposed groups of males and females. Feed consumption by females exposed to 7,800 ppm or greater was less than that by the vehicle controls during the first week of the study. By the end of the study, feed consumption by all exposed groups of mice was greater than that by the vehicle controls. The increased feed consumption may have been due to the mice scattering feed, an indication of poor palatability. Dietary concentrations of 3,900, 7,800, 15,600, and 31,300 ppm resulted in average daily doses of approximately 745, 1,840, 3,915, and 8,110 mg citral/kg body weight to males and 790, 1,820, 3,870, and 7,550 mg/kg to females. Mice in the 15,600 and 31,300 ppm groups were generally thin and lethargic; a few males in the 7,800 ppm group were also thin.

At week 14, treatment-related decreases in lymphocyte counts were observed in all groups of exposed males and in females exposed to 15,600 or 31,300 ppm (Table F2). The decreased lymphocyte counts resulted in reduced leukocyte counts in these groups. The marked suppression in mean body weights of mice exposed to 7,800 ppm or greater and decreases in the lymphocyte counts may reflect a physiological response consistent with a stress-related and/or corticosteroid-induced lymphopenia.

Differences in organ weights between exposed mice and the vehicle controls reflected body weight differences and were not toxicologically significant (Table G2).

The wall of the forestomach of many male and female mice exposed to 15,600 or 31,300 ppm citral was

TABLE 8
Survival, Body Weights, and Feed Consumption of Mice in the 14-Week Feed Study of Citral

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Vehicle Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 14
Male							
Vehicle Control	10/10	20.6 ± 0.3	33.2 ± 0.8	12.6 ± 0.7		4.4	4.5
3,900	10/10	20.3 ± 0.3	28.1 ± 0.6**	7.9 ± 0.6**	85	4.6	5.0
7,800	10/10	20.3 ± 0.4	25.6 ± 0.6**	5.2 ± 0.4**	77	4.3	5.9
15,600	10/10	20.0 ± 0.3	21.3 ± 0.6**	1.3 ± 0.5**	64	4.0	6.2
31,300	6/10[d]	19.8 ± 0.3	17.1 ± 0.4**	-2.9 ± 0.4**	52	4.1	6.2
Female							
Vehicle Control	10/10	16.4 ± 0.1	29.8 ± 0.7	13.4 ± 0.8		3.4	3.6
3,900	10/10	16.6 ± 0.2	26.1 ± 0.4**	9.5 ± 0.4**	88	3.3	5.1
7,800	10/10	17.0 ± 0.3	21.2 ± 0.4**	4.2 ± 0.4**	71	2.3	6.4
15,600	10/10	16.8 ± 0.2	18.2 ± 0.2**	1.4 ± 0.3**	61	2.3	6.5
31,300	10/10	16.5 ± 0.2	16.2 ± 0.2**	-0.2 ± 0.2**	55	2.1	5.3

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Feed consumption is expressed as grams per animal per day.
[d] Week of death: 2

variably thickened (2 to 5 times normal) and the mucosa (squamous epithelium) and submucosa were often rugose. Although thickened, all three main components (mucosa, submucosa, and muscle) appeared proportional to each other and to those of control animals. Therefore, this alteration was considered the result of a contracted stomach rather than a pathological alteration. There did, however, appear to be an excessive amount of keratin (hyperkeratosis) on the surface of the epithelium of these animals, but the minimal hyperkeratosis was relatively insignificant. The incidences of ovarian atrophy were significantly increased in females exposed to 15,600 or 31,300 ppm (vehicle control, 0/10; 3,900 ppm, 0/0; 7,800 ppm, 0/10; 15,600 ppm, 7/10; 31,300 ppm, 10/10); the atrophy was moderate in 15,600 ppm females (2.6) and marked in 31,300 ppm females (3.8). The basis for the diagnosis of atrophy was an absence of or reduction in the number of corpora lutea with no effect on primary, secondary, or antral follicles. The NTP Pathology Working Group considered that the ovarian lesions most probably represented hypoplasia rather than atrophy and were most likely a secondary effect due to the poor condition of the exposed mice.

Exposure Concentration Selection Rationale: Based on lower final mean body weights in all exposed groups of mice, exposure concentrations selected for the 2-year feed study in mice were 500, 1,000, and 2,000 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 9 and in the Kaplan-Meier survival curves (Figure 4). Survival of exposed groups of males and females was similar to that of the vehicle control groups.

TABLE 9
Survival of Mice in the 2-Year Feed Study of Citral

	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	4	2	6	3
Natural deaths	3	8	2	7
Animals surviving to study termination	43[d]	40	42	40
Percent probability of survival at end of study[a]	86	80	84	80
Mean survival (days)[b]	695	695	715	701
Survival analysis[c]	P=0.660	P=0.586	P=1.000	P=0.596
Female				
Animals initially in study	50	50	50	50
Missing[e]	1	0	0	0
Moribund	5	2	4	5
Natural deaths	3	3	3	5
Animals surviving to study termination	41	45	43	40
Percent probability of survival at end of study	84	90	86	80
Mean survival (days)	703	719	718	700
Survival analysis	P=0.439	P=0.540N	P=0.964N	P=0.769

[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. The results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the exposed group columns. A lower mortality in an exposure group is indicated by **N**.
[d] Includes one animal that died during the last week of the study
[e] Censored from survival analyses

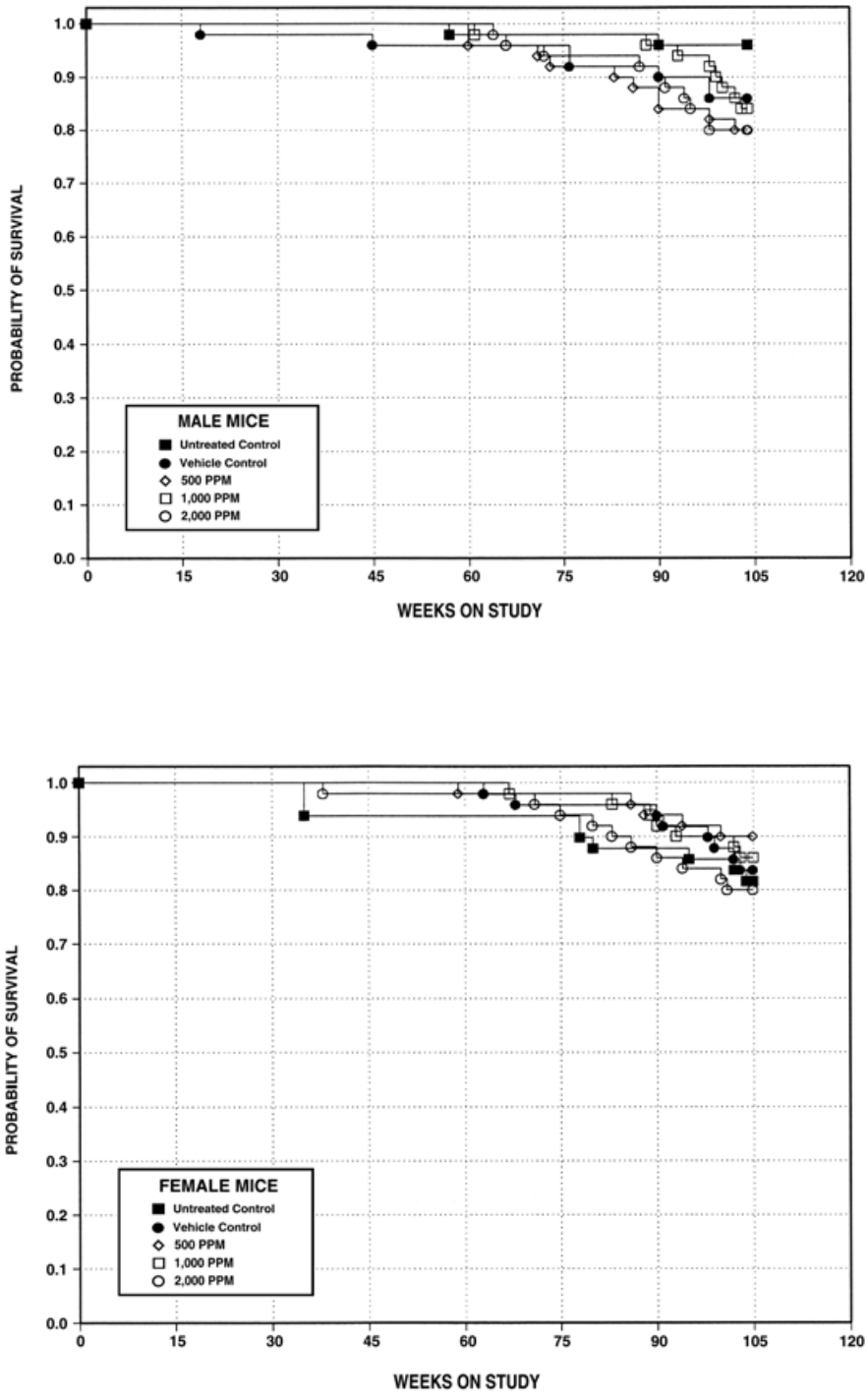


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Citral in Feed for 2 Years

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of mice exposed to 2,000 ppm were generally less throughout the study compared to those of the vehicle controls, mean body weights of mice exposed to 1,000 ppm were generally less during year 2 of the study (males) or from week 14 to the end of the study (females), and mean body weights of 500 ppm females were less from week 30 (Figure 5; Tables 10 and 11). Feed consumption by the exposed groups was similar to that by the vehicle controls (Tables I3 and I4). Dietary concentrations of 500, 1,000, and 2,000 ppm delivered average daily doses of approximately 60, 120, and 260 mg citral/kg body weight to males and females. No clinical findings were attributed to citral exposure.

Untreated Controls Versus Vehicle Controls

The incidences of bone marrow hyperplasia (males: untreated control, 9/50; vehicle control, 19/50; females: 2/50, 11/49) were significantly greater in the vehicle control groups compared to those in the untreated control groups (Tables C4 and D5). In male mice, incidences of kidney infarct (2/50, 8/50) and renal tubule mineralization (45/50, 48/50) were significantly greater in vehicle controls compared to untreated controls. The reason for these differences is unknown, but they are likely due to individual animal variation. There were no differences in the incidences of neoplasms in vehicle controls compared to untreated controls (Tables C1 and D1).

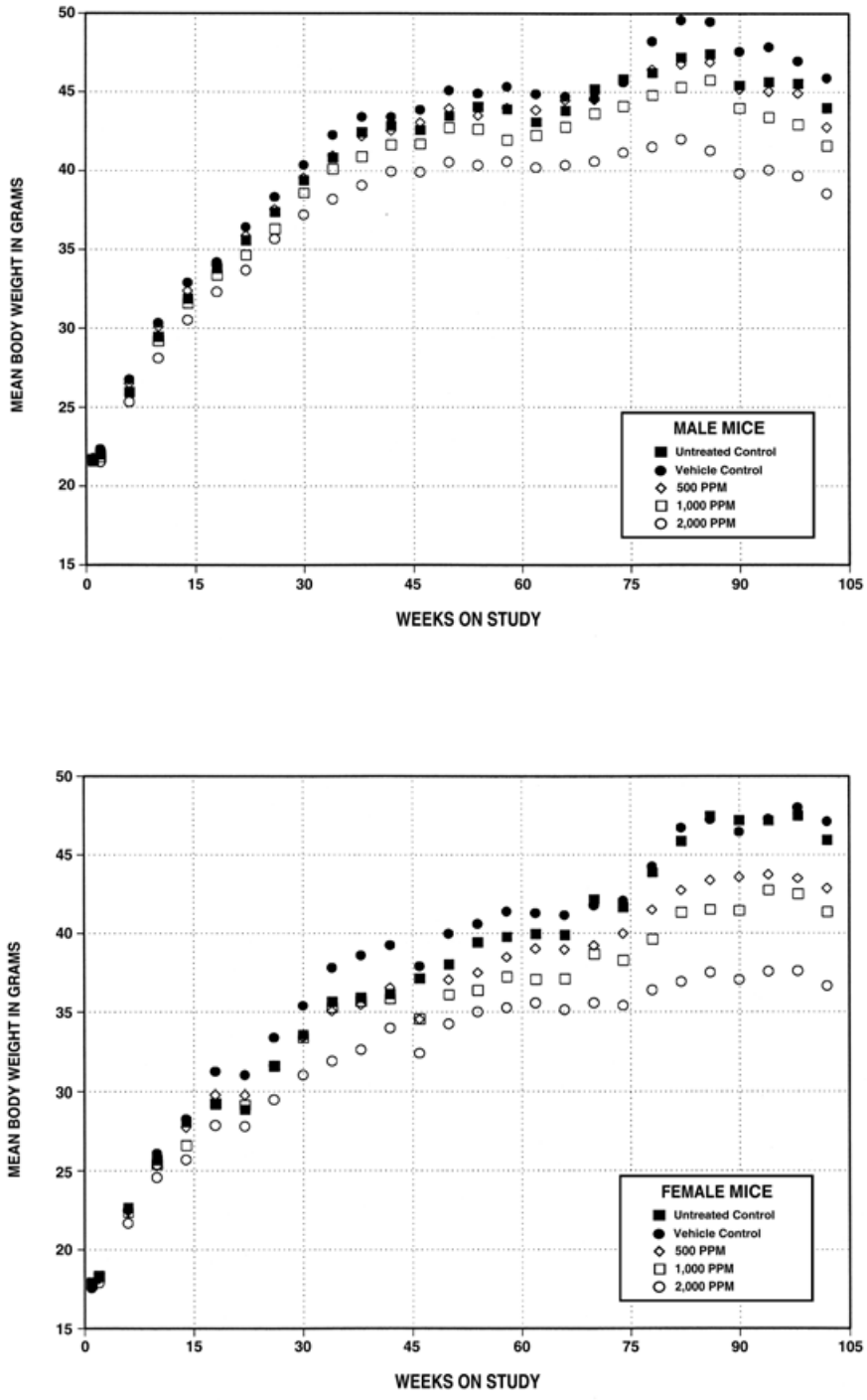


FIGURE 5
Growth Curves for Male and Female Mice Exposed to Citral in Feed for 2 Years

TABLE 10
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Citral

Weeks on Study	Vehicle Control		500 ppm			1,000 ppm			2,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	21.7	50	21.8	101	50	21.7	100	50	21.7	100	50
2	22.3	50	22.4	100	50	21.8	98	50	21.5	96	50
6	26.8	50	26.5	99	50	26.0	97	50	25.4	95	50
10	30.4	50	30.1	99	50	29.2	96	50	28.1	92	50
14	32.9	50	32.4	99	50	31.6	96	50	30.5	93	50
18	34.2	50	34.0	99	50	33.4	98	50	32.3	94	50
22	36.4	49	35.9	99	50	34.6	95	50	33.7	93	50
26	38.3	49	37.6	98	50	36.3	95	50	35.7	93	50
30	40.4	49	39.6	98	50	38.6	96	50	37.2	92	50
34	42.3	49	41.0	97	50	40.1	95	50	38.2	90	50
38	43.4	49	42.2	97	50	40.9	94	50	39.1	90	50
42	43.4	49	42.6	98	50	41.6	96	50	40.0	92	50
46	43.9	48	43.1	98	50	41.7	95	50	39.9	91	50
50	45.1	48	44.0	98	50	42.7	95	50	40.6	90	50
54	44.9	48	43.5	97	50	42.6	95	50	40.4	90	50
58	45.3	48	44.0	97	50	42.0	93	50	40.6	90	50
62	44.9	48	43.9	98	48	42.2	94	49	40.2	90	50
66	44.7	48	44.5	100	48	42.8	96	49	40.4	90	48
70	44.6	48	44.5	100	48	43.6	98	49	40.6	91	48
74	45.6	48	45.8	100	46	44.1	97	49	41.2	90	47
78	48.2	46	46.4	96	46	44.8	93	49	41.5	86	47
82	49.6	46	46.8	94	46	45.3	91	49	42.0	85	47
86	49.5	46	46.9	95	45	45.7	92	49	41.3	83	47
90	47.6	46	45.2	95	44	44.0	92	48	39.8	84	46
94	47.9	45	45.0	94	42	43.4	91	47	40.1	84	43
98	47.0	45	44.9	96	41	42.9	91	47	39.7	85	42
102	45.9	43	42.8	93	41	41.6	91	44	38.6	84	40
Mean for weeks											
1-13	25.3		25.2	100		24.7	98		24.2	96	
14-52	40.0		39.2	98		38.2	96		36.7	92	
53-102	46.6		44.9	96		43.5	93		40.5	87	

TABLE 11
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Citral

Weeks on Study	Vehicle Control		500 ppm			1,000 ppm			2,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	17.6	50	17.7	101	50	17.8	101	50	17.6	100	50
2	18.2	50	18.1	100	50	18.3	101	50	17.9	98	50
6	22.5	50	22.5	100	50	22.4	100	50	21.7	96	50
10	26.1	50	25.3	97	50	25.4	97	50	24.6	94	50
14	28.3	50	27.8	98	50	26.6	94	50	25.7	91	50
18	31.2	49	29.8	96	50	29.2	94	50	27.9	89	50
22	31.0	49	29.8	96	50	29.1	94	50	27.8	90	50
26	33.4	49	31.6	95	50	31.6	95	50	29.5	88	50
30	35.4	49	33.4	94	50	33.4	94	50	31.0	88	50
34	37.8	49	35.1	93	50	35.3	93	50	31.9	84	50
38	38.6	49	35.5	92	50	35.7	93	50	32.6	85	50
42	39.2	49	36.5	93	50	35.8	91	50	34.0	87	49
46	37.9	49	34.5	91	50	34.6	91	50	32.4	86	49
50	40.0	49	37.0	93	50	36.1	90	50	34.2	86	49
54	40.6	49	37.5	92	50	36.4	90	50	35.0	86	49
58	41.4	49	38.5	93	50	37.2	90	50	35.3	85	49
62	41.3	49	39.0	94	49	37.0	90	50	35.6	86	49
66	41.1	48	39.0	95	49	37.1	90	50	35.1	85	49
70	41.8	47	39.2	94	49	38.7	93	49	35.6	85	49
74	42.1	47	40.0	95	49	38.3	91	49	35.4	84	48
78	44.3	47	41.5	94	49	39.6	89	49	36.4	82	47
82	46.7	47	42.8	92	49	41.3	88	49	36.9	79	46
86	47.2	47	43.4	92	49	41.5	88	48	37.5	79	45
90	46.5	47	43.6	94	47	41.4	89	47	37.0	80	44
94	47.3	45	43.8	93	47	42.8	91	45	37.6	80	43
98	48.0	44	43.5	91	46	42.5	89	45	37.6	78	42
102	47.1	43	42.9	91	45	41.4	88	45	36.6	78	40
Mean for weeks											
1-13	21.1		20.9	99		21.0	100		20.5	97	
14-52	35.3		33.1	94		32.7	93		30.7	87	
53-102	44.3		41.1	93		39.6	89		36.3	82	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of malignant lymphoma and neoplasms and/or nonneoplastic lesions of the liver, oral mucosa, bone, adrenal cortex, kidney, and lung. Summaries of the incidences of neoplasms and/or nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Malignant Lymphoma: The incidences of malignant lymphoma in females occurred with a positive trend. The incidence in 2,000 ppm females was significantly greater than that in the vehicle control group but was within the historical ranges in controls (all routes) given NTP-2000 diet or feed controls given NIH-07 diet (Tables 12, D3, and D4). Tissues most commonly affected by malignant lymphoma were the spleen, mesenteric lymph node, thymus, and, to a lesser extent, the ovary. The three earliest cases of malignant lymphoma were observed in moribund animals in the 1,000 (469 days on study) and 2,000 (491 and 523 days on study) ppm groups; all remaining malignant lymphomas were observed at the end of the study. To further characterize the nature of the lymphomas in vehicle control and exposed mice, all cases of lymphoma were sectioned and immunostained using CD-3 to identify T cells and CD-45R (B220 clone) to identify B cells. Special stains did not reveal any differences in the origin of lymphomas in vehicle controls or females exposed to citral.

TABLE 12
Incidences of Malignant Lymphoma in Mice in the 2-Year Feed Study of Citral

	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Male				
Malignant Lymphoma				
Overall rate[a]	0/50 (0%)	2/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rate[b]	0.0%	4.4%	6.3%	2.2%
Terminal rate[c]	0/43 (0%)	1/40 (3%)	2/42 (5%)	0/40 (0%)
First incidence (days)	—[e]	576	720	500
Poly-3 test[d]	P=0.450	P=0.235	P=0.126	P=0.501
Female				
Malignant Lymphoma[f]				
Overall rate	3/49 (6%)	5/50 (10%)	9/50 (18%)	12/50 (24%)
Adjusted rate	6.5%	10.4%	18.6%	25.7%
Terminal rate	2/41 (5%)	5/45 (11%)	7/43 (16%)	10/40 (25%)
First incidence (days)	719	733 (T)	469	491
Poly-3 test	P=0.004	P=0.376	P=0.070	P=0.011

(T) Terminal sacrifice
[a] Number of animals with neoplasm per number of animals necropsied
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the 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 differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group
[f] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 98/659 (14.0% ± 7.1%), range 6%-32%; with feed controls given NIH-07 diet: 167/953 (17.5% ± 7.7%), range 6%-30%

Liver: There was a positive trend in the incidence of hepatocellular adenoma in females (3/49, 2/50, 8/50, 8/50), but neither pairwise comparisons for hepatocellular adenoma nor trends for hepatocellular carcinoma or hepatocellular adenoma or carcinoma (combined) were significant (Table D3). Therefore, it is unlikely that this was a chemical-related effect.

Oral Mucosa: Inflammation and ulceration of the oral mucosa were present in all groups of mice. The incidences of inflammation in 2,000 ppm males and inflammation and ulceration in all groups of exposed females were significantly increased (Tables 13, C4, and D5). With rare exceptions, the areas of inflammation and ulceration were directly medial to the molar teeth. The inflammation was minimal to mild and was characterized by an accumulation of mixed inflammatory cells within and just beneath the oral mucosa adjacent to the medial aspect of the teeth. In a majority of the cases, hair shafts were present in the inflamed areas and appeared to have penetrated the tooth socket. Ulcers were minimal to mild in severity and consisted of focal areas with loss of mucosa. The ulcers were almost always located at the points where hair shafts penetrated the oral mucosa. The inflammation and ulceration were considered to be secondary to embedded hair shafts present either in the actual section or in an adjacent plane of section. These same lesions, with similar severity, were observed in vehicle controls. Thus, the inflammation and ulceration were probably not a direct toxic effect of citral, but citral may have exacerbated the secondary inflammatory response in females. The significance of this effect is unknown.

Bone: The incidences of bone fibrosis were significantly increased in 500 and 1,000 ppm females (11/49, 22/50, 21/50, 18/50; Table D5). The significance of this observation is unknown.

Adrenal Cortex: The incidences of adrenal cortical focal hyperplasia were increased in exposed males versus the vehicle controls, and the increase was significant in the 2,000 ppm group (0/50, 3/50, 2/50, 5/50; Table C4). Because the incidences are very low for this common background lesion, they are not considered to reflect a toxic response to citral exposure.

TABLE 13
Incidences of Selected Nonneoplastic Lesions of the Oral Mucosa in Mice in the 2-Year Feed Study of Citral

	Vehicle Control		500 ppm		1,000 ppm		2,000 ppm	
Male								
Number Necropsied	50		50		50		50	
Inflammation, Chronic Active[a]	12	(1.8)[b]	16	(1.9)	21	(1.9)	21*	(1.5)
Ulcer	9	(1.8)	8	(1.6)	12	(1.4)	10	(1.6)
Female								
Number Necropsied	49		50		50		50	
Inflammation, Chronic Active	14	(1.4)	32**	(1.9)	35**	(1.8)	32**	(1.5)
Ulcer	6	(1.2)	15*	(1.9)	22**	(1.6)	15*	(1.5)

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

Kidney: There was an exacerbation of minimal nephropathy in exposed females, and the incidence was significantly increased in the 2,000 ppm group (Tables 14 and D5). The 500 and 1,000 ppm females had significantly increased incidences of minimal renal tubule mineralization compared to that in the vehicle controls. The toxicological significance of these effects is unclear.

Lung: The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) was significantly decreased in 2,000 ppm males compared to that in the vehicle controls (12/50, 9/50, 7/50, 4/50; Table C3), but this incidence was not significantly different from that in the untreated controls (8/50). Incidences of focal alveolar epithelial hyperplasia (males: 1/50, 1/50, 4/50, 2/50; females: 0/49, 3/50, 2/50, 2/50) were low and similar across all groups of mice (Tables C4 and D5).

GENETIC TOXICOLOGY

Citral (1 to 220 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without Aroclor-induced rat or hamster liver S9 enzymes (Table E1; Zeiger *et al*., 1987). In cytogenetic tests with cultured Chinese hamster ovary cells, citral induced sister chromatid exchanges (SCEs) with and without S9 (Table E2); citral was toxic to these cells, and higher doses required an extended culture period to permit accumulation of sufficient second-division metaphase cells for analysis. In contrast to the positive results in the SCE assay, chromosomal aberrations were not significantly increased after exposure to citral, with or without S9 (Table E3). As a result of citral-induced cell cycle delay, the cultures treated in the presence of S9 were permitted to grow for a longer than normal period of time to allow additional accumulation of first-division metaphase cells for analysis. Negative results were obtained in an *in vivo* bone marrow micronucleus test in male $B6C3F_1$ mice treated by intraperitoneal injection with 250 to 750 mg/kg daily for 3 days (Table E4); the next higher dose tested, 1,000 mg/kg, was lethal. Likewise, no increases in the frequency of micronucleated erythrocytes were observed in peripheral blood samples collected from male and female mice within 24 hours of the final exposure in the 14-week study (Table E5).

In conclusion, citral gave negative results in *in vitro* and *in vivo* tests for genotoxicity with one exception. The *in vitro* mammalian cell test for SCEs was positive with and without S9.

TABLE 14
Incidences of Selected Nonneoplastic Lesions of the Kidney in Female Mice in the 2-Year Feed Study of Citral

	Vehicle Control		500 ppm		1,000 ppm		2,000 ppm	
Number Examined Microscopically	49		50		50		50	
Nephropathy[a]	9	(1.0)[b]	16	(1.0)	15	(1.2)	17*	(1.0)
Renal Tubule, Mineralization	4	(1.0)	14*	(1.0)	18**	(1.0)	6	(1.2)

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

DISCUSSION AND CONCLUSIONS

Citral, a β-substituted vinyl aldehyde, occurs naturally among several plant and fruit species (*Fenaroli's*, 1975; Opdyke, 1979). Citral is used as a flavoring agent in a wide range of consumer products including baked goods, ice cream, beverages, perfumes, and soaps (Opdyke, 1979). Citral is also used in the synthesis of vitamin A, ionone, and methylionone (*Merck Index*, 1989). Toxicology and carcinogenicity studies of citral were performed because of widespread human exposure from its use as a food and fragrance additive and as a representative β-substituted vinyl aldehyde.

Because the most significant human exposure to citral occurs through ingestion as a food additive, dosed feed was the preferred route of exposure for the rodent studies. In a stability study of citral in NIH-07 diet (Kuhn *et al*., 1991), a 41% loss of citral was observed after one day, which was attributed to volatility and reactivity of the aldehydic moiety of citral with components in the feed. Thus, citral was given in starch microcapsules mixed with the diet, increasing the stability of citral in the diet to 95% after seven days.

To determine if the toxicity of citral was altered by microencapsulation, 14-day continuous feed and comparative corn oil gavage studies were performed (Dieter *et al.*, 1993). No mortality and only slight changes in body and organ weights were observed in rats and mice exposed to 2,280 and 8,550 mg citral/kg body weight. In the corn oil gavage study, some mice exposed to 1,068 mg/kg and all mice exposed to 2,137 mg/kg died. Additionally, adverse clinical signs and some mortality were observed in mice gavaged with 1,068 mg/kg in corn oil. Mild hyperplasia and squamous metaplasia of the respiratory epithelium was observed in rats exposed to 1,140 and 2,280 mg/kg. This was not observed in the present studies. Administration of citral in corn oil by gavage also caused stomach inflammation and necrosis/ulceration and hyperplasia of the squamous mucosa. These responses could potentially compromise interpretation of carcinogenic responses in long-term studies. Therefore, microencapsulated citral was chosen as the route of administration for long-term studies because it allowed for higher doses and minimized gastric irritation. The doses used in the present studies exceeded the Acceptable Daily Intake of citral in humans, which is approximately 5 mg/kg per day (Council of Europe, 1973). Studies with cinnamaldehyde also have shown that the bioavailability and toxicity of the test article were not altered when administered in microcapsules compared to corn oil gavage administration (Yuan *et al.*, 1993; Hébert *et al.*, 1994).

Between the untreated and vehicle controls in the 2-year studies, there were significant differences in the incidences of uterine stromal polyps in rats and in some nonneoplastic lesions in rats and mice. The incidence of uterine stromal polyp in female rats was significantly lower in the vehicle controls (10%) than that in untreated controls (28%) and was outside the lower end of the historical control range for the NTP-2000 diet (12%-31%). While this response is statistically significant, it is not believed to be biologically relevant as the incidences are on the low and high ends of the range and probably reflect normal biological variation. An informal review of all nonneoplastic lesions from other NTP studies was performed to approximate a range for the nonneoplastic lesions that were significantly different between vehicle and untreated controls. In most cases, the lesions occurred at the frequencies expected by chance, suggesting that the differences were due to biological variation and not to ingestion of microcapsules. However, in vehicle control male and female mice, significant increases in the incidences of bone marrow hyperplasia were observed compared to untreated controls. In control mice from 2-year NTP feed studies using the NIH-07 diet, bone marrow hyperplasia was reported in 32 studies (male: range, 0%-71%; female: range, 0%-68%) and bone marrow hypercellularity was reported in five studies (male: range, 0%-18%; female: range, 0%-32%). The incidences observed in male (38%) and female (22%) mice from the vehicle control groups in the current study were within these ranges.

In the current 14-week rat study, all males and females in the 31,300 ppm group were killed moribund during the second week of the study. Dose-related decreases in mean body weights, from which they never recovered, occurred in male and female rats exposed to 7,800 ppm or greater. Based on this information, the highest dose

selected for the 2-year study was 4,000 ppm. In addition to decreased mean body weights, nephropathy and renal tubule granular casts were observed in 3 of 10 male rats exposed to 3,900 ppm and most male rats exposed to 7,800 or 15,600 ppm. In the current 2-year study, no compound-related neoplasms or nonneoplastic lesions were observed in male or female rats exposed to 1,000, 2,000, or 4,000 ppm citral.

The incidences of clitoral gland hyperplasia and adenoma or carcinoma (combined) were significantly decreased in 4,000 ppm female rats compared to those in the vehicle controls. In addition, an exposure-related decrease in the incidence of mammary gland fibroadenoma in rats was observed in the 4,000 ppm group. While the significance of these effects is unknown, it is possible that a relationship exists between these events and the antiestrogenic effects of citral (Geldof *et al*., 1992).

Citral has been extensively studied for its effect on the induction of benign and atypical hyperplasia in the ventral prostate of male rats (Servadio *et al*., 1986; Engelstein *et al*., 1996; Kessler *et al*., 1998). In the present study, careful examination did not reveal any effect on male accessory glands, including all lobes of the prostate. A comparative study of citral-induced benign and atypical hyperplasia in Wistar, Sprague-Dawley, Fischer 344, and ACI/Ztm rats demonstrated that strain genotype and endocrine background play a role in the development of this disease (Scolnik *et al*., 1994); the animal model chosen for the current study, the Fischer 344/N rat, was shown to be refractory to citral-induced prostatic hyperplasia.

In the 14-week mouse study, compound-related deaths occurred in 4 of 10 males exposed to 31,300 ppm. Mean body weights of all exposed groups of males and females were less than those of the vehicle controls. Typically, in the absence of other information, high exposure concentrations for 2-year studies are chosen based on the concentration that causes less than a 10% decrease in body weight. Because male and female mice exposed to 3,900 ppm exceeded this percentage, the highest exposure concentration chosen for the 2-year studies was 2,000 ppm.

In the 14-week studies, significant increases in relative liver weights occurred in 31,300 ppm male rats and in exposed groups of mice. This response was most likely due to significant decreases in body weights resulting from toxicity at high exposure concentrations and decreased feed consumption. No treatment-related hepatic histopathologic changes indicative of a direct or indirect effect of citral exposure were observed in the present studies. However, other studies have shown that citral is a peroxisome proliferator (Jackson *et al*., 1987; Roffey *et al*., 1990). A characteristic hallmark of toxicity for this chemical class is an increase in liver weight. This effect has been observed in male Wistar albino rats dermally exposed to 1,500 mg citral/kg body weight per day for 5 days (Roffey *et al*., 1990), male B6C3F_1 mice orally gavaged with 1,068 or 2,137 mg/kg per day for 14 days (Dieter *et al*., 1993), and Wistar and Long-Evans male rats gastrically intubated with 2,400 mg/kg per day for 3 to 10 days (Jackson *et al*., 1987). However, in 13-week studies, liver weights of Fischer 344 rats exposed by inhalation to concentrations up to 10 ppm (Gaworski *et al*., 1993) and Osborne-Mendel rats exposed to dietary concentrations up to 10,000 ppm (Hagan *et al*., 1967) were not affected. Thus, it is unlikely that citral induced peroxisome proliferation in the present studies.

In the 2-year mouse study, the incidences of malignant lymphoma in females occurred with a positive trend. When detected in lymph nodes and thymus glands, lymphomas are easily diagnosed. However, malignant lymphoma in the spleen is often difficult to distinguish from lymphoid hyperplasia. This prompted a comprehensive, blind peer review of all diagnosed lymphomas and lymphoid hyperplasia in all lymphoid tissues. The final count of lymphomas was based upon an independent assessment of affected lymphoid tissues by up to 10 pathologists and represents a consensus opinion in all cases.

Several arguments support an association of malignant lymphoma in female mice with citral exposure. In addition to the positive trend in the incidences of malignant lymphoma, the incidence in the 2,000 ppm group was significantly greater than that in the vehicle controls and exceeded the incidences of lymphoma in control female mice in all but one study using the NTP-2000 diet. The incidences of malignant lymphoma in 1,000 and 2,000 ppm females were significantly greater than that in untreated and vehicle control groups combined.

Conversely, other arguments weaken the association of malignant lymphoma with citral exposure in female mice. Although the incidence of malignant lymphoma in the 2,000 ppm group was significantly increased, it

was within the historical ranges for control female mice given the NTP-2000 and NIH-07 diets for 2 years, and the incidence in the vehicle controls was at the lower end of these historical control ranges.

The total weight of evidence supports the call of equivocal evidence of carcinogenicity because malignant lymphoma is a common tumor in mice, the increased incidence of lymphoma observed in the present study was marginal and within the historical control ranges for NTP-2000 and NIH-07 diets, and the incidence in the concurrent vehicle control group was at the low end of the historical control ranges. Citral is readily absorbed from the gastrointestinal tract and is similarly distributed in the gastrointesinal tract, liver, and kidneys in rats and mice (Phillips *et al.*, 1976). However, mice have a wider distribution throughout all organs and excrete citral less rapidly than rats. Because citral has a longer residence time and has a more extensive distribution pattern in mice, it is possible that the response observed in female mice could be related to these differences. However, it could not be determined if there was a difference in distribution or clearance of citral between genders because the studies in the literature were performed in male rats and mice only (Phillips *et al.*, 1976; Diliberto *et al*., 1988, 1990). Toxicokinetic studies were attempted by the NTP; however, citral was unstable in blood. In the absence of this information, adequate modeling studies to elucidate gender differences in response to citral could not be performed.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of citral in male or female F344/N rats exposed to 1,000, 2,000, or 4,000 ppm. There was *no evidence of carcinogenic activity* of citral in male B6C3F$_1$ mice exposed to 500, 1,000, or 2,000 ppm. There was *equivocal evidence of carcinogenic activity* in female B6C3F$_1$ mice based on increased incidences of malignant lymphoma.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and 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 CITRAL

TABLE A1	Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Citral	66
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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Citral[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	18	22	15	11	10
Natural deaths	2	6	3	4	6
Survivors					
Terminal sacrifice	30	22	32	35	34
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)				
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin	1 (2%)				
Intestine large, cecum	(50)	(50)	(50)	(49)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Leiomyoma		1 (2%)			
Leiomyosarcoma					1 (2%)
Intestine small, ileum	(50)	(50)	(49)	(50)	(50)
Liver	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Mesentery	(8)	(13)	(11)	(11)	(5)
Fibrosarcoma					1 (20%)
Fibrous histiocytoma, metastatic, skin		1 (8%)			
Oral mucosa		(1)	(2)		
Squamous cell carcinoma		1 (100%)	1 (50%)		
Pharyngeal, squamous cell papilloma			1 (50%)		
Pancreas	(50)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		1 (2%)	1 (2%)
Fibroma		1 (2%)			
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, skin		1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Leiomyosarcoma		1 (2%)			
Squamous cell papilloma			1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Tongue	(1)		(1)	(1)	
Squamous cell papilloma	1 (100%)		1 (100%)	1 (100%)	
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Schwannoma malignant			2 (4%)	1 (2%)	

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Pheochromocytoma complex	1 (2%)				1 (2%)
Pheochromocytoma benign	5 (10%)	3 (6%)	2 (4%)	2 (4%)	8 (16%)
Bilateral, pheochromocytoma benign	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Islets, pancreatic	(49)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	2 (4%)	1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)	(49)
Carcinoma, metastatic, Zymbal's gland		1 (2%)			
Pars distalis, adenoma	8 (16%)	9 (18%)	7 (14%)	9 (18%)	6 (12%)
Pars intermedia, adenoma	1 (2%)		1 (2%)		2 (4%)
Pars nervosa, adenoma				1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)			
C-cell, adenoma	7 (14%)	4 (8%)	9 (18%)	10 (20%)	10 (20%)
C-cell, carcinoma	2 (4%)	2 (4%)		2 (4%)	1 (2%)
Follicular cell, adenoma	3 (6%)			2 (4%)	
Follicular cell, carcinoma	1 (2%)				2 (4%)
General Body System					
None					
Genital System					
Coagulating gland			(1)	(1)	(1)
Adenoma					1 (100%)
Epididymis	(50)	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(49)	(50)	(50)
Adenoma	4 (8%)	3 (6%)	5 (10%)	4 (8%)	3 (6%)
Carcinoma	1 (2%)			1 (2%)	1 (2%)
Prostate	(50)	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)		
Bilateral, interstitial cell, adenoma	46 (92%)	42 (84%)	46 (92%)	41 (82%)	44 (88%)
Interstitial cell, adenoma	3 (6%)	5 (10%)	3 (6%)	4 (8%)	3 (6%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Lymph node	(15)	(20)	(10)	(10)	(12)
Mediastinal, fibrous histiocytoma, metastatic, skin		1 (5%)			
Lymph node, mandibular	(50)	(49)	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Hemangioma	1 (2%)				
Spleen	(50)	(50)	(50)	(50)	(49)
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Thymus	(50)	(47)	(49)	(47)	(49)

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Integumentary System					
Mammary gland	(50)	(50)	(50)	(49)	(50)
Adenocarcinoma		1 (2%)			
Adenoma	1 (2%)				
Carcinoma		1 (2%)			
Fibroadenoma	3 (6%)	2 (4%)		3 (6%)	2 (4%)
Fibroadenoma, multiple		3 (6%)			
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)	2 (4%)	1 (2%)	
Basal cell carcinoma			1 (2%)		
Keratoacanthoma	4 (8%)	3 (6%)	2 (4%)	5 (10%)	4 (8%)
Keratoacanthoma, multiple	1 (2%)		1 (2%)		
Squamous cell papilloma	1 (2%)			1 (2%)	
Trichoepithelioma	1 (2%)		1 (2%)		
Dermis, schwannoma malignant				1 (2%)	
Epidermis, melanoma malignant	1 (2%)				
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	2 (4%)		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrous histiocytoma	1 (2%)	1 (2%)			
Subcutaneous tissue, fibrous histiocytoma, metastatic, skin		1 (2%)			
Subcutaneous tissue, lipoma			1 (2%)		
Subcutaneous tissue, myxoma		1 (2%)			
Subcutaneous tissue, myxosarcoma			1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)	1 (2%)		1 (2%)
Subcutaneous tissue, schwannoma malignant		2 (4%)			
Subcutaneous tissue, pinna, melanoma malignant				1 (2%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)	
Rib, carcinoma, metastatic, mammary gland		1 (2%)			
Skeletal muscle					(2)
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland		1 (2%)			
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	2 (4%)		
Alveolar/bronchiolar carcinoma			1 (2%)	1 (2%)	
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Osteosarcoma, metastatic, bone				1 (2%)	
Pheochromocytoma complex, metastatic, adrenal medulla					1 (2%)
Schwannoma malignant, metastatic, skin		1 (2%)			
Bronchiole, carcinoma	1 (2%)				

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Respiratory System (continued)					
Nose	(50)	(50)	(50)	(50)	(50)
Adenoma				1 (2%)	
Trachea	(50)	(50)	(50)	(50)	(50)
Special Senses System					
Eye	(1)	(3)	(3)	(2)	(3)
Melanoma malignant				1 (50%)	
Zymbal's gland		(1)			(1)
Carcinoma		1 (100%)			1 (100%)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Lipoma					1 (2%)
Renal tubule, adenoma				1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)	(50)
Lipoma				1 (2%)	
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Leukemia mononuclear	33 (66%)	35 (70%)	39 (78%)	32 (64%)	29 (58%)
Lymphoma malignant					1 (2%)
Mesothelioma malignant	2 (4%)	2 (4%)	4 (8%)	4 (8%)	2 (4%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	50	49	50	49	50
Total primary neoplasms	143	134	143	138	129
Total animals with benign neoplasms	50	47	50	48	48
Total benign neoplasms	97	86	91	92	87
Total animals with malignant neoplasms	35	41	41	37	33
Total malignant neoplasms	46	48	52	46	42
Total animals with metastatic neoplasms	1	4		1	1
Total metastatic neoplasms	1	17		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 A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: Untreated Control

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

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

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

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 0 2	0 0 2 7	0 1 2	0 1 3	0 1 7	0 2 7	0 3 2	0 4 8	0 0 5	0 0 8	0 1 6	0 2 4	0 2 6	0 2 8	0 3 6	0 3 8	0 5 0	0 0 6	0 3 5	0 4 9	0 1 4	0 1 8	0 2 0	0 3 3	0 3 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X																		1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																	+		+					+		8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex						X																				1
Pheochromocytoma benign		X												X				X								5
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X		X					X						X				X					8
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X					X			X				X	X								X		X	7
C-cell, carcinoma						X					X															2
Follicular cell, adenoma																						X				3
Follicular cell, carcinoma																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: Untreated Control

	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
Number of Days on Study	5	0	4	8	0	1	1	1	3	3	5	6	6	7	7	7	8	9	9	1	2	2	2	2	2
	0	5	9	9	0	0	0	7	9	9	3	0	0	4	4	4	8	3	5	2	6	6	6	6	6
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	4	3	4	4	3	2	3	4	4	4	4	0	1	0	1	1	4	2	0	0	1	2	2	2	3
	5	9	0	3	1	1	4	6	1	4	2	3	5	1	0	9	7	3	4	9	1	2	5	9	0
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													X
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																						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+	+							+	+	+		+	+	+	+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma		X							X																X
Keratoacanthoma, multiple																									
Squamous cell papilloma																									
Trichoepithelioma																									
Epidermis, melanoma malignant																		X							
Subcutaneous tissue, fibroma						X																			
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, fibrous histiocytoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 0 2	0 0 2 7	0 0 1 2	0 1 1 3	0 1 1 7	0 2 3 7	0 3 4 2	0 4 0 8	0 0 0 5	0 0 0 8	0 0 1 6	0 1 2 4	0 2 2 6	0 2 2 8	0 2 3 6	0 3 3 8	0 3 5 0	0 5 0 6	0 3 3 5	0 3 4 9	0 4 1 4	0 1 1 8	0 1 2 0	0 2 3 3	0 3 3 7	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X															X								4
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	46
Interstitial cell, adenoma															X												3
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+						+	+						+	+								15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																		X									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																											1
Fibroadenoma		X									X			X													3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																			X								4
Keratoacanthoma, multiple																							X				1
Squamous cell papilloma												X															1
Trichoepithelioma																X											1
Epidermis, melanoma malignant																											1
Subcutaneous tissue, fibroma																											1
Subcutaneous tissue, fibrosarcoma																X			X								2
Subcutaneous tissue, fibrous histiocytoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	450	505	549	589	600	611	610	617	639	643	653	660	667	674	677	744	748	763	769	771	772	776	776	776	776
Carcass ID Number	04505	03509	04400	04403	03301	02411	03414	04416	04401	04404	04402	04403	01005	01501	01004	01909	01907	04207	02304	00409	00411	01912	02225	02209	03330
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Bronchiole, carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X	X		X		X	X	X	X	X	X	X	X	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 Citral: Untreated Control

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 0 2	0 0 1 7	0 1 1 2	0 1 1 3	0 1 1 7	0 2 3 7	0 3 3 2	0 4 3 8	0 0 4 5	0 0 5 8	0 0 6 8	0 1 6 6	0 2 4 4	0 2 6 6	0 2 6 8	0 3 6 6	0 3 6 8	0 5 6 0	0 0 6 6	0 3 6 5	0 4 6 9	0 1 7 4	0 1 7 8	0 2 8 0	0 3 8 3	0 3 8 7	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X															2
Bronchiole, carcinoma						X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X			X		X	X	X		X		X		X	X				X	X	X		33
Mesothelioma malignant																											2

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

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

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

Number of Days on Study	7 0 7	7 0 9	7 2 2	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 9 0	0 7 4	0 6 3	0 6 4	0 6 8	0 7 2	0 7 3	0 8 1	0 8 3	0 9 9	0 5 6	0 5 9	0 6 2	0 7 5	0 7 6	0 8 7	0 8 9	0 9 2	0 6 1	0 6 5	0 8 6	0 5 4	0 7 8	0 8 2	1 0 0	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
Leiomyoma																				X						1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Mesentery	+	+									+						+				+					13
Fibrous histiocytoma, metastatic, skin																										1
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Fibroma											X															1
Fibrous histiocytoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																		X								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X																			3
Bilateral, pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X			X								2
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Pars distalis, adenoma	X	X										X			X		X	X							X	9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma						X																				1
C-cell, adenoma					X															X					4
C-cell, carcinoma								X																		2

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

Number of Days on Study	3 6 5	4 4 6	5 0 9	5 3 2	6 1 0	6 1 7	6 2 3	6 2 8	6 3 2	6 3 7	6 3 9	6 3 9	6 5 3	6 6 0	6 6 0	6 6 0	6 6 3	6 7 4	6 7 4	6 7 8	6 8 8	6 8 8	6 9 4	6 9 5	6 9 5
Carcass ID Number	0 7 0	0 9 7	0 9 1	0 9 5	0 5 8	0 8 8	0 6 9	0 9 6	0 9 4	0 7 9	0 6 0	0 9 3	0 9 8	0 5 2	0 6 6	0 6 7	0 5 7	0 5 1	0 5 5	0 5 3	0 7 7	0 8 0	0 8 4	0 7 1	0 8 5
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X											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
Interstitial cell, adenoma														X	X					X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Lymph node		+	+		+		+				+		+		+				+		+	+	+		+
Mediastinal, fibrous histiocytoma, metastatic, skin																							X		
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Carcinoma																								X	
Fibroadenoma																									
Fibroadenoma, multiple																									X
Fibrous histiocytoma, metastatic, skin																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma						X												X							
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrous histiocytoma																							X		
Subcutaneous tissue, fibrous histiocytoma, metastatic, skin																							X		
Subcutaneous tissue, myxoma																									
Subcutaneous tissue, sarcoma	X																								
Subcutaneous tissue, schwannoma malignant								X	X																

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

Number of Days on Study	7 0 7	7 0 9	7 2 2	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 9 0	0 7 4	0 6 3	0 6 4	0 6 8	0 7 2	0 7 3	0 8 1	0 8 3	0 9 9	0 5 6	0 5 9	0 6 2	0 7 5	0 7 6	0 8 7	0 8 9	0 9 2	0 6 1	0 6 5	0 8 6	0 5 4	0 7 8	0 8 2	1 0 0	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												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	X		X	X	X	X	42
Interstitial cell, adenoma												X									X					5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Lymph node	+	+	+					+	+			+					+						+			20
Mediastinal, fibrous histiocytoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																	X									1
Carcinoma																										1
Fibroadenoma															X							X				2
Fibroadenoma, multiple						X			X																	3
Fibrous histiocytoma, metastatic, skin																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma						X																				1
Keratoacanthoma																								X		3
Subcutaneous tissue, fibroma				X																						1
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, fibrous histiocytoma, metastatic, skin																										1
Subcutaneous tissue, myxoma			X																							1
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, schwannoma malignant																										2

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

Number of Days on Study	3 6 5	4 4 6	5 0 9	5 3 2	6 1 0	6 1 7	6 2 3	6 2 8	6 3 2	6 3 7	6 3 9	6 3 9	6 5 3	6 6 0	6 6 0	6 6 0	6 6 3	6 7 4	6 7 4	6 7 8	6 8 8	6 8 8	6 9 4	6 9 5	6 9 5
Carcass ID Number	0 7 0	0 9 7	0 9 1	0 9 5	0 5 8	0 8 8	0 6 9	0 9 6	0 9 4	0 7 9	0 6 0	0 9 3	0 9 8	0 5 2	0 6 6	0 6 7	0 5 7	0 5 1	0 5 5	0 5 3	0 7 7	0 8 0	0 8 4	0 7 1	0 8 5
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, carcinoma, metastatic, mammary gland																							X		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland						X																			
Peripheral nerve							+			+															
Spinal cord							+			+															
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Fibrous histiocytoma, metastatic, skin																							X		
Schwannoma malignant, metastatic, skin								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																			+				+		
Zymbal's gland						+																			
Carcinoma						X																			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X		X	X		X	X		X	X	X	X		X	X	X	X	X		X	X
Mesothelioma malignant																	X								

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

Number of Days on Study	7 0 7	7 0 9	7 2 2	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 9 0	0 7 4	0 6 3	0 6 4	0 6 8	0 7 2	0 7 3	0 8 1	0 8 3	0 9 9	0 5 6	0 5 9	0 6 2	0 7 5	0 7 6	0 8 7	0 8 9	0 9 2	0 6 1	0 6 5	0 8 6	0 5 4	0 7 8	0 8 2	1 0 0	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, carcinoma, metastatic, mammary gland																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Fibrous histiocytoma, metastatic, skin																										1
Schwannoma malignant, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								3
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X		X	X	X	X	X		X					X	X	X		X	X	X	X	X	35
Mesothelioma malignant								X																		2

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

Number of Days on Study	478	505	526	639	639	660	671	674	688	692	694	695	695	709	709	716	720	725	726	726	726	726	726	726	726
Carcass ID Number	13 38	10 5	11 2	10 1	14 9	11 0	12 3	14 1	12 4	11 9	10 7	10 9	14 0	12 8	12 9	15 0	13 0	13 4	10 2	10 4	11 7	11 8	12 5	13 2	13 3
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																		+							
Squamous cell carcinoma																		X							
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									+
Squamous cell papilloma																									X
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant		X																							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X						X						
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X									X		X	X		X	
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X					X	X	X	X	X	

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

Number of Days on Study	726	726	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	729	729	729	729	730	
Carcass ID Number	142	145	108	114	115	116	120	135	136	139	144	147	103	106	111	113	127	131	137	148	121	122	126	146	143	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+				+					+										+			+		11
Oral mucosa																									+	2
Squamous cell carcinoma																										1
Pharyngeal, squamous cell papilloma																									X	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Tooth																				+						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant												X														2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										2
Bilateral, pheochromocytoma benign													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X								X				2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma														X						X						7
Pars intermedia, adenoma				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X							X	X												9

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

Number of Days on Study	478	505	526	639	639	660	671	774	788	692	694	695	695	709	709	716	720	725	726	726	726	726	726	726
Carcass ID Number	13 8	10 5	11 2	10 1	14 9	11 0	12 3	14 1	12 4	11 9	10 7	10 9	14 0	12 8	12 9	15 0	13 0	13 4	10 2	10 4	11 7	11 8	12 5	13 2	13 3
General Body System																									
None																									
Genital System																									
Coagulating gland										+															
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X		X		X							X		X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
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
Interstitial cell, adenoma	X	X													X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+			+	+			+	+			+	+									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																						X			
Basal cell carcinoma																X									
Keratoacanthoma																								X	
Keratoacanthoma, multiple																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma																	X								
Subcutaneous tissue, fibrosarcoma														X											
Subcutaneous tissue, lipoma																					X				
Subcutaneous tissue, myxosarcoma																									
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	726	726	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	729	729	729	729	730	
Carcass ID Number	14202	14405	10408	11414	11515	11616	12020	13535	13636	13939	14404	14407	10403	10006	11411	11613	12037	13131	13737	14818	12201	12212	12626	14606	14603		Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Coagulating gland																											1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma																											5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																						X					1
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		46
Interstitial cell, adenoma																											3
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node											+												+	+			10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Basal cell adenoma																X											2
Basal cell carcinoma																											1
Keratoacanthoma												X															2
Keratoacanthoma, multiple															X												1
Trichoepithelioma									X																		1
Subcutaneous tissue, fibroma													X									X					3
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, lipoma																											1
Subcutaneous tissue, myxosarcoma																					X						1
Subcutaneous tissue, sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

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

Number of Days on Study	478	505	526	639	639	660	671	674	688	692	694	695	695	709	709	716	720	725	726	726	726	726	726	726	726
Carcass ID Number	13 8	10 5	11 2	10 1	14 9	11 0	12 3	14 1	12 4	11 9	10 7	10 9	14 0	12 8	12 9	15 0	13 0	13 4	10 2	10 4	11 7	11 8	12 5	13 2	13 3
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																			+						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X	X	X	X	X	X		X	X			X	X		X	X	X			X	X	X
Mesothelioma malignant								X																	

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

Number of Days on Study	726	726	727	727	727	727	727	727	727	727	727	727	728	728	728	728	728	728	728	728	728	729	729	729	729	730	
Carcass ID Number	14 42	14 45	10 38	11 14	11 15	11 16	12 00	13 35	13 36	13 39	14 44	14 47	10 03	00 06	11 01	11 13	12 07	23 01	13 37	14 48	22 01	22 02	22 06	44 06	14 43	Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																								X		2
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye										+															+	3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X	X	X	X	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	39
Mesothelioma malignant		X								X												X				4

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: 2,000 ppm

Number of Days on Study	573	600	624	639	660	674	688	701	709	709	712	720	720	722	723	726	726	726	726	726	726	726	726	726	727
Carcass ID Number	162	158	182	177	197	195	165	171	185	189	166	173	198	176	192	156	160	163	175	178	184	186	188	200	153
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+					+	+		+	+	+				+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																X									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X					X				X		X													
Pars nervosa, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma	X			X					X	X		X			X	X							X		
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
None																									

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

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 5 4	1 5 5 9	1 6 6 7	1 7 7 0	1 7 7 2	1 9 0 0	1 9 9 3	1 9 9 4	1 1 6 1	1 6 6 4	1 7 7 4	1 7 7 9	1 8 8 0	1 8 8 3	1 9 9 9	1 5 5 2	1 6 6 8	1 8 8 7	1 9 9 1	1 9 9 6	1 5 6 1	1 5 5 5	1 5 5 7	1 6 6 9	1 8 8 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery															+	+			+			+				11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+																			1
Squamous cell papilloma							X																			1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																						X			X	2
Bilateral, pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X							X			X				X				X							9
Pars nervosa, adenoma				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X														X						10
C-cell, carcinoma								X			X															2
Follicular cell, adenoma																		X		X						2
General Body System																										
None																										

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

Number of Days on Study	5 7 3	6 0 0	6 2 4	6 3 9	6 6 0	6 7 4	6 8 8	7 0 1	7 0 9	7 0 9	7 1 2	7 2 0	7 2 0	7 2 2	7 2 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7
Carcass ID Number	1 6 2	1 5 8	1 8 2	1 7 7	1 9 7	1 9 5	1 6 5	1 7 1	1 8 5	1 8 9	1 6 6	1 7 3	1 9 8	1 7 6	1 9 2	1 5 6	1 6 0	1 6 3	1 7 5	1 7 8	1 8 4	1 8 6	1 8 8	2 0 0	1 5 3
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
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
Interstitial cell, adenoma						X																			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+	+		+		+		+			+	+				+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							X											X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma							X		X																
Squamous cell papilloma																									X
Dermis, schwannoma malignant																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma												X													
Subcutaneous tissue, pinna, melanoma malignant											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 2 7	7 2 7 7	7 2 7 7	7 2 7 7	7 2 7 7	7 2 7 7	7 2 7 7	7 2 7 7	7 2 8 8	7 2 8 8	7 2 8 8	7 2 8 8	7 2 8 8	7 2 8 8	7 2 8 8	7 2 9 9	7 2 9 9	7 2 9 9	7 2 9 9	7 2 9 9	7 3 0 0	7 3 0 0	7 3 0 0	7 3 0 0	7 3 0 0	
Carcass ID Number	1 5 5 4	1 5 5 9	1 6 6 7	1 7 7 0	1 7 7 2	1 9 9 0	1 9 9 3	1 9 9 4	1 6 6 1	1 6 6 4	1 7 7 4	1 7 7 9	1 8 8 0	1 8 8 3	1 9 9 9	1 5 5 2	1 6 6 8	1 8 8 7	1 9 9 1	1 9 9 6	1 5 5 1	1 5 5 5	1 5 5 7	1 6 6 9	1 8 8 1	Total Tissues/ Tumors
Genital System																										
Coagulating gland											+															1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X							X													X		4
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	41
Interstitial cell, adenoma	X				X						X															4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+																			10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Fibroadenoma							X																			3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma									X																	1
Keratoacanthoma		X														X						X				5
Squamous cell papilloma																										1
Dermis, schwannoma malignant							X																			1
Subcutaneous tissue, fibroma										X							X									2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, pinna, melanoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	573	600	624	639	660	674	688	701	709	709	712	720	720	722	723	726	726	726	726	726	726	726	726	726	727
Carcass ID Number	16252	15258	18252	17277	19297	19295	16265	17271	18285	18289	16266	17273	19298	17276	19292	15256	16260	16263	17275	17278	18284	18286	18288	20200	15253
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																X									
Osteosarcoma, metastatic, bone			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+			+									
Melanoma malignant													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma							X																		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X		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 Citral: 2,000 ppm

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 4	1 5 9	1 6 7	1 7 0	1 7 2	1 9 0	1 9 3	1 9 4	1 6 1	1 6 4	1 7 4	1 7 9	1 8 0	1 8 3	1 9 9	1 5 2	1 6 8	1 8 7	1 9 1	1 9 6	1 5 1	1 5 5	1 5 7	1 6 9	1 8 1	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Melanoma malignant																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X			X		X	X	X	X	X	X		X						X	X	X	X	32
Mesothelioma malignant															X									X		4

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: 4,000 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: 4,000 ppm

Number of Days on Study	726	727	727	727	727	727	727	727	727	727	728	728	728	728	729	729	729	729	729	729	730	730	730	730	730	
Carcass ID Number	250	203	214	215	217	218	225	233	238	246	213	224	227	230	231	207	208	237	244	245	201	212	228	243	249	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																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+																+	5
Fibrosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
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 complex																										1
Pheochromocytoma benign													X			X		X	X			X				8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X			X			X		X					X											6
Pars intermedia, adenoma												X														2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X								X			X					X							X	10
C-cell, carcinoma																										1
Follicular cell, carcinoma		X								X																2
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: 4,000 ppm

Number of Days on Study	3	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	9	2	4	9	2	3	3	5	7	8	8	9	0	0	2	2	2	2	2	2	2	2	2	2	2
	7	0	4	6	8	6	9	5	4	0	4	5	9	9	0	3	6	6	6	6	6	6	6	6	6
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
	0	0	1	2	4	0	3	2	4	4	1	0	2	2	3	0	1	1	2	2	3	3	3	4	4
	2	9	6	9	0	6	9	0	2	7	1	5	1	2	6	4	0	9	3	6	2	4	5	1	8
Genital System																									
Coagulating gland																									
Adenoma																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																					X	
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
Interstitial cell, adenoma		X				X																			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+		+	+				+												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma												X								X		X			
Subcutaneous tissue, fibroma												X													
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: 4,000 ppm

Number of Days on Study	726	727	727	727	727	727	727	727	727	727	728	728	728	728	729	729	729	729	729	729	730	730	730	730	730	
Carcass ID Number	25 00	20 03	21 04	21 15	21 17	21 18	22 25	23 33	23 38	24 46	21 33	22 24	22 27	23 07	23 31	20 17	20 08	23 37	24 44	24 45	20 01	21 12	22 28	24 39	24 49	Total Tissues/ Tumors
Genital System																										
Coagulating gland																		+								1
Adenoma																		X								1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											3
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	44
Interstitial cell, adenoma																		X								3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+									+				+		+			+	+			12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma						X					X															2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma													X													4
Subcutaneous tissue, fibroma										X																2
Subcutaneous tissue, fibrosarcoma																					X					1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																	+					+				2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: 4,000 ppm

Number of Days on Study	3 9 7	5 2 0	5 4 4	5 9 6	6 2 8	6 3 6	6 3 9	6 5 5	6 7 4	6 8 0	6 8 4	6 9 5	7 0 9	7 0 9	7 2 0	7 2 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6
Carcass ID Number	2 0 2	2 0 9	2 1 6	2 2 9	2 4 0	2 0 6	2 3 9	2 2 0	2 4 2	2 4 7	2 1 1	2 0 5	2 2 1	2 2 2	2 3 6	2 0 4	2 1 0	2 1 9	2 2 3	2 2 6	2 3 2	2 3 4	2 3 5	2 4 1	2 4 8
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex, metastatic, adrenal medulla								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																+			+						
Zymbal's gland	+																								
Carcinoma	X																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X	X		X	X	X	X		X	X	X	X					X	X	X	X	
Lymphoma malignant																									
Mesothelioma malignant											X									X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Citral: 4,000 ppm

Number of Days on Study	726	727	727	727	727	727	727	727	727	727	728	728	728	728	728	729	729	729	729	729	729	730	730	730	730	730	
Carcass ID Number	25 00	20 03	21 04	21 15	21 17	21 18	22 25	23 33	23 38	24 46	21 33	22 24	22 27	23 00	23 31	20 17	20 08	23 37	24 44	24 45	20 01	21 12	22 28	24 33	24 49	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye													+													3
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																					X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X		X	X		X	X			X			X	X		X	X	X		X			29
Lymphoma malignant																						X				1
Mesothelioma malignant																										2

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Adrenal Medulla: Benign Pheochromocytoma					
Overall rate[a]	6/50 (12%)	4/50 (8%)	3/50 (6%)	3/50 (6%)	8/50 (16%)
Adjusted rate[b]	13.6%	9.5%	6.5%	6.3%	17.6%
Terminal rate[c]	3/30 (10%)	2/22 (9%)	2/32 (6%)	3/35 (9%)	8/34 (24%)
First incidence (days)	639	610	695	726 (T)	726 (T)
Poly-3 test[d]		P=0.086	P=0.453N	P=0.436N	P=0.213
Adrenal Medulla: Benign or Complex Pheochromocytoma					
Overall rate	7/50 (14%)	4/50 (8%)	3/50 (6%)	3/50 (6%)	9/50 (18%)
Adjusted rate	15.8%	9.5%	6.5%	6.3%	19.7%
Terminal rate	4/30 (13%)	2/22 (9%)	2/32 (6%)	3/35 (9%)	8/34 (24%)
First incidence (days)	639	610	695	726 (T)	655
Poly-3 test		P=0.044	P=0.453N	P=0.436N	P=0.147
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	4.6%	2.4%	6.5%	2.1%	0.0%
Terminal rate	1/30 (3%)	0/22 (0%)	2/32 (6%)	1/35 (3%)	0/34 (0%)
First incidence (days)	695	637	709	726 (T)	—[e]
Poly-3 test		P=0.175N	P=0.338	P=0.733N	P=0.484N
Mammary Gland: Fibroadenoma					
Overall rate	3/50 (6%)	5/50 (10%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	6.9%	12.0%	0.0%	6.3%	4.4%
Terminal rate	3/30 (10%)	4/22 (18%)	0/32 (0%)	2/35 (6%)	2/34 (6%)
First incidence (days)	726 (T)	695	—	688	726 (T)
Poly-3 test		P=0.289N	P=0.023N	P=0.287N	P=0.183N
Mammary Gland: Fibroadenoma or Adenoma					
Overall rate	4/50 (8%)	5/50 (10%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	9.2%	12.0%	0.0%	6.3%	4.4%
Terminal rate	3/30 (10%)	4/22 (18%)	0/32 (0%)	2/35 (6%)	2/34 (6%)
First incidence (days)	688	695	—	688	726 (T)
Poly-3 test		P=0.289N	P=0.005N	P=0.110N	P=0.060N
Mammary Gland: Fibroadenoma, Adenoma, Adenocarcinoma, or Carcinoma					
Overall rate	4/50 (8%)	7/50 (14%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	9.2%	16.7%	0.0%	6.3%	4.4%
Terminal rate	3/30 (10%)	5/22 (23%)	0/32 (0%)	2/35 (6%)	2/34 (6%)
First incidence (days)	688	695	—	688	726 (T)
Poly-3 test		P=0.110N	P=0.005N	P=0.110N	P=0.060N
Oral Cavity (Oral Mucosa, Tongue, Pharynx): Squamous Cell Papilloma or Squamous Cell Carcinoma					
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	2.3%	2.4%	6.5%	2.1%	0.0%
Terminal rate	0/30 (0%)	0/22 (0%)	2/32 (6%)	1/35 (3%)	0/34 (0%)
First incidence (days)	660	532	725	726 (T)	—
Poly-3 test		P=0.177N	P=0.335	P=0.734N	P=0.485N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	8/50 (16%)	9/50 (18%)	7/50 (14%)	9/50 (18%)	6/49 (12%)
Adjusted rate	18.4%	21.3%	15.2%	18.7%	13.2%
Terminal rate	7/30 (23%)	5/22 (23%)	6/32 (19%)	5/35 (14%)	5/34 (15%)
First incidence (days)	688	660	692	573	636
Poly-3 test		P=0.248N	P=0.321N	P=0.480N	P=0.236N

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Preputial Gland: Adenoma					
Overall rate	4/50 (8%)	3/50 (6%)	5/49 (10%)	4/50 (8%)	3/50 (6%)
Adjusted rate	9.2%	7.1%	10.8%	8.4%	6.5%
Terminal rate	3/30 (10%)	1/22 (5%)	0/32 (0%)	3/35 (9%)	2/34 (6%)
First incidence (days)	660	639	505	709	544
Poly-3 test		P=0.432N	P=0.412	P=0.566	P=0.621N
Preputial Gland: Adenoma or Carcinoma					
Overall rate	5/50 (10%)	3/50 (6%)	5/49 (10%)	5/50 (10%)	4/50 (8%)
Adjusted rate	11.3%	7.1%	10.8%	10.5%	8.7%
Terminal rate	3/30 (10%)	1/22 (5%)	0/32 (0%)	3/35 (9%)	2/34 (6%)
First incidence (days)	617	639	505	674	544
Poly-3 test		P=0.540	P=0.412	P=0.427	P=0.549
Skin: Keratoacanthoma					
Overall rate	5/50 (10%)	3/50 (6%)	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adjusted rate	11.3%	7.1%	6.5%	10.5%	8.8%
Terminal rate	3/30 (10%)	1/22 (5%)	3/32 (9%)	3/35 (9%)	3/34 (9%)
First incidence (days)	505	617	726 (T)	688	695
Poly-3 test		P=0.412	P=0.624N	P=0.425	P=0.541
Skin: Squamous Cell Papilloma or Keratoacanthoma					
Overall rate	6/50 (12%)	3/50 (6%)	3/50 (6%)	6/50 (12%)	4/50 (8%)
Adjusted rate	13.5%	7.1%	6.5%	12.6%	8.8%
Terminal rate	4/30 (13%)	1/22 (5%)	3/32 (9%)	4/35 (11%)	3/34 (9%)
First incidence (days)	505	617	726 (T)	688	695
Poly-3 test		P=0.401	P=0.624N	P=0.305	P=0.541
Skin: Trichoepithelioma or Basal Cell Adenoma					
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	2.3%	2.4%	6.5%	2.1%	0.0%
Terminal rate	1/30 (3%)	1/22 (5%)	3/32 (9%)	1/35 (3%)	0/34 (0%)
First incidence (days)	726 (T)	726 (T)	726 (T)	726 (T)	—
Poly-3 test		P=0.173N	P=0.341	P=0.731N	P=0.483N
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma					
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rate	2.3%	2.4%	8.7%	2.1%	0.0%
Terminal rate	1/30 (3%)	1/22 (5%)	3/32 (9%)	1/35 (3%)	0/34 (0%)
First incidence (days)	726 (T)	726 (T)	716	726 (T)	—
Poly-3 test		P=0.133N	P=0.210	P=0.731N	P=0.483N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma					
Overall rate	7/50 (14%)	4/50 (8%)	7/50 (14%)	7/50 (14%)	4/50 (8%)
Adjusted rate	15.8%	9.5%	15.3%	14.7%	8.8%
Terminal rate	5/30 (17%)	2/22 (9%)	6/32 (19%)	5/35 (14%)	3/34 (9%)
First incidence (days)	505	617	716	688	695
Poly-3 test		P=0.413N	P=0.310	P=0.334	P=0.601N
Skin (Subcutaneous Tissue): Fibroma					
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.3%	2.4%	6.5%	4.2%	4.4%
Terminal rate	0/30 (0%)	1/22 (5%)	2/32 (6%)	2/35 (6%)	1/34 (3%)
First incidence (days)	610	726 (T)	720	726 (T)	695
Poly-3 test		P=0.545	P=0.341	P=0.545	P=0.531

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma					
Overall rate	3/50 (6%)	1/50 (2%)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted rate	6.8%	2.4%	8.7%	6.3%	6.6%
Terminal rate	2/30 (7%)	1/22 (5%)	2/32 (6%)	2/35 (6%)	2/34 (6%)
First incidence (days)	610	726 (T)	709	720	695
Poly-3 test		P=0.408	P=0.210	P=0.354	P=0.338
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibrosarcoma, Myxosarcoma, or Sarcoma					
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	6.9%	4.7%	6.5%	2.1%	4.3%
Terminal rate	2/30 (7%)	0/22 (0%)	1/32 (3%)	0/35 (0%)	1/34 (3%)
First incidence (days	674	365	688	720	520
Poly-3 test		P=0.473N	P=0.535	P=0.463N	P=0.666N
Skin (Subcutaneous Tissue): Fibroma, Myxoma, Fibrous Histiocytoma, Fibrosarcoma, Myxosarcoma, or Sarcoma					
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	3/50 (6%)	4/50 (8%)
Adjusted rate	9.1%	9.4%	13.0%	6.3%	8.7%
Terminal rate	2/30 (7%)	1/22 (5%)	3/32 (9%)	2/35 (6%)	2/34 (6%)
First incidence (days)	610	365	688	720	520
Poly-3 test		P=0.405N	P=0.419	P=0.442N	P=0.599N
Testes: Adenoma					
Overall rate	49/50 (98%)	47/50 (94%)	49/50 (98%)	45/50 (90%)	47/50 (94%)
Adjusted rate	99.5%	98.5%	98.6%	91.7%	95.9%
Terminal rate	30/30 (100%)	22/22 (100%)	32/32 (100%)	34/35 (97%)	34/34 (100%)
First incidence (days)	505	532	478	600	520
Poly-3 test		P=0.225N	P=0.877	P=0.110N	P=0.428N
Thyroid Gland (C-Cell): Adenoma					
Overall rate	7/50 (14%)	5/50 (10%)	9/50 (18%)	10/50 (20%)	10/50 (20%)
Adjusted rate	16.1%	11.9%	19.6%	20.7%	21.8%
Terminal rate	7/30 (23%)	3/22 (14%)	8/32 (25%)	4/35 (11%)	6/34 (18%)
First incidence (days)	726 (T)	623	709	573	636
Poly-3 test		P=0.187	P=0.242	P=0.202	P=0.170
Thyroid Gland (C-Cell): Adenoma or Carcinoma					
Overall rate	9/50 (18%)	7/50 (14%)	9/50 (18%)	12/50 (24%)	11/50 (22%)
Adjusted rate	20.7%	16.6%	19.6%	24.8%	23.9%
Terminal rate	9/30 (30%)	4/22 (18%)	8/32 (25%)	6/35 (17%)	7/34 (21%)
First incidence (days)	726 (T)	623	709	573	636
Poly-3 test		P=0.227	P=0.463	P=0.242	P=0.276
Thyroid Gland (Follicular Cell): Adenoma					
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.8%	0.0%	0.0%	4.2%	0.0%
Terminal rate	1/30 (3%)	0/22 (0%)	0/32 (0%)	2/35 (6%)	0/34 (0%)
First incidence (days)	450	—	—[f]	726 (T)	—
Poly-3 test		P=0.622	—	P=0.267	—
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma					
Overall rate	4/50 (8%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.0%	0.0%	0.0%	4.2%	4.4%
Terminal rate	1/30 (3%)	0/22 (0%)	0/32 (0%)	2/35 (6%)	2/34 (6%)
First incidence (days)	450	—	—	726 (T)	726 (T)
Poly-3 test		P=0.095	—	P=0.267	P=0.257

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
All Organs: Mononuclear Cell Leukemia					
Overall rate	33/50 (66%)	35/50 (70%)	39/50 (78%)	32/50 (64%)	29/50 (58%)
Adjusted rate	68.0%	75.3%	79.5%	65.5%	61.0%
Terminal rate	16/30 (53%)	15/22 (68%)	26/32 (81%)	21/35 (60%)	18/34 (53%)
First incidence (days)	450	446	478	600	596
Poly-3 test		P=0.030N	P=0.400	P=0.198N	P=0.096N
All Organs: Malignant Mesothelioma					
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	4/50 (8%)	2/50 (4%)
Adjusted rate	4.6%	4.8%	8.7%	8.4%	4.4%
Terminal rate	0/30 (0%)	1/22 (5%)	3/32 (9%)	2/35 (6%)	1/34 (3%)
First incidence (days)	610	663	674	709	684
Poly-3 test		P=0.454N	P=0.382	P=0.398	P=0.663N
All Organs: Benign Neoplasms					
Overall rate	50/50 (100%)	47/50 (94%)	50/50 (100%)	48/50 (96%)	48/50 (96%)
Adjusted rate	100.0%	98.5%	100.0%	96.0%	98.0%
Terminal rate	30/30 (100%)	22/22 (100%)	32/32 (100%)	34/35 (97%)	34/34 (100%)
First incidence (days)	450	532	478	573	520
Poly-3 test		P=0.421N	P=0.740	P=0.441N	P=0.774N
All Organs: Malignant Neoplasms					
Overall rate	35/50 (70%)	41/50 (82%)	41/50 (82%)	37/50 (74%)	33/50 (66%)
Adjusted rate	71.5%	83.6%	83.5%	74.9%	67.4%
Terminal rate	17/30 (57%)	15/22 (68%)	27/32 (84%)	24/35 (69%)	20/34 (59%)
First incidence (days)	450	365	478	600	397
Poly-3 test		P=0.017N	P=0.602N	P=0.203N	P=0.047N
All Organs: Benign or Malignant Neoplasms					
Overall rate	50/50 (100%)	49/50 (98%)	50/50 (100%)	49/50 (98%)	50/50 (100%)
Adjusted rate	100.0%	99.3%	100.0%	98.0%	100.0%
Terminal rate	30/30 (100%)	22/22 (100%)	32/32 (100%)	34/35 (97%)	34/34 (100%)
First incidence (days)	450	365	478	573	397
Poly-3 test		P=0.659	P=0.970	P=0.631N	P=0.970

(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, testis, 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 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 A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Citral[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	18	22	15	11	10
Natural deaths	2	6	3	4	6
Survivors					
Terminal sacrifice	30	22	32	35	34
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Dysplasia				1 (2%)	
Inflammation			1 (2%)		
Parasite metazoan	4 (8%)		4 (8%)	2 (4%)	
Ulcer			1 (2%)		
Artery, inflammation				1 (2%)	
Lymphoid tissue, hyperplasia		1 (2%)			
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Inflammation	1 (2%)				1 (2%)
Parasite metazoan	7 (14%)	3 (6%)	7 (14%)	8 (16%)	8 (16%)
Intestine large, cecum	(50)	(50)	(50)	(49)	(50)
Edema			1 (2%)		
Inflammation					2 (4%)
Parasite metazoan			1 (2%)		
Ulcer	1 (2%)	2 (4%)			
Intestine small, duodenum	(50)	(50)	(50)	(50)	(50)
Inflammation			1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Inflammation	1 (2%)	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, granulomatous		1 (2%)			
Intestine small, ileum	(50)	(50)	(49)	(50)	(50)
Erosion				1 (2%)	
Inflammation		2 (4%)	1 (2%)	1 (2%)	2 (4%)
Parasite metazoan		1 (2%)		1 (2%)	
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis		5 (10%)	1 (2%)	4 (8%)	1 (2%)
Basophilic focus	33 (66%)	24 (48%)	33 (66%)	33 (66%)	29 (58%)
Clear cell focus	14 (28%)	7 (14%)	11 (22%)	16 (32%)	9 (18%)
Degeneration, cystic	3 (6%)	2 (4%)	1 (2%)	1 (2%)	5 (10%)
Developmental malformation				1 (2%)	
Eosinophilic focus	6 (12%)	3 (6%)	5 (10%)	3 (6%)	6 (12%)
Fatty change	2 (4%)	4 (8%)		1 (2%)	
Hematopoietic cell proliferation		3 (6%)	1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	6 (12%)	3 (6%)	7 (14%)	4 (8%)	7 (14%)
Inflammation	21 (42%)	22 (44%)	28 (56%)	27 (54%)	28 (56%)
Mixed cell focus	5 (10%)	1 (2%)	8 (16%)	5 (10%)	7 (14%)
Necrosis	1 (2%)				1 (2%)
Vacuolization cytoplasmic	7 (14%)	6 (12%)	7 (14%)	8 (16%)	3 (6%)
Bile duct, fibrosis					1 (2%)
Bile duct, hyperplasia	48 (96%)	45 (90%)	50 (100%)	45 (90%)	47 (94%)
Centrilobular, degeneration	22 (44%)	19 (38%)	14 (28%)	15 (30%)	16 (32%)

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Alimentary System (continued)					
Mesentery	(8)	(13)	(11)	(11)	(5)
Inflammation		1 (8%)	1 (9%)		
Fat, necrosis	7 (88%)	11 (85%)	7 (64%)	9 (82%)	3 (60%)
Oral mucosa		(1)	(2)		
Inflammation, chronic active			1 (50%)		
Pancreas	(50)	(50)	(50)	(50)	(50)
Atrophy	22 (44%)	18 (36%)	17 (34%)	14 (28%)	16 (32%)
Cytoplasmic alteration	1 (2%)	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Hyperplasia	3 (6%)	2 (4%)	7 (14%)		2 (4%)
Inflammation	2 (4%)	1 (2%)			
Metaplasia, hepatocyte				2 (4%)	
Thrombosis		1 (2%)			
Artery, inflammation		1 (2%)	3 (6%)		2 (4%)
Salivary glands	(50)	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	2 (4%)		1 (2%)
Cytoplasmic alteration					1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	1 (2%)	2 (4%)	
Inflammation		1 (2%)	3 (6%)	1 (2%)	2 (4%)
Ulcer	1 (2%)	3 (6%)	2 (4%)	3 (6%)	3 (6%)
Epithelium, hyperplasia	1 (2%)	6 (12%)	7 (14%)	8 (16%)	3 (6%)
Epithelium, hyperplasia, basal cell	1 (2%)	1 (2%)			1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Atrophy					1 (2%)
Erosion	2 (4%)	7 (14%)	3 (6%)	2 (4%)	2 (4%)
Inflammation			1 (2%)	1 (2%)	1 (2%)
Necrosis					1 (2%)
Thrombosis					1 (2%)
Ulcer	3 (6%)	4 (8%)	2 (4%)	5 (10%)	1 (2%)
Epithelium, ulcer				1 (2%)	
Tongue	(1)		(1)	(1)	
Inflammation			1 (100%)		
Tooth	(1)	(1)	(1)		
Degeneration		1 (100%)			
Malformation			1 (100%)		
Peridontal tissue, inflammation	1 (100%)	1 (100%)			
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Inflammation				2 (4%)	
Jugular vein, thrombosis			1 (2%)		
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	39 (78%)	43 (86%)	45 (90%)	50 (100%)	47 (94%)
Fibrosis					1 (2%)
Inflammation		2 (4%)			1 (2%)
Thrombosis		6 (12%)	2 (4%)	2 (4%)	2 (4%)
Valve, inflammation		1 (2%)			

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)		1 (2%)
Atrophy					1 (2%)
Hematopoietic cell proliferation		2 (4%)			
Hyperplasia	12 (24%)	13 (26%)	20 (40%)	11 (22%)	14 (28%)
Hypertrophy				1 (2%)	
Necrosis	3 (6%)	1 (2%)	1 (2%)		2 (4%)
Thrombosis		1 (2%)			
Vacuolization cytoplasmic	4 (8%)	7 (14%)	1 (2%)	2 (4%)	3 (6%)
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Hyperplasia	12 (24%)	16 (32%)	23 (46%)	14 (28%)	15 (30%)
Necrosis					1 (2%)
Thrombosis					1 (2%)
Islets, pancreatic	(49)	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)				
Parathyroid gland	(48)	(45)	(47)	(45)	(45)
Hyperplasia	1 (2%)		2 (4%)	1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)	(49)
Atrophy					1 (2%)
Cyst	5 (10%)	4 (8%)	5 (10%)	4 (8%)	2 (4%)
Necrosis	1 (2%)				
Pars distalis, cyst				1 (2%)	
Pars distalis, hemorrhage					1 (2%)
Pars distalis, hyperplasia	15 (30%)	22 (44%)	24 (48%)	19 (38%)	18 (37%)
Pars intermedia, hyperplasia				1 (2%)	1 (2%)
Pars nervosa, hyperplasia		1 (2%)			
Rathke's cleft, hyperplasia		1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Inflammation					1 (2%)
C-cell, hyperplasia	32 (64%)	38 (76%)	41 (82%)	41 (82%)	34 (68%)
Follicular cell, hyperplasia	1 (2%)	2 (4%)	1 (2%)	4 (8%)	3 (6%)
General Body System					
None					
Genital System					
Coagulating gland			(1)	(1)	(1)
Inflammation			1 (100%)		
Epididymis	(50)	(50)	(50)	(50)	(50)
Atrophy					1 (2%)
Inflammation	1 (2%)		3 (6%)	1 (2%)	2 (4%)
Preputial gland	(50)	(50)	(49)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)		1 (2%)	2 (4%)
Inflammation	47 (94%)	48 (96%)	47 (96%)	49 (98%)	47 (94%)
Duct, ectasia	1 (2%)		2 (4%)		1 (2%)
Prostate	(50)	(50)	(50)	(50)	(50)
Cyst	4 (8%)	1 (2%)	8 (16%)	1 (2%)	2 (4%)
Hyperplasia	2 (4%)	3 (6%)		3 (6%)	
Inflammation				1 (2%)	2 (4%)
Inflammation, chronic active	29 (58%)	33 (66%)	30 (60%)	28 (56%)	22 (44%)
Dorsal, inflammation, chronic active	1 (2%)		1 (2%)		
Ventral, hyperplasia	1 (2%)				

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Genital System (continued)					
Seminal vesicle	(50)	(50)	(50)	(50)	(50)
Atrophy				1 (2%)	
Hyperplasia				1 (2%)	
Inflammation	1 (2%)				
Testes	(50)	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)	
Atrophy	2 (4%)	2 (4%)		3 (6%)	1 (2%)
Hyperplasia		1 (2%)			
Interstitial cell, hyperplasia	4 (8%)	7 (14%)	4 (8%)	9 (18%)	5 (10%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Atrophy			3 (6%)	1 (2%)	2 (4%)
Hemorrhage					1 (2%)
Hyperplasia	14 (28%)	16 (32%)	20 (40%)	14 (28%)	13 (26%)
Myelofibrosis	2 (4%)	2 (4%)	1 (2%)	1 (2%)	
Necrosis		1 (2%)			
Lymph node	(15)	(20)	(10)	(10)	(12)
Deep cervical, hyperplasia, plasma cell					1 (8%)
Inguinal, ectasia					1 (8%)
Inguinal, necrosis		1 (5%)			
Mediastinal, ectasia		1 (5%)			1 (8%)
Mediastinal, necrosis		2 (10%)			
Renal, necrosis		1 (5%)			
Lymph node, mandibular	(50)	(49)	(50)	(50)	(50)
Atrophy		1 (2%)			
Ectasia	4 (8%)	3 (6%)	2 (4%)	9 (18%)	1 (2%)
Hyperplasia		1 (2%)			
Hyperplasia, plasma cell	17 (34%)	13 (27%)	13 (26%)	18 (36%)	20 (40%)
Inflammation					1 (2%)
Necrosis	1 (2%)	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		1 (2%)	
Ectasia	3 (6%)	1 (2%)		5 (10%)	1 (2%)
Inflammation			1 (2%)		
Inflammation, granulomatous		1 (2%)			
Necrosis		1 (2%)		1 (2%)	
Spleen	(50)	(50)	(50)	(50)	(49)
Accessory spleen				1 (2%)	1 (2%)
Angiectasis					1 (2%)
Congestion		1 (2%)		1 (2%)	
Fibrosis	2 (4%)	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation	3 (6%)	8 (16%)	2 (4%)	4 (8%)	5 (10%)
Hemorrhage				1 (2%)	
Infarct	2 (4%)	2 (4%)		1 (2%)	2 (4%)
Necrosis		2 (4%)			
Pigmentation			2 (4%)	1 (2%)	1 (2%)
Lymphoid follicle, atrophy		2 (4%)	1 (2%)	1 (2%)	
Red pulp, depletion cellular		1 (2%)	2 (4%)		
Thymus	(50)	(47)	(49)	(47)	(49)
Atrophy	45 (90%)	38 (81%)	47 (96%)	44 (94%)	45 (92%)
Inflammation		1 (2%)			
Epithelial cell, hyperplasia					1 (2%)
Vein, inflammation					1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Integumentary System					
Mammary gland	(50)	(50)	(50)	(49)	(50)
Hyperplasia	3 (6%)	7 (14%)	5 (10%)	9 (18%)	6 (12%)
Skin	(50)	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)			
Hyperkeratosis		4 (8%)		3 (6%)	
Hyperplasia	1 (2%)	1 (2%)		1 (2%)	
Inflammation		3 (6%)	1 (2%)	4 (8%)	
Inflammation, chronic active	1 (2%)				
Parakeratosis				1 (2%)	
Ulcer				2 (4%)	
Dermis, fibrosis				1 (2%)	
Dermis, necrosis				1 (2%)	
Epidermis, hyperplasia	2 (4%)	1 (2%)			
Epidermis, inflammation, acute	1 (2%)	1 (2%)			
Subcutaneous tissue, fibrosis			1 (2%)	1 (2%)	
Subcutaneous tissue, mineralization				1 (2%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Necrosis				1 (2%)	
Osteopetrosis			1 (2%)	1 (2%)	
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Hemorrhage	5 (10%)	9 (18%)	1 (2%)	2 (4%)	2 (4%)
Necrosis		1 (2%)		1 (2%)	1 (2%)
Spinal cord		(2)			
Hemorrhage		2 (100%)			
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Embolus, cartilagenous			1 (2%)		
Foreign body	1 (2%)				
Hemorrhage	6 (12%)	2 (4%)	1 (2%)		2 (4%)
Inflammation	12 (24%)	12 (24%)	6 (12%)	8 (16%)	5 (10%)
Necrosis		1 (2%)			
Thrombosis	1 (2%)	3 (6%)			1 (2%)
Alveolar epithelium, hyperplasia	7 (14%)	6 (12%)	10 (20%)	10 (20%)	11 (22%)
Artery, inflammation		1 (2%)			
Bronchiole, hyperplasia				1 (2%)	
Bronchus, hyperplasia		1 (2%)			
Mediastinum, inflammation		1 (2%)			
Nose	(50)	(50)	(50)	(50)	(50)
Dysplasia		1 (2%)			
Foreign body	7 (14%)	7 (14%)	6 (12%)	9 (18%)	7 (14%)
Inflammation	13 (26%)	11 (22%)	9 (18%)	14 (28%)	8 (16%)
Trachea	(50)	(50)	(50)	(50)	(50)
Inflammation	1 (2%)	1 (2%)			

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Special Senses System					
Eye	(1)	(3)	(3)	(2)	(3)
Cataract	1 (100%)	3 (100%)	2 (67%)	1 (50%)	3 (100%)
Retina, degeneration	1 (100%)	3 (100%)	2 (67%)	1 (50%)	3 (100%)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet		2 (4%)		2 (4%)	3 (6%)
Cyst				4 (8%)	
Infarct		3 (6%)	1 (2%)		
Mineralization	45 (90%)	42 (84%)	45 (90%)	48 (96%)	50 (100%)
Necrosis		1 (2%)			
Nephropathy	49 (98%)	50 (100%)	50 (100%)	49 (98%)	50 (100%)
Pigmentation	3 (6%)	2 (4%)		2 (4%)	6 (12%)
Thrombosis		2 (4%)			
Renal tubule, hyperplasia			2 (4%)	1 (2%)	2 (4%)

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

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	12	10	11	11	12
Natural deaths	3		3	3	2
Survivors					
Died last week of study	1				
Terminal sacrifice	34	40	36	36	36
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Polyp adenomatous	1 (2%)			1 (2%)	
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Leiomyosarcoma, metastatic, uterus				1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(49)	(50)
Sarcoma		1 (2%)			
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, skin				1 (2%)	
Mesentery	(10)	(5)	(1)	(5)	(7)
Oral mucosa			(1)		
Pharyngeal, squamous cell papilloma			1 (100%)		
Pancreas	(50)	(50)	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Tongue		(1)			(1)
Squamous cell carcinoma					1 (100%)
Squamous cell papilloma		1 (100%)			
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Schwannoma malignant	1 (2%)		1 (2%)	2 (4%)	1 (2%)
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)			
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Pheochromocytoma benign	2 (4%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)	(49)
Adenoma				2 (4%)	1 (2%)
Parathyroid gland	(43)	(43)	(40)	(43)	(47)
Adenoma	2 (5%)				
Pituitary gland	(50)	(50)	(50)	(50)	(49)
Pars distalis, adenoma	12 (24%)	17 (34%)	11 (22%)	17 (34%)	13 (27%)
Pars distalis, carcinoma				1 (2%)	
Pars intermedia, adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)	

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Endocrine System (continued)					
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Leiomyosarcoma, metastatic, uterus				1 (2%)	
Bilateral, C-cell, adenoma	1 (2%)				
C-cell, adenoma	7 (14%)	13 (26%)	9 (18%)	9 (18%)	11 (22%)
C-cell, carcinoma			2 (4%)		
Follicular cell, adenoma			1 (2%)		
Follicular cell, carcinoma		1 (2%)		1 (2%)	
General Body System					
None					
Genital System					
Clitoral gland	(49)	(49)	(49)	(50)	(49)
Adenoma	9 (18%)	5 (10%)	2 (4%)	4 (8%)	1 (2%)
Carcinoma		1 (2%)			
Bilateral, adenoma		1 (2%)	1 (2%)		
Ovary	(50)	(50)	(50)	(50)	(50)
Uterus	(50)	(50)	(50)	(50)	(50)
Adenoma		1 (2%)			
Fibroma				1 (2%)	
Hemangioma		1 (2%)			
Polyp stromal	13 (26%)	4 (8%)	8 (16%)	8 (16%)	10 (20%)
Polyp stromal, multiple		1 (2%)			
Schwannoma malignant				1 (2%)	
Cervix, leiomyosarcoma				1 (2%)	
Cervix, polyp stromal	1 (2%)				
Vagina		(2)	(1)	(2)	
Schwannoma malignant, metastatic, skin				1 (50%)	
Schwannoma malignant, metastatic, uterus				1 (50%)	
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Lymph node	(7)	(4)	(7)	(10)	(5)
Mediastinal, carcinoma, metastatic, mammary gland				1 (10%)	
Lymph node, mandibular	(50)	(50)	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, skin				1 (2%)	
Thymus	(49)	(47)	(49)	(48)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)			
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Carcinoma			1 (2%)	3 (6%)	
Fibroadenoma	22 (44%)	21 (42%)	16 (32%)	18 (36%)	15 (30%)
Fibroadenoma, multiple	4 (8%)	6 (12%)	6 (12%)		1 (2%)
Hemangioma		1 (2%)			

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Integumentary System (continued)					
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)	
Keratoacanthoma					2 (4%)
Squamous cell papilloma		1 (2%)			
Subcutaneous tissue, fibroma		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, lipoma	2 (4%)				
Subcutaneous tissue, schwannoma malignant				1 (2%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)	
Skeletal muscle				(1)	
Schwannoma malignant, metastatic, skin				1 (100%)	
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland				1 (2%)	
Meningioma malignant		1 (2%)			
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)			
Carcinoma, metastatic, mammary gland				1 (2%)	
Carcinoma, metastatic, thyroid gland			2 (4%)		
Schwannoma malignant, metastatic, skin				1 (2%)	
Mediastinum, carcinoma, metastatic, mammary gland				1 (2%)	
Nose	(50)	(50)	(50)	(50)	(50)
Adenoma		1 (2%)			
Osteosarcoma, metastatic, bone				1 (2%)	
Special Senses System					
Eye	(2)	(3)	(1)		(2)
Retrobulbar, schwannoma malignant					1 (50%)
Zymbal's gland				(1)	
Carcinoma				1 (100%)	
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Renal tubule, adenoma		1 (2%)			
Renal tubule, carcinoma		1 (2%)			
Urinary bladder	(50)	(50)	(50)	(50)	(50)
Leiomyosarcoma, metastatic, uterus				1 (2%)	
Transitional epithelium, carcinoma			1 (2%)		

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Leukemia mononuclear	14 (28%)	10 (20%)	22 (44%)	14 (28%)	15 (30%)
Lymphoma malignant	1 (2%)		1 (2%)		
Neoplasm Summary					
Total animals with primary neoplasms[c]	47	45	47	46	43
Total primary neoplasms	95	96	88	93	75
Total animals with benign neoplasms	37	41	39	37	38
Total benign neoplasms	79	80	60	67	57
Total animals with malignant neoplasms	15	15	26	22	17
Total malignant neoplasms	16	16	28	26	18
Total animals with metastatic neoplasms		1	2	6	
Total metastatic neoplasms		1	2	14	

[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 Citral: Untreated Control

Number of Days on Study	508	519	588	595	609	622	627	635	636	650	686	719	719	719	722	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	284	525	595	598	585	300	766	555	597	655	633	577	770	774	789	545	604	601	644	666	622	733	811	833	911
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous													X												
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery						+		+										+			+		+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant														X											
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	M	+	M	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X								X	X	X			X			X		X		
Pars intermedia, adenoma																				X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma												X													
C-cell, adenoma																					X				
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X					X				X	X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal														X		X	X		X	X		X			
Cervix, polyp stromal	X																								

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

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

Number of Days on Study	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	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 9 4	2 9 6	2 9 9	2 5 1	2 5 3	2 6 2	2 6 7	2 7 1	2 7 5	2 7 8	2 7 9	2 8 0	2 8 2	2 8 6	2 8 7	2 9 0	2 5 6	2 5 8	2 5 9	2 6 8	2 6 9	2 7 7	2 8 8	2 9 2	2 9 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+						+		+							+				+			10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign									X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenoma	X																			X						2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma								X			X											X	X	X		12
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma				X		X	X	X		X			X													7
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X					X				X						X	X							9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X					X							X	X	X	X		X		13
Cervix, polyp stromal																										1

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

Number of Days on Study	508	519	588	595	609	622	627	635	636	650	668	711	719	719	722	732	732	733	733	733	733	733	733	733	733	733
Carcass ID Number	28 4	25 2	29 5	29 8	28 5	30 0	27 6	25 5	29 7	26 5	26 3	25 7	27 0	27 4	28 9	25 4	26 0	26 1	26 4	26 6	27 2	27 3	28 1	28 3	29 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+		+		+			+	+	+														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					X							X	X	X		X			X	X		X	X		
Fibroadenoma, multiple															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X			X	X	X	X	X			X				X							X
Lymphoma malignant						X																			

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

Number of Days on Study	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	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	
Carcass ID Number	2 9 4	2 9 6	2 9 9	2 5 1	2 5 3	2 6 2	2 6 7	2 7 1	2 7 5	2 7 8	2 7 9	2 8 0	2 8 2	2 8 6	2 8 7	2 9 0	2 5 6	2 5 8	2 5 9	2 6 8	2 6 9	2 7 7	2 8 8	2 9 2	2 9 3	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma			X	X				X		X		X		X	X			X	X		X	X		X	X	22
Fibroadenoma, multiple							X		X								X									4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lipoma															X											2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													1
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	X									14
Lymphoma malignant																										1

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

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

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

Number of Days on Study	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	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	
Carcass ID Number	3 0 0 6	3 0 0 7	3 0 0 9	3 0 2 1	3 0 3 1	3 0 3 5	3 0 4 2	3 0 4 9	3 0 5 0	3 0 1	3 0 0 8	3 0 1 0	3 0 1 3	3 0 1 4	3 0 1 7	3 0 1 8	3 0 2 2	3 0 2 4	3 0 2 6	3 0 2 7	3 0 2 9	3 0 3 0	3 0 3 9	3 0 4 1	3 0 4 4	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
Sarcoma													X													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																				+						5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X				X			X								X		X	X			17
Pars intermedia, adenoma														X												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X	X				X			X	X				X			X	X	X					13
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X		X																	X	5
Carcinoma	X																									1
Bilateral, adenoma																						X				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Hemangioma																										1
Polyp stromal				X	X						X					X										4
Polyp stromal, multiple								X																		1
Vagina	+																	+								2

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

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

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

Number of Days on Study	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	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	3 0 0 6	3 0 0 7	3 0 0 9	3 2 0 1	3 3 1 1	3 3 1 5	3 4 2 2	3 4 2 9	3 5 0 0	3 0 1 1	3 0 1 8	3 1 0 0	3 1 1 3	3 1 1 4	3 1 1 7	3 1 1 8	3 2 2 2	3 2 2 4	3 2 2 6	3 2 2 7	3 2 2 9	3 3 0 0	3 3 3 9	3 4 4 1	3 4 4 4	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+																							4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma	X		X	X	X						X		X			X			X					X	X	21
Fibroadenoma, multiple							X					X								X						6
Hemangioma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+																						3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X																								1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X													X	X								10

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

Number of Days on Study	400	401	558	559	612	645	659	662	687	694	708	708	708	712	732	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	391	396	663	585	889	864	883	893	935	957	972	974	998	970	566	600	699	711	775	776	788	822	885	888	894
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																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								+	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	M	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X					X				X				X			X		X	X
Pars intermedia, adenoma									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X					X		X	X	X					X				
C-cell, carcinoma													X												
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Bilateral, adenoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X									X											
Vagina																									

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

Number of Days on Study	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	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	7 3 4	7 3 4	
Carcass ID Number	3 9 5	3 5 1	3 5 2	3 5 4	3 5 9	3 6 1	3 6 2	3 7 7	3 7 9	3 8 0	3 8 6	3 8 7	3 9 2	3 9 7	4 0 0	3 5 3	3 6 5	3 6 7	3 6 8	3 7 3	3 8 1	3 8 4	3 9 0	3 9 6	3 9 9	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												+														1
Oral mucosa									+																	1
Pharyngeal, squamous cell papilloma									X																	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																									X	1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X																	X			X			11
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X									X								X		9
C-cell, carcinoma	X																									2
Follicular cell, adenoma		X																								1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X		X																						2
Bilateral, adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X										X	X		X			X					X			8
Vagina															+											1

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

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

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

Number of Days on Study	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	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	7 3 4	7 3 4	
Carcass ID Number	3 9 5	3 5 1	3 5 2	3 5 4	3 5 9	3 6 1	3 6 2	3 7 7	3 7 9	3 8 0	3 8 6	3 8 7	3 9 2	3 9 7	4 0 0	3 5 3	3 6 5	3 6 7	3 6 8	3 7 3	3 8 1	3 8 4	3 9 0	3 9 6	3 9 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma						X	X		X			X				X		X						X	X	16
Fibroadenoma, multiple			X					X						X							X					6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																						X				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X															2
Carcinoma, metastatic, thyroid gland	X																									2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma											X															1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X				X	X	X			X		X					X	X	22
Lymphoma malignant																										1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Citral: 2,000 ppm

Number of Days on Study	445	453	504	510	595	638	649	673	690	694	694	714	719	721	732	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	416	447	413	443	428	410	435	438	418	422	425	409	414	431	402	405	407	411	412	417	419	421	424	426	430
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous															X										
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus						X																			
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin													X												
Mesentery									+	+	+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+												
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant								X																	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign															X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X				X			X			X		X	X	X	X	X				X			X	
Pars distalis, carcinoma										X															
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus						X																			
C-cell, adenoma						X												X						X	
Follicular cell, carcinoma																									
General Body System																									
None																									

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

Number of Days on Study	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 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	
Carcass ID Number	4 3 6	4 4 0	4 4 2	4 4 4	4 4 6	4 0 3	4 0 4	4 0 8	4 1 5	4 2 0	4 3 3	4 3 4	4 3 7	4 3 9	4 4 5	4 5 0	4 0 1	4 4 6	4 2 3	4 2 7	4 2 9	4 3 2	4 4 1	4 4 8	4 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Mesentery		+								+																5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth								+																		2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																		X								2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign														X												2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X				X								2
Parathyroid gland	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X				X			X			X				X							17
Pars distalis, carcinoma																										1
Pars intermedia, adenoma				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
C-cell, adenoma			X		X	X											X							X	X	9
Follicular cell, carcinoma																		X								1
General Body System																										
None																										

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

Number of Days on Study	445	453	504	510	559	638	649	673	690	699	694	714	719	721	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	416	447	413	443	428	410	435	438	418	422	425	409	414	413	402	405	407	411	411	417	419	421	424	426	430
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X											X	X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X									
Polyp stromal							X															X			X
Schwannoma malignant				X																					
Cervix, leiomyosarcoma						X																			
Vagina				+									+												
Schwannoma malignant, metastatic, skin													X												
Schwannoma malignant, metastatic, uterus				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+		+		+	+	+				+												
Mediastinal, carcinoma, metastatic, mammary gland		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin													X												
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																							
Fibroadenoma								X			X			X	X		X	X				X		X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								X	
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, schwannoma malignant													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma												X													
Skeletal muscle													+												
Schwannoma malignant, metastatic, skin													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland										X															
Spinal cord			+																						

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

Number of Days on Study	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 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 3 6	4 4 0	4 4 2	4 4 4	4 4 6	4 0 3	4 0 4	4 0 8	4 1 5	4 2 0	4 3 3	4 3 4	4 3 7	4 3 9	4 4 5	4 5 0	4 0 1	4 0 6	4 2 3	4 2 7	4 2 9	4 3 2	4 4 1	4 4 8	4 4 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Polyp stromal						X			X			X		X						X						8
Schwannoma malignant																										1
Cervix, leiomyosarcoma																										1
Vagina																										2
Schwannoma malignant, metastatic, skin																										1
Schwannoma malignant, metastatic, uterus																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+	+							+								10
Mediastinal, carcinoma, metastatic, mammary gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X		X												3
Fibroadenoma									X					X	X	X		X			X		X	X	X	18
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Subcutaneous tissue, fibroma																X										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Schwannoma malignant, metastatic, skin																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Spinal cord																										1

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

Number of Days on Study	44 45	44 53	50 34	51 40	59 05	63 38	64 89	67 33	69 00	69 04	69 44	71 44	71 19	72 91	73 22	73 22	73 22	73 22	73 22	73 22	73 22	73 22	73 22	73 22
Carcass ID Number	41 66	44 67	41 33	44 33	42 88	41 00	43 55	43 88	41 88	42 02	42 25	40 99	41 44	43 11	40 22	40 55	40 77	41 11	41 22	41 72	41 91	42 14	42 46	43 00
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar adenoma, multiple																								
Carcinoma, metastatic, mammary gland		X																						
Schwannoma malignant, metastatic, skin													X											
Mediastinum, carcinoma, metastatic, mammary gland		X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Zymbal's gland	+																							
Carcinoma	X																							
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus						X																		
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X		X	X	X			X							X	X				

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

Number of Days on Study	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 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	
Carcass ID Number	4 3 6	4 4 0	4 4 2	4 4 4	4 4 6	4 0 3	4 0 4	4 0 8	4 1 5	4 2 0	4 3 3	4 3 4	4 3 7	4 3 9	4 4 5	4 5 0	4 0 1	4 0 6	4 2 3	4 2 7	4 2 9	4 3 2	4 4 1	4 4 8	4 4 9	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma							X																				1
Alveolar/bronchiolar adenoma, multiple	X																										1
Carcinoma, metastatic, mammary gland																											1
Schwannoma malignant, metastatic, skin																											1
Mediastinum, carcinoma, metastatic, mammary gland																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Osteosarcoma, metastatic, bone																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leiomyosarcoma, metastatic, uterus																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear						X	X	X		X	X							X									14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Citral: 4,000 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Citral: 4,000 ppm

Number of Days on Study	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	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	
Carcass ID Number	4 6 1	4 6 5	4 7 2	4 7 9	4 8 3	4 8 5	4 8 9	4 9 3	4 5 1	4 5 2	4 5 3	4 5 6	4 5 9	4 6 0	4 6 2	4 6 3	4 6 8	4 7 3	4 7 5	4 7 8	4 8 0	4 8 4	4 8 6	4 9 4	4 9 6	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										+	+											+				7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Tooth																										2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																		X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X							1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X		X	X		X							X	X			X							13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X								X				X	X						11
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									X	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X					X													X		X	X	10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Citral: 4,000 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Citral: 4,000 ppm

Number of Days on Study	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	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	
Carcass ID Number	4 6 1	4 6 5	4 7 2	4 7 9	4 8 3	4 8 5	4 8 9	4 9 3	4 5 1	4 5 2	4 5 3	4 5 6	4 5 9	4 6 0	4 6 2	4 6 3	4 6 8	4 7 3	4 7 5	4 7 8	4 8 0	4 8 4	4 8 6	4 9 4	4 9 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																			+							5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma	X					X		X	X			X	X		X			X				X				15
Fibroadenoma, multiple			X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																		X								2
Subcutaneous tissue, fibroma																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																2
Retrobulbar, schwannoma malignant																										1
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X					X	X									X			X				15

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Clitoral Gland: Adenoma					
Overall rate[a]	9/49 (18%)	6/49 (12%)	3/49 (6%)	4/50 (8%)	1/49 (2%)
Adjusted rate[b]	20.2%	13.0%	6.7%	8.8%	2.3%
Terminal rate[c]	8/35 (23%)	5/40 (13%)	3/35 (9%)	3/36 (8%)	1/35 (3%)
First incidence (days)	719	708	732 (T)	690	732 (T)
Poly-3 test[d]		P=0.063N	P=0.260N	P=0.383N	P=0.068N
Clitoral Gland: Adenoma or Carcinoma					
Overall rate	9/49 (18%)	7/49 (14%)	3/49 (6%)	4/50 (8%)	1/49 (2%)
Adjusted rate	20.2%	15.1%	6.7%	8.8%	2.3%
Terminal rate	8/35 (23%)	6/40 (15%)	3/35 (9%)	3/36 (8%)	1/35 (3%)
First incidence (days)	719	708	732 (T)	690	732 (T)
Poly-3 test		P=0.035N	P=0.173N	P=0.273N	P=0.038N
Mammary Gland: Fibroadenoma					
Overall rate	26/50 (52%)	27/50 (54%)	22/50 (44%)	18/50 (36%)	16/50 (32%)
Adjusted rate	56.7%	56.6%	47.6%	39.5%	35.2%
Terminal rate	21/35 (60%)	22/40 (55%)	20/36 (56%)	15/36 (42%)	13/36 (36%)
First incidence (days)	609	687	582	673	491
Poly-3 test		P=0.019N	P=0.252N	P=0.071N	P=0.028N
Mammary Gland: Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	2.2%	6.5%	0.0%
Terminal rate	0/35 (0%)	0/40 (0%)	0/36 (0%)	2/36 (6%)	0/36 (0%)
First incidence (days)	—[e]	—	645	453	—[f]
Poly-3 test		P=0.596	P=0.495	P=0.114	—
Mammary Gland: Fibroadenoma or Carcinoma					
Overall rate	26/50 (52%)	27/50 (54%)	23/50 (46%)	20/50 (40%)	16/50 (32%)
Adjusted rate	56.7%	56.6%	49.5%	43.1%	35.2%
Terminal rate	21/35 (60%)	22/40 (55%)	20/36 (56%)	16/36 (44%)	13/36 (36%)
First incidence (days)	609	687	582	453	491
Poly-3 test		P=0.019N	P=0.311N	P=0.133N	P=0.028N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	12/50 (24%)	17/50 (34%)	11/50 (22%)	17/50 (34%)	13/49 (27%)
Adjusted rate	26.2%	35.8%	23.7%	36.3%	29.8%
Terminal rate	8/35 (23%)	14/40 (35%)	8/36 (22%)	11/36 (31%)	12/35 (34%)
First incidence (days)	609	677	612	445	617
Poly-3 test		P=0.457N	P=0.145N	P=0.566	P=0.352N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma					
Overall rate	12/50 (24%)	17/50 (34%)	11/50 (22%)	18/50 (36%)	13/49 (27%)
Adjusted rate	26.2%	35.8%	23.7%	38.3%	29.8%
Terminal rate	8/35 (23%)	14/40 (35%)	8/36 (22%)	11/36 (31%)	12/35 (34%)
First incidence (days)	609	677	612	445	617
Poly-3 test		P=0.471N	P=0.145N	P=0.485	P=0.352N
Thyroid Gland (C-Cell): Adenoma					
Overall rate	8/50 (16%)	13/50 (26%)	9/50 (18%)	9/50 (18%)	11/50 (22%)
Adjusted rate	17.7%	27.6%	19.5%	19.8%	24.6%
Terminal rate	7/35 (20%)	13/40 (33%)	6/36 (17%)	8/36 (22%)	7/36 (19%)
First incidence (days)	719	732 (T)	659	638	687
Poly-3 test		P=0.474N	P=0.251N	P=0.261N	P=0.463N

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Thyroid Gland (C-Cell): Adenoma or Carcinoma					
Overall rate	8/50 (16%)	13/50 (26%)	11/50 (22%)	9/50 (18%)	11/50 (22%)
Adjusted rate	17.7%	27.6%	23.8%	19.8%	24.6%
Terminal rate	7/35 (20%)	13/40 (33%)	7/36 (19%)	8/36 (22%)	7/36 (19%)
First incidence (days)	719	732 (T)	659	638	687
Poly-3 test		P=0.410N	P=0.429N	P=0.261N	P=0.463N
Uterus: Stromal Polyp					
Overall rate	14/50 (28%)	5/50 (10%)	8/50 (16%)	8/50 (16%)	10/50 (20%)
Adjusted rate	30.5%	10.6%	17.4%	17.6%	22.3%
Terminal rate	12/35 (34%)	5/40 (13%)	6/36 (17%)	7/36 (19%)	7/36 (19%)
First incidence (days)	508	732 (T)	612	649	588
Poly-3 test		P=0.101	P=0.262	P=0.253	P=0.108
All Organs: Mononuclear Cell Leukemia					
Overall rate	14/50 (28%)	10/50 (20%)	22/50 (44%)	14/50 (28%)	15/50 (30%)
Adjusted rate	28.8%	21.1%	44.9%	29.7%	31.8%
Terminal rate	5/35 (14%)	9/40 (23%)	13/36 (36%)	8/36 (22%)	7/36 (19%)
First incidence (days)	508	652	400	504	386
Poly-3 test		P=0.391	P=0.010	P=0.234	P=0.173
All Organs: Benign Neoplasms					
Overall rate	37/50 (74%)	41/50 (82%)	39/50 (78%)	37/50 (74%)	38/50 (76%)
Adjusted rate	78.8%	85.4%	81.2%	77.6%	80.9%
Terminal rate	30/35 (86%)	34/40 (85%)	30/36 (83%)	28/36 (78%)	28/36 (78%)
First incidence (days)	508	677	582	445	491
Poly-3 test		P=0.333N	P=0.390N	P=0.230N	P=0.374N
All Organs: Malignant Neoplasms					
Overall rate	15/50 (30%)	15/50 (30%)	26/50 (52%)	22/50 (44%)	17/50 (34%)
Adjusted rate	30.6%	31.1%	52.6%	44.2%	35.9%
Terminal rate	5/35 (14%)	12/40 (30%)	15/36 (42%)	10/36 (28%)	8/36 (22%)
First incidence (days)	508	491	400	445	386
Poly-3 test		P=0.498N	P=0.024	P=0.130	P=0.391
All Organs: Benign or Malignant Neoplasms					
Overall rate	47/50 (94%)	45/50 (90%)	47/50 (94%)	46/50 (92%)	43/50 (86%)
Adjusted rate	94.0%	91.8%	94.0%	92.0%	87.1%
Terminal rate	32/35 (91%)	36/40 (90%)	33/36 (92%)	32/36 (89%)	30/36 (83%)
First incidence (days)	508	491	400	445	386
Poly-3 test		P=0.196N	P=0.489	P=0.631	P=0.332N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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 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 B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Citral[a]

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	12	10	11	11	12
Natural deaths	3		3	3	2
Survivors					
Died last week of study	1				
Terminal sacrifice	34	40	36	36	36
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Inflammation				1 (2%)	
Parasite metazoan	2 (4%)	2 (4%)			2 (4%)
Ulcer				1 (2%)	
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Parasite metazoan	7 (14%)	4 (8%)	1 (2%)	6 (12%)	3 (6%)
Intestine large, cecum	(50)	(50)	(50)	(50)	(49)
Inflammation			1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)	(50)	(50)
Inflammation			1 (2%)		
Parasite metazoan					1 (2%)
Intestine small, jejunum	(50)	(50)	(50)	(49)	(50)
Dysplasia			1 (2%)		
Inflammation			1 (2%)		
Polyp inflammatory			1 (2%)		
Ulcer					1 (2%)
Lymphatic, cyst			1 (2%)		
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Inflammation		1 (2%)			
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis		3 (6%)	1 (2%)	1 (2%)	1 (2%)
Basophilic focus	42 (84%)	48 (96%)	44 (88%)	45 (90%)	42 (84%)
Clear cell focus		1 (2%)			
Degeneration, cystic	1 (2%)	2 (4%)			
Eosinophilic focus	8 (16%)	8 (16%)	7 (14%)	3 (6%)	9 (18%)
Fatty change				1 (2%)	4 (8%)
Fibrosis			1 (2%)		
Hematopoietic cell proliferation	1 (2%)	3 (6%)			
Hepatodiaphragmatic nodule	10 (20%)	8 (16%)	8 (16%)	4 (8%)	5 (10%)
Inflammation	40 (80%)	44 (88%)	44 (88%)	41 (82%)	43 (86%)
Mixed cell focus	16 (32%)	18 (36%)	11 (22%)	16 (32%)	15 (30%)
Necrosis			2 (4%)		1 (2%)
Vacuolization cytoplasmic	5 (10%)	12 (24%)	7 (14%)	4 (8%)	6 (12%)
Bile duct, hyperplasia	25 (50%)	15 (30%)	17 (34%)	13 (26%)	13 (26%)
Centrilobular, degeneration	5 (10%)	6 (12%)	9 (18%)	7 (14%)	7 (14%)
Mesentery	(10)	(5)	(1)	(5)	(7)
Hemorrhage	1 (10%)				
Inflammation		2 (40%)			
Thrombosis					1 (14%)
Fat, necrosis	8 (80%)	3 (60%)	1 (100%)	4 (80%)	5 (71%)

[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 Citral

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Alimentary System (continued)					
Pancreas	(50)	(50)	(50)	(50)	(50)
Atrophy	8 (16%)	12 (24%)	20 (40%)	8 (16%)	10 (20%)
Cyst		2 (4%)			
Cytoplasmic alteration	2 (4%)	1 (2%)	1 (2%)		2 (4%)
Hyperplasia	1 (2%)	2 (4%)	2 (4%)		
Inflammation	1 (2%)		1 (2%)		
Metaplasia, hepatocyte					1 (2%)
Salivary glands	(50)	(50)	(50)	(50)	(50)
Atrophy	2 (4%)				1 (2%)
Inflammation		2 (4%)			
Stomach, forestomach	(50)	(49)	(50)	(50)	(50)
Edema	1 (2%)				
Hyperplasia					1 (2%)
Inflammation			1 (2%)		1 (2%)
Ulcer	2 (4%)		2 (4%)		1 (2%)
Epithelium, hyperplasia	6 (12%)	1 (2%)	4 (8%)	3 (6%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Erosion	2 (4%)	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Fibrosis	1 (2%)				
Inflammation			1 (2%)		
Mineralization		1 (2%)	1 (2%)		
Ulcer				1 (2%)	
Epithelium, mineralization	1 (2%)				
Tooth			(1)	(2)	(2)
Inflammation				2 (100%)	1 (50%)
Malformation				1 (50%)	
Peridontal tissue, inflammation			1 (100%)		1 (50%)
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Inflammation					1 (2%)
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	41 (82%)	48 (96%)	40 (80%)	42 (84%)	39 (78%)
Fibrosis				1 (2%)	
Hemorrhage			1 (2%)		
Necrosis					1 (2%)
Thrombosis			1 (2%)		1 (2%)
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)	1 (2%)	3 (6%)	10 (20%)
Atrophy			1 (2%)		
Atypia cellular					1 (2%)
Degeneration, cystic				1 (2%)	
Hyperplasia	14 (28%)	16 (32%)	13 (26%)	12 (24%)	8 (16%)
Hypertrophy	10 (20%)	4 (8%)	3 (6%)	3 (6%)	4 (8%)
Thrombosis			1 (2%)		
Vacuolization cytoplasmic	1 (2%)	2 (4%)	6 (12%)	2 (4%)	

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Endocrine System (continued)					
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Hyperplasia	8 (16%)	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Infiltration cellular, lymphocyte		1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)				
Parathyroid gland	(43)	(43)	(40)	(43)	(47)
Hyperplasia	1 (2%)				
Pituitary gland	(50)	(50)	(50)	(50)	(49)
Cyst	1 (2%)		2 (4%)	3 (6%)	3 (6%)
Hyperplasia				1 (2%)	
Pars distalis, cyst	1 (2%)	1 (2%)		1 (2%)	
Pars distalis, hyperplasia	27 (54%)	29 (58%)	31 (62%)	23 (46%)	27 (55%)
Pars intermedia, hyperplasia		1 (2%)	1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)	(50)
C-cell, hyperplasia	45 (90%)	45 (90%)	39 (78%)	43 (86%)	36 (72%)
Follicular cell, hyperplasia		1 (2%)	2 (4%)		
General Body System					
None					
Genital System					
Clitoral gland	(49)	(49)	(49)	(50)	(49)
Hyperplasia	7 (14%)	17 (35%)	8 (16%)	15 (30%)	4 (8%)
Inflammation	13 (27%)	22 (45%)	20 (41%)	19 (38%)	24 (49%)
Metaplasia			1 (2%)		
Bilateral, cyst		1 (2%)			
Duct, cyst	5 (10%)	5 (10%)	3 (6%)	6 (12%)	4 (8%)
Ovary	(50)	(50)	(50)	(50)	(50)
Atrophy			2 (4%)	1 (2%)	
Cyst	3 (6%)	11 (22%)	6 (12%)	4 (8%)	5 (10%)
Infiltration cellular, lymphocyte				1 (2%)	2 (4%)
Uterus	(50)	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)				
Hemorrhage		1 (2%)		1 (2%)	
Hyperplasia					1 (2%)
Hyperplasia, cystic	1 (2%)				
Inflammation		1 (2%)			
Cervix, prolapse				1 (2%)	
Endometrium, hyperplasia, cystic	9 (18%)	12 (24%)	15 (30%)	9 (18%)	14 (28%)
Vagina		(2)	(1)	(2)	
Dilatation		1 (50%)			
Hyperplasia				1 (50%)	
Hypertrophy		1 (50%)			
Inflammation, acute			1 (100%)		

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)				
Atrophy	1 (2%)	1 (2%)		2 (4%)	1 (2%)
Hyperplasia	11 (22%)	9 (18%)	12 (24%)	10 (20%)	10 (20%)
Myelofibrosis	1 (2%)		1 (2%)		1 (2%)
Necrosis				1 (2%)	
Lymph node	(7)	(4)	(7)	(10)	(5)
Lumbar, hyperplasia, histiocytic		1 (25%)			
Mediastinal, congestion		1 (25%)			
Mediastinal, hyperplasia, plasma cell				1 (10%)	
Lymph node, mandibular	(50)	(50)	(50)	(50)	(50)
Ectasia		10 (20%)	3 (6%)	5 (10%)	7 (14%)
Hyperplasia, plasma cell	6 (12%)	17 (34%)	17 (34%)	7 (14%)	17 (34%)
Necrosis					1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(50)
Atrophy		1 (2%)			
Ectasia			1 (2%)		
Hyperplasia, lymphoid			1 (2%)		
Spleen	(50)	(50)	(50)	(50)	(50)
Accessory spleen		1 (2%)			
Ectopic tissue		1 (2%)			
Fibrosis	1 (2%)	1 (2%)			
Granuloma	1 (2%)				
Hematopoietic cell proliferation	11 (22%)	11 (22%)	8 (16%)	5 (10%)	5 (10%)
Hemorrhage				1 (2%)	
Hyperplasia, histiocytic	1 (2%)				
Hyperplasia, adenomatous					1 (2%)
Infarct	1 (2%)				
Infiltration cellular, lipocyte					1 (2%)
Necrosis			1 (2%)		
Pigmentation	1 (2%)		1 (2%)	3 (6%)	
Red pulp, depletion cellular	1 (2%)				
Thymus	(49)	(47)	(49)	(48)	(49)
Atrophy	45 (92%)	46 (98%)	45 (92%)	44 (92%)	46 (94%)
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Galactocele	3 (6%)	1 (2%)	2 (4%)	3 (6%)	
Hyperplasia		1 (2%)	4 (8%)		1 (2%)
Hyperplasia, focal	4 (8%)	5 (10%)	10 (20%)	6 (12%)	3 (6%)
Hyperplasia, lobular			1 (2%)		
Skin	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			1 (2%)		
Fibrosis		1 (2%)			
Hyperkeratosis	1 (2%)				
Hyperplasia	1 (2%)				
Inflammation	1 (2%)				
Dermis, fibrosis	1 (2%)				
Subcutaneous tissue, inflammation		1 (2%)			

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

	Untreated Control	Vehicle Control	1,000 ppm	2,000 ppm	4,000 ppm
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteopetrosis	3 (6%)	3 (6%)	12 (24%)	5 (10%)	8 (16%)
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Hemorrhage	3 (6%)	2 (4%)	4 (8%)	4 (8%)	
Necrosis		1 (2%)		4 (8%)	
Spinal cord				(1)	
Hemorrhage				1 (100%)	
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Fibrosis					1 (2%)
Hemorrhage	2 (4%)		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)		
Inflammation	9 (18%)	7 (14%)	17 (34%)	9 (18%)	9 (18%)
Alveolar epithelium, hyperplasia	9 (18%)	10 (20%)	9 (18%)	10 (20%)	11 (22%)
Nose	(50)	(50)	(50)	(50)	(50)
Foreign body	3 (6%)	1 (2%)	4 (8%)	1 (2%)	3 (6%)
Inflammation	4 (8%)	5 (10%)	5 (10%)	2 (4%)	3 (6%)
Trachea	(50)	(50)	(50)	(50)	(50)
Inflammation	1 (2%)	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Special Senses System					
Eye	(2)	(3)	(1)		(2)
Cataract	2 (100%)	2 (67%)	1 (100%)		1 (50%)
Cornea, inflammation		1 (33%)			
Retina, degeneration	2 (100%)	2 (67%)	1 (100%)		1 (50%)
Harderian gland					(1)
Atrophy					1 (100%)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)		1 (2%)	
Cyst		1 (2%)			1 (2%)
Hydronephrosis				2 (4%)	1 (2%)
Inflammation	1 (2%)	1 (2%)			1 (2%)
Mineralization	41 (82%)	43 (86%)	43 (86%)	38 (76%)	41 (82%)
Necrosis					2 (4%)
Nephropathy	41 (82%)	44 (88%)	45 (90%)	48 (96%)	44 (88%)
Pigmentation	2 (4%)	1 (2%)	4 (8%)		1 (2%)
Renal tubule, hyperplasia		1 (2%)			1 (2%)
Transitional epithelium, hyperplasia				1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)	(50)
Calculus gross observation					1 (2%)
Hemorrhage	1 (2%)		1 (2%)		
Inflammation				1 (2%)	
Ulcer				1 (2%)	
Transitional epithelium, hyperplasia				1 (2%)	1 (2%)

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

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	1	4	2	6	3
Natural deaths	1	3	8	2	7
Survivors					
Died last week of study	1	1			
Terminal sacrifice	47	42	40	42	40
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine small, duodenum	(50)	(50)	(50)	(49)	(50)
Polyp adenomatous	1 (2%)	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)	2 (4%)		1 (2%)	
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas				1 (2%)	
Hemangiosarcoma	2 (4%)				
Hepatocellular carcinoma	3 (6%)	9 (18%)	12 (24%)	4 (8%)	9 (18%)
Hepatocellular carcinoma, multiple	1 (2%)		1 (2%)	1 (2%)	
Hepatocellular adenoma	9 (18%)	8 (16%)	8 (16%)	11 (22%)	10 (20%)
Hepatocellular adenoma, multiple	1 (2%)	2 (4%)	3 (6%)		3 (6%)
Mesentery	(6)	(3)	(2)	(3)	(3)
Pancreas	(50)	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)	
Stomach, forestomach	(50)	(50)	(49)	(50)	(50)
Carcinoma, metastatic, pancreas				1 (2%)	
Squamous cell papilloma				1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)	
Hepatocellular carcinoma, metastatic, liver			1 (2%)		
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Subcapsular, adenoma	1 (2%)	1 (2%)	1 (2%)		
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Pheochromocytoma benign			1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Adenoma		1 (2%)			
Pituitary gland	(50)	(48)	(49)	(47)	(50)
Pars intermedia, adenoma				1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas				1 (2%)	
Preputial gland	(50)	(50)	(50)	(50)	(50)
Prostate	(50)	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas				1 (2%)	
Testes	(50)	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)				
Hemangiosarcoma					1 (2%)
Interstitial cell, adenoma	1 (2%)				
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma				2 (4%)	1 (2%)
Mast cell tumor malignant		1 (2%)		1 (2%)	
Lymph node	(2)		(1)	(2)	(1)
Mediastinal, carcinoma, metastatic, pancreas				1 (50%)	
Lymph node, mandibular	(48)	(45)	(47)	(47)	(49)
Lymph node, mesenteric	(48)	(47)	(49)	(48)	(50)
Spleen	(50)	(50)	(49)	(50)	(50)
Hemangiosarcoma				3 (6%)	2 (4%)
Mast cell tumor malignant		1 (2%)			
Thymus	(50)	(49)	(48)	(48)	(46)
Thymoma benign				1 (2%)	
Integumentary System					
Skin	(50)	(50)	(50)	(50)	(50)
Pinna, melanoma malignant					1 (2%)
Subcutaneous tissue, hemangioma	1 (2%)				
Subcutaneous tissue, sarcoma			1 (2%)		
Tail, fibrosarcoma		1 (2%)		1 (2%)	
Tail, neurofibrosarcoma					1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Chondrosarcoma				1 (2%)	
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Astrocytoma benign					1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	8 (16%)	5 (10%)	6 (12%)	2 (4%)
Alveolar/bronchiolar carcinoma	4 (8%)	5 (10%)	4 (8%)	1 (2%)	3 (6%)
Carcinoma, metastatic, pancreas				1 (2%)	
Hemangiosarcoma		1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)	1 (2%)	1 (2%)	2 (4%)
Special Senses System					
Harderian gland	(2)	(2)	(1)	(3)	
Adenoma	2 (100%)	2 (100%)	1 (100%)	2 (67%)	
Carcinoma				1 (33%)	
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(49)	(50)	(50)
Hemangioma				1 (2%)	
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Lymphoma malignant	4 (8%)		2 (4%)	3 (6%)	1 (2%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	27	28	35	33	26
Total primary neoplasms	37	43	39	44	35
Total animals with benign neoplasms	20	20	18	21	14
Total benign neoplasms	22	23	19	23	16
Total animals with malignant neoplasms	14	18	20	17	18
Total malignant neoplasms	15	20	20	21	19
Total animals with metastatic neoplasms		1	1	2	2
Total metastatic neoplasms		1	2	7	2

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

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

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

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

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

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	00004	00008	00019	00020	00022	00037	00039	00045	00029	00033	00037	00010	00011	00012	00013	00014	00016	00018	00024	00026	00028	00038	00041	00047	00048	00050	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
Carcinoma																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X					2
Hepatocellular carcinoma													X							X							3
Hepatocellular carcinoma, multiple								X																			1
Hepatocellular adenoma				X		X					X					X			X							X	9
Hepatocellular adenoma, multiple																											1
Mesentery																			+				+				6
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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												1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																				X							1
General Body System																											
None																											

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

Number of Days on Study	3 9 7	6 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	0 3 1	0 0 6	0 0 3	0 0 9	0 2 1	0 2 7	0 3 5	0 4 3	0 4 4	0 4 5	0 0 1	0 0 2	0 1 1	0 1 5	0 1 7	0 2 3	0 2 5	0 3 0	0 3 2	0 3 4	0 3 6	0 4 0	0 4 2	0 4 6	0 4 9
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																				X						
Interstitial cell, adenoma								X																		
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+																								
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																	X				
Alveolar/bronchiolar carcinoma									X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Citral: Untreated Control

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	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	7 3 1	7 3 1	
Carcass ID Number	0 0 0 4	0 0 0 8	0 0 1 9	0 0 2 0	0 0 2 2	0 0 3 7	0 0 3 9	0 0 0 5	0 0 2 9	0 0 3 3	0 0 3 7	0 0 1 0	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 6	0 0 1 8	0 0 2 4	0 0 2 6	0 0 2 8	0 0 3 8	0 0 4 1	0 0 4 7	0 0 4 8	0 0 5 0	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																											1
Interstitial cell, adenoma																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Subcutaneous tissue, hemangioma																				X							1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X				X						4
Alveolar/bronchiolar carcinoma										X									X				X				4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland																											2
Adenoma																											2
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 Citral: Vehicle Control

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

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	06 65	07 71	07 72	08 22	08 86	08 88	09 91	09 92	09 96	07 70	07 78	09 95	05 51	05 53	05 54	05 56	06 61	06 64	07 44	07 75	07 76	08 81	08 84	08 89	09 90	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
Carcinoma										X																2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X		X						X					X					X		9
Hepatocellular adenoma						X					X					X										8
Hepatocellular adenoma, multiple			X																							2
Mesentery			+																							3
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	43
Pituitary gland	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	1212	3101	5300	5300	6226	6288	6822	7227	7227	7227	7227	7227	7227	7227	7228	7228	7228	7228	7228	7228	7228	7228	7228	7228	7228	7228
Carcass ID Number	0066	0079	0052	0067	0097	0087	0094	0057	0059	0060	0073	0077	0080	0098	0055	0058	0062	0063	0068	0069	0083	0085	0093	0099	0100	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																										
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	
Lymph node, mesenteric	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mast cell tumor malignant																									X	
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	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tail, fibrosarcoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma				X					X					X	X							X				
Alveolar/bronchiolar carcinoma				X																				X		
Hemangiosarcoma																										
Hepatocellular carcinoma, metastatic, liver																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																							+			
Harderian gland																+										
Adenoma																X										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	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	
Carcass ID Number	0 6 5	0 7 1	0 7 2	0 8 2	0 8 6	0 8 8	0 9 1	0 9 2	0 9 6	0 7 0	0 7 8	0 9 5	0 5 1	0 5 3	0 5 4	0 5 6	0 6 1	0 6 4	0 7 4	0 7 5	0 7 6	0 8 1	0 8 4	0 8 9	0 9 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																						X				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																										1
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	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tail, fibrosarcoma																	X									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X							X							X				8
Alveolar/bronchiolar carcinoma																	X			X			X			5
Hemangiosarcoma									X																	1
Hepatocellular carcinoma, metastatic, liver								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																+										2
Adenoma																X										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Citral: 500 ppm

Number of Days on Study	418	419	491	511	576	601	626	629	680	701	722	727	722	727	722	728	728	728	728	728	728	728	728	728
Carcass ID Number	10004	10007	10025	10044	10041	10036	10049	10022	10028	10003	10006	10014	10045	10117	10237	10101	10118	10119	10200	10300	10313	10323	10344	10345
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					X	X		X	X					X			X						
Hepatocellular carcinoma, multiple								X																
Hepatocellular adenoma		X		X						X					X	X		X					X	
Hepatocellular adenoma, multiple												X												
Mesentery												+												
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																								X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	M	+	+	+	M	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Citral: 500 ppm

Number of Days on Study	728	728	729	729	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	13 37	14 07	10 02	14 03	10 09	13 33	10 05	11 01	11 02	11 03	11 06	12 01	12 04	12 06	12 07	12 08	12 09	13 08	13 09	14 00	14 02	14 05	14 06	14 08	15 00	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	48
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							X							X		X		X						X		12
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma										X																8
Hepatocellular adenoma, multiple		X																							X	3
Mesentery			+																							2
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver														X												1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Citral: 500 ppm

Number of Days on Study	418	419	491	511	576	601	626	629	680	711	722	727	722	727	722	728	722	728	722	728	722	728	722	728	722	728	722	728
Carcass ID Number	10404	10047	10225	10444	10441	10336	10449	10222	10208	10003	10036	10044	10115	10515	10717	10323	10101	10110	10118	10919	10120	10230	10331	10312	10334	10124	10335	
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma			X																									
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																												
Alveolar/bronchiolar carcinoma														X			X											
Hepatocellular carcinoma, metastatic, liver																												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																												
Harderian gland																												
Adenoma																												
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant					X																							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Citral: 500 ppm

Number of Days on Study	728	728	729	729	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	13 47	14 77	10 22	14 43	10 09	13 33	10 55	11 11	11 12	11 13	11 16	12 11	12 14	12 26	12 27	12 28	12 29	13 38	13 39	14 04	14 22	14 25	14 26	14 28	15 10	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																												1
Lymph node, mandibular	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X				X							X				X				X							5
Alveolar/bronchiolar carcinoma											X													X				4
Hepatocellular carcinoma, metastatic, liver														X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																												
Harderian gland																								+				1
Adenoma																								X				1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																								X				2

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

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

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

Number of Days on Study	728	729	729	729	729	729	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	19 8	15 1	16 1	16 2	16 6	17 3	17 8	18 1	19 0	16 4	17 1	19 9	15 8	16 0	16 9	17 0	17 7	17 9	18 0	18 3	18 4	18 5	19 2	19 4	20 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Hepatocellular carcinoma							X														X		X			4
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X		X						X			X				X					X		X	11
Mesentery		+																	+							3
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	427	616	650	682	889	697	710	720	722	727	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	728
Carcass ID Number	159	163	157	193	191	188	165	174	168	172	176	186	187	152	153	154	155	156	167	175	182	189	195	196	197
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X								
Mast cell tumor malignant																										
Lymph node			+					+																		
Mediastinal, carcinoma, metastatic, pancreas			X																							
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																										
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tail, fibrosarcoma													X													
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondrosarcoma																	X									
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve		+																								
Spinal cord		+																								
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																						
Alveolar/bronchiolar carcinoma																							X			
Carcinoma, metastatic, pancreas			X																							
Hepatocellular carcinoma, metastatic, liver					X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland																			+							
Adenoma																										
Carcinoma																			X							
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																										
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 Citral: 1,000 ppm

Number of Days on Study	728	729	729	729	729	729	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	19 98	15 91	16 11	16 12	16 26	17 73	17 78	18 81	19 10	16 04	17 11	19 19	15 58	16 00	16 09	17 00	17 07	17 79	18 00	18 03	18 41	18 51	19 21	19 41	20 01	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																						2
Mast cell tumor malignant																	X										1
Lymph node																											2
Mediastinal, carcinoma, metastatic, pancreas																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																X						3
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		48
Thymoma benign													X														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
Tail, fibrosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondrosarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																											1
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X		X			X					X			X												6
Alveolar/bronchiolar carcinoma																											1
Carcinoma, metastatic, pancreas																											1
Hepatocellular carcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland														+											+		3
Adenoma														X											X		2
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																						X					1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																											3

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

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

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

Number of Days on Study	728	728	728	728	728	728	729	729	729	729	729	729	729	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	22 23	22 29	23 30	23 32	23 34	24 46	21 92	21 99	22 22	22 25	22 26	23 39	24 49	20 55	24 44	20 44	20 66	21 13	21 77	21 81	23 33	23 71	24 13	24 43	24 47	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	X																X									9
Hepatocellular adenoma									X							X		X		X	X				X	10
Hepatocellular adenoma, multiple														X			X									3
Mesentery	+																									3
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																								1

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

Number of Days on Study	447	456	500	600	626	633	652	661	681	682	722	727	722	727	722	737	722	737	722	727	722	728	722	728	722	728	722	728
Carcass ID Number	22308	23306	24308	22207	24505	22404	23808	21000	20909	22101	20012	20007	21104	22300	23101	23505	24000	24202	25020	20001	20013	20038	21101	21105	21106
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										X		
Lymph node			+																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hemangiosarcoma																			X						X			
Thymus	+	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	M		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Pinna, melanoma malignant																												
Tail, neurofibrosarcoma									X																			
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Astrocytoma benign										X																		
Spinal cord																									+			
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Alveolar/bronchiolar adenoma																												
Alveolar/bronchiolar carcinoma																												
Hepatocellular carcinoma, metastatic, liver								X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Special Senses System																												
None																												
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymphoma malignant			X																									

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

Number of Days on Study	728	728	728	728	728	728	729	729	729	729	729	729	729	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	22 23	22 29	23 30	23 32	23 34	24 46	21 12	21 19	22 22	22 25	22 26	23 39	24 09	20 05	24 44	20 04	20 06	21 13	21 17	21 18	23 33	23 37	24 41	24 43	24 47	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
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
Pinna, melanoma malignant									X																	1
Tail, neurofibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma benign																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X						X								2
Alveolar/bronchiolar carcinoma												X									X				X	3
Hepatocellular carcinoma, metastatic, liver	X																									2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Harderian Gland: Adenoma or Carcinoma					
Overall rate[a]	2/50 (4%)	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate[b]	4.1%	4.3%	2.2%	6.3%	0.0%
Terminal rate[c]	2/48 (4%)	2/43 (5%)	1/40 (3%)	3/42 (7%)	0/40 (0%)
First incidence (days)	727 (T)	727 (T)	727 (T)	727 (T)	—[e]
Poly-3 test[d]		P=0.241N	P=0.508N	P=0.518	P=0.239N
Liver: Hepatocellular Adenoma					
Overall rate	10/50 (20%)	10/50 (20%)	11/50 (22%)	11/50 (22%)	13/50 (26%)
Adjusted rate	20.5%	21.4%	23.6%	22.6%	28.2%
Terminal rate	10/48 (21%)	9/43 (21%)	8/40 (20%)	10/42 (24%)	11/40 (28%)
First incidence (days)	727 (T)	530	419	427	681
Poly-3 test		P=0.266	P=0.498	P=0.543	P=0.303
Liver: Hepatocellular Carcinoma					
Overall rate	4/50 (8%)	9/50 (18%)	13/50 (26%)	5/50 (10%)	9/50 (18%)
Adjusted rate	8.2%	19.3%	27.5%	10.4%	19.1%
Terminal rate	4/48 (8%)	8/43 (19%)	7/40 (18%)	3/42 (7%)	5/40 (13%)
First incidence (days)	727 (T)	530	418	689	626
Poly-3 test		P=0.346N	P=0.243	P=0.176N	P=0.597N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	13/50 (26%)	15/50 (30%)	22/50 (44%)	15/50 (30%)	21/50 (42%)
Adjusted rate	26.6%	32.1%	45.1%	30.6%	44.3%
Terminal rate	13/48 (27%)	14/43 (33%)	14/40 (35%)	12/42 (29%)	15/40 (38%)
First incidence (days)	727 (T)	530	418	427	626
Poly-3 test		P=0.242	P=0.136	P=0.526N	P=0.156
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	4/50 (8%)	8/50 (16%)	5/50 (10%)	6/50 (12%)	2/50 (4%)
Adjusted rate	8.2%	17.1%	11.1%	12.5%	4.4%
Terminal rate	4/48 (8%)	7/43 (16%)	5/40 (13%)	5/42 (12%)	2/40 (5%)
First incidence (days)	727 (T)	530	727 (T)	682	727 (T)
Poly-3 test		P=0.046N	P=0.299N	P=0.364N	P=0.049N
Lung: Alveolar/bronchiolar Carcinoma					
Overall rate	4/50 (8%)	5/50 (10%)	4/50 (8%)	1/50 (2%)	3/50 (6%)
Adjusted rate	8.2%	10.7%	8.9%	2.1%	6.6%
Terminal rate	4/48 (8%)	4/43 (9%)	4/40 (10%)	1/42 (2%)	3/40 (8%)
First incidence (days)	727 (T)	530	727 (T)	727 (T)	727 (T)
Poly-3 test		P=0.233N	P=0.522N	P=0.096N	P=0.368N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	8/50 (16%)	12/50 (24%)	9/50 (18%)	7/50 (14%)	4/50 (8%)
Adjusted rate	16.4%	25.7%	19.9%	14.5%	8.7%
Terminal rate	8/48 (17%)	11/43 (26%)	9/40 (23%)	6/42 (14%)	4/40 (10%)
First incidence (days)	727 (T)	530	727 (T)	682	727 (T)
Poly-3 test		P=0.018N	P=0.343N	P=0.136N	P=0.028N
Spleen: Hemangiosarcoma					
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	0.0%	6.3%	4.4%
Terminal rate	0/48 (0%)	0/43 (0%)	0/40 (0%)	3/42 (7%)	2/40 (5%)
First incidence (days)	—	—	—[f]	727 (T)	727 (T)
Poly-3 test		P=0.096		P=0.126	P=0.236

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
All Organs: Hemangiosarcoma					
Overall rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rate	4.1%	2.2%	0.0%	6.3%	6.6%
Terminal rate	2/48 (4%)	1/43 (2%)	0/40 (0%)	3/42 (7%)	3/40 (8%)
First incidence (days)	727 (T)	727 (T)	—	727 (T)	727 (T)
Poly-3 test		P=0.109	P=0.504N	P=0.320	P=0.303
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	4/50 (8%)	1/50 (2%)	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted rate	8.2%	2.2%	0.0%	8.3%	6.6%
Terminal rate	4/48 (8%)	1/43 (2%)	0/40 (0%)	4/42 (10%)	3/40 (8%)
First incidence (days)	727 (T)	727 (T)	—	727 (T)	727 (T)
Poly-3 test		P=0.111	P=0.504N	P=0.191	P=0.303
All Organs: Malignant Lymphoma					
Overall rate	4/50 (8%)	0/50 (0%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	8.0%	0.0%	4.4%	6.3%	2.2%
Terminal rate	2/48 (4%)	0/43 (0%)	1/40 (3%)	2/42 (5%)	0/40 (0%)
First incidence (days)	397	—	576	720	500
Poly-3 test		P=0.450	P=0.235	P=0.126	P=0.501
All Organs: Benign Neoplasms					
Overall rate	20/50 (40%)	20/50 (40%)	18/50 (36%)	21/50 (42%)	14/50 (28%)
Adjusted rate	41.0%	41.9%	38.6%	42.9%	30.3%
Terminal rate	20/48 (42%)	17/43 (40%)	15/40 (38%)	19/42 (45%)	12/40 (30%)
First incidence (days)	727 (T)	530	419	427	681
Poly-3 test		P=0.162N	P=0.453N	P=0.542	P=0.170N
All Organs: Malignant Neoplasms					
Overall rate	14/50 (28%)	18/50 (36%)	20/50 (40%)	17/50 (34%)	18/50 (36%)
Adjusted rate	28.0%	38.0%	41.2%	35.0%	37.6%
Terminal rate	12/48 (25%)	16/43 (37%)	12/40 (30%)	13/42 (31%)	12/40 (30%)
First incidence (days)	397	530	418	650	500
Poly-3 test		P=0.461N	P=0.456	P=0.465N	P=0.567N
All Organs: Benign or Malignant Neoplasms					
Overall rate	27/50 (54%)	28/50 (56%)	35/50 (70%)	33/50 (66%)	26/50 (52%)
Adjusted rate	54.0%	58.7%	70.0%	66.7%	54.1%
Terminal rate	25/48 (52%)	25/43 (58%)	25/40 (63%)	27/42 (64%)	19/40 (48%)
First incidence (days)	397	530	418	427	500
Poly-3 test		P=0.232N	P=0.169	P=0.272	P=0.404N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and spleen; 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 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 C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Citral[a]

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	1	4	2	6	3
Natural deaths	1	3	8	2	7
Survivors					
Died last week of study	1	1			
Terminal sacrifice	47	42	40	42	40
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Gallbladder	(50)	(50)	(48)	(48)	(49)
Epithelium, cytoplasmic alteration			1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Serosa, inflammation, granulomatous				1 (2%)	
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Ulcer				1 (2%)	
Intestine large, cecum	(50)	(50)	(50)	(50)	(50)
Edema				1 (2%)	
Serosa, inflammation, granulomatous	1 (2%)				
Intestine small, duodenum	(50)	(50)	(50)	(49)	(50)
Epithelium, hyperplasia, focal	1 (2%)				
Epithelium, hypertrophy	1 (2%)				
Epithelium, metaplasia, focal, squamous	1 (2%)				
Epithelium, necrosis, focal	2 (4%)				
Peyer's patch, inflammation, granulomatous			1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Muscularis, atrophy	1 (2%)				
Muscularis, inflammation, chronic				1 (2%)	1 (2%)
Peyer's patch, hyperplasia, lymphoid		1 (2%)		1 (2%)	
Peyer's patch, infiltration cellular, plasma cell				1 (2%)	
Peyer's patch, inflammation, suppurative	1 (2%)				
Serosa, inflammation, granulomatous	1 (2%)	2 (4%)			
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)	1 (2%)
Inflammation, granulomatous				1 (2%)	
Serosa, inflammation, granulomatous			1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis					2 (4%)
Basophilic focus			1 (2%)		
Clear cell focus	8 (16%)	9 (18%)	3 (6%)	7 (14%)	2 (4%)
Eosinophilic focus	3 (6%)	4 (8%)	2 (4%)	5 (10%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)		2 (4%)		
Infiltration cellular, mast cell	1 (2%)	1 (2%)			
Infiltration cellular, lymphocyte	2 (4%)	1 (2%)	4 (8%)	5 (10%)	4 (8%)
Inflammation, granulomatous	9 (18%)	7 (14%)	12 (24%)	12 (24%)	7 (14%)
Mixed cell focus	9 (18%)	10 (20%)	8 (16%)	9 (18%)	7 (14%)
Necrosis, focal	3 (6%)	1 (2%)	4 (8%)	5 (10%)	1 (2%)
Vacuolization cytoplasmic, focal	6 (12%)	11 (22%)	7 (14%)	4 (8%)	4 (8%)

[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 Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Alimentary System (continued)					
Liver (continued)	(50)	(50)	(50)	(50)	(50)
Bile duct, cyst			1 (2%)		
Bile duct, cytoplasmic alteration					1 (2%)
Bile duct, hyperplasia		1 (2%)			
Centrilobular, degeneration	1 (2%)	1 (2%)	1 (2%)		
Periportal, degeneration		1 (2%)			
Periportal, fibrosis					1 (2%)
Mesentery	(6)	(3)	(2)	(3)	(3)
Inflammation, chronic	1 (17%)	1 (33%)		1 (33%)	
Inflammation, granulomatous	3 (50%)	1 (33%)	1 (50%)		1 (33%)
Artery, inflammation, chronic			1 (50%)		1 (33%)
Fat, necrosis	1 (17%)	1 (33%)		2 (67%)	1 (33%)
Oral mucosa	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active	6 (12%)	12 (24%)	16 (32%)	21 (42%)	21 (42%)
Ulcer	4 (8%)	9 (18%)	8 (16%)	12 (24%)	10 (20%)
Pancreas	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)	
Duct, hypertrophy, focal		1 (2%)			
Stomach, forestomach	(50)	(50)	(49)	(50)	(50)
Inflammation, chronic				1 (2%)	
Inflammation, suppurative		2 (4%)			2 (4%)
Ulcer	1 (2%)			2 (4%)	
Epithelium, cyst		2 (4%)			
Epithelium, hyperkeratosis, diffuse	1 (2%)	1 (2%)			2 (4%)
Epithelium, hyperplasia, diffuse	1 (2%)			2 (4%)	
Epithelium, hyperplasia, focal	1 (2%)	5 (10%)		2 (4%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic, focal			1 (2%)		
Ulcer				2 (4%)	
Epithelium, hyperplasia, focal	2 (4%)				1 (2%)
Epithelium, inflammation, acute, focal		1 (2%)			
Glands, ectasia	1 (2%)	1 (2%)			
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Aorta, adventitia, inflammation, chronic				1 (2%)	
Heart	(50)	(50)	(50)	(50)	(50)
Artery, inflammation, chronic			1 (2%)		1 (2%)
Atrium, thrombosis		1 (2%)			
Coronary artery, inflammation, chronic	1 (2%)				1 (2%)
Myocardium, degeneration	1 (2%)	2 (4%)		3 (6%)	1 (2%)
Myocardium, inflammation, chronic				1 (2%)	
Valve, inflammation, chronic		2 (4%)	1 (2%)	1 (2%)	2 (4%)

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Fibrosis, focal	1 (2%)			1 (2%)	
Hyperplasia				1 (2%)	
Hyperplasia, focal	1 (2%)		3 (6%)	2 (4%)	5 (10%)
Hypertrophy		1 (2%)			
Hypertrophy, focal	25 (50%)	25 (50%)	17 (34%)	28 (56%)	22 (44%)
Inflammation, granulomatous			1 (2%)		
Mineralization, focal			1 (2%)		
Vacuolization cytoplasmic, focal	1 (2%)				1 (2%)
Subcapsular, hyperplasia	36 (72%)	42 (84%)	40 (80%)	47 (94%)	39 (78%)
Subcapsular, hyperplasia, focal	1 (2%)				
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Hyperplasia, focal				1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Hyperplasia	15 (30%)	18 (36%)	28 (56%)	30 (60%)	9 (18%)
Parathyroid gland	(43)	(43)	(39)	(44)	(37)
Cyst					2 (5%)
Hyperplasia, focal		1 (2%)			
Pituitary gland	(50)	(48)	(49)	(47)	(50)
Cyst	1 (2%)		1 (2%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal			1 (2%)		3 (6%)
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Granuloma sperm		1 (2%)			1 (2%)
Inflammation, chronic active	1 (2%)				
Inflammation, granulomatous				1 (2%)	
Preputial gland	(50)	(50)	(50)	(50)	(50)
Atrophy				1 (2%)	
Cyst	17 (34%)	14 (28%)	19 (38%)	18 (36%)	12 (24%)
Inflammation, granulomatous		3 (6%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative	2 (4%)	3 (6%)	2 (4%)	1 (2%)	4 (8%)
Prostate	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)		1 (2%)		
Artery, inflammation, chronic			1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	3 (6%)	
Testes	(50)	(50)	(50)	(50)	(50)
Germinal epithelium, degeneration	4 (8%)	2 (4%)		4 (8%)	4 (8%)
Germinal epithelium, mineralization			1 (2%)		1 (2%)
Tunic, mineralization				1 (2%)	1 (2%)

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Hyperplasia	9 (18%)	19 (38%)	18 (36%)	14 (28%)	14 (28%)
Inflammation, focal, suppurative	1 (2%)				
Lymph node, mandibular	(48)	(45)	(47)	(47)	(49)
Infiltration cellular, mast cell	1 (2%)				
Lymph node, mesenteric	(48)	(47)	(49)	(48)	(50)
Congestion				1 (2%)	
Hematopoietic cell proliferation					1 (2%)
Hyperplasia, lymphoid			1 (2%)		
Infiltration cellular, plasma cell	1 (2%)			1 (2%)	
Infiltration cellular, histiocyte	1 (2%)			1 (2%)	
Inflammation, granulomatous	1 (2%)			1 (2%)	
Spleen	(50)	(50)	(49)	(50)	(50)
Hematopoietic cell proliferation	17 (34%)	13 (26%)	18 (37%)	13 (26%)	11 (22%)
Infiltration cellular, mast cell	1 (2%)	1 (2%)			
Lymphoid follicle, atrophy	3 (6%)	4 (8%)	5 (10%)	3 (6%)	6 (12%)
Lymphoid follicle, hyperplasia	6 (12%)	8 (16%)	3 (6%)	3 (6%)	5 (10%)
Thymus	(50)	(49)	(48)	(48)	(46)
Atrophy	41 (82%)	43 (88%)	39 (81%)	32 (67%)	41 (89%)
Ectopic parathyroid gland			1 (2%)		
Hyperplasia, lymphoid			1 (2%)		
Inflammation, suppurative				1 (2%)	
Integumentary System					
Skin	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)	
Dermis, inflammation, chronic, focal				1 (2%)	
Epidermis, hyperplasia, focal	2 (4%)		1 (2%)		
Subcutaneous tissue, inflammation, granulomatous			1 (2%)	1 (2%)	
Subcutaneous tissue, inflammation, suppurative					1 (2%)
Subcutaneous tissue, necrosis			1 (2%)		
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Fibrosis		1 (2%)	3 (6%)		1 (2%)
Inflammation, granulomatous				1 (2%)	
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)	
Peripheral nerve				(1)	
Axon, degeneration				1 (100%)	

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Hemorrhage			6 (12%)	2 (4%)	
Inflammation, chronic, focal	1 (2%)				
Inflammation, granulomatous		1 (2%)		1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia				1 (2%)	
Alveolar epithelium, hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	1 (2%)				
Bronchiole, inflammation, suppurative	1 (2%)				
Serosa, fibrosis	2 (4%)			1 (2%)	
Serosa, fibrosis, focal		1 (2%)			
Serosa, inflammation, chronic		1 (2%)			
Nose	(50)	(50)	(50)	(50)	(50)
Infiltration cellular, mast cell	1 (2%)				
Inflammation, suppurative		1 (2%)	1 (2%)		
Sinus, inflammation, suppurative	1 (2%)				
Special Senses System					
Eye		(1)			
Anterior chamber, infiltration cellular, histiocyte		1 (100%)			
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Infarct	2 (4%)	8 (16%)	5 (10%)	6 (12%)	3 (6%)
Infiltration cellular, mast cell		1 (2%)			
Inflammation, granulomatous	1 (2%)			1 (2%)	
Inflammation, suppurative				1 (2%)	
Metaplasia, osseous	2 (4%)	3 (6%)	3 (6%)		1 (2%)
Nephropathy	45 (90%)	46 (92%)	36 (72%)	46 (92%)	38 (76%)
Artery, inflammation, chronic			1 (2%)		
Artery, inflammation, suppurative					1 (2%)
Capsule, inflammation, chronic				1 (2%)	
Papilla, hemorrhage	1 (2%)				
Pelvis, hemorrhage	1 (2%)				
Renal tubule, cyst	8 (16%)	4 (8%)	6 (12%)	6 (12%)	4 (8%)
Renal tubule, cytoplasmic alteration			1 (2%)		
Renal tubule, hyperplasia	2 (4%)		1 (2%)	2 (4%)	2 (4%)
Renal tubule, mineralization	45 (90%)	48 (96%)	43 (86%)	50 (100%)	33 (66%)
Urinary bladder	(50)	(50)	(49)	(50)	(50)
Inflammation, chronic			1 (2%)		
Transitional epithelium, cytoplasmic alteration			1 (2%)		1 (2%)
Transitional epithelium, hyperplasia		1 (2%)			1 (2%)

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

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Accidental death	1				
Moribund	4	5	2	4	5
Natural deaths	5	3	3	3	5
Survivors					
Terminal sacrifice	40	41	45	43	40
Missing		1			
Animals examined microscopically	50	49	50	50	50
Alimentary System					
Intestine large, rectum	(50)	(49)	(50)	(50)	(50)
Intestine large, cecum	(50)	(49)	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)		
Intestine small, jejunum	(50)	(49)	(50)	(50)	(50)
Carcinoma			1 (2%)		1 (2%)
Intestine small, ileum	(50)	(49)	(50)	(50)	(50)
Liver	(50)	(49)	(50)	(50)	(50)
Fibrous histiocytoma				1 (2%)	
Hemangiosarcoma				1 (2%)	
Hepatocellular carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hepatocellular carcinoma, multiple		1 (2%)			
Hepatocellular adenoma	5 (10%)	2 (4%)	2 (4%)	8 (16%)	7 (14%)
Hepatocellular adenoma, multiple		1 (2%)			1 (2%)
Histiocytic sarcoma					1 (2%)
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)	
Mesentery	(5)	(3)	(1)	(6)	(2)
Fibrous histiocytoma				1 (17%)	
Sarcoma, metastatic, skin				1 (17%)	
Pancreas	(50)	(49)	(50)	(50)	(50)
Salivary glands	(49)	(49)	(50)	(50)	(49)
Stomach, forestomach	(50)	(49)	(50)	(50)	(50)
Squamous cell carcinoma				1 (2%)	
Squamous cell papilloma	1 (2%)				2 (4%)
Stomach, glandular	(50)	(49)	(50)	(50)	(50)
Adenoma			1 (2%)		
Tongue		(1)			(1)
Squamous cell carcinoma		1 (100%)			1 (100%)
Cardiovascular System					
Heart	(50)	(49)	(50)	(50)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Endocrine System					
Adrenal cortex	(50)	(49)	(50)	(50)	(50)
Adrenal medulla	(50)	(49)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)				
Pituitary gland	(49)	(48)	(50)	(49)	(49)
Pars distalis, adenoma	4 (8%)	4 (8%)	5 (10%)	2 (4%)	3 (6%)
Pars intermedia, adenoma	1 (2%)	1 (2%)	1 (2%)		
Thyroid gland	(48)	(49)	(50)	(50)	(49)
Follicle, adenoma			1 (2%)		1 (2%)
General Body System					
None					
Genital System					
Clitoral gland	(47)	(48)	(50)	(47)	(49)
Carcinoma	1 (2%)				
Ovary	(50)	(49)	(50)	(49)	(50)
Carcinoma, metastatic, stomach, forestomach				1 (2%)	
Cystadenoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)	
Granulosa cell tumor benign	1 (2%)				
Histiocytic sarcoma					1 (2%)
Luteoma	1 (2%)				
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)	
Uterus	(50)	(49)	(50)	(50)	(50)
Adenoma			1 (2%)		
Carcinoma			1 (2%)		
Leiomyosarcoma					1 (2%)
Polyp stromal		2 (4%)	1 (2%)		1 (2%)
Hematopoietic System					
Bone marrow	(50)	(49)	(50)	(50)	(50)
Lymph node	(2)	(1)		(7)	(5)
Lumbar, histiocytic sarcoma					1 (20%)
Mediastinal, histiocytic sarcoma					1 (20%)
Mediastinal, sarcoma, metastatic, skin				1 (14%)	
Renal, histiocytic sarcoma					1 (20%)
Lymph node, mandibular	(49)	(49)	(48)	(47)	(44)
Histiocytic sarcoma					1 (2%)
Lymph node, mesenteric	(49)	(47)	(48)	(50)	(49)
Histiocytic sarcoma					1 (2%)
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)	
Spleen	(50)	(49)	(50)	(49)	(50)
Histiocytic sarcoma					1 (2%)
Thymus	(47)	(48)	(49)	(48)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Integumentary System					
Mammary gland	(50)	(49)	(50)	(49)	(49)
Carcinoma			1 (2%)		
Skin	(50)	(49)	(50)	(50)	(50)
Fibrous histiocytoma				1 (2%)	
Sebaceous gland, adenoma			1 (2%)		
Subcutaneous tissue, hemangioma	1 (2%)				
Subcutaneous tissue, sarcoma		2 (4%)	2 (4%)	1 (2%)	2 (4%)
Tail, sarcoma			1 (2%)		
Musculoskeletal System					
Bone	(50)	(49)	(50)	(50)	(50)
Fibrosarcoma	1 (2%)				
Skeletal muscle	(1)	(1)		(1)	(2)
Sarcoma	1 (100%)				
Nervous System					
Brain	(50)	(48)	(50)	(50)	(50)
Respiratory System					
Lung	(50)	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	7 (14%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma	3 (6%)	3 (6%)	1 (2%)		
Carcinoma, metastatic, harderian gland	1 (2%)				
Fibrous histiocytoma				1 (2%)	
Hepatocellular carcinoma, metastatic, liver		1 (2%)			
Histiocytic sarcoma					1 (2%)
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)				
Sarcoma, metastatic, skin		1 (2%)			
Nose	(50)	(49)	(50)	(50)	(50)
Special Senses System					
Harderian gland	(2)	(3)	(2)	(3)	(1)
Adenoma	1 (50%)	2 (67%)	1 (50%)	2 (67%)	1 (100%)
Carcinoma	1 (50%)			1 (33%)	
Urinary System					
Kidney	(50)	(49)	(50)	(50)	(50)
Histiocytic sarcoma					1 (2%)
Urinary bladder	(50)	(49)	(50)	(50)	(50)
Systemic Lesions					
Multiple organs[b]	(50)	(49)	(50)	(50)	(50)
Histiocytic sarcoma					1 (2%)
Lymphoma malignant	4 (8%)	3 (6%)	5 (10%)	9 (18%)	12 (24%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Neoplasm Summary					
Total animals with primary neoplasms[c]	23	22	27	23	30
Total primary neoplasms	32	28	36	34	36
Total animals with benign neoplasms	16	12	19	13	14
Total benign neoplasms	19	16	22	16	17
Total animals with malignant neoplasms	12	12	13	13	18
Total malignant neoplasms	13	12	14	18	19
Total animals with metastatic neoplasms	2	2		2	
Total metastatic neoplasms	2	2		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 D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: Untreated Control

Number of Days on Study	0 0 9	2 4 2	2 4 2	2 4 3	5 4 4	5 4 5	5 5 7	6 6 0	7 0 9	7 2 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	7 3 4
Carcass ID Number	2 8 7	2 5 3	2 5 4	2 5 2	2 6 9	2 6 7	2 6 4	2 7 6	2 5 6	2 9 6	2 5 5	2 6 0	2 6 2	2 6 3	2 7 5	2 7 9	2 8 1	2 8 3	2 8 6	2 8 9	2 9 1	2 9 2	2 9 3	2 9 4	2 5 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																									
Hepatocellular adenoma																				X		X			
Mesentery							+	+	+																
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant						X																			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																							X		
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Carcinoma											X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign														X											
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: 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 Citral: Untreated Control

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	257	265	266	268	271	272	274	277	285	288	295	297	258	259	261	270	273	278	280	282	284	290	298	299	300	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																						X				1
Hepatocellular adenoma	X							X								X										5
Mesentery			+												+											5
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma									X																	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth															+											1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	43
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma											X						X					X				4
Pars intermedia, adenoma															X											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																			X							1
Granulosa cell tumor benign																										1
Luteoma																					X					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

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 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	
Carcass ID Number	2 5 7	2 6 5	2 6 6	2 6 8	2 7 1	2 7 2	2 7 4	2 7 7	2 8 5	2 8 8	2 9 5	2 9 7	2 5 8	2 5 9	2 6 1	2 7 0	2 7 3	2 7 8	2 8 0	2 8 2	2 8 4	2 9 0	2 9 8	2 9 9	3 0 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node															+											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma										X																1
Skeletal muscle																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X												X						3
Alveolar/bronchiolar carcinoma											X	X												X		3
Carcinoma, metastatic, harderian gland															X											1
Pheochromocytoma malignant, metatastic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland															+											2
Adenoma																										1
Carcinoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant									X						X											4

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

Number of Days on Study	4 4 1	4 7 0	6 2 5	6 3 3	6 8 0	6 8 8	7 0 9	7 1 9	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	7 3 4	7 3 4	7 3 4
Carcass ID Number	3 4 2	3 4 6	3 1 5	3 2 8	3 3 2	3 1 4	3 0 2	3 2 4	3 0 4	3 0 8	3 1 2	3 1 7	3 1 8	3 1 9	3 2 0	3 2 2	3 2 6	3 3 3	3 3 8	3 4 0	3 4 1	3 4 1	3 0 1	3 0 3	3 0 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 carcinoma					X																				
Hepatocellular carcinoma, multiple							X																		
Hepatocellular adenoma																					X				
Hepatocellular adenoma, multiple																									
Mesentery	+																		+						
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	M	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma																	X								
Pars intermedia, adenoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									

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

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 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 5	7 3 5	7 3 5	
Carcass ID Number	3 0 7	3 1 1	3 1 3	3 2 7	3 3 4	3 3 5	3 4 4	3 4 8	3 5 0	3 0 6	3 0 9	3 1 0	3 1 6	3 2 1	3 2 3	3 2 5	3 2 9	3 3 1	3 3 6	3 3 7	3 3 9	3 4 3	3 4 5	3 4 7	3 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Hepatocellular carcinoma									X																	2
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X																							2
Hepatocellular adenoma, multiple										X																1
Mesentery			+																							3
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue				+																						1
Squamous cell carcinoma				X																						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma						X																	X	X		4
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																							X			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal																								X	X	2

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

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

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

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 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 5	7 3 5	
Carcass ID Number	3 0 7	3 1 1	3 1 3	3 2 7	3 3 4	3 3 5	3 4 4	3 4 8	3 5 0	3 0 6	3 0 9	3 1 0	3 1 6	3 2 1	3 2 3	3 2 5	3 2 9	3 3 1	3 3 6	3 3 7	3 3 9	3 4 3	3 4 5	3 4 7	3 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																									X	2
Alveolar/bronchiolar carcinoma					X														X							3
Hepatocellular carcinoma, metastatic, liver																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland	+		+																							3
Adenoma	X																									2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant			X																							3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 500 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 500 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 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 5	
Carcass ID Number	3 7 1	3 7 2	3 7 4	3 7 6	3 7 8	3 7 9	3 8 6	3 8 7	3 8 9	3 9 1	3 9 2	3 9 9	4 0 0	3 5 9	3 6 2	3 6 6	3 6 8	3 6 9	3 7 0	3 8 5	3 8 8	3 9 3	3 9 4	3 9 7	3 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																									X	1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma			X																				X			2
Mesentery																										1
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X				X																	X			5
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicle, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																								X		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Carcinoma																										1
Polyp stromal					X																					1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 500 ppm

Number of Days on Study	4 1 3	6 0 0	6 1 5	6 5 3	6 9 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 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 8 1	3 9 5	3 5 7	3 6 3	3 6 7	3 5 4	3 6 0	3 6 4	3 6 5	3 7 3	3 7 5	3 7 7	3 8 0	3 8 2	3 8 3	3 8 4	3 9 0	3 9 6	3 5 1	3 5 2	3 5 3	3 5 5	3 5 6	3 5 8	3 6 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X																						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																									
Subcutaneous tissue, sarcoma																									
Tail, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland										+							+								
Adenoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant															X		X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 500 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 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 5	
Carcass ID Number	3 7 1	3 7 2	3 7 4	3 7 6	3 7 8	3 7 9	3 8 6	3 8 7	3 8 9	3 9 1	3 9 2	3 9 9	4 0 0	3 5 9	3 6 2	3 6 6	3 6 8	3 6 9	3 7 0	3 8 5	3 8 8	3 9 3	3 9 4	3 9 7	3 9 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, adenoma																					X					1
Subcutaneous tissue, sarcoma														X									X			2
Tail, sarcoma																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X						X			X			X	X									7
Alveolar/bronchiolar carcinoma									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										2
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant				X	X								X													5

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 1,000 ppm

Number of Days on Study	4	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	7	1	2	4	0	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	5	8	5	5	9	7	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	1	1	0	1	3	2	0	1	1	1	2	2	2	3	3	3	4	4	4	4	5	0	0	0
	3	8	1	7	4	8	0	2	3	5	9	2	6	8	3	5	7	1	2	4	5	0	3	5	6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma										X															
Hemangiosarcoma																									
Hepatocellular carcinoma			X																						
Hepatocellular adenoma										X		X	X							X		X			
Squamous cell carcinoma, metastatic, stomach, forestomach							X																		
Mesentery										+						+		+							
Fibrous histiocytoma										X															
Sarcoma, metastatic, skin																									
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, stomach, forestomach							X																		
Cystadenoma																				X					
Squamous cell carcinoma, metastatic, stomach, forestomach							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 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 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 5	7 3 5	
Carcass ID Number	4 0 8	4 1 0	4 1 6	4 2 7	4 3 6	4 3 9	4 4 0	4 4 3	4 4 9	4 0 1	4 0 4	4 0 9	4 1 2	4 1 7	4 2 1	4 2 4	4 2 5	4 2 9	4 3 0	4 3 1	4 3 2	4 3 4	4 4 6	4 4 7	4 4 8	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
Fibrous histiocytoma																										1
Hemangiosarcoma								X																		1
Hepatocellular carcinoma																										1
Hepatocellular adenoma			X													X	X									8
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Mesentery	+					+											+									6
Fibrous histiocytoma																										1
Sarcoma, metastatic, skin	X																									1
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	M	+	M	+	+	+	M	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																	X								X	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, stomach, forestomach																										1
Cystadenoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	4 6 9	5 7 5	6 1 8	6 2 5	6 4 5	7 0 9	7 1 7	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	7 3 3	7 3 4	7 4 4	7 3 4
Carcass ID Number	4 2 3	4 1 8	4 1 1	4 0 7	4 1 4	4 3 8	4 2 0	4 0 2	4 1 3	4 1 5	4 1 9	4 2 2	4 2 6	4 2 8	4 3 3	4 3 5	4 3 7	4 4 1	4 4 2	4 4 4	4 4 5	4 5 0	4 0 3	4 0 5	4 0 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+					+				+				+	+										
Mediastinal, sarcoma, metastatic, skin																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach							X																		
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma										X															
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Fibrous histiocytoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X					X				X				X	X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 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 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 5	7 3 5	
Carcass ID Number	4 0 8	4 1 0	4 1 6	4 2 7	4 3 6	4 3 9	4 4 0	4 4 3	4 4 9	4 0 1	4 0 4	4 0 9	4 1 2	4 1 7	4 2 1	4 2 4	4 2 5	4 2 9	4 3 0	4 3 1	4 3 2	4 3 4	4 4 6	4 4 7	4 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+																							7
Mediastinal, sarcoma, metastatic, skin	X																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Subcutaneous tissue, sarcoma	X																									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+																									1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X										X										3
Fibrous histiocytoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland				+						+			+													3
Adenoma										X			X													2
Carcinoma				X																						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X		X			X		X																9

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 2,000 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 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	
Carcass ID Number	4 5 2	4 5 8	4 6 2	4 6 6	4 6 7	4 7 2	4 7 3	4 7 4	4 7 8	4 8 2	4 8 7	4 9 3	4 5 3	4 5 5	4 6 4	4 6 8	4 7 0	4 7 7	4 7 9	4 8 0	4 8 3	4 8 6	4 9 0	4 9 2	4 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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma											X															1
Hepatocellular adenoma					X											X										7
Hepatocellular adenoma, multiple										X																1
Histiocytic sarcoma																										1
Mesentery											+															2
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma									X								X									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																									X	3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicle, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma													X													1
Polyp stromal																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Citral: 2,000 ppm

Number of Days on Study	264	491	523	557	576	597	628	656	700	706	733	733	733	733	733	733	733	733	733	733	733	733	733	733	734
Carcass ID Number	457	484	461	475	500	459	491	494	495	459	454	456	460	463	465	469	471	476	481	485	488	489	497	498	451
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+			+													
Lumbar, histiocytic sarcoma									X																
Mediastinal, histiocytic sarcoma									X																
Renal, histiocytic sarcoma									X																
Lymph node, mandibular	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma				X						X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+						+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve					+	+																			
Spinal cord					+	+																			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Histiocytic sarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
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 Citral: 2,000 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 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	
Carcass ID Number	4 5 2	4 5 8	4 6 2	4 6 6	4 6 7	4 7 2	4 7 3	4 7 4	4 7 8	4 8 2	4 8 7	4 9 3	4 5 3	4 5 5	4 6 4	4 6 8	4 7 0	4 7 7	4 7 9	4 8 0	4 8 3	4 8 6	4 9 0	4 9 2	4 9 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+														+							+				5
Lumbar, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland	+																									1
Adenoma	X																									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant	X	X					X								X				X			X	X			12

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Harderian Gland: Adenoma or Carcinoma					
Overall rate[a]	2/50 (4%)	2/49 (4%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate[b]	4.6%	4.3%	2.1%	6.3%	2.2%
Terminal rate[c]	2/40 (5%)	2/41 (5%)	1/45 (2%)	3/43 (7%)	1/40 (3%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)	733 (T)
Poly-3 test[d]		P=0.489N	P=0.488N	P=0.512	P=0.507N
Liver: Hepatocellular Adenoma					
Overall rate	5/50 (10%)	3/49 (6%)	2/50 (4%)	8/50 (16%)	8/50 (16%)
Adjusted rate	11.4%	6.5%	4.2%	16.9%	17.6%
Terminal rate	5/40 (13%)	3/41 (7%)	2/45 (4%)	8/43 (19%)	7/40 (18%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)	656
Poly-3 test		P=0.023	P=0.484N	P=0.107	P=0.094
Liver: Hepatocellular Carcinoma					
Overall rate	1/50 (2%)	3/49 (6%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	2.3%	6.5%	2.1%	2.1%	2.2%
Terminal rate	1/40 (3%)	1/41 (2%)	1/45 (2%)	0/43 (0%)	1/40 (3%)
First incidence (days)	733 (T)	680	733 (T)	618	733 (T)
Poly-3 test		P=0.246N	P=0.295N	P=0.295N	P=0.315N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	6/50 (12%)	6/49 (12%)	3/50 (6%)	9/50 (18%)	9/50 (18%)
Adjusted rate	13.7%	12.9%	6.3%	18.8%	19.8%
Terminal rate	6/40 (15%)	4/41 (10%)	3/45 (7%)	8/43 (19%)	8/40 (20%)
First incidence (days)	733 (T)	680	733 (T)	618	656
Poly-3 test		P=0.097	P=0.228N	P=0.309	P=0.272
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	3/50 (6%)	2/49 (4%)	7/50 (14%)	3/50 (6%)	1/50 (2%)
Adjusted rate	6.8%	4.3%	14.6%	6.3%	2.2%
Terminal rate	3/40 (8%)	2/41 (5%)	7/45 (16%)	3/43 (7%)	0/40 (0%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)	656
Poly-3 test		P=0.184N	P=0.088	P=0.512	P=0.505N
Lung: Alveolar/bronchiolar Carcinoma					
Overall rate	3/50 (6%)	3/49 (6%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.8%	6.5%	2.1%	0.0%	0.0%
Terminal rate	3/40 (8%)	3/41 (7%)	1/45 (2%)	0/43 (0%)	0/40 (0%)
First incidence (days)	733 (T)	733 (T)	733 (T)	—[e]	—
Poly-3 test		P=0.043N	P=0.293N	P=0.114N	P=0.122N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	6/50 (12%)	5/49 (10%)	8/50 (16%)	3/50 (6%)	1/50 (2%)
Adjusted rate	13.7%	10.8%	16.7%	6.3%	2.2%
Terminal rate	6/40 (15%)	5/41 (12%)	8/45 (18%)	3/43 (7%)	0/40 (0%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)	656
Poly-3 test		P=0.033N	P=0.299	P=0.342N	P=0.105N
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	4/49 (8%)	4/48 (8%)	5/50 (10%)	2/49 (4%)	3/49 (6%)
Adjusted rate	9.3%	8.9%	10.4%	4.3%	6.7%
Terminal rate	4/39 (10%)	4/40 (10%)	5/45 (11%)	2/42 (5%)	3/40 (8%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)	733 (T)
Poly-3 test		P=0.328N	P=0.536	P=0.325N	P=0.504N

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
All Organs: Malignant Lymphoma					
Overall rate	4/50 (8%)	3/49 (6%)	5/50 (10%)	9/50 (18%)	12/50 (24%)
Adjusted rate	9.1%	6.5%	10.4%	18.6%	25.7%
Terminal rate	4/40 (10%)	2/41 (5%)	5/45 (11%)	7/43 (16%)	10/40 (25%)
First incidence (days)	733 (T)	719	733 (T)	469	491
Poly-3 test		P=0.004	P=0.376	P=0.070	P=0.011
All Organs: Benign Neoplasms					
Overall rate	16/50 (32%)	12/49 (24%)	19/50 (38%)	13/50 (26%)	14/50 (28%)
Adjusted rate	36.4%	26.0%	39.7%	27.4%	30.7%
Terminal rate	16/40 (40%)	12/41 (29%)	19/45 (42%)	13/43 (30%)	13/40 (33%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)	656
Poly-3 test		P=0.537	P=0.115	P=0.531	P=0.392
All Organs: Malignant Neoplasms					
Overall rate	12/50 (24%)	12/49 (24%)	13/50 (26%)	13/50 (26%)	18/50 (36%)
Adjusted rate	26.9%	25.5%	26.9%	26.7%	38.0%
Terminal rate	11/40 (28%)	7/41 (17%)	12/45 (27%)	9/43 (21%)	13/40 (33%)
First incidence (days)	545	625	615	469	491
Poly-3 test		P=0.100	P=0.528	P=0.540	P=0.138
All Organs: Benign or Malignant Neoplasms					
Overall rate	23/50 (46%)	22/49 (45%)	27/50 (54%)	23/50 (46%)	30/50 (60%)
Adjusted rate	51.6%	46.7%	55.9%	47.2%	62.9%
Terminal rate	22/40 (55%)	17/41 (42%)	26/45 (58%)	19/43 (44%)	24/40 (60%)
First incidence (days)	545	625	615	469	491
Poly-3 test		P=0.100	P=0.243	P=0.563	P=0.081

(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 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

TABLE D4
Historical Incidence of Malignant Lymphoma in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
Acrylonitrile (gavage)	4/50
Citral (feed)	7/99
p,p′-Dichlorodiphenyl sulfone (feed)	6/50
Indium phosphide (inhalation)	8/50
60-Hz Magnetic fields (whole body exposure)	32/100
Methacrylonitrile (gavage)	9/50
o-Nitrotoluene (feed)	8/60
p-Nitrotoluene (feed)	3/50
Riddelliine (gavage)	7/50
Sodium nitrite (drinking water)	7/50
Vanadium pentoxide (inhalation)	7/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	98/659 (14.9%)
Mean ± standard deviation	14.0% ± 7.1%
Range	6%-32%
Historical Incidence in Feed Controls Given NIH-07 Diet at Battelle Columbus Laboratories[b]	
Anthraquinone	14/50
4,4′-Thiobis-(6-*t*-butyl-*m*-cresol)	13/51
Manganese (II) sulfate monohydrate	15/51
Oxazepam	3/50
Primidone	8/50
Triamterene	12/50
Triamterene	9/50
Tricresyl phosphate	4/50
Overall Historical Incidence in Feed Controls Given NIH-07 Diet	
Total (%)	167/953 (17.5%)
Mean ± standard deviation	17.5% ± 7.7%
Range	6%-30%

[a] Data as of December 22, 2000; includes histiocytic, lymphocytic, mixed, unspecified, and undifferentiated cell type malignant lymphoma
[b] Data as of December 23, 1999; includes histiocytic, lymphocytic, mixed, unspecified, and undifferentiated cell type malignant lymphoma

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

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Accidental death	1				
Moribund	4	5	2	4	5
Natural deaths	5	3	3	3	5
Survivors					
Terminal sacrifice	40	41	45	43	40
Missing		1			
Animals examined microscopically	50	49	50	50	50
Alimentary System					
Esophagus	(50)	(49)	(50)	(50)	(50)
Hyperplasia, basal cell		1 (2%)			
Intestine small, duodenum	(50)	(49)	(50)	(50)	(49)
Ectasia	1 (2%)				
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Ulcer				1 (2%)	
Epithelium, hyperplasia, focal	1 (2%)	1 (2%)			
Epithelium, metaplasia, squamous	1 (2%)				
Intestine small, jejunum	(50)	(49)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)			
Ulcer		1 (2%)			1 (2%)
Muscularis, infiltration cellular, lymphocyte					1 (2%)
Peyer's patch, hyperplasia, lymphoid	2 (4%)			2 (4%)	
Peyer's patch, infiltration cellular, plasma cell				1 (2%)	
Intestine small, ileum	(50)	(49)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)				
Inflammation, granulomatous	1 (2%)				
Ulcer	1 (2%)				
Liver	(50)	(49)	(50)	(50)	(50)
Basophilic focus				1 (2%)	
Clear cell focus	3 (6%)		2 (4%)	6 (12%)	
Eosinophilic focus			1 (2%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		3 (6%)	
Hemorrhage		1 (2%)		1 (2%)	
Infarct		1 (2%)			
Infiltration cellular, lymphocyte	16 (32%)	18 (37%)	12 (24%)	27 (54%)	25 (50%)
Inflammation, granulomatous	20 (40%)	14 (29%)	20 (40%)	16 (32%)	11 (22%)
Mineralization		1 (2%)			
Mixed cell focus	4 (8%)	5 (10%)	1 (2%)	4 (8%)	3 (6%)
Necrosis, focal	2 (4%)	3 (6%)	2 (4%)	3 (6%)	
Vacuolization cytoplasmic, focal	4 (8%)	3 (6%)	5 (10%)	3 (6%)	5 (10%)
Bile duct, cyst			1 (2%)		
Bile duct, inflammation, granulomatous	1 (2%)				
Centrilobular, degeneration	1 (2%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Alimentary System (continued)					
Mesentery	(5)	(3)	(1)	(6)	(2)
Infiltration cellular, mast cell	1 (20%)				
Inflammation, granulomatous	1 (20%)			1 (17%)	
Thrombosis					1 (50%)
Artery, inflammation, chronic		1 (33%)		1 (17%)	
Fat, necrosis	3 (60%)	2 (67%)	1 (100%)	2 (33%)	1 (50%)
Oral mucosa	(50)	(49)	(50)	(50)	(50)
Infiltration cellular, mast cell	1 (2%)			1 (2%)	
Inflammation, chronic active	20 (40%)	14 (29%)	32 (64%)	35 (70%)	32 (64%)
Ulcer	6 (12%)	6 (12%)	15 (30%)	22 (44%)	15 (30%)
Pancreas	(50)	(49)	(50)	(50)	(50)
Fibrosis, focal			1 (2%)		
Hypertrophy, focal		1 (2%)			
Infiltration cellular, mast cell	1 (2%)				
Inflammation, chronic			1 (2%)		
Acinus, atrophy	1 (2%)				2 (4%)
Acinus, hypertrophy, focal	1 (2%)			2 (4%)	
Duct, cyst	2 (4%)	1 (2%)	1 (2%)		1 (2%)
Duct, inflammation, chronic	1 (2%)				
Salivary glands	(49)	(49)	(50)	(50)	(49)
Artery, inflammation, chronic		1 (2%)		1 (2%)	
Parotid gland, inflammation, chronic		1 (2%)			
Stomach, forestomach	(50)	(49)	(50)	(50)	(50)
Edema, diffuse					1 (2%)
Edema, focal	1 (2%)				
Infiltration cellular, lymphocyte	1 (2%)				
Inflammation, chronic, focal			1 (2%)		
Ulcer	1 (2%)	1 (2%)	1 (2%)		2 (4%)
Epithelium, hyperplasia, focal	3 (6%)	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Stomach, glandular	(50)	(49)	(50)	(50)	(50)
Edema, diffuse					1 (2%)
Mineralization		1 (2%)			
Ulcer	1 (2%)	1 (2%)			
Artery, inflammation, chronic	1 (2%)				
Epithelium, hyperplasia, atypical, focal		1 (2%)			
Glands, ectasia		1 (2%)			1 (2%)
Muscularis, inflammation, acute		1 (2%)			
Tooth	(1)				
Pulp, inflammation, chronic	1 (100%)				
Cardiovascular System					
Blood vessel	(50)	(49)	(50)	(50)	(50)
Aorta, mineralization		1 (2%)	1 (2%)	1 (2%)	
Aorta, adventitia, inflammation, chronic	1 (2%)				
Pulmonary vein, hemorrhage	1 (2%)				
Heart	(50)	(49)	(50)	(50)	(50)
Artery, inflammation, chronic		1 (2%)	2 (4%)	1 (2%)	2 (4%)
Artery, mineralization			1 (2%)		
Atrium, inflammation, chronic			1 (2%)		1 (2%)
Atrium, thrombosis		1 (2%)			
Coronary artery, inflammation, chronic			1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Cardiovascular System (continued)					
Heart (continued)	(50)	(49)	(50)	(50)	(50)
Myocardium, degeneration	3 (6%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Myocardium, inflammation, chronic					1 (2%)
Myocardium, mineralization			1 (2%)	1 (2%)	
Valve, inflammation, chronic	2 (4%)	2 (4%)	4 (8%)		1 (2%)
Endocrine System					
Adrenal cortex	(50)	(49)	(50)	(50)	(50)
Accessory adrenal cortical nodule				1 (2%)	
Atrophy			1 (2%)		
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)		
Hyperplasia, focal	1 (2%)			2 (4%)	2 (4%)
Hypertrophy, focal	3 (6%)	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, granulomatous					1 (2%)
Vacuolization cytoplasmic, focal			1 (2%)		
Subcapsular, hyperplasia	47 (94%)	49 (100%)	50 (100%)	49 (98%)	49 (98%)
Subcapsular, hyperplasia, focal					1 (2%)
Adrenal medulla	(50)	(49)	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)	1 (2%)		2 (4%)	2 (4%)
Islets, pancreatic	(50)	(49)	(50)	(50)	(50)
Hyperplasia	2 (4%)		3 (6%)	1 (2%)	2 (4%)
Parathyroid gland	(43)	(42)	(35)	(40)	(43)
Inflammation, granulomatous	1 (2%)				
Pituitary gland	(49)	(48)	(50)	(49)	(49)
Angiectasis					1 (2%)
Cyst			1 (2%)	1 (2%)	
Pars distalis, hyperplasia, focal	7 (14%)	7 (15%)	7 (14%)	10 (20%)	9 (18%)
Pars nervosa, mineralization			1 (2%)		
Thyroid gland	(48)	(49)	(50)	(50)	(49)
Inflammation, chronic, focal		1 (2%)			
Inflammation, granulomatous	2 (4%)				
Follicle, hyperplasia			1 (2%)		
General Body System					
None					
Genital System					
Clitoral gland	(47)	(48)	(50)	(47)	(49)
Cyst			1 (2%)		
Inflammation, granulomatous			1 (2%)		
Inflammation, suppurative					1 (2%)
Ovary	(50)	(49)	(50)	(49)	(50)
Angiectasis		1 (2%)		2 (4%)	
Cyst	19 (38%)	20 (41%)	23 (46%)	16 (33%)	17 (34%)
Dysplasia, focal	1 (2%)	1 (2%)			
Necrosis, focal	1 (2%)				
Thrombosis			2 (4%)		
Interstitial cell, hyperplasia				1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Genital System (continued)					
Uterus	(50)	(49)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)		
Thrombosis		1 (2%)		1 (2%)	
Ulcer				1 (2%)	
Endometrium, hyperplasia, cystic	43 (86%)	45 (92%)	43 (86%)	44 (88%)	35 (70%)
Hematopoietic System					
Bone marrow	(50)	(49)	(50)	(50)	(50)
Hyperplasia	2 (4%)	11 (22%)	6 (12%)	6 (12%)	13 (26%)
Lymph node	(2)	(1)		(7)	(5)
Lumbar, hyperplasia, lymphoid				1 (14%)	
Pancreatic, hyperplasia, lymphoid				1 (14%)	
Renal, hyperplasia, lymphoid				1 (14%)	
Lymph node, mandibular	(49)	(49)	(48)	(47)	(44)
Amyloid deposition	1 (2%)				
Hyperplasia, lymphoid		1 (2%)			
Lymph node, mesenteric	(49)	(47)	(48)	(50)	(49)
Atrophy	1 (2%)				
Fibrosis	1 (2%)				
Hematopoietic cell proliferation		1 (2%)			
Hyperplasia, lymphoid	1 (2%)		1 (2%)		
Infiltration cellular, plasma cell	3 (6%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, polymorphonuclear				1 (2%)	
Inflammation, granulomatous	1 (2%)				
Spleen	(50)	(49)	(50)	(49)	(50)
Hematopoietic cell proliferation	17 (34%)	14 (29%)	19 (38%)	10 (20%)	19 (38%)
Lymphoid follicle, atrophy	8 (16%)	4 (8%)	7 (14%)	2 (4%)	4 (8%)
Lymphoid follicle, hyperplasia	8 (16%)	14 (29%)	7 (14%)	12 (24%)	13 (26%)
Thymus	(47)	(48)	(49)	(48)	(50)
Atrophy	26 (55%)	31 (65%)	33 (67%)	24 (50%)	19 (38%)
Hyperplasia, lymphoid	11 (23%)	7 (15%)	5 (10%)	16 (33%)	14 (28%)
Integumentary System					
Mammary gland	(50)	(49)	(50)	(49)	(49)
Hyperplasia		1 (2%)			
Hyperplasia, cystic	1 (2%)				1 (2%)
Skin	(50)	(49)	(50)	(50)	(50)
Necrosis		1 (2%)			
Dermis, fibrosis, focal	1 (2%)				
Subcutaneous tissue, fibrosis				1 (2%)	
Musculoskeletal System					
Bone	(50)	(49)	(50)	(50)	(50)
Fibrosis	19 (38%)	11 (22%)	22 (44%)	21 (42%)	18 (36%)
Fracture	1 (2%)				
Joint, inflammation, chronic				1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Nervous System					
Brain	(50)	(48)	(50)	(50)	(50)
Hemorrhage, focal	1 (2%)				
Hydrocephalus			1 (2%)	1 (2%)	
Necrosis, focal	1 (2%)				
Artery, meninges, inflammation, chronic				1 (2%)	
Hypothalamus, compression		1 (2%)			1 (2%)
Meninges, inflammation, acute	1 (2%)				
Peripheral nerve		(1)			(2)
Axon, degeneration		1 (100%)			2 (100%)
Spinal cord		(1)			(2)
Artery, inflammation, chronic		1 (100%)			
Axon, degeneration		1 (100%)			1 (50%)
Respiratory System					
Lung	(50)	(49)	(50)	(50)	(50)
Hemorrhage	1 (2%)		2 (4%)	1 (2%)	
Inflammation, acute, focal				1 (2%)	
Inflammation, granulomatous	1 (2%)		2 (4%)	3 (6%)	2 (4%)
Metaplasia, osseous				1 (2%)	
Mineralization		1 (2%)			
Alveolar epithelium, hyperplasia, focal	2 (4%)		3 (6%)	2 (4%)	2 (4%)
Alveolus, inflammation, chronic, focal	1 (2%)				
Nose	(50)	(49)	(50)	(50)	(50)
Hemorrhage		1 (2%)			
Inflammation, suppurative					1 (2%)
Trachea	(50)	(49)	(50)	(50)	(49)
Glands, inflammation, suppurative	1 (2%)				
Special Senses System					
Eye	(1)				
Synechia	1 (100%)				
Retrobulbar, fibrosis	1 (100%)				
Urinary System					
Kidney	(50)	(49)	(50)	(50)	(50)
Hydronephrosis	1 (2%)				
Infarct	4 (8%)	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Inflammation, suppurative			1 (2%)		
Metaplasia, osseous			3 (6%)	1 (2%)	
Nephropathy	13 (26%)	9 (18%)	16 (32%)	15 (30%)	17 (34%)
Artery, inflammation, chronic		1 (2%)			
Artery, mineralization			1 (2%)		
Capsule, inflammation, granulomatous				1 (2%)	
Glomerulus, inflammation, chronic	1 (2%)				
Papilla, fibrosis, focal		1 (2%)			
Papilla, necrosis				1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Citral

	Untreated Control	Vehicle Control	500 ppm	1,000 ppm	2,000 ppm
Urinary System (continued)					
Kidney (continued)	(50)	(49)	(50)	(50)	(50)
Pelvis, inflammation, granulomatous	1 (2%)				
Renal tubule, cyst	1 (2%)	1 (2%)			
Renal tubule, cytoplasmic alteration					1 (2%)
Renal tubule, degeneration, focal				1 (2%)	
Renal tubule, mineralization	3 (6%)	4 (8%)	14 (28%)	18 (36%)	6 (12%)
Renal tubule, necrosis			1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)				

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al*. (1987). Citral was sent to the laboratory as a coded aliquot by Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37º 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 37º C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of citral. 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). Citral 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 four doses of citral; 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 26 hours with citral in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing citral 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 citral, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no citral. Incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant citral-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

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 citral for 8.5 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 citral and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 18.5 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. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: because cell cycle delay was anticipated in the presence of S9 at the concentrations tested, the incubation period was extended.

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 ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) 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.

Mouse Bone Marrow Micronucleus Test Protocol

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by citral exposure. The standard three-exposure protocol is described in detail by Shelby *et al*. (1993). Male $B6C3F_1$ mice were injected intraperitoneally three times at 24-hour intervals with 250 to 1,000 mg citral/kg body weight dissolved in corn oil. Solvent control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of four or five animals per dose group.

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

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented by MacGregor *et al*. (1990). At the end of the 14-week 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 normochromatic erythrocytes (NCEs) per animal. In addition, the percentage of PCEs among the total erythrocyte population in the peripheral blood was scored for each exposure group as a measure of toxicity.

The results for NCEs were tabulated as described for PCEs in the bone marrow micronucleus test. Results of the 14-week studies were accepted without repeat tests, because additional test data could not be obtained.

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

Citral (1 to 220 μg/plate) was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without Aroclor-induced rat or hamster liver S9 enzymes (Table E1; Zeiger *et al*., 1987). In cytogenetic tests with CHO cells, citral induced SCEs with and without S9 (Table E2); citral was toxic to these cells, and higher doses required an extended culture period to permit accumulation of sufficient second-division metaphase cells for analysis. In contrast to the positive results in the SCE assay, Abs were not significantly increased after exposure to citral, with or without S9 (Table E3). As a result of citral-induced cell cycle delay, the cultures treated in the presence of S9 were permitted to grow for a longer than normal period of time to allow additional accumulation of first-division metaphase cells for analysis. Negative results were obtained in an *in vivo* bone marrow micronucleus test in male B6C3F_1 mice treated by intraperitoneal injection with 250 to 750 mg/kg citral daily for 3 days (Table E4); the next higher dose tested, 1,000 mg/kg, was lethal. Likewise, no increases in the frequency of micronucleated erythrocytes were observed in peripheral blood samples collected from male and female mice within 24 hours of the final exposure in the 14-week study (Table E5).

In conclusion, citral gave negative results in *in vitro* and *in vivo* tests for genotoxicity with one exception. The *in vitro* mammalian cell test for SCEs was positive with and without S9.

TABLE E1
Mutagenicity of Citral in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100							
	0.0	155 ± 3.2	154 ± 6.1	148 ± 9.0	146 ± 5.8	122 ± 7.9	150 ± 8.4
	1.0	152 ± 16.8	146 ± 9.4				
	3.3	136 ± 7.2	141 ± 2.4	157 ± 4.8	149 ± 2.2	111 ± 11.3	128 ± 3.5
	10.0	140 ± 6.9	143 ± 7.1	145 ± 9.7	134 ± 8.4	126 ± 2.8	122 ± 1.7
	33.0	134 ± 3.8	147 ± 14.0[d]	145 ± 0.9	142 ± 5.2	123 ± 8.1	138 ± 2.1
	50.0		132 ± 12.9				
	67.0	Toxic					
	100.0			151 ± 5.9	142 ± 6.3[d]	129 ± 1.0	150 ± 9.4[d]
	160.0				141 ± 1.9		126 ± 5.5
	220.0			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		1,386 ± 11.9	1,349 ± 18.9	900 ± 38.1	439 ± 24.6	774 ± 9.1	434 ± 32.4
TA1535							
	0.0	29 ± 4.5	25 ± 2.6	17 ± 2.6	9 ± 1.7	14 ± 7.9	150 ± 1.9
	1.0	25 ± 1.9	18 ± 3.0				
	3.3	27 ± 3.8	23 ± 1.7	14 ± 2.0	11 ± 1.2	17 ± 0.6	12 ± 0.9
	10.0	27 ± 3.8	23 ± 4.1	13 ± 2.9	12 ± 3.8	8 ± 0.3	9 ± 2.1
	33.0	26 ± 3.8	23 ± 4.3[d]	16 ± 2.3	12 ± 0.3	13 ± 1.5	13 ± 3.8
	50.0		16 ± 2.0				
	67.0	19 ± 2.3[d]					
	100.0			18 ± 3.0	14 ± 2.7[d]	11 ± 1.2	18 ± 0.6[d]
	160.0				11 ± 3.7		10 ± 1.3
	220.0			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,277 ± 17.6	1,098 ± 39.7	119 ± 5.2	57 ± 2.8	99 ± 6.2	71 ± 5.3
TA1537							
	0.0	10 ± 0.3	5 ± 0.9	10 ± 3.2	7 ± 0.9	9 ± 1.5	7 ± 1.0
	1.0	9 ± 1.5	5 ± 0.7				
	3.3	9 ± 0.9	6 ± 1.7	10 ± 3.7	3 ± 0.7	9 ± 1.2	6 ± 1.0
	10.0	8 ± 1.7	6 ± 0.9	13 ± 2.8	8 ± 1.0	8 ± 0.9	7 ± 1.2
	33.0	6 ± 1.3	7 ± 0.3[d]	12 ± 2.0	5 ± 0.9	6 ± 0.6	5 ± 1.0
	50.0		3 ± 1.2				
	67.0	Toxic					
	100.0			9 ± 0.6	6 ± 1.5[d]	9 ± 0.7	7 ± 1.9[d]
	160.0				5 ± 0.7		7 ± 0.6
	220.0			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		547 ± 36.5	516 ± 58.9	74 ± 1.2	30 ± 0.3	54 ± 3.2	34 ± 6.4

TABLE E1
Mutagenicity of Citral in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA98							
	0.0	33 ± 2.6	15 ± 1.8	40 ± 1.5	24 ± 2.0	29 ± 1.5	23 ± 0.9
	1.0	28 ± 1.0	18 ± 2.3				
	3.3	25 ± 2.2	13 ± 2.8	32 ± 4.1	25 ± 4.4	34 ± 2.7	20 ± 3.6
	10.0	26 ± 5.4	17 ± 1.8	38 ± 3.4	28 ± 4.6	34 ± 2.5	22 ± 0.9
	33.0	30 ± 2.8	16 ± 0.6	40 ± 5.5	25 ± 3.3	31 ± 6.2	21 ± 1.2
	50.0		13 ± 1.2				
	67.0	23 ± 0.9[d]					
	100.0			30 ± 1.5	29 ± 4.1	34 ± 3.0	21 ± 1.0
	160.0				21 ± 3.4[d]		23 ± 1.5[d]
	220.0			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,510 ± 60.1	1,171 ± 55.0	890 ± 39.3	288 ± 6.8	679 ± 19.5	328 ± 20.3

[a] Study was performed at EG&G Mason Research Institute. The detailed protocol and these data are presented by Zeiger *et al.* (1987).
[b] 0 µg/plate was the solvent control.
[c] Revertants are presented as mean ± standard error from three plates.
The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.
[d] Slight toxicity

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

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide[c]		50	1,036	393	0.37	7.9	26.0	
Citral	0.289	50	1,036	476	0.45	9.5	26.0	21.12*
	0.868	50	1,041	480	0.46	9.6	26.0	21.55*
	2.890	50	1,025	570	0.55	11.4	26.0	46.59*
	8.860	Toxic						
					P<0.001[d]			
Mitomycin-C[e]	1.5	50	1,044	703	0.67	14.1	26.0	77.51*
	10.0	5	105	229	2.18	45.8	26.0	474.93*
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,046	494	0.47	9.9	26.0	
Citral	2.5	50	1,046	512	0.48	10.2	26.0	3.64
	5.0	50	1,043	544	0.52	10.9	26.0	10.44
	7.5	50	1,047	720	0.68	14.4	26.0[f]	45.61*
	10.0	50	1,026	789	0.76	15.8	33.0[f]	62.83*
	20.0	Toxic						
					P<0.001			
Mitomycin-C	0.0015	50	1,046	692	0.66	13.8	26.0	40.08*
	0.010	5	104	222	2.13	44.4	26.0	351.99*

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Citral

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9								
Trial 1								
Summary: Weakly Positive								
Dimethylsulfoxide		50	1,039	468	0.45	9.4	26.0	
Citral	0.87	50	1,042	509	0.48	10.2	26.0	8.45
	2.89	50	1,035	546	0.52	10.9	26.0	17.12
	8.68	50	1,035	693	0.66	13.9	26.0	48.65*
	28.90	Toxic						
					P<0.001			
Cyclophosphamide[e]	0.4	50	1,038	650	0.62	13.0	26.0	39.02*
	2.0	5	105	147	1.40	29.4	26.0	210.81*
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,032	478	0.46	9.6	26.0	
Citral	15.1	50	1,024	651	0.63	13.0	26.0[f]	37.26*
	20.1	50	1,026	771	0.75	15.4	34.0[f]	62.24*
	25.2	50	1,015	739	0.72	14.8	34.0[f]	57.19*
	30.2	25	508	402	0.79	16.1	34.0[f]	70.85*
	40.2	25	510	387	0.75	15.5	34.0[f]	63.83*
					P<0.001			
Cyclophosphamide	0.4	50	1,025	764	0.74	15.3	26.0	60.93*
	2.0	5	101	135	1.33	27.0	26.0	188.58*

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

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

Compound	Dose (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
-S9					
Harvest time: 10.5 hours					
Summary: Negative					
Dimethylsulfoxide[b]		100	4	0.04	2.0
Citral	12.5	100	1	0.01	1.0
	20.2	100	5	0.05	5.0
	25.3	100	9	0.09	6.0
	40.3	Toxic			
					P=0.023[c]
Mitomycin-C[d]	0.15	100	12	0.12	11.0
	0.50	25	7	0.28	28.0
+S9					
Harvest time: 20.5 hours[e]					
Summary: Negative					
Dimethylsulfoxide		100	1	0.01	1.0
Citral	30.3	100	6	0.06	6.0
	40.3	100	3	0.03	3.0
	50.5	75	6	0.08	6.6
	60.6	100	5	0.05	5.0
	70.7	Toxic			
					P=0.103
Cyclophosphamide[d]	3.8	100	4	0.04	4.0
	62.5	25	18	0.72	52.0*

* Positive response ($P \leq 0.05$) versus the solvent control
a Study was performed at Litton Bionetics, Inc. The detailed protocol is 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
e Due to cell cycle delay, harvest time was extended to maximize the number of first-division metaphase cells available for analysis.

TABLE E4
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with Citral by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]
Corn oil[d]		4	0.50 ± 0.35	
Citral	250	5	1.10 ± 0.29	0.0828
	500	4	1.75 ± 0.60	0.0092
	750	5	1.30 ± 0.34	0.0413
			P=0.040[e]	
Cyclophosphamide[f]	25	5	11.30 ± 1.35	

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al*. (1993).
[b] PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control. Dosed group values are significant at P≤0.008 (ILS, 1990).
[e] Vehicle control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
Positive control

TABLE E5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Administration of Citral in Feed for 14 Weeks[a]

Concentration (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male				
Untreated Control	10	1.30 ± 0.32		2.2
Vehicle Control	10	1.90 ± 0.22		2.1
3,900	10	1.50 ± 0.32	0.5818	2.2
7,800	10	1.70 ± 0.28	0.4199	1.9
15,600	10	2.50 ± 0.25	0.0458	1.8
31,300	6	1.83 ± 0.28	0.3482	1.8
		P=0.145[d]		
Female				
Untreated Control	10	1.00 ± 0.35		2.3
Vehicle Control	10	1.50 ± 0.32		2.6
3,900	10	1.00 ± 0.24	0.7251	2.4
7,800	10	1.10 ± 0.36	0.6382	2.4
15,600	10	0.90 ± 0.22	0.8022	2.3
31,300	10	1.60 ± 0.29	0.2196	2.2
		P=0.217		

[a] Study was performed at Integrated Laboratory Systems, Inc. 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 combined controls; significant at P≤0.006 (ILS, 1990)
Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed Cochran-Armitage 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 14-Week Feed Study of Citral 224
TABLE F2 Hematology Data for Mice in the 14-Week Feed Study of Citral 230

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral[a]

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male						
n						
Day 4	10	10	10	10	10	10
Day 22	10	10	10	10	8	0
Week 14	10	10	10	10	10	0
Hematology						
Hematocrit (%)						
Day 4	38.7 ± 0.6	38.9 ± 0.6	40.1 ± 0.4	42.4 ± 0.5**	44.7 ± 0.5**	45.8 ± 0.7**
Day 22	43.7 ± 0.9	44.3 ± 0.4	44.1 ± 0.8	43.8 ± 0.4	51.1 ± 2.7	
Week 14	44.7 ± 0.4	44.7 ± 0.5	44.9 ± 0.8	44.6 ± 0.5	45.4 ± 0.5	
Hemoglobin (g/dL)						
Day 4	12.4 ± 0.2	12.4 ± 0.2	12.8 ± 0.1	13.6 ± 0.2**	14.2 ± 0.2**	14.6 ± 0.2**
Day 22	14.3 ± 0.2	14.5 ± 0.2	14.2 ± 0.3	14.3 ± 0.1	16.2 ± 0.8	
Week 14	15.1 ± 0.1	15.0 ± 0.1	15.2 ± 0.2	15.2 ± 0.1	15.3 ± 0.1	
Erythrocytes (10^6/µL)						
Day 4	6.38 ± 0.08	6.41 ± 0.10	6.65 ± 0.07	7.18 ± 0.12**	7.60 ± 0.06**	7.72 ± 0.13**
Day 22	7.17 ± 0.15	7.25 ± 0.07	7.18 ± 0.14	7.21 ± 0.08	8.60 ± 0.48	
Week 14	8.35 ± 0.09	8.45 ± 0.11	8.39 ± 0.15	8.35 ± 0.08	8.39 ± 0.09	
Reticulocytes (10^5/µL)						
Day 4	4.18 ± 0.31	4.25 ± 0.27	2.93 ± 0.43*	1.84 ± 0.22**	2.12 ± 0.14**	2.01 ± 0.26**
Day 22	1.86 ± 0.13	2.09 ± 0.26	1.66 ± 0.23	2.42 ± 0.29	1.72 ± 0.39	
Week 14	1.38 ± 0.11	1.15 ± 0.15	1.25 ± 0.11	1.06 ± 0.15	1.18 ± 0.10	
Nucleated erythrocytes (10^3/µL)						
Day 4	0.11 ± 0.05	0.15 ± 0.06	0.07 ± 0.03	0.01 ± 0.01*	0.00 ± 0.00**	0.00 ± 0.00**
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	
Mean cell volume (fL)						
Day 4	60.8 ± 0.5	60.8 ± 0.2	60.4 ± 0.4	59.2 ± 0.5**	58.8 ± 0.4**	59.5 ± 0.4**
Day 22	61.2 ± 0.2	61.3 ± 0.2	61.3 ± 0.2	61.0 ± 0.3	59.5 ± 0.4**	
Week 14	53.8 ± 0.2	52.9 ± 0.1	53.5 ± 0.2*	53.6 ± 0.2**	54.3 ± 0.2**	
Mean cell hemoglobin (pg)						
Day 4	19.5 ± 0.1	19.4 ± 0.1	19.2 ± 0.2	18.9 ± 0.2	18.6 ± 0.1**	18.9 ± 0.1**
Day 22	20.0 ± 0.2	20.0 ± 0.2	19.8 ± 0.2	19.8 ± 0.2	18.9 ± 0.2**	
Week 14	18.0 ± 0.1	17.8 ± 0.2	18.1 ± 0.1	18.2 ± 0.1	18.2 ± 0.1	
Mean cell hemoglobin concentration (g/dL)						
Day 4	32.0 ± 0.2	31.9 ± 0.2	31.9 ± 0.2	32.1 ± 0.3	31.6 ± 0.1	31.8 ± 0.2
Day 22	32.8 ± 0.3	32.7 ± 0.3	32.3 ± 0.3	32.7 ± 0.1	31.8 ± 0.3	
Week 14	33.7 ± 0.2	33.6 ± 0.2	33.9 ± 0.2	34.0 ± 0.2	33.6 ± 0.2	
Platelets (10^3/µL)						
Day 4	855.2 ± 25.4	871.2 ± 18.0	877.8 ± 46.9	990.6 ± 25.3**	1,054.3 ± 16.6**	1,137.5 ± 43.4**
Day 22	836.8 ± 14.3	844.1 ± 16.9	852.8 ± 28.0	881.5 ± 15.0	822.4 ± 26.0	
Week 14	721.0 ± 14.9	698.6 ± 8.0	708.0 ± 18.3	707.7 ± 10.3	707.8 ± 8.1	
Leukocytes (10^3/µL)						
Day 4	9.65 ± 0.38	10.45 ± 0.46	10.44 ± 0.34	11.23 ± 0.50	11.52 ± 0.57	9.04 ± 0.71
Day 22	11.84 ± 0.68	12.16 ± 0.53	10.49 ± 0.61	12.25 ± 0.77	11.63 ± 0.52	
Week 14	11.41 ± 0.23	12.95 ± 0.58	12.95 ± 0.44	10.92 ± 0.43*	10.71 ± 0.46**	
Segmented neutrophils (10^3/µL)						
Day 4	1.30 ± 0.14	1.66 ± 0.14	1.69 ± 0.23	1.70 ± 0.18	1.72 ± 0.17	1.38 ± 0.14
Day 22	1.08 ± 0.13	1.49 ± 0.11	1.12 ± 0.06*	1.36 ± 0.10	1.13 ± 0.11	
Week 14	1.58 ± 0.19	1.97 ± 0.26	2.07 ± 0.21	1.50 ± 0.13	1.45 ± 0.15	

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male (continued)						
n						
Day 4	10	10	10	10	10	10
Day 22	10	10	10	10	8	0
Week 14	10	10	10	10	10	0
Hematology (continued)						
Bands (10^3/μL)						
Day 4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Lymphocytes (10^3/μL)						
Day 4	8.21 ± 0.30	8.51 ± 0.43	8.61 ± 0.27	9.21 ± 0.38	9.52 ± 0.54	7.47 ± 0.59
Day 22	10.54 ± 0.61	10.31 ± 0.43	8.98 ± 0.55	10.56 ± 0.71	10.33 ± 0.48	
Week 14	9.43 ± 0.31	10.59 ± 0.40	10.52 ± 0.41	8.96 ± 0.43*	9.01 ± 0.40*	
Monocytes (10^3/μL)						
Day 4	0.12 ± 0.03	0.25 ± 0.03	0.12 ± 0.04	0.27 ± 0.07	0.24 ± 0.05	0.12 ± 0.03
Day 22	0.19 ± 0.05	0.34 ± 0.09	0.33 ± 0.07	0.26 ± 0.04	0.15 ± 0.03	
Week 14	0.26 ± 0.05	0.13 ± 0.04	0.31 ± 0.09	0.39 ± 0.08*	0.18 ± 0.04	
Basophils (10^3/μL)						
Day 4	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 22	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	
Eosinophils (10^3/μL)						
Day 4	0.03 ± 0.02	0.03 ± 0.02	0.02 ± 0.01	0.05 ± 0.03	0.04 ± 0.02	0.07 ± 0.02
Day 22	0.04 ± 0.03	0.02 ± 0.02	0.06 ± 0.04	0.07 ± 0.03	0.01 ± 0.01	
Week 14	0.14 ± 0.03	0.26 ± 0.05	0.05 ± 0.02**	0.07 ± 0.02**	0.07 ± 0.03**	
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 4	11.4 ± 0.4	9.4 ± 0.9	12.6 ± 0.3**	14.1 ± 0.5**	13.5 ± 0.7**	22.8 ± 1.7**
Day 22	14.0 ± 0.3	11.1 ± 0.4	12.4 ± 0.4*	13.3 ± 0.3**	19.3 ± 1.5**	
Week 14	19.4 ± 0.6	15.9 ± 0.5	16.3 ± 0.8	15.9 ± 0.5	18.2 ± 0.6*	
Creatinine (mg/dL)						
Day 4	0.57 ± 0.02	0.55 ± 0.02	0.56 ± 0.02	0.58 ± 0.01	0.58 ± 0.01	0.56 ± 0.02
Day 22	0.60 ± 0.00	0.60 ± 0.00	0.61 ± 0.01	0.62 ± 0.01	0.59 ± 0.01	
Week 14	0.66 ± 0.02	0.67 ± 0.02	0.70 ± 0.03	0.80 ± 0.04**	0.79 ± 0.01**	
Total protein (g/dL)						
Day 4	5.0 ± 0.1	4.9 ± 0.1	5.1 ± 0.0	5.0 ± 0.1	5.2 ± 0.1**	5.2 ± 0.0**
Day 22	6.0 ± 0.1	6.1 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.4 ± 0.2	
Week 14	6.6 ± 0.0	6.5 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	6.3 ± 0.1	
Albumin (g/dL)						
Day 4	3.8 ± 0.1	3.7 ± 0.0	4.0 ± 0.0**	3.9 ± 0.0**	4.1 ± 0.0**	4.2 ± 0.0**
Day 22	4.4 ± 0.0	4.5 ± 0.1	4.6 ± 0.0	4.6 ± 0.0	4.9 ± 0.1**	
Week 14	4.7 ± 0.0	4.7 ± 0.1	4.8 ± 0.1	5.0 ± 0.1**	4.8 ± 0.1	
Alanine aminotransferase (IU/L)						
Day 4	91 ± 2	90 ± 2	99 ± 3	95 ± 3	100 ± 7	74 ± 3*
Day 22	64 ± 2	62 ± 2	63 ± 2	70 ± 2	58 ± 8	
Week 14	64 ± 3	72 ± 3	70 ± 8	57 ± 2*	68 ± 3	

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male (continued)						
n						
Day 4	10	10	10	10	10	10
Day 22	10	10	10	10	8	0
Week 14	10	10	10	10	10	0
Clinical Chemistry (continued)						
Alkaline phosphatase (IU/L)						
Day 4	2,049 ± 55	2,172 ± 80	2,198 ± 35	2,026 ± 58	1,735 ± 39**	1,362 ± 40**
Day 22	1,256 ± 19*	1,361 ± 33	1,328 ± 31	1,479 ± 31	1,163 ± 143	
Week 14	536 ± 16	574 ± 12	551 ± 14	607 ± 20	619 ± 25	
Creatine kinase (IU/L)						
Day 4	283 ± 25	345 ± 37	423 ± 95	424 ± 105	681 ± 163	831 ± 164**[b]
Day 22	501 ± 87	384 ± 42	519 ± 116	319 ± 40	484 ± 79	
Week 14	155 ± 19	159 ± 20	312 ± 106	325 ± 101	257 ± 36	
Sorbitol dehydrogenase (IU/L)						
Day 4	18 ± 1	18 ± 1	19 ± 1	18 ± 1	18 ± 1	20 ± 1
Day 22	21 ± 1	23 ± 1	21 ± 1	18 ± 1**	20 ± 1**	
Week 14	24 ± 1	27 ± 1	27 ± 3	23 ± 1	23 ± 1	
Bile acids (μmol/L)						
Day 4	39.2 ± 3.1	33.9 ± 2.7	43.7 ± 3.8	36.8 ± 4.3	54.6 ± 10.2	38.6 ± 3.4[b]
Day 22	33.4 ± 2.1	28.8 ± 3.5	31.8 ± 2.1	33.8 ± 2.9	28.6 ± 4.9	
Week 14	18.4 ± 1.5	27.1 ± 2.9	25.1 ± 2.2	27.6 ± 2.1	30.9 ± 1.6	
Female						
Hematology						
n						
Day 4	10	9	9	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	10	0
Hematocrit (%)						
Day 4	41.5 ± 0.5	41.6 ± 0.9	43.4 ± 1.0	46.3 ± 0.9**	48.2 ± 0.8**	47.3 ± 0.7**
Day 22	46.1 ± 0.6	46.4 ± 0.6	46.1 ± 0.9	44.9 ± 0.5	44.8 ± 0.4	
Week 14	43.6 ± 0.3	43.2 ± 0.3	44.7 ± 0.5	43.1 ± 0.4	44.0 ± 0.3	
Hemoglobin (g/dL)						
Day 4	13.0 ± 0.2	13.2 ± 0.3	13.6 ± 0.4	14.8 ± 0.3**	15.2 ± 0.2**	15.0 ± 0.2**
Day 22	15.1 ± 0.1	15.3 ± 0.2	15.2 ± 0.3	15.1 ± 0.1	15.0 ± 0.2	
Week 14	14.9 ± 0.1	14.8 ± 0.1	15.2 ± 0.1	14.9 ± 0.1	15.1 ± 0.1	
Erythrocytes (10^6/μL)						
Day 4	6.71 ± 0.10	6.79 ± 0.17	7.09 ± 0.18	7.81 ± 0.16**	8.10 ± 0.15**	7.89 ± 0.08**
Day 22	7.51 ± 0.10	7.73 ± 0.12	7.64 ± 0.16	7.61 ± 0.1	7.84 ± 0.09	
Week 14	7.64 ± 0.06	7.61 ± 0.06	7.87 ± 0.06*	7.59 ± 0.06	7.89 ± 0.1*	
Reticulocytes (10^5/μL)						
Day 4	3.49 ± 0.32	3.16 ± 0.40	3.23 ± 0.32	2.01 ± 0.15*	1.98 ± 0.21*	2.09 ± 0.11*
Day 22	1.48 ± 0.09	1.36 ± 0.14	1.30 ± 0.13	1.19 ± 0.08	1.41 ± 0.13	
Week 14	0.93 ± 0.09	1.10 ± 0.12	0.98 ± 0.11	0.86 ± 0.11	0.90 ± 0.11	

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Female (continued)						
Hematology (continued)						
n						
Day 4	10	9	9	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	10	0
Nucleated erythrocytes (10^3/μL)						
Day 4	0.03 ± 0.02	0.05 ± 0.03	0.03 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00*
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.00 ± 0.00	
Mean cell volume (fL)						
Day 4	61.9 ± 0.5	61.2 ± 0.4	61.3 ± 0.4	59.4 ± 0.3**	59.7 ± 0.4*	59.9 ± 0.4*
Day 22	61.3 ± 0.3	60.1 ± 0.3	60.5 ± 0.3	59.0 ± 0.4	57.2 ± 0.2**	
Week 14	57.1 ± 0.2	57.0 ± 0.3	56.7 ± 0.2	56.8 ± 0.1	56.1 ± 0.2*	
Mean cell hemoglobin (pg)						
Day 4	19.4 ± 0.2	19.4 ± 0.1	19.2 ± 0.1	19.0 ± 0.1	18.8 ± 0.2	19.0 ± 0.1
Day 22	20.1 ± 0.1	19.8 ± 0.1	19.9 ± 0.1	19.8 ± 0.1	19.1 ± 0.1**	
Week 14	19.6 ± 0.1	19.5 ± 0.1	19.3 ± 0.1	19.7 ± 0.1	19.3 ± 0.1	
Mean cell hemoglobin concentration (g/dL)						
Day 4	31.4 ± 0.1	31.6 ± 0.2	31.4 ± 0.2	32.0 ± 0.1	31.6 ± 0.3	31.8 ± 0.1
Day 22	32.8 ± 0.3	33.0 ± 0.2	33.0 ± 0.1	33.6 ± 0.2	33.4 ± 0.2	
Week 14	34.3 ± 0.1	34.3 ± 0.2	34.1 ± 0.2	34.7 ± 0.1	34.3 ± 0.2	
Platelets (10^3/μL)						
Day 4	821.5 ± 23.7	759.2 ± 45.3	798.8 ± 29.8	899.0 ± 31.7**	990.4 ± 31.0**	1,067.9 ± 22.8**
Day 22	788.8 ± 18.5	758.5 ± 17.3	737.7 ± 20.6	821.1 ± 23.2	789.4 ± 19.8	
Week 14	638.8 ± 11.4	636.7 ± 13.8	660.4 ± 11.9	618.2 ± 12.2	676.2 ± 13.9	
Leukocytes (10^3/μL)						
Day 4	10.71 ± 0.39	10.96 ± 0.69	10.30 ± 0.43	13.59 ± 0.59*	14.01 ± 0.73*	11.30 ± 0.79
Day 22	12.43 ± 0.54	12.29 ± 0.46	13.06 ± 0.21	12.04 ± 0.71	13.36 ± 0.55	
Week 14	9.51 ± 0.75	8.55 ± 0.30	8.68 ± 0.48	8.40 ± 0.50	10.89 ± 0.51*	
Segmented neutrophils (10^3/μL)						
Day 4	1.49 ± 0.18	1.60 ± 0.28	1.12 ± 0.15	1.42 ± 0.11	1.21 ± 0.09	1.55 ± 0.13
Day 22	1.54 ± 0.14	1.25 ± 0.18	1.73 ± 0.17	1.32 ± 0.15	0.93 ± 0.11	
Week 14	1.38 ± 0.12	1.15 ± 0.08	1.06 ± 0.11	0.96 ± 0.11	1.04 ± 0.18	
Bands (10^3/μL)						
Day 4	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Lymphocytes (10^3/μL)						
Day 4	9.03 ± 0.32	9.23 ± 0.42	9.09 ± 0.35	12.07 ± 0.59*	12.62 ± 0.69**	9.67 ± 0.73
Day 22	10.60 ± 0.48	10.82 ± 0.44	11.01 ± 0.29	10.38 ± 0.72	12.15 ± 0.54	
Week 14	7.87 ± 0.69	7.18 ± 0.28	7.42 ± 0.44	7.23 ± 0.49	9.61 ± 0.43**	
Monocytes (10^3/μL)						
Day 4	0.08 ± 0.03	0.05 ± 0.03	0.06 ± 0.03	0.09 ± 0.04	0.12 ± 0.04	0.05 ± 0.02
Day 22	0.20 ± 0.06	0.16 ± 0.04	0.22 ± 0.05	0.30 ± 0.08	0.21 ± 0.06	
Week 14	0.24 ± 0.07	0.17 ± 0.06	0.14 ± 0.05	0.13 ± 0.04	0.22 ± 0.05	

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Female (continued)						
Hematology (continued)						
n						
Day 4	10	9	9	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	10	0
Basophils (10^3/μL)						
Day 4	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 22	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	
Eosinophils (10^3/μL)						
Day 4	0.08 ± 0.04	0.07 ± 0.02	0.03 ± 0.02	0.00 ± 0.00*	0.07 ± 0.03	0.03 ± 0.02
Day 22	0.10 ± 0.04	0.06 ± 0.03	0.09 ± 0.004	0.04 ± 0.02	0.07 ± 0.03	
Week 14	0.01 ± 0.01	0.05 ± 0.03	0.07 ± 0.02	0.08 ± 0.03	0.02 ± 0.01	
Clinical Chemistry						
n						
Day 4	10	10	10	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	10	0
Urea nitrogen (mg/dL)						
Day 4	10.3 ± 0.3	7.6 ± 0.4	10.9 ± 0.5**	11.2 ± 0.4**	13.6 ± 1.2**	26.7 ± 2.4**
Day 22	13.4 ± 0.5	13.4 ± 0.2	13.2 ± 0.5	13.6 ± 0.5	14.8 ± 0.4*	
Week 14	14.8 ± 0.6	15.2 ± 0.6	15.6 ± 0.5	15.6 ± 0.5	16.6 ± 0.7	
Creatinine (mg/dL)						
Day 4	0.56 ± 0.02	0.58 ± 0.01	0.59 ± 0.01	0.60 ± 0.00	0.56 ± 0.02	0.53 ± 0.02*
Day 22	0.58 ± 0.01	0.60 ± 0.02	0.60 ± 0.02	0.63 ± 0.02	0.60 ± 0.00	
Week 14	0.67 ± 0.02	0.67 ± 0.02	0.70 ± 0.00	0.69 ± 0.02	0.73 ± 0.02*	
Total protein (g/dL)						
Day 4	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.2 ± 0.0
Day 22	5.9 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.0	6.1 ± 0.1	
Week 14	6.6 ± 0.1	6.5 ± 0.1	6.5 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	
Albumin (g/dL)						
Day 4	4.1 ± 0.1	4.1 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.3 ± 0.0
Day 22	4.5 ± 0.0	4.5 ± 0.0	4.7 ± 0.1	4.7 ± 0.0	4.8 ± 0.1**	
Week 14	5.0 ± 0.1	5.0 ± 0.1	5.1 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	
Alanine aminotransferase (IU/L)						
Day 4	84 ± 3	81 ± 3	95 ± 4*	92 ± 2	91 ± 4	72 ± 4
Day 22	54 ± 1	54 ± 2	56 ± 2	60 ± 1*	74 ± 3**	
Week 14	90 ± 9	78 ± 8	63 ± 2	62 ± 2	68 ± 3	
Alkaline phosphatase (IU/L)						
Day 4	1,772 ± 35	1,768 ± 54	1,816 ± 66	1,725 ± 29	1,473 ± 46**	1,031 ± 41**
Day 22	912 ± 16	902 ± 22	966 ± 31	1,110 ± 16**	1,107 ± 14**	
Week 14	567 ± 9	544 ± 16	534 ± 18	651 ± 18**	626 ± 20**	

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of Citral

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Female (continued)						
Clinical Chemistry (continued)						
n						
Day 4	10	10	10	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	10	0
Creatine kinase (IU/L)						
Day 4	318 ± 40	381 ± 31	392 ± 42	473 ± 80	542 ± 99	446 ± 45
Day 22	209 ± 11	270 ± 37	255 ± 30	508 ± 112*	247 ± 17	
Week 14	227 ± 44	194 ± 27	284 ± 46	273 ± 31	242 ± 44	
Sorbitol dehydrogenase (IU/L)						
Day 4	16 ± 1	18 ± 1	18 ± 1	19 ± 1	18 ± 1	20 ± 1
Day 22	16 ± 1	17 ± 1	17 ± 1	19 ± 1	15 ± 1	
Week 14	33 ± 4	27 ± 3	20 ± 1	22 ± 1	21 ± 2	
Bile acids (µmol/L)						
Day 4	36.0 ± 3.6	35.8 ± 4.3	34.5 ± 5.0	47.2 ± 5.0	57.2 ± 3.5**[b]	53.5 ± 7.1*
Day 22	32.7 ± 2.5	29.6 ± 3.7	20.9 ± 3.1	34.9 ± 1.7	52.1 ± 2.4**	
Week 14	25.7 ± 2.0	41.4 ± 5.7	30.6 ± 4.0	35.2 ± 2.9	41.8 ± 4.7	

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

TABLE F2
Hematology Data for Mice in the 14-Week Feed Study of Citral[a]

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male						
n	10	10	10	10	10	6
Hematocrit (%)	50.3 ± 0.8	50.4 ± 0.8	47.1 ± 0.4*	49.1 ± 0.4	49.4 ± 0.9	48.8 ± 1.7
Hemoglobin (g/dL)	17.1 ± 0.2	17.2 ± 0.2	16.5 ± 0.2	17.0 ± 0.1	16.9 ± 0.3	17.1 ± 0.5
Erythrocytes (10^6/µL)	11.23 ± 0.20	11.24 ± 0.17	10.38 ± 0.10**	10.87 ± 0.10	10.76 ± 0.19	10.75 ± 0.35
Reticulocytes (10^5/µL)	0.86 ± 0.10	0.84 ± 0.12	0.74 ± 0.12	0.69 ± 0.09	0.75 ± 0.10	0.64 ± 0.11
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)	45.0 ± 0.2	45.0 ± 0.2	45.4 ± 0.2	45.4 ± 0.2	46.0 ± 0.0**	45.5 ± 0.2*
Mean cell hemoglobin (pg)	15.3 ± 0.2	15.3 ± 0.1	15.9 ± 0.1**	15.6 ± 0.1	15.7 ± 0.1	15.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.1 ± 0.4	34.2 ± 0.2	35.1 ± 0.2*	34.6 ± 0.1	34.1 ± 0.2	35.1 ± 0.2*
Platelets (10^3/µL)	724.5 ± 22.0	798.9 ± 54.1	719.2 ± 21.4	667.7 ± 26.1	722.3 ± 40.0	913.0 ± 61.6
Leukocytes (10^3/µL)	5.48 ± 0.56	5.40 ± 0.72	3.40 ± 0.44	3.65 ± 0.84	2.27 ± 0.17**	1.70 ± 0.09**
Segmented neutrophils (10^3/µL)	1.28 ± 0.30	1.18 ± 0.31	1.61 ± 0.43	0.57 ± 0.11	0.38 ± 0.08*	0.45 ± 0.09
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/µL)	4.08 ± 0.58	4.15 ± 0.58	1.76 ± 0.15**	3.02 ± 0.74*	1.86 ± 0.13**	1.21 ± 0.09**
Monocytes (10^3/µL)	0.05 ± 0.03	0.04 ± 0.02	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 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 ± 0.03	0.03 ± 0.02	0.01 ± 0.01	0.05 ± 0.02	0.01 ± 0.01	0.03 ± 0.01
Female						
n	10	10	10	10	10	10
Hematocrit (%)	45.0 ± 0.7	45.8 ± 0.7	45.4 ± 1.2	46.6 ± 0.9	44.9 ± 0.4	46.8 ± 0.8
Hemoglobin (g/dL)	15.8 ± 0.2	16.3 ± 0.2	16.0 ± 0.4	16.2 ± 0.2	15.8 ± 0.1	16.0 ± 0.2
Erythrocytes (10^6/µL)	9.88 ± 0.16	10.09 ± 0.15	9.81 ± 0.26	10.07 ± 0.21	9.86 ± 0.06	10.29 ± 0.16
Reticulocytes (10^5/µL)	0.95 ± 0.21	0.98 ± 0.16	0.90 ± 0.17	1.07 ± 0.20	1.14 ± 0.15	1.04 ± 0.16
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)	45.5 ± 0.2	45.4 ± 0.2	46.4 ± 0.2**	46.3 ± 0.2**	45.7 ± 0.2	45.7 ± 0.2
Mean cell hemoglobin (pg)	16.0 ± 0.1	16.2 ± 0.1	16.3 ± 0.1	16.1 ± 0.1	16.0 ± 0.1	15.6 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	35.2 ± 0.2	35.7 ± 0.3	35.2 ± 0.2	34.8 ± 0.2*	35.2 ± 0.2	34.3 ± 0.2**
Platelets (10^3/µL)	760.5 ± 33.8	742.7 ± 31.0	700.2 ± 51.2	608.9 ± 27.8	829.3 ± 35.8	657.0 ± 50.2
Leukocytes (10^3/µL)	4.91 ± 0.32	4.11 ± 0.24	4.28 ± 0.28	4.38 ± 0.28	3.16 ± 0.28*	2.56 ± 0.26**
Segmented neutrophils (10^3/µL)	0.98 ± 0.19	0.58 ± 0.07	0.53 ± 0.08	0.39 ± 0.05	0.48 ± 0.10	0.36 ± 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)	3.74 ± 0.24	3.44 ± 0.19	3.68 ± 0.30	3.86 ± 0.26	2.65 ± 0.21*	2.13 ± 0.19**
Monocytes (10^3/µL)	0.08 ± 0.02	0.06 ± 0.02	0.03 ± 0.01	0.04 ± 0.02	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)	0.11 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.09 ± 0.02	0.02 ± 0.01	0.05 ± 0.02

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

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

TABLE G1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Feed Study of Citral 232
TABLE G2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Feed Study of Citral 233

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Feed Study of Citral[a]

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm
n	10	10	10	10	10
Male					
Necropsy body wt	340 ± 7	347 ± 6	330 ± 7*	304 ± 4**	258 ± 5**
Heart					
Absolute	1.031 ± 0.017	1.038 ± 0.026	1.013 ± 0.028	0.920 ± 0.019**	0.812 ± 0.021**
Relative	3.036 ± 0.051	2.991 ± 0.053	3.069 ± 0.047	3.032 ± 0.057	3.145 ± 0.057
R. Kidney					
Absolute	1.111 ± 0.025	1.114 ± 0.017	1.134 ± 0.027	1.169 ± 0.018	1.037 ± 0.026
Relative	3.268 ± 0.043	3.213 ± 0.038	3.441 ± 0.067**	3.854 ± 0.035**	4.014 ± 0.057**
Liver					
Absolute	12.218 ± 0.413	12.686 ± 0.336	12.481 ± 0.310	12.580 ± 0.282	9.996 ± 0.212**
Relative	35.902 ± 0.899	36.537 ± 0.541	37.819 ± 0.309	41.482 ± 0.913**	38.721 ± 0.499**
Lung					
Absolute	1.792 ± 0.065	1.879 ± 0.094	1.776 ± 0.084	1.643 ± 0.052*	1.400 ± 0.061**
Relative	5.299 ± 0.242	5.401 ± 0.218	5.365 ± 0.161	5.408 ± 0.125	5.423 ± 0.217
R. Testis					
Absolute	1.503 ± 0.029	1.486 ± 0.027	1.505 ± 0.017	1.456 ± 0.021	1.457 ± 0.020
Relative	4.421 ± 0.042	4.287 ± 0.062	4.570 ± 0.057**	4.802 ± 0.057**	5.653 ± 0.093**
Thymus					
Absolute	0.354 ± 0.016	0.342 ± 0.013	0.328 ± 0.014	0.283 ± 0.009**	0.260 ± 0.011**
Relative	1.039 ± 0.037	0.987 ± 0.038	0.994 ± 0.034	0.932 ± 0.027	1.006 ± 0.041
Female					
Necropsy body wt	204 ± 3	194 ± 4	182 ± 4	188 ± 3	170 ± 2**
Heart					
Absolute	0.681 ± 0.020	0.641 ± 0.009	0.620 ± 0.016	0.645 ± 0.011	0.581 ± 0.010**
Relative	3.343 ± 0.102	3.314 ± 0.052	3.410 ± 0.074	3.435 ± 0.055	3.423 ± 0.055
R. Kidney					
Absolute	0.686 ± 0.016	0.628 ± 0.015	0.639 ± 0.011	0.662 ± 0.012	0.629 ± 0.009
Relative	3.366 ± 0.063	3.239 ± 0.056	3.514 ± 0.035**	3.525 ± 0.056**	3.706 ± 0.027**
Liver					
Absolute	7.218 ± 0.132	6.577 ± 0.189	6.310 ± 0.251	6.666 ± 0.133	6.220 ± 0.098
Relative	35.419 ± 0.588	33.896 ± 0.491	34.587 ± 0.861	35.501 ± 0.773	36.670 ± 0.684*
Lung					
Absolute	1.208 ± 0.042[b]	1.148 ± 0.042	1.154 ± 0.054	1.152 ± 0.036	1.035 ± 0.043
Relative	5.912 ± 0.195[b]	5.936 ± 0.222	6.355 ± 0.284	6.146 ± 0.236	6.089 ± 0.213
Thymus					
Absolute	0.279 ± 0.009	0.269 ± 0.015	0.248 ± 0.008	0.268 ± 0.008	0.249 ± 0.006
Relative	1.367 ± 0.031	1.383 ± 0.059	1.372 ± 0.057	1.427 ± 0.039	1.467 ± 0.031

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test; pairwise comparisons between the untreated and vehicle control 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). No data are available for the 31,300 ppm groups due to 100% mortality.
[b] n=9

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Feed Study of Citral[a]

	Untreated Control	Vehicle Control	3,900 ppm	7,800 ppm	15,600 ppm	31,300 ppm
Male						
n	10	10	10	10	10	6
Necropsy body wt	31.8 ± 0.8	34.2 ± 0.8	29.0 ± 0.5**	26.4 ± 0.5**	23.1 ± 0.5**	18.7 ± 0.8**
Heart						
Absolute	0.154 ± 0.003	0.173 ± 0.010	0.157 ± 0.006	0.160 ± 0.004	0.174 ± 0.008	0.152 ± 0.007
Relative	4.863 ± 0.133	5.073 ± 0.267	5.432 ± 0.181	6.075 ± 0.187**	7.548 ± 0.362**	8.138 ± 0.240**
R. Kidney						
Absolute	0.293 ± 0.011	0.289 ± 0.008	0.279 ± 0.007	0.255 ± 0.007**	0.226 ± 0.006**	0.188 ± 0.010**
Relative	9.232 ± 0.295	8.488 ± 0.253	9.644 ± 0.131**	9.667 ± 0.193**	9.783 ± 0.161**	10.041 ± 0.227**
Liver						
Absolute	1.407 ± 0.027	1.496 ± 0.044	1.431 ± 0.023	1.418 ± 0.038	1.324 ± 0.036**	1.282 ± 0.083**
Relative	44.421 ± 0.806	43.743 ± 0.740	49.466 ± 0.649**	53.783 ± 0.969**	57.425 ± 1.284**	68.435 ± 2.091**
Lung						
Absolute	0.304 ± 0.007	0.315 ± 0.025	0.305 ± 0.005	0.294 ± 0.008	0.276 ± 0.010	0.229 ± 0.025**
Relative	9.631 ± 0.333	9.151 ± 0.651	10.560 ± 0.243	11.170 ± 0.330*	11.965 ± 0.432**	12.253 ± 1.330**
R. Testis						
Absolute	0.124 ± 0.004	0.118 ± 0.003	0.113 ± 0.004	0.110 ± 0.004	0.097 ± 0.004**	0.068 ± 0.003**
Relative	3.944 ± 0.181	3.476 ± 0.098	3.899 ± 0.130	4.164 ± 0.112	4.209 ± 0.123	3.680 ± 0.205
Thymus						
Absolute	0.042 ± 0.002	0.047 ± 0.002	0.040 ± 0.002*	0.042 ± 0.001*	0.041 ± 0.003*	0.029 ± 0.003**
Relative	1.323 ± 0.058	1.378 ± 0.045	1.366 ± 0.038	1.597 ± 0.041	1.795 ± 0.115**	1.532 ± 0.162*
Female						
n	10	10	10	10	10	10
Necropsy body wt	29.9 ± 0.9	30.3 ± 0.4	27.0 ± 0.4**	22.5 ± 0.4**	18.8 ± 0.2**	17.4 ± 0.1**
Heart						
Absolute	0.138 ± 0.007	0.139 ± 0.004	0.148 ± 0.004	0.146 ± 0.005	0.138 ± 0.004	0.128 ± 0.003
Relative	4.611 ± 0.171	4.585 ± 0.099	5.491 ± 0.191**	6.505 ± 0.280**	7.350 ± 0.184**	7.377 ± 0.169**
R. Kidney						
Absolute	0.190 ± 0.006	0.176 ± 0.004	0.206 ± 0.005	0.183 ± 0.005	0.155 ± 0.003**	0.152 ± 0.006**
Relative	6.340 ± 0.120	5.830 ± 0.121	7.604 ± 0.151**	8.144 ± 0.138**	8.237 ± 0.154**	8.725 ± 0.293**
Liver						
Absolute	1.343 ± 0.050	1.271 ± 0.037	1.358 ± 0.027	1.244 ± 0.038	1.234 ± 0.044	1.037 ± 0.040**
Relative	44.910 ± 1.179	41.973 ± 0.786	50.333 ± 1.094**	55.261 ± 1.313**	65.860 ± 2.437**	59.771 ± 2.280**
Lung						
Absolute	0.243 ± 0.020	0.260 ± 0.015	0.262 ± 0.018	0.264 ± 0.011	0.222 ± 0.009	0.219 ± 0.010*
Relative	8.204 ± 0.743	8.590 ± 0.502	9.715 ± 0.700	11.706 ± 0.434**	11.868 ± 0.485**	12.617 ± 0.537**
Thymus						
Absolute	0.055 ± 0.004	0.051 ± 0.002	0.054 ± 0.003	0.050 ± 0.002	0.058 ± 0.002	0.058 ± 0.003
Relative	1.856 ± 0.130	1.703 ± 0.086	2.006 ± 0.081*	2.229 ± 0.078**	3.092 ± 0.102**	3.362 ± 0.161**

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test; pairwise comparisons between the untreated and vehicle control 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 H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization of Citral

Citral was obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI), in two lots. Lot 06930PG was used during the 14-week studies, and lot 04402AQ was used during the 2-year studies. The manufacturer indicated a purity of 96.5% for each lot. The chemical was microencapsulated by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and the loaded microcapsules were assigned separate lot numbers. Lot 20295 was prepared for use in the 14-week studies, and lot MRI 020196MC was prepared for use in the 2-year studies. Identity, purity, moisture content, and stability analyses of the neat chemical and the loaded microcapsules were conducted by the analytical chemistry laboratory and the study laboratory. Reports on analyses performed in support of the citral studies are on file at the National Institute of Environmental Health Sciences.

Analyses of Neat Chemical

The chemical, a colorless liquid, was identified as citral by the analytical chemistry laboratory using infrared, ultraviolet/visible (lot 04402AQ), and nuclear magnetic resonance spectroscopy and gas chromatography/mass spectrometry (GC/MS) by system A (Table H1) (lot 04402AQ). All spectra were consistent with the structure of citral and with the literature spectra (*Aldrich*, 1985, 1993; Sadtler Research Laboratories, 1966). GC/MS spectra for the two components of lot 04402AQ were consistent with NBS library spectra for the two isomers of citral, neral and geranial. The infrared and nuclear magnetic resonance spectra are presented in Figures H1 and H2. The boiling point for lot 04402AQ was determined to be 213.3° C at 744.5 mm mercury.

The purity of lot 06930PG was determined by the analytical chemistry laboratory using gas chromatography by system B. The purity of lot 04402AQ was determined by the analytical chemistry laboratory using functional group titration, thin-layer chromatography (TLC), and GC by system B. Moisture content was determined using Karl Fischer titration. Functional group titration was performed using *Food Chemicals Codex* (1981) methods. TLC was performed on Silica Gel 60 F-254 plates with a solvent system of 90:5:5 toluene:ethyl acetate:glacial acetic acid. The plates were examined using 254 nm ultraviolet light and a spray of 0.4% 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid. Vanillin was used as a reference standard.

For lot 06930PG, GC indicated two major peaks and seven impurities with a combined area of 2.4% relative to the combined major peak area. The isomer ratio was approximately 2:1 geranial:neral. For lot 04402AQ, Karl Fischer titration indicated 0.12% ± 0.05% water. Functional group titration indicated 92.2% ± 0.4% aldehydes. TLC indicated a major spot, a minor spot, and two trace impurities. GC analyses resolved two major peaks and 20 impurities with areas of 0.72% or less of the major peak area and a combined area of 5.78% relative to the combined major peak area; geranial and neral were identified on the basis of the elution order indicated by a literature reference (*Food Chemicals Codex*, 1981). The overall purity of lot 04402AQ was determined to be approximately 94%, with an isomer composition of approximately 63% geranial and 37% neral.

Accelerated stability studies of the neat chemical were performed by the analytical chemistry laboratory using GC by system C. These studies indicated no degradation after storage for 2 weeks at temperatures up to 60° C when stored protected from light.

Microcapsule Formulation and Analyses

Microcapsules loaded with neat citral and placebos (empty microcapsules) were prepared in several batches at the analytical chemistry laboratory by a proprietary process using food-grade sugar and starch to produce dry microspheres. The batches were homogenized and passed through 40- over 140-mesh sieves and were stored in amber glass bottles at room temperature before shipping to the study laboratory. Lot MRI 020196MC microcapsules were examined microscopically for appearance, and particle sizes were profiled. Particles were clear or translucent white spheres approximately 50 to 100 µm in diameter. Less than 3% were agglomerated. The

surfaces were smooth and shiny. About 25% had a few adherent, small particles, and 50% had a heavy coating of smaller particles. Only two or three broken microcapsules and no leaking microcapsules were observed. Microcapsules were passed through U.S. standard sieves (Nos. 30, 40, 60, 80, and 120). Greater than 99% of the microcapsules were retained by sieves with pores ranging from less than 125 to 250 µm.

The chemical load of the microcapsules was determined by the analytical chemistry laboratory using GC by systems D (lot 20295) and E (lot MRI 020196MC). Microcapsule samples were dissolved in 50 mL of a 60:40 acetonitrile:water solution by sonicating for 10 minutes, with the samples in a 45° C water bath for the second 5 minutes, and then shaking for 15 minutes. An additional 50 mL of acetonitrile was added and the solution was mixed and centrifuged. A 4-mL aliquot of the supernatant was combined with 7 mL of an internal standard solution of 0.70 mg octadecane in 98:2 acetonitrile:chloroform and filtered. The chemical load was determined to be 31.3% for lot 20295 and 31.9% for lot MRI 020196MC. An impurity profile analysis of lot MRI 020196MC was performed by the analytical chemistry laboratory using GC by a system similar to system E; 15 impurities with areas of 0.1% or greater relative to the combined peak area were detected. The identity of lot MRI 020196MC was confirmed as microencapsulated citral by the study laboratory using GC/MS (system F). The spectra were consistent with the instrument's spectral library for isomers of citral. The chemical load for lot MRI 020196MC was analyzed by the study laboratory using high-performance liquid chromatography (HPLC) with an Inertsil ODS-2 column using ultraviolet light detection (292 nm) and a solvent system of Milli-Q water:methanol (30:70) at a flow rate of 1 mL/minute. Milli-Q water has a conductivity of 18 MΩ/cm or less. The chemical load was determined to be 32.3%, which confirms the 31.9% from the analytical chemistry laboratory.

A 1-year shelf-life study conducted by the analytical chemistry laboratory using GC by systems G and H indicated that lot CIT-4B of microcapsules (not used in the current studies) retained approximately 94% of its chemical load when stored for up to 6 months at room temperature, protected from light; microcapsules stored at room temperature for 6 months and then at approximately 5° C for 6 months retained 95.8% of the zero-time chemical load. No change in the ratio of the isomers geranial and neral was noted at either time point. Microcapsules stored at room temperature, open to air and light, for up to 28 days after 6 months of storage at room temperature, after 6 months at room temperature plus 6 months at 5° C, or after seven freeze-thaw cycles showed no changes in chemical retention. Slight increases were observed in the concentrations of total impurities in samples stored for 6 months (1.30%) or 12 months (1.57%) compared to freshly prepared microcapsules (1.15%). The microcapsules were stored in amber glass bottles, protected from light, at approximately 5° C. The stability of the microcapsules was monitored by the analytical chemistry laboratory using GC by systems D and E for the 14-week studies and by the study laboratory using HPLC as described for the chemical load determination for the 2-year studies; no loss of citral from the microcapsules was detected.

Preparation and Analysis of Dose Formulations

The dose formulations of citral microcapsules were prepared with nonirradiated NTP-2000 feed every 2 to 4 weeks during the 14-week studies and with irradiated NTP-2000 feed approximately every 4 weeks during the 2-year studies (Table H2). Placebo and/or loaded microcapsules were combined with feed to a concentration of 10% microcapsules for the 14-week studies and 1.25% microcapsules for the 2-year studies. A premix was prepared by hand and then blended with additional feed in a Patterson-Kelly twin-shell blender for 15 minutes. Dose formulations were stored in polyethylene bags inside sealed plastic buckets at room temperature (14-week studies) or at approximately 5° C (2-year studies) for up to 35 days.

Homogeneity and stability studies of an 830 ppm dose formulation and homogeneity studies of the 4,000 and 31,300 ppm dose formulations in nonirradiated NTP-2000 feed were performed by the analytical chemistry laboratory using GC by systems similar to systems E and G. Homogeneity was confirmed. Samples stored at approximately 5° C or –20° C showed chemical losses of approximately 4% at day 4, after which no losses occurred; however, samples stored at room temperature showed steady losses of approximately 11% over 35 days. The study laboratory conducted homogeneity studies of the 500 and 4,000 ppm dose formulations and stability

studies of the 500 ppm dose formulation in irradiated NTP-2000 feed for the 2-year studies using GC by a system similar to system E. Homogeneity was confirmed. The concentrations of samples stored at –5° C or room temperature were less than the initial values at all time points. Samples stored at room temperature showed chemical losses of approximately 15% between days 21 and 38. Samples stored under animal room conditions (room temperature, open to air and light) showed chemical losses of approximately 10% after 1 day and did not decrease further after 4 days; samples contaminated by rodent urine and feces showed losses of 20% to 30%.

Periodic analyses of the dose formulations of citral used during the 14-week studies were conducted by the analytical chemistry laboratory using GC systems similar to system E. The dose formulations were analyzed at the beginning, midpoint, and end of the studies; animal room samples of these dose formulations were also analyzed (Table H3). All 29 dose formulations analyzed were within 10% of the target concentrations. Of the animal room samples, 7 of 21 for rats and 4 of 29 for mice were within 10% of the target concentrations. Periodic analyses of the dose formulations used during the 2-year studies were conducted by the study laboratory using GC by a system similar to system E. During the 2-year studies, the dose formulations were analyzed approximately every 9 to 12 weeks; animal room samples were also analyzed (Table H4). All 36 and 33 dose formulations analyzed for rats and mice, respectively, were within 10% of the target concentrations. Of the animal room samples, 8 of 12 for rats and 6 of 12 for mice were within 10% of the target concentrations. In the 14-week and 2-year studies, loss of citral in the animal room samples was attributed to contamination with urine and feces, which softened the microcapsules. This was observed early in each study and continued longer with mice than with rats. Also, in the 14-week studies, high concentrations of citral in the animal room samples were attributed to the animals' ability to avoid microcapsules mixed with the feed.

TABLE H1
Gas Chromatography Systems Used in the Feed Studies of Citral[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Mass spectrometry with positive ion electron impact ionization (35 to 550 amu; scan rate 0.6 seconds)	DB-5, 30 m × 0.32 mm, 1.0-µm film (J&W Scientific, Folsom, CA)	Helium at 30 mL/second	35° C for 4 minutes, then 10° C/minute to 300° C, held 7 minutes
System B			
Flame ionization	DB-WAX, 30 m × 0.53 mm, 1.0-µm film (J&W Scientific)	Helium at approximately 10 mL/minute	60° C for 6 minutes, then 5° C/minute to 225° C, held 6 minutes
System C			
Flame ionization	3% Silar 5 CP, 1.8 m × 4.0 mm	Nitrogen at 70 mL/minute	100° C, then 10° C/minute to 160° C
System D			
Flame ionization	DB-WAX, 30 m × 0.53 mm, 1.0-µm film (J&W Scientific)	Helium at 10 mL/minute	Isothermal at 250° C
System E			
Flame ionization	DB-WAX, 30 m × 0.53 mm, 1.0-µm film (J&W Scientific)	Helium at 10 mL/minute	80° C for 6 minutes, then 10° C/minute to 125° C, held 13 minutes
System F			
Mass spectrometry with positive ion electron impact ionization (25 to 200 amu)	Stabiliwax-DA, 30 m × 0.25 mm, 0.25-µm film (Restek, Bellefonte, PA)	Helium at approximately 10 mL/minute	80° C for 6 minutes, then 10° C/minute to 125° C, held 13 minutes
System G			
Flame ionization	10% Carbowax 20 M on 80/100 mesh chromosorb W AW, 1.8 m × 2 mm	Nitrogen at 30 mL/minute	Isothermal at 145° C
System H			
Flame ionization	10% Carbowax 20 M-TPA on 80/100 mesh chromosorb W AW, 1.8 m × 4 mm	Nitrogen at 70 mL/minute	100° C to 160° C at 5° C/minute, held for 21 minutes, or 60° C for 6 minutes, then 5° C/minute to 225° C, held for 21 minutes

[a] The gas chromatographs were manufactured by Hewlett Packard (Palo Alto, CA) (system A), Varian, Inc. (Palo Alto, CA) (systems B-E, G, and H), and Fisons P.L.C. (Loughborough, Leicestershire, UK) (system F).

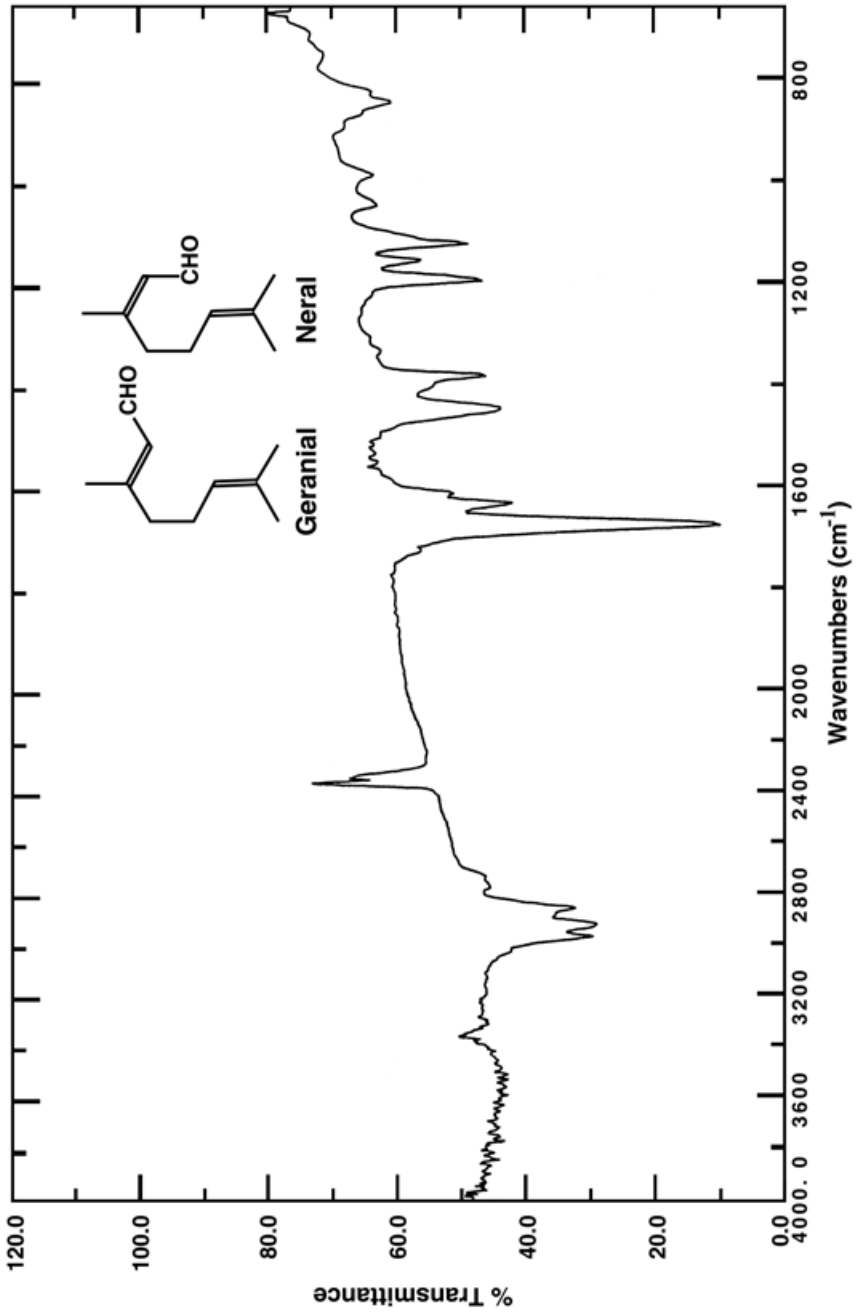

FIGURE H1
Infrared Absorption Spectrum of Citral

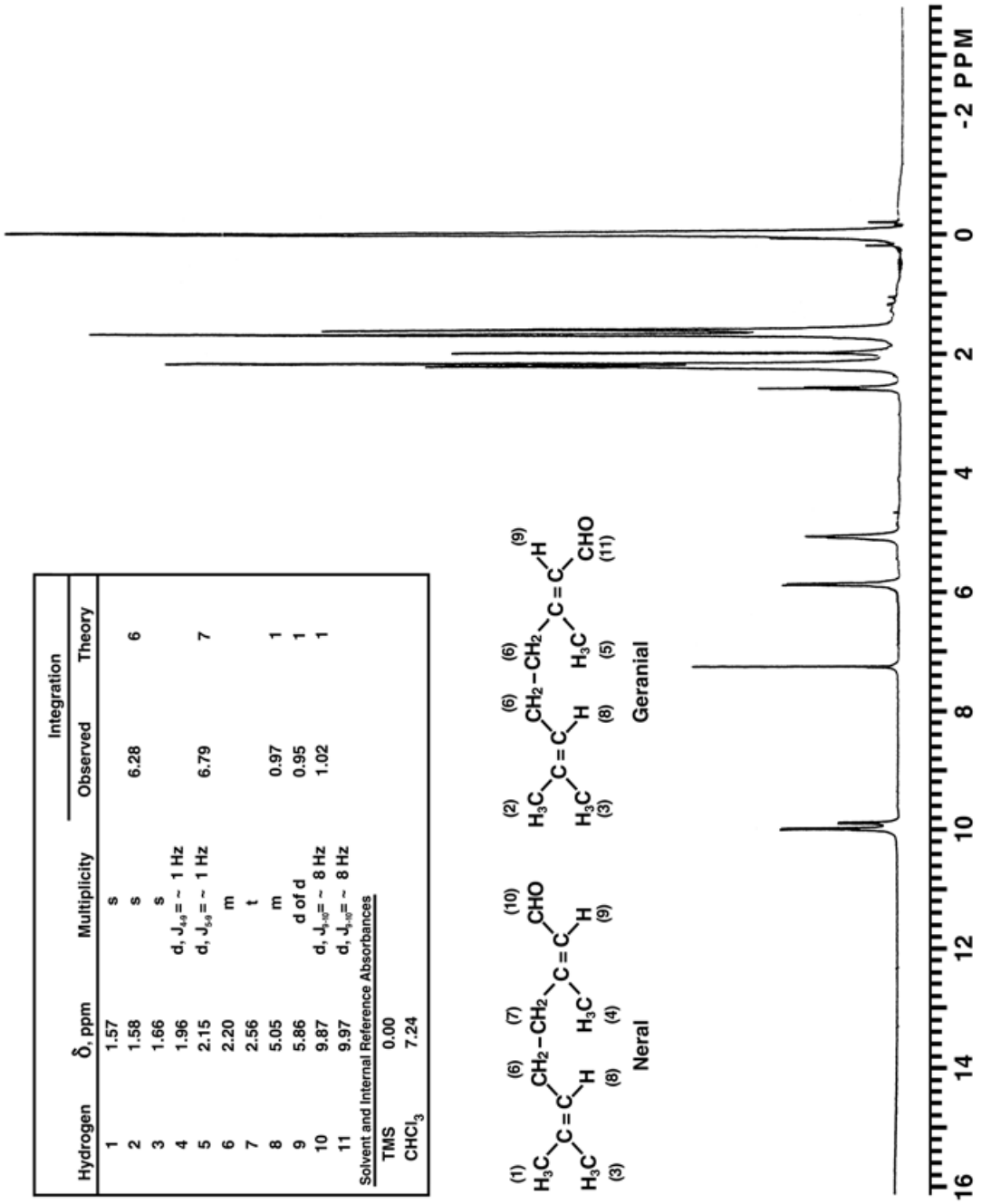

Figure H2
Nuclear Magnetic Resonance Spectrum of Citral

TABLE H2
Preparation and Storage of Dose Formulations in the Feed Studies of Citral

	14-Week Studies	2-Year Studies
Preparation	A premix of citral and feed was prepared by hand and then layered into the remaining feed and blended with additional feed in a twin-shell blender for 15 minutes. The dose formulations were prepared every 2 or 4 weeks.	Same as 14-week studies, except dose formulations were prepared approximately every 4 weeks
Chemical Lot Number	Neat: 06930PG Microcapsules: 20295	Neat: 04402AQ Microcapsules: MRI 020196MC
Maximum Storage Time	35 days	35 days
Storage Conditions	Stored in polyethylene bags inside sealed plastic buckets at room temperature	Stored in polyethylene bags inside sealed plastic buckets at approximately 5° C
Study Laboratory	Battelle Columbus Operations (Columbus, OH)	Battelle Columbus Operations (Columbus, OH)

TABLE H3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Feed Studies of Citral[a]

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[b] (ppm)	Difference from Target (%)
Rats				
May 24, 1995	May 25 and 30, 1995	3,900	3,631	–7
		3,900	3,693	–5
		3,900	3,725	–4
		7,800	7,324	–6
		7,800	7,418	–5
		7,800	7,512	–4
		15,600	15,494	–1
		15,600	15,462	–1
		15,600	15,368	–1
		31,300	30,737	–2
		31,300	28,953	–7
		31,300	30,236	–3
	June 22-23, 1995[c]	3,900	4,914	+26
		3,900	4,476	+15
		7,800	9,390	+20
		7,800	8,326	+7
		7,800	7,982	+2
		15,600	5,509	–65
		15,600	6,072	–61
		15,600	5,227	–66
June 28, 1995	June 29-30, 1995	3,900	3,881	0
		3,900	3,850	–1
		3,900	3,819	–2
		7,800	7,794	0
		7,800	7,825	+1
		7,800	7,919	+2
		15,600	15,400	–1
		15,600	15,494	–1
		15,600	15,306	–2
	August 3, 1995[c]	3,900	4,601	+18
		7,800	9,390	+20
		7,800	9,359	+20
		7,800	10,016	+28
		15,600	10,986	–30
		15,600	15,587	0
		15,600	7,293	–53

TABLE H3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Feed Studies of Citral

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
August 9, 1995	August 10-11, 1995	3,900	3,693	–5
		3,900	3,725	–4
		7,800	7,324	–6
		7,800	7,199	–8
		15,600	14,805	–5
		15,600	14,555	–7
	September 13, 1995[c]	3,900	4,570	+17
		3,900	4,163	+7
		7,800	7,669	–2
		7,800	8,326	+7
		15,600	15,118	–3
		15,600	11,112	–29
Mice				
May 24, 1995	May 25 and 30, 1995	3,900	3,631	–7
		3,900	3,693	–5
		3,900	3,725	–4
		7,800	7,324	–6
		7,800	7,418	–5
		7,800	7,512	–4
		15,600	15,494	–1
		15,600	15,462	–1
		15,600	15,368	–1
		31,300	30,737	–2
		31,300	28,953	–7
		31,300	30,236	–3
	June 22-23, 1995[c]	3,900	3,944	+1
		3,900	3,913	0
		3,900	3,913	0
		7,800	5,634	–28
		7,800	7,387	–5
		7,800	6,792	–13
		15,600	17,872	+15
		15,600	17,372	+11
		15,600	20,595	+32
		31,300	45,385	+45
		31,300	42,881	+37
		31,300	40,690	+30

TABLE H3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Feed Studies of Citral

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
June 28, 1995	June 29-30, 1995	3,900	3,881	0
		3,900	3,850	–1
		3,900	3,819	–2
		7,800	7,794	0
		7,800	7,825	0
		7,800	7,919	+2
		15,600	15,400	–1
		15,600	15,494	–1
		15,600	15,306	–2
		31,300	31,237	0
	August 3, 1995[c]	3,900	2,911	–25
		3,900	3,349	–14
		3,900	3,193	–18
		7,800	3,036	–61
		7,800	3,161	–59
		7,800	5,008	–36
		15,600	5,478	–65
		15,600	8,326	–47
		15,600	4,852	–69
		31,300	27,575	–12
August 9, 1995	August 10-11, 1995	3,900	3,693	–5
		3,900	3,725	–4
		7,800	7,324	–6
		7,800	7,199	–8
		15,600	14,805	–5
		15,600	14,555	–7
		31,300	29,798	–5
	September 13, 1995[c]	3,900	3,349	–14
		3,900	3,349	–14
		7,800	4,445	–43
		7,800	2,661	–66
		15,600	7,262	–53
		15,600	7,230	–54
		31,300	26,136	–16

[a] Analyses were performed by Midwest Research Institute (Kansas City, MO).
[b] Results of single analyses through June 23, 1995; results of duplicate analyses thereafter
[c] Animal room samples

TABLE H4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Citral[a]

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[b] (ppm)	Difference from Target (%)
Rats				
May 30, 1996	May 31-June 1,1996	1,000	960	–4
		2,000	2,003	0
		4,000	3,988	0
	May 14-15, 1996[c]	1,000	960	–4
		2,000	1,764	–12
		4,000	4,179	+4
June 11, 1996	June 11-12, 1996	1,000	1,037	+4
		2,000	2,058	+3
		4,000	4,051	+1
August 12, 1996	August 13, 1996	1,000	925	–7
		2,000	1,844	–8
		4,000	3,764	–6
November 4, 1996	November 4-5, 1996	1,000	1,014	+1
		2,000	2,038	+2
		4,000	4,019	0
January 6, 1997	January 7, 1997	1,000	992	–1
		2,000	2,016	+1
		4,000	3,988	0
	February 6-7, 1997[c]	1,000	775	–22
		2,000	1,595	–20
		4,000	3,254	–19
April 1, 1997	April 2, 1997	1,000	989	–1
		2,000	1,959	–2
		4,000	4,115	+3
June 3, 1997	June 4, 1997	1,000	989	–1
		2,000	1,860	–7
		4,000	3,700	–7
August 25, 1997	August 28, 1997	1,000	1,021	+2
		2,000	1,997	0
		4,000	3,988	0
	September 24-25, 1997[c]	1,000	986	–1
		2,000	1,940	–3
		4,000	4,019	0
October 27 and 30, 1997	October 30-31, 1997	1,000	1,024	+2
		2,000	2,077	+4
		4,000	4,243	+6

TABLE H4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Citral

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
January 19, 1998	January 22, 1998	1,000	995	0
		2,000	1,991	0
		4,000	4,019	0
March 24, 1998	March 26, 1998	1,000	957	–4
		2,000	1,914	–4
		4,000	3,796	–5
	April 22-23, 1998[c]	1,000	1,002	0
		2,000	2,007	0
		4,000	4,307	+8
May 26, 1998	May 27, 1998	1,000	1,027	+3
		2,000	2,077	+4
		4,000	4,147	+4
Mice				
June 11, 1996	June 11-12, 1996	500	501	0
		1,000	1,037	+4
		2,000	2,058	+3
	July 17, 1996[c]	500	230	–54
		1,000	695	–30
		2,000	587	–71
August 12, 1996	August 13, 1996	500	453	–9
		1,000	925	–7
		2,000	1,844	–8
November 4, 1996	November 4-5, 1996	500	501	+1
		1,000	1,014	+1
		2,000	2,038	+2
January 6, 1997	January 7, 1997	500	498	0
		1,000	992	–1
		2,000	2,016	+1
	February 6-7, 1997[c]	500	456	–9
		1,000	928	–7
		2,000	1,761	–12
April 1, 1997	April 2, 1997	500	475	–5
		1,000	989	–1
		2,000	1,959	–2

TABLE H4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Citral

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
June 3, 1997	June 4, 1997	500	501	0
		1,000	989	–1
		2,000	1,860	–7
August 25, 1997	August 28, 1997	500	498	0
		1,000	1,021	+2
		2,000	1,997	0
	September 24-25, 1997[c]	500	434	–13
		1,000	817	–18
		2,000	1,901	–5
October 27 and 30, 1997	October 30-31, 1997	500	485	–3
		1,000	1,024	+2
		2,000	2,077	+4
January 19, 1998	January 22, 1998	500	498	0
		1,000	995	0
		2,000	1,991	0
March 24, 1998	March 26, 1998	500	485	–3
		1,000	957	–4
		2,000	1,914	–4
	April 22-23, 1998[c]	500	542	+8
		1,000	986	–1
		2,000	2,045	+2
May 26, 1998	May 27, 1998	500	504	+1
		1,000	1,027	+3
		2,000	2,077	+4

[a] Analyses were performed by Midwest Research Institute (Kansas City, MO).
[b] Results of duplicate analyses
[c] Animal room samples

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

TABLE I1	Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Citral	250
TABLE I2	Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Citral	252
TABLE I3	Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Citral	254
TABLE I4	Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Citral	256

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

Week	Untreated Control		Vehicle Control		1,000 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]
1	17.3	124	16.8	126	17.2	126	136
2	20.3	162	20.4	161	20.4	163	125
5	22.3	267	20.9	266	20.4	262	78
9	19.9	330	20.3	330	20.1	327	61
13	19.4	363	19.6	363	19.5	362	54
17	20.1	391	19.4	390	19.9	390	51
21	19.0	409	19.7	410	19.6	406	48
25	21.0	427	21.2	424	20.8	421	49
29	19.1	434	18.8	435	19.2	426	45
33	19.8	442	20.1	439	20.5	438	47
37	20.0	455	19.9	453	20.0	451	44
41	20.6	463	20.2	462	19.9	458	43
45	21.4	472	21.2	469	21.8	464	47
49	20.0	480	19.4	479	19.3	473	41
53	19.3	486	19.2	487	19.0	479	40
57	19.8	487	19.3	483	20.1	477	42
61	19.1	490	19.6	490	19.2	483	40
65	18.9	493	19.4	490	19.1	484	39
69	19.6	489	19.4	486	19.2	479	40
73	18.0	484	18.2	480	17.6	475	37
77	17.7	486	18.2	490	18.3	480	38
81	16.8	479	17.4	486	17.2	480	36
85	17.2	483	16.6	485	16.7	479	35
89	16.7	484	16.2	478	17.6	481	36
93	16.6	473	16.1	466	16.5	475	35
97	16.1	482	15.9	473	16.4	475	34
101	16.9	476	17.0	479	16.2	470	34
Mean for weeks							
1-13	19.8	249	19.6	249	19.5	248	91
14-52	20.1	441	20.0	440	20.1	436	46
53-101	17.9	484	17.9	482	17.9	478	37

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

Week	2,000 ppm			4,000 ppm		
	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
1	17.1	125	273	17.0	126	539
2	20.1	160	251	20.3	157	518
5	20.6	260	158	24.2	258	375
9	19.9	319	124	22.5	315	284
13	19.1	354	108	21.8	349	249
17	19.7	381	103	21.4	376	227
21	19.8	400	99	20.1	392	204
25	20.2	412	98	20.1	399	201
29	19.6	420	93	20.1	413	194
33	20.1	432	93	19.4	420	184
37	19.4	444	87	19.7	430	183
41	20.1	452	89	20.2	436	185
45	20.8	458	91	22.4	445	200
49	19.3	465	83	19.6	450	174
53	18.9	472	80	18.7	456	164
57	19.5	472	82	19.5	448	173
61	19.3	478	80	20.3	458	177
65	18.9	482	78	19.2	460	167
69	19.1	478	79	19.3	456	169
73	17.6	474	74	18.2	453	160
77	17.2	476	72	18.7	456	163
81	16.2	472	68	17.5	455	153
85	17.2	478	72	17.1	453	151
89	16.8	474	70	17.9	452	158
93	16.8	469	71	17.3	448	154
97	16.7	467	71	17.3	452	153
101	16.3	461	70	17.0	440	154
Mean for weeks						
1-13	19.4	244	183	21.2	241	393
14-52	19.9	429	93	20.3	418	195
53-101	17.7	473	75	18.3	453	161

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

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

Week	Untreated Control		Vehicle Control		1,000 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]
1	13.3	107	13.3	106	13.1	107	122
2	12.3	125	12.4	125	12.2	124	99
5	13.5	166	13.4	166	12.6	162	78
9	12.3	187	12.6	187	12.5	186	67
13	12.0	198	12.3	201	11.7	196	59
17	12.3	207	12.2	208	11.4	203	56
21	11.4	213	11.2	213	11.2	210	53
25	12.6	219	12.5	219	11.8	214	55
29	14.2	231	12.8	226	12.2	223	54
33	11.9	230	12.4	230	11.9	226	52
37	12.5	236	12.4	238	11.8	232	51
41	12.7	240	12.8	242	12.1	237	51
45	13.0	250	13.4	253	12.9	245	52
49	12.9	257	13.0	259	12.8	252	50
53	13.0	268	13.6	270	12.7	260	49
57	13.1	274	12.8	276	12.0	268	45
61	13.8	281	14.2	286	13.4	275	48
65	13.4	286	13.5	290	13.5	283	48
69	13.5	298	13.8	302	13.1	291	45
73	12.7	307	13.2	309	12.3	298	41
77	12.4	314	13.0	318	13.2	307	43
81	12.6	320	13.1	327	12.3	313	39
85	13.0	327	13.0	332	12.1	319	38
89	12.2	325	13.0	334	12.8	324	39
93	13.3	329	12.8	332	12.5	324	38
97	13.2	334	12.8	331	12.0	322	37
101	12.9	335	13.1	335	12.9	326	39
Mean for weeks							
1-13	12.7	156	12.8	157	12.4	155	85
14-52	12.6	232	12.5	232	12.0	227	53
53-101	13.0	308	13.2	311	12.7	301	42

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

Week	2,000 ppm			4,000 ppm		
	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
1	12.9	107	239	13.2	108	486
2	12.2	124	195	12.7	122	412
5	12.5	162	154	13.3	159	333
9	12.4	185	134	12.8	178	287
13	12.0	198	121	11.8	190	249
17	11.6	204	113	11.8	198	238
21	11.4	212	108	11.4	203	225
25	11.6	215	108	11.7	207	226
29	12.1	224	108	11.8	211	224
33	11.6	226	103	11.7	216	217
37	11.8	232	101	11.6	221	210
41	12.0	235	102	11.8	222	212
45	12.7	244	104	13.1	229	227
49	12.7	252	101	12.3	235	209
53	12.5	257	97	11.8	236	199
57	12.3	264	93	12.4	240	206
61	13.4	274	98	12.3	246	199
65	13.0	282	92	12.5	253	196
69	13.3	291	91	14.1	263	214
73	12.1	296	82	12.5	266	187
77	12.8	305	84	13.3	275	192
81	12.5	311	80	12.1	282	171
85	12.6	318	79	12.4	286	173
89	12.8	322	79	13.0	291	178
93	12.6	322	78	12.9	291	177
97	12.4	323	77	12.3	289	169
101	12.6	323	78	13.5	298	180
Mean for weeks						
1-13	12.4	155	169	12.8	152	353
14-52	12.0	227	105	11.9	216	221
53-101	12.7	299	85	12.7	271	188

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

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

Week	Untreated Control		Vehicle Control		500 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]
2	4.6	22.0	4.7	22.3	4.7	22.4	104
6	5.1	25.9	5.2	26.8	5.3	26.5	99
10	5.0	29.5	5.2	30.4	5.1	30.1	85
14	4.8	31.9	5.1	32.9	5.1	32.4	78
18	4.5	33.8	4.3	34.2	4.3	34.0	63
22	4.6	35.6	4.8	36.4	4.7	35.9	65
26	4.8	37.4	4.9	38.3	4.7	37.6	63
30	4.8	39.4	5.0	40.4	4.7	39.6	60
34	4.6	40.8	4.8	42.3	4.6	41.0	55
38	4.5	42.4	4.7	43.4	4.5	42.2	53
42	4.6	42.9	4.4	43.4	4.5	42.6	53
46	4.7	42.6	4.8	43.9	4.6	43.1	54
50	4.5	43.5	4.7	45.1	4.5	44.0	51
54	4.7	44.1	4.7	44.9	4.5	43.5	52
58	4.7	43.9	4.7	45.3	4.7	44.0	53
62	4.4	43.1	4.7	44.9	4.6	43.9	52
66	4.5	43.8	4.6	44.7	4.6	44.5	52
70	4.6	45.2	4.5	44.6	4.6	44.5	51
74	4.4	45.8	4.3	45.6	4.2	45.8	46
78	4.2	46.2	4.6	48.2	4.3	46.4	46
82	4.4	47.2	4.6	49.6	4.4	46.8	47
86	4.7	47.4	5.1	49.5	4.7	46.9	49
90	4.7	45.4	4.8	47.6	4.8	45.2	53
94	4.6	45.6	4.9	47.9	4.6	45.0	51
98	4.8	45.5	4.9	47.0	4.7	44.9	52
102	5.1	44.0	5.3	45.9	5.2	42.8	60
Mean for weeks							
2-13	4.9	25.8	5.0	26.5	5.0	26.3	96
14-52	4.6	39.0	4.8	40.0	4.6	39.2	59
53-102	4.6	45.2	4.7	46.6	4.6	44.9	51

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

Week	1,000 ppm Feed (g)	1,000 ppm Body Weight (g)	1,000 ppm Dose (mg/kg)	2,000 ppm Feed (g)	2,000 ppm Body Weight (g)	2,000 ppm Dose (mg/kg)
2	4.6	21.8	210	4.5	21.5	421
6	5.2	26.0	198	5.3	25.4	416
10	5.1	29.2	175	5.2	28.1	370
14	5.1	31.6	160	5.1	30.5	330
18	4.6	33.4	137	4.5	32.3	278
22	4.8	34.6	137	4.7	33.7	281
26	4.7	36.3	128	4.7	35.7	261
30	4.8	38.6	124	4.7	37.2	251
34	4.6	40.1	114	4.5	38.2	233
38	4.4	40.9	106	4.3	39.1	221
42	4.6	41.6	109	4.5	40.0	222
46	4.6	41.7	110	4.4	39.9	218
50	4.5	42.7	105	4.4	40.6	214
54	4.5	42.6	106	4.3	40.4	212
58	4.6	42.0	108	4.5	40.6	220
62	4.5	42.2	105	4.4	40.2	219
66	4.6	42.8	107	4.3	40.4	213
70	4.6	43.6	105	4.3	40.6	210
74	4.2	44.1	95	4.1	41.2	198
78	4.3	44.8	96	4.1	41.5	197
82	4.4	45.3	96	4.4	42.0	210
86	4.7	45.7	102	4.4	41.3	212
90	4.8	44.0	108	4.6	39.8	229
94	4.4	43.4	101	4.4	40.1	217
98	4.6	42.9	106	4.4	39.7	220
102	5.1	41.6	122	4.8	38.6	250
Mean for weeks						
2-13	5.0	25.7	195	5.0	25.0	402
14-52	4.7	38.2	123	4.6	36.7	251
53-102	4.6	43.5	104	4.4	40.5	216

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

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

Week	Untreated Control		Vehicle Control		500 ppm		
	Feed (g)[a]	Body Weight (g)	Feed (g)	Body Weight (g)	Feed (g)	Body Weight (g)	Dose (mg/kg)[b]
1	3.8	17.9	3.7	17.6	3.7	17.7	103
2	3.9	18.3	4.6	18.2	4.0	18.1	108
6	4.9	22.7	5.5	22.5	4.8	22.5	106
10	5.0	25.7	5.0	26.1	4.9	25.3	96
14	4.4	28.1	4.7	28.3	4.5	27.8	80
18	3.9	29.2	4.2	31.2	4.2	29.8	70
22	4.6	28.8	4.1	31.0	4.3	29.8	72
26	4.7	31.5	4.7	33.4	4.6	31.6	72
30	4.6	33.5	4.3	35.4	4.2	33.4	63
34	4.5	35.6	4.4	37.8	4.3	35.1	61
38	3.8	35.9	4.1	38.6	3.9	35.5	55
42	3.8	36.1	3.7	39.2	3.9	36.5	53
46	4.2	37.1	3.3	37.9	2.8	34.5	40
50	4.4	38.0	4.2	40.0	4.1	37.0	56
54	4.3	39.4	4.4	40.6	4.3	37.5	57
58	4.5	39.8	4.5	41.4	4.0	38.5	51
62	4.0	39.9	4.0	41.3	4.2	39.0	53
66	4.3	39.9	4.2	41.1	4.0	39.0	51
70	4.1	42.2	3.9	41.8	3.7	39.2	47
74	4.3	41.7	4.0	42.1	4.2	40.0	52
78	4.1	43.9	3.8	44.3	3.6	41.5	43
82	4.0	45.9	4.1	46.7	3.7	42.8	43
86	4.2	47.4	4.3	47.2	3.5	43.4	41
90	5.5	47.2	4.8	46.5	4.6	43.6	52
94	4.6	47.2	4.9	47.3	4.1	43.8	47
98	4.8	47.5	4.8	48.0	4.6	43.5	52
102	5.2	45.9	5.3	47.1	5.0	42.9	58
Mean for weeks							
1-13	4.4	21.2	4.7	21.1	4.3	20.9	103
14-52	4.3	33.4	4.2	35.3	4.1	33.1	62
53-102	4.5	43.7	4.4	44.3	4.1	41.1	50

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

Week	1,000 ppm			2,000 ppm		
	Feed (g)	Body Weight (g)	Dose (mg/kg)	Feed (g)	Body Weight (g)	Dose (mg/kg)
1	3.6	17.8	204	3.5	17.6	402
2	4.0	18.3	219	3.8	17.9	419
6	4.7	22.4	207	4.9	21.7	451
10	4.7	25.4	185	5.2	24.6	423
14	4.2	26.6	158	4.4	25.7	339
18	3.8	29.2	131	4.4	27.9	312
22	4.2	29.1	144	4.4	27.8	314
26	4.6	31.6	146	4.4	29.5	299
30	4.3	33.4	127	4.4	31.0	282
34	4.0	35.3	114	4.1	31.9	256
38	3.8	35.7	106	4.0	32.6	243
42	3.8	35.8	105	3.9	34.0	231
46	3.1	34.6	90	3.3	32.4	201
50	3.9	36.1	108	3.8	34.2	224
54	4.1	36.4	113	4.1	35.0	234
58	3.9	37.2	106	3.8	35.3	213
62	4.1	37.0	110	4.1	35.6	230
66	3.6	37.1	97	3.6	35.1	202
70	3.6	38.7	94	3.6	35.6	200
74	4.1	38.3	108	3.9	35.4	222
78	3.4	39.6	85	3.7	36.4	201
82	3.7	41.3	88	3.6	36.9	194
86	3.7	41.5	89	4.2	37.5	221
90	4.5	41.4	109	4.4	37.0	234
94	4.2	42.8	97	4.2	37.6	223
98	4.4	42.5	102	4.7	37.6	250
102	4.8	41.4	116	5.1	36.6	276
Mean for weeks						
1-13	4.3	21.0	204	4.4	20.4	424
14-52	4.0	32.7	123	4.1	30.7	270
53-102	4.0	39.6	101	4.1	36.3	223

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

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

TABLE J1	Ingredients of NTP-2000 Rat and Mouse Ration	260
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TABLE J1
Ingredients of NTP-2000 Rat and Mouse Ration

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

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

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

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

[a] Per kg of finished product

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.6 ± 0.52	12.6 – 14.7	26
Crude fat (% by weight)	8.2 ± 0.29	7.6 – 9.0	26
Crude fiber (% by weight)	9.6 ± 0.68	8.3 – 11.1	26
Ash (% by weight)	5.2 ± 0.29	4.6 – 5.9	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)	4,888 ± 1,345	2,570 – 8,140	26
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	82.2 ± 14.08	62.2 – 107.0	8
Thiamine (ppm)[b]	8.5 ± 1.11	6.6 – 11.7	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)[b]	9.04 ± 2.37	6.4 – 12.4	8
Folic acid (ppm)	1.64 ± 0.38	1.26 – 2.32	8
Biotin (ppm)	0.333 ± 0.15	0.225 – 0.704	8
Vitamin B_{12} (ppb)	68.7 ± 63.0	18.3 – 174.0	8
Choline (as chloride) (ppm)	3,155 ± 325	2,700 – 3,790	8
Minerals			
Calcium (%)	0.993 ± 0.053	0.884 – 1.080	26
Phosphorus (%)	0.569 ± 0.030	0.487 – 0.616	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)	0.724 ± 0.529	0.330 – 2.000	8
Cobalt (ppm)	0.45 ± 0.628	0.20 – 2.0	8

[a] From formulation
[b] As hydrochloride

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

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.26 ± 0.127	0.10 – 0.62	26
Cadmium (ppm)	0.04 ± 0.005	0.04 – 0.06	26
Lead (ppm)	0.09 ± 0.046	0.05 – 0.28	26
Mercury (ppm)	<0.02		26
Selenium (ppm)	0.17 ± 0.037	0.12 – 0.29	26
Aflatoxins (ppb)	<5.00		26
Nitrate nitrogen (ppm)[c]	15.9 ± 8.35	9.04 – 43.2	26
Nitrite nitrogen (ppm)[c]	<0.61		26
BHA (ppm)[d]	1.1 ± 0.48	0.01 – 3.37	26
BHT (ppm)[d]	1.1 ± 0.29	0.01 – 2.29	26
Aerobic plate count (CFU/g)[e]	66,929 ± 96,279	5 – 210,000	5
Coliform (MPN/g)[f]	20.3 ± 20.5	3 – 43	3
Escherichia coli (MPN/g)	<10		26
Salmonella (MPN/g)	Negative		26
Total nitrosoamines (ppb)[g]	5.0 ± 2.21	2.7 – 12.6	26
N-Nitrosodimethylamine (ppb)[g]	2.1 ± 1.08	0.9 – 5.1	26
N-Nitrosopyrrolidine (ppb)[g]	3.0 ± 1.79	1.0 – 8.7	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

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

	Mean ± Standard Deviation	Range	Number of Samples
Pesticides (ppm) (continued)			
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.10		26
Methyl chlorpyrifos	0.097 ± 0.082	0.020 – 0.300	24
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion	0.235 ± 0.470	0.020 – 2.430	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

[a] 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] Data for two nonirradiated samples and three irradiated samples. Microbial counts for 21 of 24 irradiated samples were below the detection limit.
[f] Data for two nonirradiated samples and one irradiated sample. Microbial counts for 23 of 24 irradiated samples were below the detection limit.
[g] All values were corrected for percent recovery.

APPENDIX K
SENTINEL ANIMAL PROGRAM

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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 14-week 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 Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
14-Week 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
Immunofluorescence Assay	
M. arthritidis	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. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
RCV/SDA	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
M. arthritidis	Study termination
Parvovirus	18 months, study termination
Hemagglutination Inhibition	
H-1	1, 6, and 12 months
KRV	1, 6, and 12 months

Method and Test	Time of Analysis
MICE	
14-Week 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
M. arthritidis	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
EDIM	1, 6, 12, and 18 months
GDVII	1, 6, 12, and 18 months
LCM	1, 6, 12, and 18 months
Mouse adenoma virus-FL	1, 6, 12, and 18 months
MHV	1, 6, 12, and 18 months
M. arthritidis	18 months
M. pulmonis	18 months
PVM	1, 6, 12, and 18 months
Reovirus 3	1, 6, 12, and 18 months
Sendai	1, 6, 12, and 18 months
Immunofluorescence Assay	
Helicobacter hepaticus	6 months
Mouse adenoma virus-FL	12 and 18 months
M. arthritidis	18 months
MCMV	18 months
Parvovirus	18 months
PVM	18 months
Hemagglutination Inhibition	
K	1, 6, and 12 months
MVM	1, 6, and 12 months
Polyoma virus	1, 6, and 12 months

Results

All test results were negative.