NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 459

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *t*-BUTYLHYDROQUINONE

(CAS NO. 1948-33-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

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

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

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

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

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). Listings of all published NTP reports and ongoing studies are also available from NTP Central Data Management. The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

t-BUTHYLHYDROQUINONE

(CAS NO. 1948-33-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

May 1997

NTP TR 459

NIH Publication No. 97-3375

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

CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

K.M. Abdo, Ph.D., Study Scientist
G.A. Boorman, D.V.M., Ph.D.
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
L.T. Burka, Ph.D.
M.R. Elwell, D.V.M., Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D.
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

Southern Research Institute

Conducted 13-week, 2-year, and long-term studies, evaluated pathology findings

J.D. Prejean, Ph.D., Principal Investigator
D.R. Farnell, D.V.M., Ph.D.
J.E. Heath, D.V.M.
R.H. James, M.S.
C. Lindamood, Ph.D.

Experimental Pathology Laboratories, Inc.

Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
S. Botts, D.V.M., Ph.D.
K. Yoshitomi, D.V.M., Ph.D.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

Analytical Sciences, Inc.

Provided statistical analyses

R.W. Morris, M.S., Principal Investigator
N.G. Mintz, B.S.
S. Rosenblum, M.S.

NTP Pathology Working Group

Evaluated slides, prepared pathology report on rats (9 January 1995)

J.C. Seely, D.V.M., Chairperson
PATHCO, Inc.
S. Botts, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
M.R. Elwell, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
A. Radovsky, D.V.M., Ph.D.
National Toxicology Program
B. Short, D.V.M., Ph.D.
SmithKline-Beecham

Evaluated slides, prepared pathology report on mice (24 February 1994)

P.K. Hildebrandt, D.V.M., Chairperson
PATHCO, Inc.
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J. Leininger, D.V.M, Ph.D.
Chemical Industry Institute of Toxicology
J. Mahler, D.V.M.
National Toxicology Program
C. Morris, D.V.M., M.S., Observer
R.P.S.
A. Radovsky, D.V.M., Ph.D.
National Toxicology Program
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

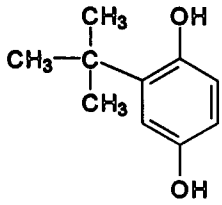
Biotechnical Services, Inc.

Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
J.R. Carlton, B.A.
L.M. Harper, B.S.
T.A. King-Hunter, B.S.
D.C. Serbus, Ph.D.

CONTENTS

ABSTRACT



t-BUTYLHYDROQUINONE
CAS No. 1948-33-0
Chemical Formula: $C_{10}H_{14}O_2$ Molecular Weight: 166.22

Synonyms: Tert-butyl-hydroquinone; 2-(1,1-dimethylethyl)-1,4-benzenediol; tert-butyl-1,4-benzenediol; mono-tertiary-butylhydroquinone; 2-(1,1-dimethyl)hydroquinone; TBHQ; MTBHQ
Trade Names: Sustane; Tenox TBHQ; Banox 20BA

t-Butylhydroquinone is used as an antioxidant in cosmetic products such as lipsticks, eye shadows, perfumes, blushers, and skin care preparations at concentrations ranging from 0.1% to 1.0%; the chemical is also used at concentrations up to 0.02% in oils, fats, and meat products to prevent rancidity, and as a polymerization inhibitor for various polyunsaturated polyesters (CIR, 1986). *t*-Butylhydroquinone was nominated for toxicity and carcinogenicity testing by the Food and Drug Administration. Toxicology and carcinogenicity studies were conducted in F344/N rats and B6C3F$_1$ mice. Mice were exposed to *t*-butylhydroquinone (99% pure) in feed for 13 weeks or 2 years. For rats, exposure to *t*-butylhydroquinone began *in utero* and continued through lactation. After weaning, pups were fed diets containing the same levels of *t*-butylhydroquinone as those given to their respective dams for 13 weeks or for up to 30 months. The oral route of administration was selected for these studies because *t*-butylhydroquinone is used as a food additive and human exposure occurs predominantly through this route. In addition to the oral route of exposure, rats were exposed prenatally because perinatal exposure to butylated hydroxytoluene (a structurally related chemical) induced hepatocellular neoplasms in rats. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells *in vitro* and in mouse bone marrow cells *in vivo*.

13-WEEK STUDY IN RATS

In the perinatal exposure phase of the 13-week study, groups of 10 female rats (F_0) were fed 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *t*-butylhydroquinone from 2 weeks prior to cohabitation until the F_1 pups were weaned. F_0 females exposed to 20,000 or 40,000 ppm did not litter. The number of pup deaths in the 5,000 and 10,000 ppm groups was greater than that in the control group, and the average number of surviving pups per litter in the 10,000 ppm group was less than that in the control group. Mean body weights of pups exposed perinatally to 5,000 or 10,000 ppm were lower than that of the controls at the time of weaning.

Groups of 10 male and 10 female F_1 rats continued to receive diets containing 0, 2,500, 5,000, or 10,000 ppm *t*-butylhydroquinone for 13 weeks following weaning. These dietary levels corresponded to approximately 200, 400, or 800 mg *t*-butylhydroquinone/kg body weight (males) or 200, 400, or 750 mg/kg (females) per day. All rats survived to the end of the study. The final mean body weights of males and females in the 5,000 and 10,000 ppm groups were significantly lower than those of the controls, as was the mean body weight gain of males exposed to 10,000 ppm. However, interpretation of these findings was complicated by the significantly

lower initial mean body weights of the 10,000 ppm groups. Differences in initial body weights were due to *in utero* exposure to *t*-butylhydroquinone. Feed consumption by exposed groups of rats was lower than that by controls at week 2, and feed consumption by 5,000 and 10,000 ppm males and 10,000 ppm females was slightly lower than that by controls at the end of the study. Hair discoloration in all exposed groups of rats, except females exposed to 2,500 ppm, was the only clinical observation considered related to chemical exposure. The mean spermatid count, spermatid heads per testis, and spermatid heads per gram of testis were significantly decreased in males exposed to 5,000 ppm. The estrous cycles of females exposed to 2,500 or 5,000 ppm were significantly longer than that of the controls. There were no biologically significant changes in clinical pathology parameters or in organ weights.

Increased incidences of hyperplasia of the nasal respiratory epithelium were observed in males exposed to 5,000 ppm and males and females exposed to 10,000 ppm, and an increased incidence of nasal exudate was observed in males in the 10,000 ppm group. Increased incidences of pigmentation were observed in the spleen of male and female rats exposed to 5,000 or 10,000 ppm. Based on lower final mean body weights and decreased feed consumption in males and females exposed to 10,000 ppm *t*-butylhydroquinone, exposure concentrations selected for the long-term rat study were 1,250, 2,500, and 5,000 ppm.

13-Week Study in Mice

Groups of 10 male and 10 female mice were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *t*-butylhydroquinone for 13 weeks. These dietary levels corresponded to approximately 440, 880, 1,950, 4,000, and 8,400 mg *t*-butylhydroquinone/kg body weight (males) or 500, 1,100, 2,200, 4,600, and 9,000 mg/kg body weight (females) per day. There were no exposure-related deaths. Final mean body weights and body weight gains of males and females exposed to 10,000, 20,000, or 40,000 ppm were significantly less than those of the controls. Feed consumption by exposed mice appeared to be similar to that by controls, but there was excessive scatter of feed by mice exposed to 10,000, 20,000, or 40,000 ppm. Therefore, feed consumption by male and female mice in these groups was likely less than that by controls. Significant increases in segmented neutrophil counts occurred at week 3 and at the end of the study in females exposed to 10,000 ppm and males and females exposed to 20,000 or 40,000 ppm. Left caudal, left epididymis, and left testis weights of males exposed to 10,000 or 40,000 ppm were generally significantly lower than those of the controls. The estrous cycle of females exposed to 40,000 ppm was significantly longer than that of the control group. There were no biologically significant differences in organ weights.

Increased incidences and severities of mucosal hyperplasia were observed in the forestomach of males exposed to 20,000 or 40,000 ppm and in females exposed to 10,000, 20,000, or 40,000 ppm, and increased incidences of inflammation were observed in the nose and skin of males and females exposed to 10,000, 20,000, or 40,000 ppm. Increased incidences of hyperplasia also occurred in the skin of males and females exposed to 10,000, 20,000, or 40,000 ppm. Based on lower final mean body weights, increased incidences of inflammation of the nose and skin, increased incidences of forestomach mucosal hyperplasia, and increased severity of nonneoplastic lesions observed in mice exposed to 10,000, 20,000, or 40,000 ppm, exposure concentrations selected for the 2-year study were 1,250, 2,500, and 5,000 ppm.

Long-Term Study in Rats

In the perinatal exposure phase of the long-term study, groups of 60 female F_0 rats were fed diets containing 0, 1,250, 2,500, or 5,000 ppm *t*-butylhydroquinone, beginning 2 weeks prior to cohabitation and continuing until F_1 pups were weaned. Following weaning, groups of 70 male and 70 female F_1 rats continued to receive diets containing 0, 1,250, or 5,000 ppm, and groups of 68 male and 68 female rats continued to receive diets containing 2,500 ppm. The duration of dosing in feed was 123 weeks postweaning for males and 129 weeks for females. These exposure concentrations resulted in daily doses of approximately 50, 100, and 200 mg *t*-butylhydroquinone/kg body weight (males) or 60, 120, and 240 mg/kg (females). Ten male and ten female F_1 rats from each exposure group were evaluated at 3 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of females exposed to 5,000 ppm was significantly greater than that of the control group. The mean body weights of males and females exposed to 5,000 ppm were generally less than those of the controls throughout the study. Feed consumption by exposed groups was similar to that by controls. Clinical findings of hair discoloration in exposed groups of males and females were considered to be related to chemical exposure.

Pathology Findings

No increased neoplasm incidences in male or female rats were attributed to *t*-butylhydroquinone exposure. The incidences of mammary gland fibroadenoma and fibroadenoma or adenoma (combined) were significantly decreased in males exposed to 1,250 ppm and in all exposed groups of females; and combined incidences of mammary gland fibroadenoma, adenoma, or carcinoma were significantly decreased in all groups of exposed females. The decreases occurred with significant negative trends. Incidences of renal cysts and inflammation were generally increased in exposed groups of male rats.

2-Year Study in Mice

Groups of 60 male and 60 female mice received 0, 1,250, 2,500, or 5,000 ppm *t*-butylhydroquinone in feed for 104 to 105 weeks. These exposure concentrations resulted in daily doses of approximately 150, 300, or 600 mg *t*-butylhydroquinone/kg body weight (males) or 150, 300, or 700 mg/kg (females). As many as 10 males and 10 females from each exposure group were evaluated at 15 months.

Survival, Body Weights, and Feed Consumption

Survival of all exposed groups of males and females was similar to that of the control groups. Mean body weights of the 5,000 ppm groups were generally lower than those of the control groups from week 13 until the end of the study. Feed consumption by exposed groups of males and females was similar to that by the controls. There were no biologically significant differences in clinical pathology parameters between control and exposed groups of mice.

Pathology Findings

No increased incidences of neoplasms or nonneoplastic lesions in male or female mice were considered to be related to *t*-butylhydroquinone exposure.

Genetic Toxicology

t-Butylhydroquinone was not mutagenic in any of four strains of *Salmonella typhimurium*, with or without liver S9 metabolic activation enzymes. It did, however, induce sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells in the presence, but not the absence, of S9. No increase in the frequency of micronucleated erythrocytes was observed in bone marrow of male mice treated with *t*-butylhydroquinone.

Conclusions

Under the conditions of this long-term feed study, there was *no evidence of carcinogenic activity** of *t*-butylhydroquinone in male or female F344/N rats exposed to 1,250, 2,500, or 5,000 ppm. Under the conditions of this 2-year feed study, there was *no evidence of carcinogenic activity* of *t*-butylhydroquinone in male or female B6C3F$_1$ mice exposed to 1,250, 2,500, or 5,000 ppm.

Exposure of rats to *t*-butylhydroquinone in feed resulted in decreased incidences of mammary gland neoplasms in males and females.

---

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

Summary of the Long-term and 2-Year Carcinogenesis and Genetic Toxicology Studies of *t*-Butylhydroquinone

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 1,250, 2,500, or 5,000 ppm (approximately 50, 100, or 200 mg/kg per day)	0, 1,250, 2,500, or 5,000 ppm (approximately 60, 120, or 240 mg/kg per day)	0, 1,250, 2,500, or 5,000 ppm (approximately 150, 300, or 600 mg/kg per day)	0, 1,250, 2,500, or 5,000 ppm (approximately 150, 300, or 700 mg/kg per day)
Body weights	5,000 ppm group less than controls	5,000 ppm group less than controls	5,000 ppm group less than controls	5,000 ppm group less than controls
Survival rates	8/60, 7/60, 1/58, 14/60	10/60, 11/60, 16/58, 17/60	39/50, 46/50, 38/51, 42/51	38/51, 35/52, 40/51, 43/54
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None
Decreased incidences	Mammary gland: fibroadenoma (10/60, 4/60, 4/58, 7/60); fibroadenoma or adenoma (11/60, 4/60, 5/58, 7/60)	Mammary gland: fibroadenoma (43/60, 33/60, 34/58, 27/60); fibroadenoma, adenoma, or carcinoma (48/60, 34/60, 34/58, 30/60)	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA97, TA98, TA100, and TA102			
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9; negative without S9			
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9; negative without S9			
Micronucleated erythrocytes Mouse bone marrow *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.

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 *t*-butylhydroquinone on 20 June 1995, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

Arnold L. Brown, M.D., Chairperson
University of Wisconsin Medical School
Madison, WI

Thomas L. Goldsworthy, Ph.D.
Department of Environmental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Meryl H. Karol, Ph.D.
Department of Environmental Occupational Health
University of Pittsburgh
Pittsburgh, PA

Curtis D. Klaassen, Ph.D.
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Claudia S. Miller, M.D., Principal Reviewer
University of Texas Health Sciences Center
San Antonio, TX

Janardan K. Reddy, M.D., Principal Reviewer
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D.
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D.
Division of Biostatistics
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D.
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Mary Jo Vodicnik, Ph.D., Principal Reviewer
University of Indiana
Indianapolis, IN

Jerrold M. Ward, D.V.M., Ph.D.
National Cancer Institute
Frederick, MD

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 20 June 1995, the draft Technical Report on the toxicology and carcinogenesis studies of *t*-butylhydroquinone received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of *t*-butylhydroquinone by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in male and female rats and mice. The proposed conclusions were that there was *no evidence of carcinogenic activity* of *t*-butylhydroquinone in male or female F344/N rats or in male or female $B6C3F_1$ mice.

Dr. Vodicnik, a principal reviewer, agreed with the proposed conclusions. She complimented the staff on the comprehensive review of the literature while recommending that a reference to a flawed study be deleted. Dr. Miller suggested the reference be kept but with the limitations of the study noted in the text (see page 19).

Dr. Reddy, the second principal reviewer, agreed with the proposed conclusions. He inquired as to whether the splenic pigmentation was hemosiderin or whether this could be the compound or lipofuscin. Dr. J.R. Hailey, NIEHS, said some stains for hemosiderin and, perhaps, lipofuscin would be done (see page 46).

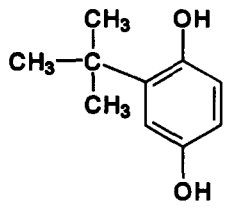
Dr. Reddy asked whether the nephropathy in male rats was associated with increased levels of $\alpha 2\mu$-globulin. Dr. Hailey responded that a minor contribution could not be ruled out absolutely, but there was no evidence in the subchronic or chronic studies that this protein played a significant role.

Dr. Miller, the third principal reviewer, agreed with the proposed conclusions. She thought a comparison of the *t*-butylhydroquinone dose levels used in rats and mice and those found in a typical human diet would be useful for the reader (see page 13).

Dr. W. Faber, Eastman Chemical Company, commended the NTP on a well conducted study. He stated that the possible effect of *t*-butylhydroquinone on the male and female reproductive systems seemed rather tenuous given the lack of a clear dose-response relationship as well as lack of findings in the teratology and multigeneration studies. He said the mention of *t*-butylhydroquinone as being structurally related to hydroquinone and butylated hydroxytoluene, which are described as carcinogenic chemicals, should be clarified to indicate these chemicals are carcinogenic in experimental animals.

Dr. Miller moved that the Technical Report on *t*-butylhydroquinone be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Reddy seconded the motion, which was accepted unanimously with 10 votes.

INTRODUCTION



t-BUTYLHYDROQUINONE
CAS No. 1948-33-0
Chemical Formula: $C_{10}H_{14}O_2$ Molecular Weight: 166.22

Synonyms: Tert-butyl-hydroquinone; 2-(1,1-dimethylethyl)-1,4-benzenediol; tert-butyl-1,4-benzendiol; mono-tertiary-butylhydroquinone; 2-(1,1-dimethyl)hydroquinone; TBHQ; MTBHQ
Trade Names: Sustane; Tenox TBHQ; Banox 20BA

CHEMICAL AND PHYSICAL PROPERTIES

t-Butylhydroquinone is a white to light tan crystalline solid with a very slight but characteristic odor and a melting point of 126.5° to 128.5° C. It is soluble in ethanol (60%), ethyl acetate (60%), propylene glycol (30%), and to a lesser extent in fats and oils (5% in lard at 50° C, 10% in cottonseed oil, corn oil, or soybean oil, and 5% in safflower oil at 25° C). *t*-Butylhydroquinone is only slightly soluble in water (less than 1% at 25° C) (Sims and Fioriti, 1980).

PRODUCTION, USE, AND HUMAN EXPOSURE

t-Butylhydroquinone can be prepared by acid-catalyzed alkylation of hydroquinone with either isobutylene or *t*-butanol (*Kirk-Othmer*, 1981; CIR, 1986).

The public portion of the Toxic Substances Control Act (TSCA) Inventory of Chemicals in Commerce lists two manufacturers of *t*-butylhydroquinone. One manufacturer reported production ranging from 100,000 to 1,000,000 pounds in 1977. No production data were provided for the other manufacturer (USEPA, 1985). The U.S. International Trade Commission reported that 47,983 pounds of *t*-butylhydroquinone were imported in 1983 (USITC, 1984). More recent information was not available. According to the National Occupational Exposure Survey, a total of 18,167 workers were potentially exposed to this chemical. Of this total, 3,687 were females (NIOSH, 1990).

t-Butylhydroquinone is used as an antioxidant in cosmetic products such as lipsticks, eye shadows, perfumes, blushers, and skin care preparations at concentrations ranging from 0.1% to 1.0%; the chemical is also used at concentrations of up to 0.02% in oils, fats, and meat products to prevent rancidity and as a polymerization inhibitor for various polyunsaturated polyesters (CIR, 1986).

t-Butylhydroquinone is permitted for use in any food at a maximum level of 200 mg *t*-butylhydroquinone/kg fat or oil content of the food (21 CFR §172.185), and the entire United States population is potentially exposed. Based on the actual usage of *t*-butylhydroquinone and its typical level in food, the potential daily intake using actual body weights of individuals surveyed has been estimated to be 0.42 mg *t*-butylhydroquinone per day (0.008 mg *t*-butylhydroquinone per kg body weight per day) (Flamm *et al.*, 1982).

The amount of *t*-butylhydroquinone approved for use as a polymerization inhibitor in cross-linked polyesters resins used as articles or components of articles

intended for use in contact with food is limited to less than or equal to 0.01% by weight of finished resin (21 CFR §177.2420). Based on the toxicology data available, the Cosmetic Ingredient Review Expert Panel concluded that *t*-butylhydroquinone may be safely used as a cosmetic ingredient at concentrations not to exceed 0.1% (CIR, 1991).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Orally administered *t*-butylhydroquinone is rapidly absorbed and excreted primarily in the urine as a sulfate conjugate and a glucuronide; small amounts are excreted as unchanged *t*-butylhydroquinone. Rats given single oral doses ranging from 0.1 to 0.4 g/kg body weight eliminated 65% to 95% of the administered dose in the urine in 3 to 4 days as 4-O-sulfate (57% to 80%), unchanged *t*-butylhydroquinone (4% to 12%), and 4-O-glucuronide (4%) (Astill *et al.*, 1975). Dogs given a single oral dose of 0.1 g/kg eliminated virtually all of the dose in the urine in 4 days as 4-O-sulfate (69% to 85%), 4-O-glucuronide (24% to 31%), and unchanged *t*-butylhydroquinone (3%) (Astill *et al.*, 1975).

Rats receiving single oral doses (0.015 to 0.92 g/kg) of *t*-butylhydroquinone radiolabeled at carbons 2, 3, 5, and 6 eliminated 82% to 88% of the label in urine, 2% to 6% in the feces, and less than 0.1% as CO_2; less than 0.2% of the radiolabel remained in the body after 4 days (Astill and Roudabush, 1973). Because the amount of *t*-butylhydroquinone eliminated as CO_2 was minimal, the authors concluded that *t*-butylhydroquinone was not catabolized via intermediary metabolic pathways. The proportion of metabolic compounds in the urine of dogs fed diets with up to 0.5% *t*-butylhydroquinone for 2 years remained unchanged throughout the study. However, in rats given up to 0.5% *t*-butylhydroquinone in the diet for 20 months, the proportion of glucuronide was somewhat elevated. Residues in liver, kidney, brain, and fat from rats in the 0.16% and 0.5% dose groups in the long-term study were negligible, suggesting that *t*-butylhydroquinone does not accumulate in the body with prolonged exposure (Astill *et al.*, 1975).

3-*t*-Butyl hydroxyanisole undergoes oxidative demethylation to *t*-butylhydroquinone by the cytochrome P_{450} system *in vivo* in dogs, rats, and man (Astill *et al.*, 1962; Verhagen *et al.*, 1989), and *in vitro* in rat liver microsomes (Rahimthula *et al.*, 1982; Armstrong and Wattenberg, 1985). *t*-Butylhydroquinone is subsequently oxidized to 2-*t*-butyl (1,4)paraquinone. The conversion of *t*-butylhydroquinone to 2-*t*-butyl-(1,4)paraquinone is substantially accelerated by prostaglandin H synthetase and lipoxygenase (Schilderman *et al.*, 1993).

Humans

Human male volunteers administered a single dose (2 mg/kg) of *t*-butylhydroquinone in high-fat food (30% corn oil) excreted 95% to 103% of the dose in the urine in 2 to 3 days as 4-O-sulfate (73% to 88%), 4-O-glucuronide (15% to 22%), and unchanged *t*-butylhydroquinone (less than 1%). Human male volunteers administered single doses (1 to 2 mg/kg) of *t*-butylhydroquinone in low-fat food (10% corn oil) eliminated 18% to 51% of the dose in urine in 2 to 3 days as 4-O-sulfate (18% to 51%), 4-O-glucuronide (0% to 6%), and unchanged *t*-butylhydroquinone (less than 1%) (Astill *et al.*, 1975). These results in human volunteers suggest that absorption of *t*-butylhydroquinone from high-fat diets is much greater than from low-fat diets. The glucuronide and sulfate derivatives of *t*-butylhydroquinone have also been identified by El-Rashidy and Niazi (1983) as metabolites of butylated hydroxyanisole in humans. The results in rats, dogs, and human volunteers suggest that these species metabolize *t*-butylhydroquinone in a similar manner.

BIOCHEMICAL EFFECTS

Experimental Animals

Feeding *t*-butylhydroquinone (up to 0.5% in the diet) to dogs for 2 years and to Sprague-Dawley rats for 20 months did not produce any significant changes in hepatic enzyme activities. No hepatic enlargement and no proliferation of hepatic smooth-surface endoplasmic reticulum were observed (Astill *et al.*, 1975). However, there was significant liver enlargement in Wistar rats receiving 0.5% *t*-butylhydroquinone in feed for 6 days, followed by a basal diet for 24 hours, but there was no concomitant increase in the activities of hepatic microsomal monooxygenase enzymes (Kawano *et al.*, 1981). *t*-Butylhydroquinone (100 mM) administered daily by gavage for 5 days to CD-1 mice caused an elevation

of glutathione transferase activity in the glandular stomach. The enzyme activity levels in the lung or kidney of CD-1 mice were unchanged (De Long *et al.*, 1985).

t-Butylhydroquinone inhibited the biosyntheses of prostaglandins E_1 and E_2 by the microsomal fraction of bovine seminal vesicles (Boehme and Branen, 1977). Astill and Mulligan (1977) studied the effect of the edible stabilizers propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, and *t*-butylhydroquinone on intragastric *N*-nitrosamine formation. Following a 12-hour fasting period, groups of 10 Sprague-Dawley rats were administered single doses of 125 mg sodium nitrite/kg body weight via gastric intubation in 2.5% (w/v) aqueous solution and 1,000 mg dimethylamine/kg body weight in 20% aqueous solution, followed immediately by the test compound in doses of 25, 75, or 225 mg/kg in corn oil. Sodium ascorbate (200 mg/kg) in 4% (w/v) aqueous solution was used as a positive control. The vehicle control group of ten animals was administered corn oil. The indices of *N*-nitrosamine formation 48 hours after dosing were the activities of serum glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), ornithine carbamoyltransferase (OCT), and the extent of hepatic necrosis. The nitrosamine-forming mixture alone induced extensive hepatic necrosis and 4-, 19-, and 24-fold increases in serum OCT, GPT, and GOT activities, respectively. Ascorbate completely suppressed enzyme induction. *t*-Butylhydroquinone administered at a dose level of 225 mg/kg gave 60% protection against hepatic necrosis and appreciably suppressed increases in enzyme activities. Administered at dose levels of 25 and 75 mg/kg, *t*-butylhydroquinone had no observable significant effect on the nitrosamine-forming system. The gross liver damage observed in the rats exposed to the nitrosamine-forming system was absent in the corn oil control group.

t-Butylhydroquinone appears to be a strong inactivator of phage DNA as well as a potent inducer of 7-hydroxy-8-oxo-2′-deoxyguanosine *in vitro* (Schilderman *et al.*, 1993). The latter compound is an oxidative DNA damage product resulting from C8 oxidation of deoxyguanosine. *t*-Butylhydroquinone induced excess production of superoxide anion in rat liver microsomes. Excess superoxide induces injury of the hepatocyte plasma membranes (Bergmann *et al.*, 1992).

Humans

No information on the biochemical effects of *t*-butylhydroquinone in humans was found in a search of the available literature.

TOXICITY

Experimental Animals

The reported oral LD_{50} for *t*-butylhydroquinone ranges from 480 to 1,000 mg/kg for rats (Epstein *et al.*, 1967; Astill *et al.*, 1975) and is 1,000 mg/kg for mice (RTECS, 1983).

Compounds structurally related to *t*-butylhydroquinone (butylated hydroxyanisole and butylated hydroxytoluene) have been shown to induce lung lesions and increased prothrombin time (Takahashi and Hiraga, 1978). No lung lesions were observed in CRL:CD-1 male mice 5 days after administration of a single intraperitoneal injection of 62.5, 125, 250, or 500 mg *t*-butylhydroquinone/kg body weight. However, the two highest doses were lethal (Krasavage and O'Donohue, 1984). Intraperitoneal injections of 50, 100, or 150 mg/kg as a 10% solution in acetone:soy oil (1:10 v/v) did not increase prothrombin time or cause hemorrhagic death in male albino rats [CRL:COB CD(SD)BR] (Krasavage, 1984).

t-Butylhydroquinone fed to rats (sex and strain not specified) at a concentration of 1% in the diet for 22 days caused a slight depression in body weight gain, but did not cause death or pathologic alterations (Astill *et al.*, 1975).

Fischer rats receiving 1% *t*-butylhydroquinone in the diet (as a 4% solution in corn oil) developed hyperplasia of the basal cell layer in the forestomach epithelium (Nera *et al.*, 1984). Similar lesions were observed in Wistar rats consuming a diet containing 2% *t*-butylhydroquinone for 28 days (Altmann *et al.*, 1985). Twice-weekly applications of 1 mL/kg hair dye formulation containing a 1:1 mixture of 0.3% *t*-butylhydroquinone with 6% hydrogen peroxide for 13 weeks to the abraded skin of male and female New Zealand rabbits did not cause any compound-related toxicity (Burnett *et al.*, 1976). Data collected in this

study included clinical pathology (complete blood count, methemoglobin concentration, fasting blood sugar, blood urea nitrogen, alkaline phosphatase, serum glutamic-oxaloacetic transaminase, urine color, urine pH, urine albumin, urine glucose, and occult blood), relative liver, kidney, adrenal, heart, thyroid, spleen, and brain weights, observations of gross abnormalities, and histopathology.

Application of 0.1 mL hydrophilic ointment containing 1% or 5% *t*-butylhydroquinone to a 3.2 cm^2 area of the skin of black guinea pigs 5 days per week for 13 weeks caused a weak depigmentation at the application site in females, but not in males. A similarly applied dose of 0.1% did not cause depigmentation in either males or females (CIR, 1991).

Humans

t-Butylhydroquinone may be a skin irritant in humans. In patch testing, five out of 1,096 patients with facial dermatitis were shown to be allergic to *t*-butylhydroquinone present in their cosmetics (White *et al.*, 1984). A 71-year-old woman who for 15 years was observed to have dermatitis at various body sites was found to be allergic to *t*-butylhydroquinone (Calnan, 1981). Of a total of 271 subjects exposed to lipstick products containing 0.054%, 0.11%, 0.14%, or 0.15% *t*-butylhydroquinone by weight, only one subject exposed to the product containing 0.14% had intense erythema, suggesting a nonspecific irritant effect (CIR, 1986).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

t-Butylhydroquinone produced no teratogenic effects when given to pregnant Sprague-Dawley rats at concentrations of 0.125%, 0.25%, or 0.5% in the diet from days 6 to 16 of gestation. Mean body weights and feed consumption of treated dams were similar to those of the controls. Average numbers of corpora lutea, implantation sites, viable fetuses, and resorptions and fetal body weights, mortality, and sex ratio were not affected at any dose. No external anomalies were observed in the 849 fetuses examined. Half of these fetuses were examined for soft-tissue abnormalities, and three were found to be abnormal. Of these three, one was from the control group and two were from a single litter in the 0.5% group. The abnormalities observed were low body weight and hydrocephalus (in the control and 0.5% groups) and transposition of a major blood vessel (in the 0.5% group) (Krasavage, 1977).

A diet containing 0% or 0.5% *t*-butylhydroquinone was fed to groups of 15 male and 15 female Sprague-Dawley rats for three successive generations (Astill *et al.*, 1975). Rats were mated to produce two litters per generation, with the next generation selected from weanlings of the second litter. Littering throughout the study produced 2,090 rats. The following parameters were assessed: gonadal functions, estrus cycles, mating, conception rates, gestation rates, parturition, and lactation; measurements of these parameters in the treated group were similar to those in the control group. Slight increases in F_1 pup weights were observed; however, no similar effect was produced in a second experiment designed to investigate these results. No difference between the treated and control groups was observed when the F_3 pups were examined grossly for skeletal muscle and soft tissue abnormalities. The F_{3a} groups were maintained on their diets for 11 months, then sacrificed. Electron microscopic examination of the livers of some animals indicated no abnormalities (Astill *et al.*, 1975). The doses used in these reproductive studies may have been too low to adequately determine the potential of *t*-butylhydroquinone to have an effect on reproduction or to cause fetal malformations.

Humans

No information on the reproductive and developmental toxicity of *t*-butylhydroquinone in humans was located in a search of the available literature.

CARCINOGENICITY

Experimental Animals

t-Butylhydroquinone at concentrations of 0%, 0.016%, 0.05%, 0.16%, or 0.5% in the diet was fed to groups of 55 male and 55 female Sprague-Dawley rats for up to 20 months. No differences in growth rate, feed intake and/or utilization, mortality, clinical chemistry, hematology, urinalysis, organ weights, or histopathology were observed between control and

treated groups at any time during the study (Terhaar and Krasavage, 1968a).

Diets containing 5% unheated or heated cottonseed oil solutions of 0.02%, 0.10%, or 0.50% *t*-butylhydroquinone were fed to groups of 15 male and 15 female Sprague-Dawley rats for 6 months (Astill *et al.*, 1975). In this study, the temperature of cottonseed oil for heated diets was raised over a 1-hour period to 375° F, and this temperature was maintained for 3 hours. Growth rate, feed utilization, mortality, organ weights, hematology, clinical chemistry, and urinalysis parameters were measured, and gross and microscopic evaluations on 27 organs were made. The three deaths in the 0.50% group were not considered to be related to *t*-butylhydroquinone. No compound-related effects on body weight, feed utilization, hematology, urinalysis, or histopathology were observed. There were slight increases in the relative weights of the testes and liver of male rats in the 0.50% *t*-butylhydroquinone/heated oil group and in the relative weights of the liver of female rats in the 0.20% and 0.50% *t*-butylhydroquinone/heated oil groups (Astill *et al.*, 1975).

These studies were considered inadequate for evaluating the carcinogenicity of *t*-butylhydroquinone for three reasons: *t*-butylhydroquinone was not tested at the maximum tolerated dose (previous short-term studies have shown that Sprague-Dawley rats can tolerate a dose of 1% *t*-butylhydroquinone); the duration of the studies was inadequate for carcinogenicity testing; and only 17 animals survived to the end of the Terhaar and Krasavage (1968a) study.

Groups of four male and four female beagle dogs were fed diets containing 0.05%, 0.15%, or 0.5% *t*-butylhydroquinone for 2 years (Astill *et al.*, 1975). Eight males and eight females served as controls. No compound-related effects on hematology, clinical chemistry, or urinalysis parameters were observed at weeks 12, 26, 52, 78, and 104 of the study. No compound-related changes (gross or microscopic) were noted in any of the tissues examined.

Recent studies have demonstrated that *t*-butylhydroquinone has a promoting effect on chemically induced tumors. The combined treatment with *t*-butylhydroquinone (1% in feed), sodium nitrite (0.3% in drinking water) and/or sodium ascorbate (1% in feed) increased the thickness of mucosae of the forestomach, glandular stomach, and esophagus of 4-week-old male F344/N rats following 4 to 6 weeks of treatment (Kawabe *et al.*, 1994; Yoshida *et al.*, 1994). In a multi-organ carcinogenesis model, *t*-butylhydroquinone (1% in the diet) significantly increased the incidences of esophageal papillary hyperplasia or nodular hyperplasias and papillomas, as well as forestomach papillomas, but significantly decreased the multiplicity of colon adenocarcinomas in male F344/N rats (Hirose *et al.*, 1993). Tumors in this study were initiated by pretreatment with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (100 mg/kg), *N*-ethyl-*N*-hydroxyethyl nitrosamine (750 mg/kg), *N*-methylbenzyl nitrosamine (two subcutaneous injections of 0.5 mg/kg), and 1,2-dimethyl hydrazine (40 mg/kg).

F344/N rats given 1% *t*-butylhydroquinone in the diet had decreased numbers and smaller sized diethyl nitrosamine-initiated preneoplastic liver foci (glutathione S-transferase placental form positive foci) than did the positive controls (Hasegawa *et al.*, 1992). Mammary gland neoplasm development was reduced in female Sprague-Dawley rats fed diets containing 0.8% *t*-butylhydroquinone for 51 weeks following initiation with dimethylbenz(a)anthracene. However, in the same study, the incidence of induced ear duct tumors was not affected by *t*-butylhydroquinone treatment (Hirose *et al.*, 1988). Six-week-old male F344/N rats treated with *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine for 4 weeks then fed diets containing 2% *t*-butylhydroquinone had greater incidences of urinary bladder papillary or nodular hyperplasia than those in controls receiving *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine only (Tamano *et al.*, 1987).

t-Butylhydroquinone is structurally related to hydroquinone, butylated hydroxyanisole, and butylated hydroxytoluene. In a 2-year carcinogenicity study, 25 or 50 mg hydroquinone/kg body weight administered by gavage was carcinogenic to F344/N rats, causing increased incidences of renal tubule cell adenomas in males and mononuclear cell leukemia in females. Hydroquinone at doses of 50 or 100 mg/kg administered by gavage was carcinogenic to female B6C3F$_1$ mice causing an increased incidence of hepatocellular neoplasms (NTP, 1989).

In 2-year carcinogenicity studies, butylated hydroxytoluene at concentrations of 3,000 or 6,000 ppm in feed was not carcinogenic to male or female F344/N rats or B6C3F$_1$ mice. There was a significant increase in the incidence of lung neoplasms in 3,000 ppm female mice, but not in 6,000 ppm females; because there was no significant dose-related positive trend, this increase could not be clearly related to butylated hydroxytoluene exposure (NCI, 1979). No evidence of carcinogenicity was observed in male or female B6C3F$_1$ mice fed diets containing 200, 1,000, or 5,000 ppm butylated hydroxytoluene for 96 weeks, followed by a basal diet for an additional 8 weeks (Shirai *et al.*, 1982). No carcinogenic effects were observed in male or female Wistar rats fed diets containing 0.25% or 1% butylated hydroxytoluene for up to 104 weeks (Hirose *et al.*, 1981). Hepatocellular neoplasms were induced in Wistar rats exposed beginning *in utero* to butylated hydroxytoluene (Olsen *et al.*, 1983). The carcinogenicity of butylated hydroxytoluene has been previously investigated in Wistar rats (Hirose *et al.*, 1981) and B6C3F$_1$ mice (Shirai *et al.*, 1982). Butylated hydroxytoluene administered in concentrations of up to 10,000 ppm (rats) and 6,000 ppm (mice) in feed did not produce carcinogenic effects. These studies were performed on one generation and were terminated at 108 weeks, while in the Olsen *et al.* (1983) study, the exposure began *in utero* and continued throughout lactation, weaning, and adulthood.

Male and female F344/N rats fed diets containing 0.5% or 2% butylated hydroxyanisole for 104 weeks followed by a basal diet for an additional 8 weeks had chemical-related increased incidences of squamous cell carcinoma of the forestomach. The incidences of these neoplasms in the 2% groups of males and females were significantly higher than those in the controls (Ito *et al.*, 1982). Feeding butylated hydroxyanisole to male F344/N rats at a concentration of 2% for 13 weeks caused proliferation of the forestomach epithelium. The rats recovered from these effects following 1 week on a basal diet (Iverson *et al.*, 1985).

GENETIC TOXICOLOGY

t-Butylhydroquinone was not mutagenic in *Salmonella typhimurium* gene mutation assays performed with or without liver S9 activation enzymes (Bonin and Baker, 1980; Hageman *et al.*, 1988; Matsuoka *et al.*, 1990; Zeiger *et al.*, 1992). Additionally, it did not produce mitotic gene conversion or mutations, with or without S9, in *Saccharomyces cerevisiae* (Rogers *et al.*, 1992). In cultured mammalian cells, no induction of mutations was noted at the HGPRT locus of Chinese hamster V79 lung cells incubated with primary hepatocytes after treatment with 0.17 to 3.4 μg *t*-butylhydroquinone/mL medium (Rogers *et al.*, 1992). However, oxidative damage was detected in single-strand phage PhiX 174 DNA (Schilderman *et al.*, 1993) and double-strand phage PhiX 174 relaxed form DNA (Li and Trush, 1994) exposed to *t*-butylhydroquinone in the presence of micromolar concentrations of Cu^{++}. No consistent induction of sister chromatid exchanges was observed in Chinese hamster V79 lung cells treated with *t*-butylhydroquinone, with or without S9 (Rogers *et al.*, 1992), but a significant increase in the frequency of chromosomal aberrations was reported in Chinese hamster cells treated with 2.5 to 50 μg/mL without S9 (Phillips *et al.*, 1989; Matsuoka *et al.*, 1990) or 20 to 40 μg/mL in the presence of S9 (Matsuoka *et al.*, 1990). The addition of catalase to the hamster cell cultures without S9 resulted in a substantial decrease in the frequency of *t*-butylhydroquinone-induced chromosomal aberrations (Phillips *et al.*, 1989), thus indicating that generation of H_2O_2 played a role in the observed induction of chromosomal damage. Because *t*-butylhydroquinone autooxidizes in solution to *t*-butylquinone, forming superoxide and H_2O_2, the mutagenic effects that are observed in cells exposed to *t*-butylhydroquinone are most likely the indirect result of the release of oxidative byproducts within the cell. Experiments with various radical scavengers provided evidence suggesting that either singlet oxygen or a singlet oxygen-like entity (possibly a copper-peroxide complex) rather than free hydroxyl radicals was responsible for DNA damage in phage induced by phenolic compounds such as *t*-butylhydroquinone (Li and Trush, 1994).

In vivo, dose-related increases in sister chromatid exchanges were induced in bone marrow cells of male Swiss albino mice given single intraperitoneal injections of 0.5 to 200 mg/kg *t*-butylhydroquinone dissolved in corn oil (Mukherjee *et al.*, 1989); the lowest effective dose in this experiment was 2 mg/kg. Induction of chromosomal aberrations (breaks, gaps,

centric fusions, and other abnormalities) was reported in bone marrow cells of male mice administered a single intraperitoneal dose of 200 mg/kg *t*-butylhydroquinone or daily gavage doses of 2 mg/kg for 30 days (Giri *et al.*, 1984); bone marrow analysis was performed 24 hours after the final dosing. Because the authors included gaps in their analyses and did not present the individual classifications of the abnormalities scored, and because for the acute dosing experiment a 24-hour post-treatment harvest time is inappropriate (12 to 17 hours is preferable), these results require independent verification.

Much of the data obtained from studies with metabolites of *t*-butylhydroquinone derive from studies of the parent compound (butylated hydroxyanisole) and concern identification of metabolic pathways, investigations of oxygen radical scavengers or catalase inhibitors on particular endpoints of metabolism, and tumor initiating properties of various butylated hydroxyanisole metabolites. One of the most active metabolites appears to be *t*-butylquinone, which is generated in redox cycling reactions with *t*-butylhydroquinone. Neither of these compounds is active in many of the standard *in vitro* mutagenicity assays. *t*-Butylquinone did not induce gene conversions or reverse mutations in *Saccharomyces cerevisiae*, nor did it induce HGPRT gene mutations or sister chromatid exchanges in V79 cells (Rogers *et al.*, 1992). However, it has been shown to be mutagenic in *S. typhimurium* strains TA98 and TA100 over a limited dose range (10 to 50 μg/plate) and to induce DNA damage in repair-deficient strains of *Bacillus subtilis*; both responses were obtained in the absence of S9 activation (Mizuno *et al.*, 1988). There is one report describing induced DNA damage in the forestomach cells of male rats. In this experiment, single strand breaks were detected by alkaline elution in the DNA of forestomach squamous epithelial cells harvested from Fischer 344 rats 3 hours after the rats received 4 mL of 0.001% or 0.00001% (approximately 0.22 or 0.0022 mg/kg) *t*-butylquinone in corn oil by gavage (Morimoto *et al.*, 1991).

In summary, *t*-butylhydroquinone and the oxidized metabolite, *t*-butylquinone, showed limited evidence of mutagenicity, primarily in mammalian cell systems sensitive to the detection of oxygen radical-induced DNA damage.

Study Rationale

t-Butylhydroquinone was nominated for toxicity and carcinogenicity testing by the Food and Drug Administration because of the potential for increased use of *t*-butylhydroquinone as a substitute for the phenolic antioxidants butylated hydroxyanisole and butylated hydroxytoluene; previous carcinogenicity studies supporting the safe use of *t*-butylhydroquinone were not considered adequate because the maximum tolerated dose was not tested, the studies were of short duration, and survival within the studies was poor. *t*-Butylhydroquinone is also structurally similar to carcinogenic chemicals such as hydroquinone and butylated hydroxyanisole. The oral route of administration was selected for these studies because *t*-butylhydroquinone is used as a food additive and human exposure occurs predominantly through this route. In addition to the oral route of exposure, rats were exposed *in utero* because butylated hydroxytoluene (a structurally related chemical) induced hepatocellular neoplasms in rats exposed *in utero*.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *t*-BUTYLHYDROQUINONE

t-Butylhydroquinone was obtained in two lots (187-1 and 1089-1) from U.O.P., Inc., (Des Plaines, IL). Lot 187-1 was used in the 13-week, long-term, and 2-year studies. Lot 1089-1 was used in the long-term and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix I). Reports on analyses performed in support of the *t*-butylhydroquinone studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

Each lot of the chemical, a fine beige powder, was identified as *t*-butylhydroquinone by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of each lot was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for *t*-butylhydroquinone. Karl Fischer water analysis indicated less than 0.4% water for lot 187-1 and 0.16% water for lot 1089-1. Functional group titration indicated a purity of 99.6% ± 0.5% for lot 187-1 and 99.1% ± 0.4% for lot 1089-1. Thin-layer chromatography of lot 187-1 indicated a major spot and two trace impurities using one system and a major spot, one minor impurity, and one trace impurity using a second system. For lot 1089-1, both thin-layer chromatography systems indicated a major spot, one minor impurity, and one trace impurity. High-performance liquid chromatography of lot 187-1 indicated a major peak and one impurity peak with an approximate area of 0.13% relative to the major peak. High-performance liquid chromatography of lot 1089-1 indicated a major peak and no impurities with peak areas greater than 0.1% relative to the major peak. Additional high-performance liquid chromatography analyses using a linear gradation in the solvent system resolved additional impurities with peak areas of 0.3% to 0.4% relative to the major peak in lots 187-1 and 1089-1. Lot 1089-1 and lot 187-1 were concomitantly analyzed by the same high-performance liquid chromatography method used for the initial purity analyses. The overall purity for each lot was 99%.

Stability studies of the bulk chemical, performed by the analytical chemistry laboratory using high-performance liquid chromatography, indicated that *t*-butylhydroquinone was stable as a bulk chemical when stored for 2 weeks, protected from light, at temperatures up to 60° C. To ensure stability, the chemical was stored at room temperature in sealed containers, protected from light. Stability was monitored 9 weeks after the beginning of the 13-week studies and within 30 days after the end of the studies. For the long-term and 2-year studies, stability was monitored at approximately 4-month intervals and within 30 days after the end of the studies. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations for the 13-week, long-term, and 2-year studies were prepared weekly (Table I1). Homogeneity and stability analyses of the dose formulations were conducted by the analytical chemistry laboratory using high-performance liquid chromatography. Homogeneity was confirmed, and the stability of the dose formulations was confirmed for at least 3 weeks when stored in sealed containers in the dark at 5° C. During the 13-week, long-term, and 2-year studies, the dose formulations were stored in sealed containers in the dark at 5° C for no longer than 3 weeks.

Periodic analyses of the dose formulations of *t*-butylhydroquinone were conducted at the study laboratory using high-performance liquid chromatography. For the 13-week studies, dose formulations were analyzed at the beginning, in the middle, and at the end of the

studies (Table I2). During the long-term and 2-year studies, dose formulations were analyzed approximately every 8 weeks (Table I3). Of the dose formulations used in the 13-week studies, 98% (43/44) were within 10% of the target concentration with no value greater than 16% from the target concentration. In the long-term studies, 219 of the 220 dose formulations used for rats and 185 of the 186 dose formulations used for mice were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

13-WEEK RAT STUDY

The 13-week study was performed to evaluate the cumulative toxic effects of *t*-butylhydroquinone with exposure to the chemical beginning *in utero* and to determine the appropriate doses to be used in the long-term study.

Male and female F344/N rats (F_0 generation) were obtained from Taconic Farms (Germantown, NY). On receipt, the rats were 38 days old. Animals were quarantined for 19 days. Females were 57 days old on the first day of the study and 71 days old on the first day of cohabitation. Before initiation of the study, five male and five female rats were randomly selected for parasite evaluation and gross observation for evidence of disease.

Males acquired for the reproductive toxicity phase were used for breeding purposes only and were not considered part of the study. Groups of 10 female rats (F_0 generation) were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *t*-butylhydroquinone for approximately 6 weeks. Feed was available *ad libitum* for F_0 females from 2 weeks prior to cohabitation until weaning of the F_1 pups. Water was available *ad libitum*. During cohabitation, two F_0 females were housed with one breeder male; F_0 females were housed individually when pregnancy was confirmed. Clinical findings, body weights, and feed consumption were recorded weekly for F_0 females during the first 2 weeks of the study (prior to cohabitation); clinical findings and body weights were also recorded weekly during lactation. Details of the study design and animal maintenance are summarized in Table 1.

During cohabitation, vaginal smears were taken daily from breeder females to determine the presence of sperm. Rats that did not litter by day 25 were killed and uteri were stained with ammonium sulfide and examined for implantation sites. After parturition, pups were examined and the number and sex of pups and the litter weight were recorded. On day 4 postpartum, litters were randomly culled to a maximum of eight rat pups per litter; pup weights were recorded on days 4, 11, 18, and 28. Pups were weaned on day 28.

Male and female F344/N rats for the 13-week base study were offspring (F_1 generation) of the breeders from the perinatal phase of the study. Rats were approximately 34 days old on the first day of the study. At the end of the study, serologic analyses were performed on five male and five female control (F_1 generation) rats using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female F_1 rats were fed diets containing 0, 2,500, 5,000, or 10,000 ppm *t*-butylhydroquinone for 13 weeks after weaning. (No F_1 offspring resulted from F_0 females fed diets containing 20,000 or 40,000 ppm, so these exposure levels were not used in the 13-week rat study.) Feed and water were available *ad libitum*. Rats were housed five per cage. Clinical findings were recorded and the animals were weighed initially, weekly, and at the end of the study; feed consumption was recorded as an average of grams per animal per day. Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected at week 13 from core study (F_1) rats for selected hematology, clinical chemistry, and coagulation analyses. Additionally, clinical pathology analyses were performed on special groups of 10 male and 10 female F_1 rats fed diets containing 0, 2,500, 5,000, or 10,000 ppm *t*-butylhydroquinone for 3 weeks after weaning. Selected hematology and clinical chemistry parameters were measured for these animals on day 5 and at week 3.

For clinical pathology analyses, rats were anesthetized with CO_2 and bled from the retroorbital sinus. Blood for hematology was collected in a tube containing ethylenediaminetetraacetic acid (EDTA); blood for clinical chemistry parameters was collected in a tube

without anticoagulant; blood for coagulation analyses was collected in a plastic syringe containing 3.8% sodium citrate. Hematology determinations were performed on whole blood using an Ortho ELT-8 analyzer (Ortho Instruments, Westwood, MA). Leukocyte and reticulocyte counts, erythrocyte counts and morphologies, and differential counts were determined from blood smears by light microscopy. Clinical chemistry parameters were determined using a Roche Cobas Fara chemistry analyzer (Roche Diagnostics Systems, Inc., Montclair, NJ). Parameters evaluated are listed in Table 1.

At the end of the study, samples from 0, 2,500, 5,000, and 10,000 ppm F_1 rats were collected for sperm motility and vaginal cytology evaluations. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluation in Toxicity Testing for Rats and Mice (NTP, 1987). For 7 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male rats and mice were evaluated for sperm count and motility. The right testis and right epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. Cauda were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study F_1 animals. The heart, right kidney, liver, lungs, 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 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all control and 10,000 ppm rats. Additionally, the following tissues from selected exposure groups were examined: the nose of all exposed groups of male rats and 5,000 ppm female rats; the spleen of 5,000 and 10,000 ppm male rats and all exposed groups of female rats; the mesenteric lymph node of 5,000 ppm female rats; and the kidneys of 2,500 and 10,000 ppm female rats. Table 1 lists the tissues and organs routinely examined.

13-Week Mouse Study

The 13-week study was performed to evaluate the cumulative toxic effects of *t*-butylhydroquinone and to determine the appropriate doses to be used in the 2-year study.

Male and female $B6C3F_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt, the mice were approximately 29 days old, and the mice were quarantined for 13 days. Mice were approximately 42 days old on the first day of the study. Prior to the start of the 13-week study, five male and five female mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the study, serologic analyses were performed on five male and five female sentinel mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female mice were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *t*-butylhydroquinone for 13 weeks. Feed and water were available *ad libitum*. Mice were housed five per cage. Clinical findings were recorded and the animals were weighed initially, weekly, and at the and of the study; feed consumption was recorded as an average of grams per animal per day.

Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected at week 13 from core study (F_1) mice for selected hematology, clinical chemistry, and coagulation analyses. Additionally, clinical pathology analyses were performed on special groups of 10 male and 10 female F_1 mice fed diets containing 0, 2,500, 5,000, or 10,000 ppm *t*-butylhydroquinone for 3 weeks after weaning. Selected hematology and clinical chemistry parameters were measured for these animals on day 5 and at week 3.

For clinical pathology analyses, mice were anesthetized with CO_2 and bled from the retroorbital sinus. Clinical pathology parameters were measured as described for the 13-week rat study and the parameters evaluated are listed in Table 1.

At the end of the study, samples from 0, 2,500, 10,000, and 40,000 ppm mice were collected for sperm motility and vaginal cytology evaluations. The parameters evaluated are listed in Table 1. Methods used were those described for the 13-week rat study.

A necropsy was performed on all core study animals. The heart, right kidney, liver, lungs, 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 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all control and 40,000 ppm mice. Additionally, the nose, skin, and forestomach of all exposed groups of male and female mice were examined. Table 1 lists the tissues and organs routinely examined.

LONG-TERM RAT STUDY

Study Design

Males acquired for the perinatal phase of the study were used for breeding purposes only. Groups of 60 female F_0 rats were fed diets containing 0, 1,250, 2,500, or 5,000 ppm *t*-butylhydroquinone, beginning 2 weeks prior to cohabitation and continuing until F_1 pups were weaned.

Following weaning, groups of as many as 70 male and 70 female F_1 rats were fed diets containing 0, 1,250, 2,500, or 5,000 ppm for 30 months or until the survival rate in any exposure group was less than 20%. Ten male and 10 female F_1 rats were evaluated at 3 months.

Source and Specification of Animals

Female F344/N F_0 rats were obtained from Taconic Farms (Germantown, NY). On receipt, the animals were approximately 31 days old. Males and females were quarantined for 18 days and were approximately 49 days old on the first day they were given dosed feed. Before the start of the study, 10 male and 10 female F_0 rats were selected for parasite evaluation and gross observation of disease. Serology samples for viral screening were collected from 10 F_0 females at the end of the reproductive phase of the study. The health of the animals was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Male and female F344/N F_1 rats were offspring (F_1 generation) of the breeders from the perinatal phase and were approximately 35 days old on the first day of exposure through feed. Pups from the F_1 generation not selected for study were used for parasite evaluation and gross observation of disease.

Animal Maintenance

During quarantine, breeder males were housed individually and F_0 females were housed two per cage. During cohabitation, one breeder male was housed with two F_0 females. F_0 females were housed individually for the remainder of the study. F_1 rats were housed five per cage. Feed and water were available *ad libitum* to F_0 and F_1 rats. Feed consumption was not measured during the perinatal phase of the study, but was measured every 4 weeks by cage for F_1 rats; additionally, control feed consumption by F_1 rats was measured weekly for the first 13 weeks of the study. Cages were changed twice weekly and racks were generally rotated once every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

During the perinatal phase of the study, clinical findings and body weights were recorded for females weekly during cohabitation and on the first day of dosing. F_1 rats were observed twice daily. Clinical

findings for F_1 rats were recorded at the beginning of the long-term study, once weekly for the first 13 weeks, and monthly thereafter. Additionally, clinical findings were recorded for F_1 rats on lactation days 4, 11, 18, and 28. As many as 10 male and 10 female rats were evaluated for hematology alterations at 3 months using the hematology methods described for the 13-week study. The parameters evaluated are listed in Table 1.

A complete necropsy and microscopic examination were performed on all F_1 rats. At the 3-month interim evaluation, the right kidney, liver, right epididymis, and right testis were weighed. 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 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ are 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 long-term rat study, a quality assessment pathologist reviewed the following organs: bone marrow (females), clitoral gland, forestomach (males), kidney (males), liver, mammary gland, nose, pituitary gland, preputial gland, spleen, and thyroid gland (males).

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. Thus, the final diagnoses represent a consensus of quality assessment pathologists, the PWG chairperson, and 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 diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

2-Year Mouse Study

Study Design

Groups of 60 male and 60 female mice were fed diets containing 0, 1,250, 2,500, or 5,000 ppm for 104 to 105 weeks. As many as 10 male and 10 female mice were evaluated at 15 months.

Source and Specification of Animals

$B6C3F_1$ mice were obtained from Taconic Farms (Germantown, NY) and were approximately 32 days old on receipt. Mice were quarantined for 12 days and were approximately 44 days old on the first day of exposure. Before the initiation of the study, five male and five female mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. The health of the animals was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Mice were housed individually. Feed and water were available *ad libitum*. Feed consumption per cage was measured every 1 to 6 weeks up to week 17 and monthly thereafter. Cages were changed twice weekly and racks were generally rotated every 2 weeks. Further details of animal maintenance are

given in Table 1. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

Mice were observed twice daily. Clinical findings were recorded at the beginning of the 2-year study, once weekly for the first 12 (females) or 13 (males) weeks, and monthly thereafter. As many as 10 male and 10 female mice were evaluated for hematology alterations at 15 months using the methods described for the 13-week study. The parameters evaluated are listed in Table 1.

A complete necropsy and microscopic examination were performed on all mice. At 15-month interim evaluations, the right kidney, liver, right epididymis, and right testis were weighed. 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 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ are 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 microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. The following organs were reviewed in mice: liver, harderian gland, and thyroid gland (females).

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 diagnosis 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. Thus, the final diagnoses represent a consensus of quality assessment pathologists, the PWG chairperson, 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 diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes 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 as presented in Tables A1, A4, B1, B4, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the 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, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

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

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

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

Analysis of Nonneoplastic Lesion Incidences

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

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoa, 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 using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure levels.

Dam and pup data from the *in utero* phases of the rat 13-week and long-term studies were analyzed using

the variance test for homogeneity of the binomial distribution (Snedecor and Cochran, 1980). Baseline maternal body weight data, litter averages for percent mortality, and pup body weights were analyzed using Bartlett's test of homogeneity of variances (Sokal and Rohlf, 1981) and the analysis of variance (Snedecor and Cochran, 1980) when appropriate [i.e., if Bartlett's test was not significant ($P>0.05$)]. If the analysis of variance was significant, Dunnett's test was used to identify the statistical significance of individual groups. If the analysis of variance was not appropriate [i.e., Bartlett's test was significant ($P\leq0.05$)], the Kruskal-Wallis test (Sokal and Rohlf, 1981) was used when 75% or fewer ties were present; when more than 75% ties were present, the Fisher exact test was used. In cases where the Kruskal-Wallis test was statistically significant ($P\leq0.05$), Dunn's method of multiple comparisons was used to identify statistical significance of individual groups. Natural delivery parameters involving discrete data were evaluated using the Kruskal-Wallis test.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, for $B6C3F_1$ mice, neoplasm incidences from the NTP historical control database (updated yearly) are included in this NTP report for neoplasms appearing to show compound-related effects during two-year studies. There are no studies of 30-month duration in the NTP historical control database for comparison to findings in the long-term F344/N rat studies.

Quality Assurance Methods

The 13-week, long-term, 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 long-term and 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of *t*-butylhydroquinone was assessed by testing the ability of the chemical to induce mutations in *Salmonella typhimurium* and cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

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

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

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *t*-Butylhydroquinone

13-Week Studies	Long-Term Rat and 2-Year Mouse Studies
Study Laboratory	
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Strain and Species	
Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$
Animal Source	
Taconic Farms (Germantown, NY)	Taconic Farms (Germantown, NY)
Time Held Before Studies	
Rats: F$_0$ - 19 days F$_1$ - No quarantine Mice: 13 days	Rats: F$_0$ - 18 days F$_1$ - No quarantine Mice: 12 days
Average Age When Studies Began	
Rats: F$_0$ - 57 days F$_1$ - 34 days Mice: 42 days	Rats: F$_0$ - 49 days F$_1$ - 35 days Mice: 44 days
Date of First Dose	
Rats: F$_0$ - 6 September 1988 F$_1$ - 21 November 1988 Mice: 5 December 1988	Rats: F$_0$ - 13 November 1989 F$_1$ - 29 January 1990 Mice: 29 November 1989
Duration of Dosing	
Rats: F$_0$ - Approximately 10 weeks F$_1$ - 87-89 days (clinical pathology study F$_1$ rats) 93-94 days (core study F$_1$ rats) Mice: 87-88 days (clinical pathology study mice) 93-95 days (core study mice)	Rats: F$_0$ - Approximately 12 weeks F$_1$ - Interim evaluation - 92 days (males) or 93 days (females) Terminal sacrifice - 123 weeks (males) or 129 weeks (females) Mice: 104 to 105 weeks
Date of Last Dose	
Rats: F$_0$ - 16-18 November 1988 F$_1$ - 15-17 February 1989 (clinical pathology study F$_1$ rats) 21-22 February 1989 (core study F$_1$ rats) Mice: 1-2 March 1989 (clinical pathology study mice) 7-9 March 1989 (core study mice)	Rats: F$_0$ - 31 January 1990 F$_1$ - 30 April 1990 (interim evaluation F$_1$ males) 1 May 1990 (interim evaluation F$_1$ females) 3 June 1992 (core study F$_1$ males) 14-15 July 1992 (core study F$_1$ females) Mice: 27-28 February 1991 (interim evaluation) 25-27 November 1991 (core study males) 2-4 December 1991 (core study females)
Necropsy Dates	
Rats: F$_1$ - 21-22 February 1989 Mice: 7-9 March 1989	Rats: F$_1$ - Interim evaluation 30 April (males) or 1 May (females) 1990 Terminal sacrifice 3 June (males) or 14-15 July (females) 1992 Mice: Interim evaluation 27 (males) or 28 (females) February (1991) Terminal sacrifice 25-27 November (males) or 2-4 December (females) 1991

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *t*-Butylhydroquinone (continued)

	13-Week Studies	Long-Term Rat and 2-Year Mouse Studies
Average Age at Necropsy	Rats: F_1 - 121-123 days (clinical pathology study rats) 127-128 days (core study rats) Mice: 129-130 days (clinical pathology study mice) 135-137 days (core study mice)	Rats: F_1 - 127-128 days (interim evaluation rats) 128 weeks (males) or 134 weeks (females) Mice: Interim evaluation - 72 weeks Core study - 110 weeks (males) or 111 weeks (females)
Size of Study Groups	Rats: F_0 generation - 10 females F_1 generation Core study - 10 males and 10 females Clinical pathology study - 10 males and 10 females Mice: Core study - 10 males and 10 females Clinical pathology study - 10 males and 10 females	Rats: F_0 - 60 females F_1 - 68-70 males and 68-70 females Mice: 60 males and 60 females
Method of Distribution	Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 13-week studies
Animals per Cage	Rats: F_0 - two females with one breeder male during cohabitation, then one female with litter per cage F_1 - five per cage Mice: five per cage	Rats: F_0 - two females with one breeder male during cohabitation, then one female with litter per cage F_1 - five per cage Mice: one per cage
Method of Animal Identification	Rats: Breeder females and pups identified by tail tattoo Mice: Toeclip	Tail tattoo
Diet	NIH-07 open formula mash diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 13-week studies
Water Distribution	Tap water (Birmingham, AL, municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI); available *ad libitum*	Same as 13-week studies
Cages	Polycarbonate (Lab Products, Inc., Maywood, NJ); changed twice weekly, except (rats only) between day 18 of gestation until completion of delivery	Same as 13-week studies
Bedding	SaniChip (P.J. Murphy Forestry Products, Corp., Montville, NJ); changed twice weekly, except (rats only) between day 18 of gestation until completion of delivery	Same as 13-week studies
Rack Filters	Reemay® spun-bonded polyester (Andico, Birmingham, AL); changed once every 2 weeks, except (rats only) between day 18 of gestation until completion of delivery	Same as 13-week studies

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *t*-Butylhydroquinone (continued)

13-Week Studies	Long-Term Rat and 2-Year Mouse Studies
Racks	
Stainless steel (Lab Products, Inc., Maywood, NJ); changed once every 2 weeks, except (rats only) between day 18 of gestation until completion of delivery	Same as 13-week studies
Animal Room Environment	
Temperature: 18.7° C to 24.2° C Relative humidity: 35.8%-79.3% Fluorescent light: 12 hours/day Room air: minimum of 10 changes per hour	Temperature: 16.7° C to 29.1° C Relative humidity: 15.8%-86.1% Fluorescent light: 12 hours/day Room air: minimum of 10 changes per hour
Doses	
Rats: F_0 - 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm F_1 - 0, 2,500, 5,000, or 10,000 ppm Mice: 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm	Rats: F_0 and F_1 - 0, 1,250, 2,500, or 5,000 ppm Mice: 0, 1,250, 2,500, or 5,000 ppm
Type and Frequency of Observation	
Rats: F_0 - Observed twice daily. Body weights and clinical findings were recorded weekly for breeder females during cohabitation and weekly for breeder females and pups during lactation. Feed consumption was recorded weekly for breeder females prior to cohabitation. F_1 - Observed twice daily. For core study animals, clinical findings were recorded and the animals were weighed initially, weekly, and at the end of the study; feed consumption was recorded as an average of grams per animal per day. Mice: Observed twice daily. Clinical findings were recorded and the animals were weighed initially, weekly, and at the end of the study; feed consumption was recorded as an average of grams per animal per day.	Rats: F_0 - Clinical findings and body weights recorded for females on the first day of the study and weekly prior to cohabitation. Feed consumption measured for breeder females weekdays through day 10 prior to cohabitation. F_1 - Clinical findings and body weights recorded individually on lactation days 4, 11, 18, and 28; at the start of the long-term study; once weekly for the first 13 weeks; and every 4 weeks thereafter. Body weights recorded on all surviving animals at the end of the study. Feed consumption measured monthly for exposed groups; feed consumption measured weekly for the first 13 weeks for animals receiving 0 ppm. Mice: Observed twice daily. Clinical findings and body weights recorded on day 1, weekly for the first 12 (females) or 13 (males) weeks, then monthly, at the interim evaluation, and the end of the study. Feed consumption measured per animal every 1-6 weeks up to week 17 and monthly thereafter.
Method of Sacrifice	
Anesthetized with CO_2 followed by exsanguination	Same as 13-week studies
Necropsy	
A necropsy was performed on all core study F_1 rats and on all core study mice. Organs weighed were the heart, right kidney, liver, lungs, right testis, and thymus.	A necropsy was performed on all F_1 rats and on all mice. At the 3-month (rats) and 15-month (mice) interim evaluations, the right kidney, liver, right epididymis, and right testis were weighed.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *t*-Butylhydroquinone (continued)

13-Week Studies	Long-Term Rat and 2-Year Mouse Studies
Clinical Pathology Blood was collected for hematology, clinical chemistry, and coagulation analyses from the retroorbital sinus of core rats and mice at the end of the studies. Blood was collected from the retroorbital sinus of special study rats and mice on day 5 and at week 3 for hematology and clinical chemistry analyses. ***Hematology:*** Hematocrit level, hemoglobin concentration, erythrocyte count, reticulocyte count, nucleated erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count, and leukocyte count and differential. ***Clinical Chemistry:*** Blood urea nitrogen, creatinine, total protein, albumin, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids. ***Coagulation:*** Thromboplastin time and activated partial thromboplastin time.	At 3 months (rats) or 15 months (mice), blood was collected from the retroorbital sinus of as many as 10 male and 10 female rats and mice. ***Hematology:*** Hematocrit level, hemoglobin concentration, erythrocyte count, reticulocyte count, nucleated erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count, and leukocyte count and differential.
Sperm Motility and Vaginal Cytology Evaluation Sperm and vaginal fluid samples were evaluated in 0, 2,500, 5,000, and 10,000 ppm F_1 rats and in 0, 2,500, 10,000, and 40,000 ppm mice at the end of the studies. The parameters evaluated in males were sperm count and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal fluid samples were collected for up to 7 consecutive days prior to the end of the studies for vaginal cytology evaluations. The parameters evaluated in females were relative frequency of estrous stages and estrous cycle length.	None
Histopathology Complete histopathologic examinations were performed on all control F_1 rats and mice, 10,000 ppm F_1 rats, and 40,000 ppm mice. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice only), heart (with aorta), large intestine (cecum, colon, rectum), kidneys, liver, lungs and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nasal cavity and turbinates, ovaries, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skeletal muscle, skin, small intestine (duodenum, jejunum, ileum), spinal cord and sciatic nerve, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. Additionally, the following tissues from selected exposure groups were examined: the nose of all exposed groups of male rats, 5,000 ppm female rats, and all exposed groups of male and female mice; the spleen of 5,000 and 10,000 ppm male rats and all exposed groups of female rats; the mesenteric lymph node of 5,000 ppm female rats; the kidneys of 2,500 and 10,000 ppm female rats; and the skin and forestomach of all exposed groups of male and female mice.	Complete histopathologic examinations were performed on all F_1 rats and on all mice. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal glands, bone (including marrow), brain, clitoral gland, esophagus, gallbladder (mice only), heart (with aorta), kidneys, large intestine (cecum, colon, rectum), liver, lungs and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nasal cavity and turbinates, ovaries, pancreas, parathyroid glands, pituitary gland, preputial gland, prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spinal cord and sciatic nerve, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

13-WEEK STUDY

In the perinatal exposure phase of the 13-week study, *t*-butylhydroquinone did not affect gestation length, the average number of pups born per litter, or the number of dams with stillborn pups for dams exposed to 2,500, 5,000, or 10,000 ppm (Table H2); dams exposed to 20,000 or 40,000 ppm did not litter. The number of pup deaths in the 5,000 and 10,000 ppm groups was greater than that in the control group, and the average number of surviving pups per litter in the 10,000 ppm group was lower than that in the control group. Mean body weights of pups in the 5,000 and 10,000 ppm groups at weaning were lower than that of the control.

All F_1 rats survived to the end of the study (Table 2). The final mean body weights of males and females in the 5,000 and 10,000 ppm groups were significantly lower than those of the controls, as was the mean body weight gain of males in the 10,000 ppm group. However, interpretation of these findings was complicated by the significantly lower initial mean body weights observed in 10,000 ppm groups. Differences in initial mean body weights were due to *in utero* exposure to *t*-butylhydroquinone.

TABLE 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of *t*-Butylhydroquinone

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[d]	
		Initial[c]	Final	Change		Week 2	Week 13
Male							
0	10/10	96 ± 5	328 ± 6	232 ± 4		17.0	14.6
2,500	10/10	92 ± 3	325 ± 3	233 ± 3	99	15.8	15.7
5,000	10/10	86 ± 4	307 ± 7*	221 ± 6	93	14.2	13.8
10,000	10/10	69 ± 3**	279 ± 5**	210 ± 5**	85	10.8	13.8
Female							
0	10/10	82 ± 3	199 ± 5	117 ± 4		11.4	12.6
2,500	10/10	81 ± 3	198 ± 3	117 ± 3	99	11.3	12.4
5,000	10/10	78 ± 3	185 ± 2**	108 ± 2	93	10.9	12.7
10,000	10/10	64 ± 2**	175 ± 3**	111 ± 3	88	9.2	10.6

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test.
** $P \leq 0.01$
a Number of animals surviving/number initially in group
b Weights and weight changes are given as mean ± standard error.
c Differences in initial body weights were due to *in utero* exposure of treated groups to *t*-butylhydroquinone.
d Feed consumption is expressed as grams of feed consumed per animal per day.

Feed consumption by exposed groups was lower than that by controls at week 2, and feed consumption by 5,000 and 10,000 ppm males and 10,000 ppm females was slightly lower than that consumed by controls at the end of the study. Dietary levels of 2,500, 5,000, and 10,000 ppm delivered daily doses of approximately 200, 400, and 800 mg *t*-butylhydroquinone/kg body weight to males and 200, 400, and 750 mg/kg to females. Hair discoloration was observed in all exposed groups of rats, with the exception of 2,500 ppm females; this was the only clinical observation considered to be related to chemical exposure.

The mean spermatid count, spermatid heads per testis, and spermatid heads per gram of testis were significantly decreased in F_1 males exposed to 5,000 ppm; the estrous cycles of F_1 females exposed to 2,500 or 5,000 ppm were significantly longer than that of the controls (Table H1). Exposure to *t*-butylhydroquinone for 13 weeks did not produce morphologic changes in reproductive organs.

Serum bile acid levels were generally significantly increased in 5,000 and 10,000 ppm male and female rats at day 5, at week 3, and at the end of the study (Table G1). Serum alanine aminotransferase activity levels were increased at day 5 in females exposed to 10,000 ppm, at week 3 in males and females exposed to 2,500, 5,000, or 10,000 ppm, and at the end of the study in males receiving 2,500 ppm. However, because the increases observed in these two parameters were marginal, and since histopathologic evaluation did not reveal evidence of liver toxicity, these marginal increases were not considered to be biologically significant changes. Differences in absolute and/or relative organ weights of control and exposed groups of rats were observed (Table F1). However, these organ weight differences were associated with histopathologic lesions and in many cases were secondary to lower body weights of exposed groups. Therefore, they were not considered clearly related to *t*-butylhydroquinone exposure.

Increased incidences of hyperplasia of the nasal respiratory epithelium were observed in males exposed to 5,000 ppm and males and females exposed to 10,000 ppm, and an increased incidence of nasal exudate was observed in males in the 10,000 ppm group (Table 3). The hyperplasia was of minimal severity and primarily involved an increase in the number of goblet cells along the nasal septum and medial aspect of the nasoturbinates. In a few male rats, there was also a mild nasal exudate composed of degenerated neutrophils and eosinophilic proteinaceous material. These nasal lesions suggest a mild irritant effect of *t*-butylhydroquinone possibly resulting from inhalation and/or aspiration of the dosed feed. Increased incidences of splenic pigmentation were observed in males and females exposed to 5,000 or 10,000 ppm, and incidences of atrophy of the red pulp were observed in these groups of females (Table 3). Because the pigment was golden brown and present within the phagocytic cells, it was considered to be hemosiderin. Atrophy of the splenic red pulp was characterized as a decrease in the number of hematopoietic cells. While the pathogenesis of these minimal changes was not determined, the biological significance is at most minimal because the bone marrow and hematologic parameters were normal. There was an exposure-related decrease in the incidences of renal mineralization in female rats (Table 3). Normally, a slight amount of mineral is observed near the corticomedullary junction in all females at 13 weeks. The pathogenesis of the observed decrease in this mineral is uncertain, although changes in feed and water consumption and decreased estrogen levels may affect mineral accumulation in the kidney.

Dose Selection Rationale: Based on lower final mean body weights and decreased feed consumption in males and females exposed to 10,000 ppm *t*-butylhydroquinone, exposure concentrations selected for the long-term rat study were 1,250, 2,500, and 5,000 ppm.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Feed Study of t-Butylhydroquinone

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male				
Nose[a]	10	10	10	10
Exudate[b]	0	0	0	4*
Nasal Respiratory Epithelial Hyperplasia	0	0	5* (1.0)[c]	10** (1.7)
Spleen	10	10	10	10
Pigmentation	0	1 (1.0)	3 (1.0)	5* (1.0)
Female				
Nose	10	—[d]	10	10
Nasal Respiratory Epithelial Hyperplasia	0	—	0	7** (1.0)
Spleen	10	10	10	10
Red Pulp, Atrophy	0	0	8** (1.8)	10** (1.8)
Pigmentation	0	5* (1.0)	8** (1.1)	10** (1.3)
Kidney	10	10	10	10
Mineralization	10 (2.0)	10 (1.9)	6 (1.3)	4** (1.2)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected rats: 1=minimal; 2=mild; 3=moderate; 4=marked
[d] Organ not examined at this exposure level

LONG-TERM STUDY

Survival

Estimates of survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves in Figure 1. Survival of females in the 5,000 ppm group was significantly greater than that of the control group. Males were killed at week 123 (28 months) post-weaning and females at week 129 (30 months) post-weaning.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 5,000 ppm groups were generally lower than those of the control groups throughout the study (Tables 5 and 6 and Figure 2). Feed consumption by exposed groups of males and females was similar to that by the controls (Tables J1 and J2). Dietary levels of 1,250, 2,500, or 5,000 ppm *t*-butylhydroquinone resulted in daily doses of approximately 50, 100, or 200 mg/kg body weight (males) or 60, 120, or 240 mg/kg (females). Clinical findings of hair discoloration in exposed groups of males and females were considered to be related to chemical exposure.

Hematology

Results of hematology assays in all exposed groups of males and females were similar to those in the control groups (Table G2).

TABLE 4
Survival of Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
Missexed[a]	0	0	2	0
Moribund	48	51	50	42
Natural deaths	4	2	7	4
Animals surviving to study termination	8	7	1	14
Percent probability of survival at the end of the study[b]	13	12	2	23
Mean survival (days)[c]	621	612	590	629
Survival analysis[d]	P=0.300N	P=0.856	P=0.075	P=0.361N
Female				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
Missexed[a]	0	0	2	0
Moribund	40	41	33	36
Natural deaths	10	8	9	7
Animals surviving to study termination	10	11	16	17
Percent probability of survival at the end of the study	17	18	28	28
Mean survival (days)	636	663	678	693
Survival analysis	P=0.017N	P=0.564N	P=0.063N	P=0.030N

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

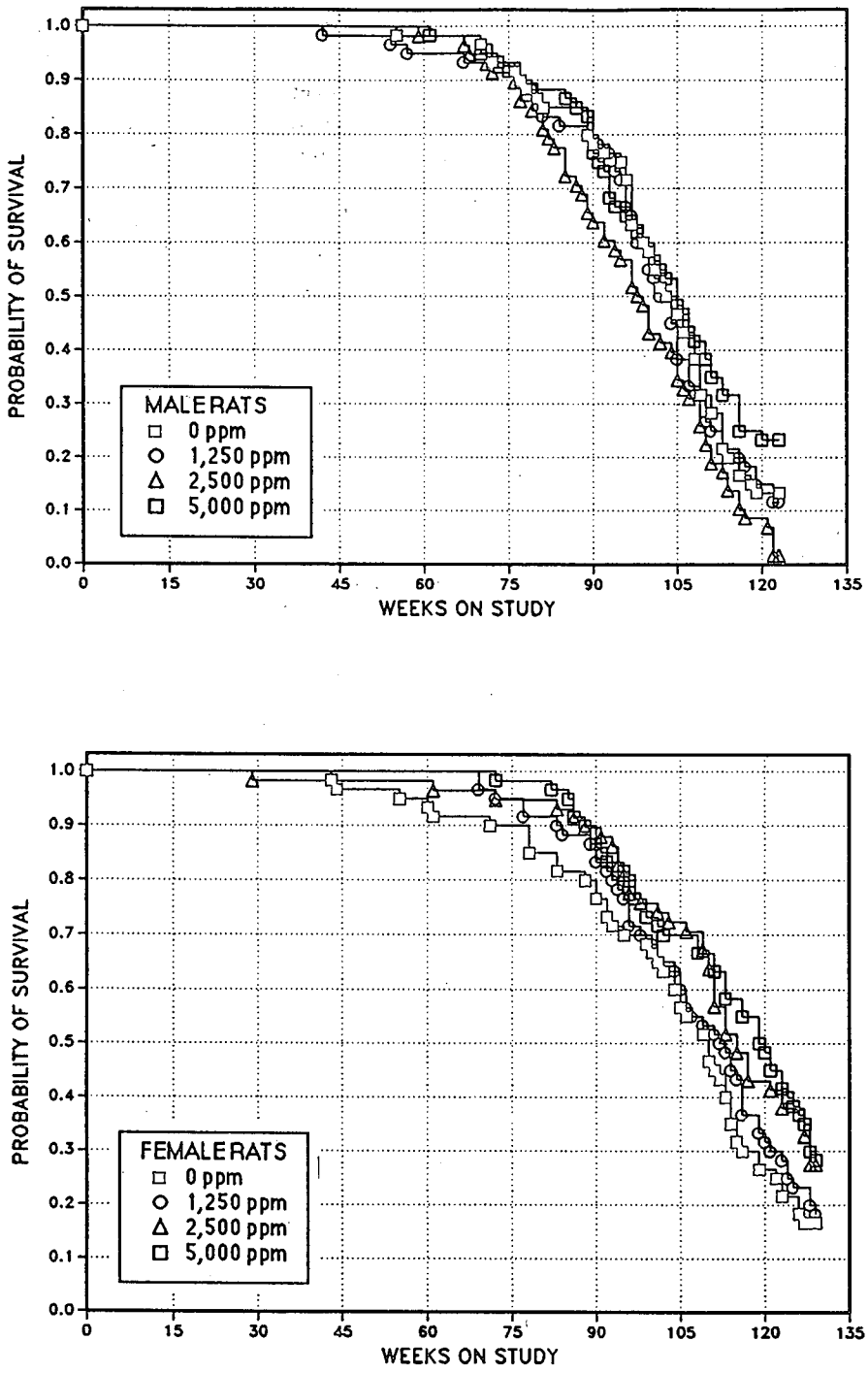


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered *t*-Butylhydroquinone in the Long-Term Feed Study

TABLE 5
Mean Body Weights and Survival of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

Weeks on Study	0 ppm		1,250 ppm			2,500 ppm			5,000 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	99	70	106	108	70	102	103	70	91	92	70
2	141	70	148	105	70	141	99	70	127	90	70
3	175	70	181	104	70	174	99	70	157	90	70
4	209	70	213	102	70	206	99	70	188	90	70
5[a]	233	70	237	102	70	232	99	68	217	93	70
6	267	70	266	100	70	260	97	68	244	91	70
7	283	70	284	100	70	277	98	68	261	92	70
8	299	70	298	100	70	294	98	68	275	92	70
9	313	70	311	100	70	307	98	68	287	92	70
10	316	70	319	101	70	320	101	68	299	95	70
11	324	70	324	100	70	323	100	68	304	94	70
12	344	70	342	100	70	337	98	68	318	92	70
13	356	70	348	98	70	343	97	68	320	90	70
17[b]	379	60	370	98	60	366	96	58	346	91	60
21	400	60	391	98	60	379	95	58	358	89	60
25	413	60	408	99	60	399	97	58	376	91	60
29	419	60	416	99	60	408	97	58	386	92	60
33	428	60	425	99	60	417	97	58	392	92	60
37	437	60	435	100	60	430	98	58	402	92	60
41	450	60	445	99	60	437	97	58	416	92	60
45	452	60	450	100	59	439	97	58	415	92	60
49	444	60	448	101	59	440	99	58	415	94	60
53	468	60	466	100	59	457	98	58	431	92	60
57	468	59	468	100	57	462	99	58	435	93	60
61	467	59	468	100	57	463	99	57	440	94	60
65	470	59	471	100	57	463	99	57	440	94	59
69	468	57	472	101	56	463	99	55	437	93	59
73	472	56	471	100	56	459	97	53	433	92	57
77	463	55	463	100	56	458	99	52	438	95	55
81	464	52	466	101	51	458	99	47	436	94	53
85	462	51	470	102	49	457	99	45	429	93	52
89	455	51	457	101	49	455	100	40	425	93	51
93	458	46	451	98	47	456	100	35	419	92	44
97	455	39	452	99	40	453	100	32	421	92	39
101	447	35	444	99	32	443	99	25	421	94	34
105	440	28	435	99	23	430	98	21	409	93	30
109	420	21	421	100	20	414	99	16	412	98	25
113	429	13	427	100	13	420	98	10	395	92	19
117	428	10	422	99	11	400	94	6	397	93	15
121	417	8	402	97	9	359	86	5	386	93	14
Mean for weeks											
1-13	258		260	101		255	99		238	92	
14-52	425		421	99		413	97		390	92	
53-121	453		451	100		443	98		422	93	

[a] Two rats in the 2,500 ppm group were missexed. These animals were removed from study during week 4.
[b] Interim evaluation occurred during week 14.

TABLE 6
Mean Body Weights and Survival of Female Rats in the Long-Term Feed Study of t-Butylhydroquinone

Weeks on Study	0 ppm		1,250 ppm			2,500 ppm			5,000 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	92	70	97	105	70	93	101	70	83	91	70
2	121	70	124	103	70	120	100	70	110	91	70
3	135	70	137	101	70	134	99	70	125	92	70
4	147	70	148	101	70	143	98	70	134	92	70
5[a]	159	70	159	100	70	155	97	68	146	92	70
6	171	70	168	98	70	162	95	68	154	90	70
7	177	70	174	98	70	170	96	68	161	91	70
8	181	70	178	99	70	174	96	68	165	92	70
9	186	70	184	99	70	180	97	68	173	93	70
10	176	70	181	103	70	183	104	68	176	100	70
11	193	70	192	99	70	187	97	68	181	94	70
12	196	70	194	99	70	188	96	68	181	92	70
13	198	70	194	98	70	191	97	68	184	93	70
17[b]	203	60	203	100	60	197	97	58	188	93	60
21	224	60	212	95	60	205	92	58	200	89	60
25	222	60	216	97	60	212	96	58	203	91	60
29	229	60	222	97	60	217	94	57	210	91	60
33	231	60	227	98	60	219	95	57	210	91	60
37	232	60	230	99	60	223	96	57	213	92	60
41	240	60	238	99	60	231	97	57	219	92	60
45	248	58	246	99	60	239	96	57	227	91	60
49	257	58	256	100	60	244	95	57	232	90	60
53	264	58	263	100	60	247	94	57	236	90	60
57	279	57	277	99	60	264	95	57	246	88	60
61	285	55	285	100	60	269	94	57	257	90	60
65	292	55	291	100	60	274	94	56	263	90	60
69	301	55	299	99	58	282	94	56	265	88	60
73	309	54	301	98	57	286	93	55	270	87	59
77	315	54	311	99	56	297	94	55	274	87	59
81	323	51	319	99	55	300	93	55	278	86	59
85	327	49	325	100	53	308	94	54	282	87	57
89	333	48	327	98	52	309	93	52	287	86	54
93	342	43	339	99	48	316	93	50	290	85	50
97	348	42	343	99	43	325	93	45	299	86	46
101	347	39	346	100	40	329	95	43	301	87	43
105	345	35	347	100	37	333	96	42	303	88	42
109	341	31	354	104	32	329	97	39	300	88	40
113	337	24	350	104	29	337	100	30	301	89	37
117	348	18	355	102	22	337	97	27	309	89	33
121	341	16	353	104	18	335	98	24	315	92	27
Mean for weeks											
1-13	164		164	100		160	98		152	93	
14-52	232		228	98		221	95		211	91	
53-121	321		321	100		304	95		282	88	

[a] Two rats in the 2,500 ppm group were missexed. These animals were removed from study during week 4.
[b] Interim evaluation occurred during week 14.

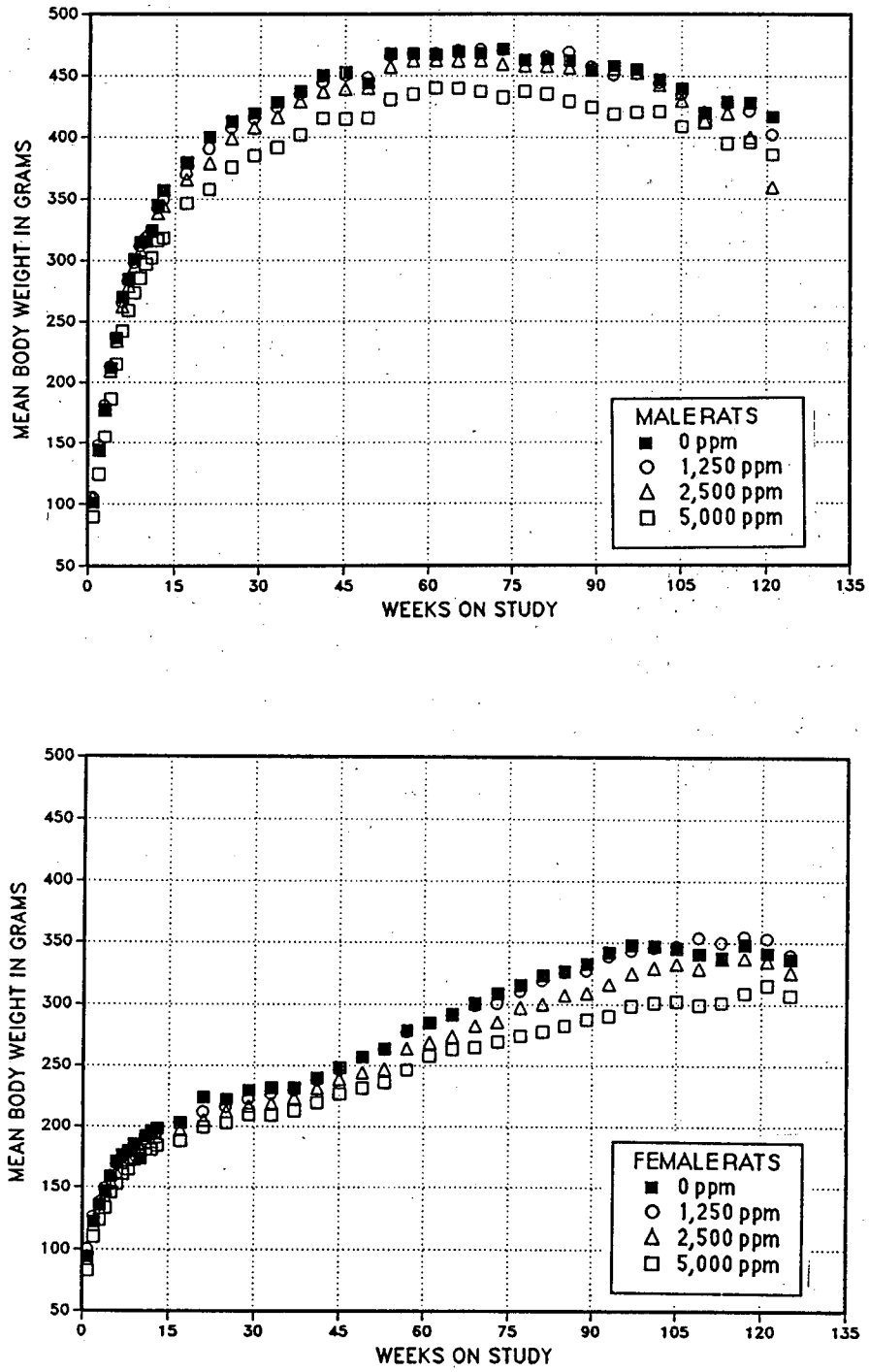


FIGURE 2
Growth Curves for Male and Female Rats Administered *t*-Butylhydroquinone in the Long-Term Feed Study

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the thyroid gland, testis, mammary gland, pituitary gland, kidney, nose, spleen, and other organs. 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.

Thyroid gland: At the end of the long-term study, follicular cell carcinomas were observed in three 5,000 ppm male rats and a follicular cell adenoma was observed in one 1,250 ppm male and one 2,500 ppm male (Table A1). However, the overall trend in neoplasm incidence was not significantly increased, and no thyroid gland hyperplasia was present in any group of male or female rats (Tables A4 and B4). At the 3-month interim evaluation, ultimobranchial cysts were found in one 1,250 ppm male and three 5,000 ppm males. These marginal effects were not considered to be chemical related (Table A4).

Testis: The incidences of testicular adenoma in exposed groups of males occurred with a statistically significant positive trend (0 ppm, 55/60; 1,250 ppm, 49/60; 2,500 ppm, 56/57; 5,000 ppm, 59/60; Table A3). This marginal effect was not considered to be chemical related. This is a neoplasm that typically occurs in male rats at 2 years of age and was observed in all control and exposed rats at terminal sacrifice. The increase was attributed to slightly improved survival in the 5,000 ppm group.

Mammary gland: Significantly decreased incidences of fibroadenoma and of fibroadenoma, adenoma, or carcinoma (combined) occurred in all exposed groups of females, and incidences of fibroadenoma and of fibroadenoma or adenoma (combined) were significantly decreased in 1,250 ppm males and marginally decreased in other exposed groups of males (Tables 9, A3, and B3). The incidences of dilatation of the mammary gland were significantly decreased in 5,000 ppm males and marginally decreased in 2,500 ppm males than in controls. In females, the incidence of mammary gland dilatation was greater in the group exposed to 1,250 ppm than in the control group (Tables 9 and B4). Mammary gland neoplasms occurred earlier in the male and female control groups than in exposed groups. Fibroadenomas of the mammary gland are benign neoplasms which occur spontaneously at a high rate in female F344/N rats, and while not generally considered life threatening, the large size of these neoplasms often necessitates removal of the animal from the study.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
Number Examined Microscopically	57	57	56	58
Dilatation[a]	23 (2.0)[b]	24 (2.2)	17 (2.4)	10** (1.7)
Hyperplasia	7 (2.4)	4 (2.0)	5 (2.2)	6 (1.7)
Fibroadenoma				
Overall rate[c]	10/60 (17%)	4/60 (7%)	4/58 (7%)	7/60 (12%)
Adjusted rate[d]	72.0%	40.7%	24.8%	40.2%
Terminal rate[e]	5/8 (63%)	2/7 (29%)	0/1 (0%)	5/14 (36%)
First incidence (days)	381	786	619	708
Logistic regression test[f]	P=0.195N	P=0.033N	P=0.183N	P=0.107N
Adenoma				
Overall rate	1/60 (2%)	0/60 (0%)	1/58 (2%)	0/60 (0%)
Fibroadenoma or Adenoma				
Overall rate	11/60 (18%)	4/60 (7%)	5/58 (9%)	7/60 (12%)
Adjusted rate	72.6%	40.7%	43.6%	40.2%
Terminal rate	5/8 (63%)	2/7 (29%)	0/1 (0%)	5/14 (36%)
First incidence (days)	381	786	619	708
Logistic regression test	P=0.145N	P=0.022N	P=0.213N	P=0.076N

(continued)

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Rats in the Long-Term Feed Study of t-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Female				
Number Examined Microscopically	60	59	58	60
Dilatation	37 (2.1)	48* (2.1)	39 (2.3)	34 (2.0)
Hyperplasia	12 (2.3)	6 (2.3)	11 (2.2)	15 (2.3)
Fibroadenoma				
Overall rate	43/60 (72%)	33/60 (55%)	34/58 (59%)	27/60 (45%)
Adjusted rate	100.0%	96.6%	86.0%	74.4%
Terminal rate	10/10 (100%)	10/11 (91%)	11/16 (69%)	9/17 (53%)
First incidence (days)	418	537	600	596
Logistic regression test	P<0.001N	P=0.006N	P=0.009N	P<0.001N
Adenoma				
Overall rate	3/60 (5%)	0/60 (0%)	1/58 (2%)	2/60 (3%)
Adjusted rate	9.9%	0.0%	2.9%	8.6%
Terminal rate	0/10 (0%)	0/11 (0%)	0/16 (0%)	1/17 (6%)
First incidence (days)	613	—[g]	774	807
Logistic regression test	P=0.562N	P=0.133N	P=0.345N	P=0.503N
Carcinoma				
Overall rate	8/60 (13%)	6/60 (10%)	2/58 (3%)	4/60 (7%)
Adjusted rate	29.3%	35.4%	10.8%	10.5%
Terminal rate	1/10 (10%)	3/11 (27%)	0/16 (0%)	0/17 (0%)
First incidence (days)	540	640	890	690
Logistic regression test	P=0.073N	P=0.345N	P=0.042N	P=0.177N
Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	48/60 (80%)	34/60 (57%)	34/58 (59%)	30/60 (50%)
Adjusted rate	100.0%	96.6%	86.0%	76.3%
Terminal rate	10/10 (100%)	10/11 (91%)	11/16 (69%)	9/17 (53%)
First incidence (days)	418	537	600	596
Logistic regression test	P<0.001N	P<0.001N	P<0.001N	P<0.001N

* Significantly different (P≤0.05) from the control group by the logistic regression test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesion in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[c] Number of animals with neoplasm per number of animals necropsied
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[g] Not applicable; no neoplasm in animal group

Pituitary gland: The incidences of pars distalis adenoma and adenoma or carcinoma (combined) in males in the 5,000 ppm group were significantly less than those in the controls (Tables 10 and A3). However, hyperplasia, adenoma, and carcinoma represent a morphological and biological continuum in the progression of proliferative lesions of the pituitary gland and incidences of hyperplasia and carcinoma were not decreased in the 5,000 ppm group. Additionally, there is a known positive correlation of pituitary gland neoplasms with body weight. The decrease in adenomas in this study may have been related to the decreased mean body weight of the 5,000 ppm group.

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Pituitary Gland (Pars Distalis) in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study				
Number Examined Microscopically	60	58	57	60
Hyperplasia, Focal[a]	10 (2.2)[b]	8 (1.9)	8 (1.6)	14 (2.2)
Adenoma				
Overall rate[c]	19/60 (32%)	16/58 (28%)	17/57 (30%)	6/60 (10%)
Adjusted rate[d]	63.8%	80.0%	100.0%	30.2%
Terminal rate[e]	2/8 (25%)	4/6 (67%)	1/1 (100%)	3/14 (21%)
First incidence (days)	528	562	562	668
Logistic regression test[f]	P=0.003N	P=0.410N	P=0.573	P=0.002N
Carcinoma				
Overall rate	0/60 (0%)	1/58 (2%)	1/57 (2%)	1/60 (2%)
Adjusted rate	0.0%	5.5%	4.2%	2.1%
Terminal rate	0/8 (0%)	0/6 (0%)	0/1 (0%)	0/14 (0%)
First incidence (days)	—[g]	766	725	627
Logistic regression test	P=0.388	P=0.488	P=0.473	P=0.491
Adenoma or Carcinoma				
Overall rate	19/60 (32%)	17/58 (29%)	18/57 (32%)	7/60 (12%)
Adjusted rate	63.8%	81.1%	100.0%	31.6%
Terminal rate	2/8 (25%)	4/6 (67%)	1/1 (100%)	3/14 (21%)
First incidence (days)	528	562	562	627
Logistic regression test	P=0.005N	P=0.494N	P=0.487	P=0.006N

[a] Number of animals with lesion
[b] Average severity grade of lesion in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[c] Number of animals with neoplasm per number of animals with pituitary gland examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[g] Not applicable; no neoplasm in animal group

Kidney: In the long-term study, there was a slight increase in the incidences of cysts and suppurative inflammation in the kidney of male rats (Tables 11 and A4). The development of a progressive nephropathy in aging F344/N rats (especially males) is well documented. A spectrum of morphological changes is identified as part of the nephropathy, including marked dilatation (cysts) of renal tubules and occasional suppurative inflammation within renal tubule lumina. In the present study, these changes were observed in kidneys of control and exposed animals with the most severe (moderate to marked) nephropathy. While this finding may suggest a slight exacerbation of the nephropathy by *t*-butylhydroquinone, the nephropathy severity grades in the controls and in the 5,000 ppm males were not markedly different (Table 11). It is not clear whether *t*-butylhydroquinone exposure contributed to these marginal increases. Additionally, the incidence and severity of renal mineralization were slightly decreased in males and females.

TABLE 11
Incidences of Nonneoplastic Lesions of the Kidney in Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

	0 ppm		1,250 ppm		2,500 ppm		5,000 ppm	
Male								
Number Examined Microscopically	60		60		58		60	
Cyst[a]	2	(3.0)[b]	3	(3.0)	7*	(2.9)	11**	(3.0)
Inflammation, Suppurative	9	(1.0)	8	(1.0)	9	(1.3)	20*	(1.2)
Mineralization	12	(1.7)	3**	(2.3)	2**	(2.0)	1**	(1.0)
Nephropathy	60	(2.6)	60	(2.6)	58	(2.4)	60	(2.8)
Transitional Epithelium, Hyperplasia	13	(1.4)	12	(1.6)	11	(2.3)	21	(1.5)
Female								
Number Examined Microscopically	60		60		57		60	
Cyst	0		1	(4.0)	0		2	(3.0)
Inflammation, Suppurative	2	(2.0)	1	(1.0)	0		0	
Mineralization	57	(2.4)	56	(2.4)	44*	(2.0)	48*	(1.6)
Nephropathy	37	(1.7)	38	(1.8)	37	(1.6)	39	(1.8)

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

Nose: At the 3-month interim evaluation, goblet cell hyperplasia occurred in the nose of male rats exposed to 5,000 ppm (Tables 12 and A4). This lesion was observed in one exposed female at 3 months (Table B4), and was morphologically similar to the lesion (epithelial hyperplasia) in rats exposed to *t*-butylhydroquinone for 13 weeks (Table 3). Incidences of goblet cell hyperplasia were not significantly increased in males at the end of the study (Tables 12 and A4). The increased incidences at earlier time points may have resulted from direct contact of the chemical with the nasal mucosa during feeding.

Spleen: The incidences of splenic pigmentation (hemosiderin) were increased in exposed groups of males and females at the 3-month interim evaluation (Tables 12, A4, and B4) and the severity increased with increasing exposure concentrations in females. This finding is similar to results from the 13-week study (Table 3). Increased incidences of pigmentation (hemosiderin, confirmed with Prussian Blue stain) were also observed in exposed groups of females at the end of the study (Tables 12 and B4), while the incidence and severity of pigmentation in exposed groups of males were similar to those of the controls (Table A4). Although the incidence differences between the female control group and the exposed female groups at the end of the long-term study were slight, the change was consistently observed at earlier time points (3-month interim evaluation and 13-week study) as well. As at earlier time points, however, other changes corroborating an anemia were not observed. The pathogenesis of this change remains uncertain, and the biological significance was considered minimal.

TABLE 12
Incidences of Nonneoplastic Lesions of the Nose and Spleen of Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

	0 ppm		1,250 ppm		2,500 ppm		5,000 ppm	
Male								
3-Month Interim Evaluation								
Nose[a]	10		10		10		10	
Goblet Cell Hyperplasia[b]	0		0		0		7**	(1.0)[c]
Spleen	10		10		10		10	
Pigmentation, Hemosiderin	0		0		3	(1.0)	5*	(1.0)
Long-Term Study								
Nose	60		60		58		60	
Goblet Cell Hyperplasia	5	(1.2)	3	(1.3)	9	(1.1)	13	(1.1)
Female								
3-Month Interim Evaluation								
Spleen	10		10		10		10	
Pigmentation, Hemosiderin	5	(1.2)	7	(1.4)	8	(1.3)	10*	(1.8)
Long-Term Study								
Spleen	60		60		57		60	
Pigmentation, Hemosiderin	24	(2.4)	27	(2.5)	33	(2.4)	41**	(2.4)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test (3-month interim evaluation) or the logistic regression test (long-term study)
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked

Other Organs: There were a number of decreased incidences of nonneoplastic lesions in various organs of male and female rats. In male rats, decreased incidences included: adrenal medulla, hyperplasia (0 ppm, 26/60; 1,250 ppm, 22/60; 2,500 ppm, 15/58; 5,000 ppm, 12/60; Table A4); liver, cystic degeneration (23/60, 16/60, 11/58, 5/60; Table A4); liver, bile duct hyperplasia (52/60, 49/60, 43/58, 25/60; Table A4); preputial gland, chronic inflammation (26/60, 16/60, 18/58, 12/60; Table A4); and prostate gland, inflammation (36/60, 39/60, 40/58, 23/60; Table A4). In exposed groups of females, the incidence of hepatocellular cytoplasmic vacuolization was decreased (14/60, 14/60, 9/58, 3/50; Table B4). In general, these nonneoplastic lesions often occur spontaneously and usually represent relatively insignificant changes within the individual organs or tissues. While the potential contribution of *t*-butylhydroquinone and/or body weight reductions as causal factors of these effects remains undetermined, the biological importance of the decreases are considered minimal.

MICE

13-WEEK STUDY

One female in each of the 10,000 and 40,000 ppm groups died before the end of the study, but the deaths were not considered to be related to *t*-butylhydroquinone exposure (Table 13). Final mean body weights and body weight gains of male and female mice in the 10,000, 20,000, and 40,000 ppm groups were significantly lower than those of the control groups. Feed consumption by exposed groups appeared to be similar to that by controls, but there was excessive scatter of feed by mice in the 10,000, 20,000, and 40,000 ppm groups. Therefore, it is likely that feed consumption by male and female mice in these groups was less than that by controls. Dietary levels of 2,500, 5,000, 10,000, 20,000, and 40,000 ppm delivered daily doses of approximately 440, 880, 1,950, 4,000, and 8,400 mg *t*-butylhydroquinone/kg body weight to males and 500, 1,100, 2,200, 4,600, and 9,000 mg/kg to females. Clinical observations of alopecia and hair discoloration were attributed to exposure to *t*-butylhydroquinone; because of feed spillage, these observations might have been due to dermal exposure to *t*-butylhydroquinone.

TABLE 13
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of *t*-Butylhydroquinone

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 2	Week 13
Male							
0	10/10	23.1 ± 0.3	32.4 ± 1.6	9.4 ± 1.7		5.0	4.5
2,500	10/10	23.0 ± 0.4	32.4 ± 0.7	9.4 ± 0.5	100	5.2	4.6
5,000	10/10	22.7 ± 0.3	31.6 ± 0.5	8.9 ± 0.4	97	6.0	4.3
10,000	10/10	23.4 ± 0.3	29.5 ± 0.4*	6.0 ± 0.2**	91	6.3	4.4
20,000	10/10	22.9 ± 0.3	26.6 ± 0.4**	3.7 ± 0.2**	82	8.0	3.8
40,000	10/10	22.4 ± 0.2	22.9 ± 0.5**	0.6 ± 0.6**	71	6.4	4.3
Female							
0	10/10	18.3 ± 0.4	29.5 ± 0.6	11.2 ± 0.4		5.8	4.2
2,500	10/10	17.7 ± 0.4	28.7 ± 0.6	11.0 ± 0.6	97	6.7	4.7
5,000	10/10	17.5 ± 0.4	28.3 ± 0.8	10.7 ± 1.0	96	6.6	4.4
10,000	9/10[d]	17.6 ± 0.1	24.0 ± 0.4**	6.3 ± 0.4**	81	6.5	3.9
20,000	10/10	17.5 ± 0.5	21.6 ± 0.4**	4.1 ± 0.5**	73	7.4	3.8
40,000	9/10[e]	17.8 ± 0.2	19.8 ± 0.5**	2.0 ± 0.4**	67	6.0	4.6

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test.
** $P \leq 0.01$
[a] Number of animals surviving/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 of feed consumed per animal per day.
[d] Week of death: 8 (accidental death)
[e] Week of death: 4 (accidental death)

Significant increases in segmented neutrophil counts occurred at week 3 and at the end of the study in the 20,000 and 40,000 ppm groups of males and females and in the 10,000 ppm female group (Table G3); this was the only clinical pathology change that was related to chemical exposure. Other clinical pathology changes were attributed to dehydration from weight loss or were considered to be otherwise unrelated. There were no biologically significant differences in organ weights (Table F3).

Left caudal, left epididymis, and left testis weights of males exposed to 10,000 or 40,000 ppm were generally significantly lower than those of the controls (Table H4). The estrous cycle of females exposed to 40,000 ppm was significantly longer than that of the controls. Additionally, no lesions were observed in the reproductive system of exposed groups of mice; thus, differences in reproductive parameters were considered to be secondary to body weight changes.

Increased incidences of mucosal hyperplasia were observed in the forestomach of male mice exposed to 20,000 or 40,000 ppm and in female mice exposed to 10,000, 20,000, or 40,000. The severity of this lesion also increased with increasing exposure concentration (Table 14). This change was characterized by a slight focal to multifocal increased thickness of the squamous epithelium of the forestomach. Probable contributors to this effect include chemical irritation and reduced mechanical action of feed in the forestomach due to decreased feed consumption in the 10,000, 20,000, and 40,000 ppm groups. Increased incidences of inflammation occurred in the nose and skin of males and females exposed to 10,000, 20,000, or 40,000 ppm (Table 14). Nasal changes involved all areas of the nasal cavity and consisted of suppurative inflammation with serous exudation. Changes in the skin included a minimal to mild chronic inflammation and increased thickening of the epithelium (hyperplasia), including the keratin layer. Both nasal (inhalation or aspiration) and skin (contamination of bedding from feed spillage) lesions were likely associated with an irritant effect of *t*-butylhydroquinone.

Dose Selection Rationale: Based on lower final mean body weights, increased incidences of inflammation of the nose and skin, increased incidences of forestomach mucosal hyperplasia, and increased severity of nonneoplastic lesions observed in mice exposed to 10,000, 20,000, or 40,000 ppm, exposure concentrations selected for the 2-year study were 1,250, 2,500, and 5,000 ppm.

TABLE 14
Incidences of Selected Nonneoplastic Lesions in Mice in the 13-Week Feed Study of *t*-Butylhydroquinone

	0 ppm		2,500 ppm		5,000 ppm		10,000 ppm		20,000 ppm		40,000 ppm	
Male												
Nose[a]	10		10		10		10		10		10	
Inflammation, Suppurative[b]	0		0		0		6**	(1.3)[c]	10**	(2.1)	10**	(2.6)
Forestomach	10		10		10		10		10		10	
Mucosal Hyperplasia	6	(1.0)	6	(1.3)	7	(1.6)	5	(1.6)	10*	(2.2)	10*	(2.5)
Skin	10		10		10		10		10		10	
Inflammation, Chronic	0		0		0		10**	(1.5)	10**	(1.8)	10**	(1.9)
Epithelial Hyperplasia	0		0		0		8**	(1.0)	10**	(1.4)	10**	(2.0)
Female												
Nose	10		10		10		10		10		10	
Inflammation, Suppurative	0		0		0		10**	(1.8)	10**	(2.1)	10**	(3.0)
Forestomach	10		10		10		10		10		10	
Mucosal Hyperplasia	3	(1.0)	4	(1.0)	6	(1.3)	9**	(2.0)	8**	(2.6)	10**	(2.9)
Skin	10		10		10		10		10		10	
Inflammation, Chronic	1	(1.0)	1	(1.0)	5	(1.0)	8**	(1.4)	10**	(1.9)	10**	(2.0)
Epithelial Hyperplasia	0		1	(1.0)	2	(1.0)	8**	(1.0)	10**	(1.7)	10**	(2.0)

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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 15 and in the Kaplan-Meier survival curves (Figure 3). Survival of males and females in all exposed groups was similar to that of the control groups.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of males and females in the 5,000 ppm groups were generally lower than those of the controls from week 13 until the end of the study (Figure 4 and Tables 16 and 17). Feed consumption by exposed groups of males and females was generally similar to that by controls (Tables J3 and J4). Dietary levels of 1,250, 2,500, or 5,000 ppm *t*-butylhydroquinone resulted in daily doses of approximately 150, 300, or 600 mg/kg body weight (males) or 150, 300, or 700 mg/kg (females). There were no clinical findings in exposed groups of male or female mice considered to be related to chemical exposure.

Hematology

The reticulocyte count in males in the 5,000 ppm group was greater than that in the control group (Table G3). There were no other biologically significant differences in hematology parameters between control and exposed groups of mice.

TABLE 15
Survival of Mice in the 2-Year Feed Study of *t*-Butylhydroquinone

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	9	9
Accidental death[a]	1	0	0	0
Moribund	6	3	7	7
Natural deaths	4	1	6	2
Animals surviving to study termination	39	46	38	42
Percent probability of survival at the end of the study[b]	80	92	75	82
Mean survival (days)[c]	711	721	700	701
Survival analysis[d]	P=0.780	P=0.143N	P=0.644	P=1.000N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	9	8	9	6
Moribund	11	7	6	6
Natural deaths	2	10	5	5
Animals surviving to study termination	38[e]	35	40	43[e]
Percent probability of survival at the end of the study	75	67	78	80
Mean survival (days)	699	689	706	695
Survival analysis	P=0.348N	P=0.571	P=0.767N	P=0.663N

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

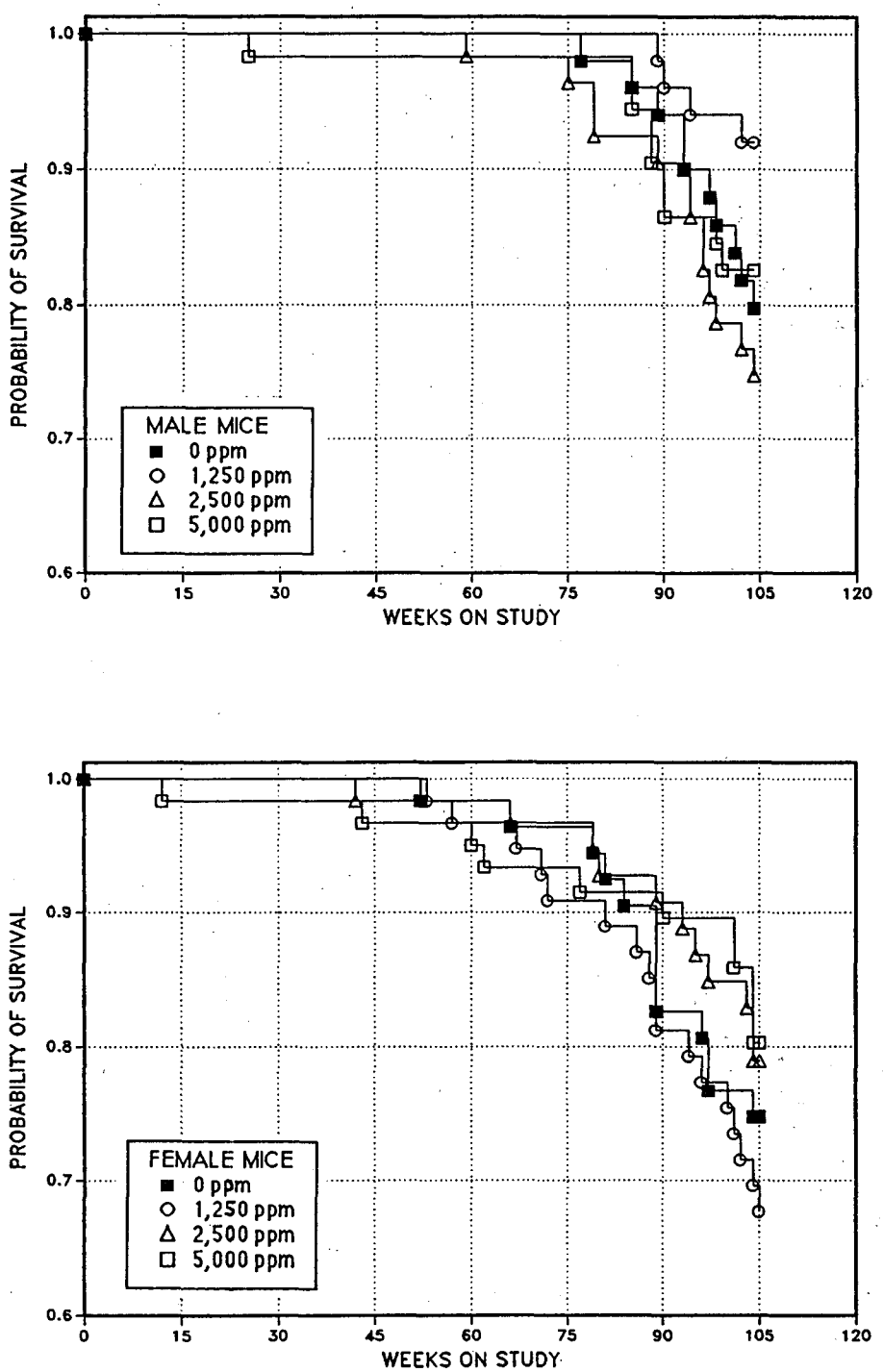


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered *t*-Butylhydroquinone in Feed for 2 Years

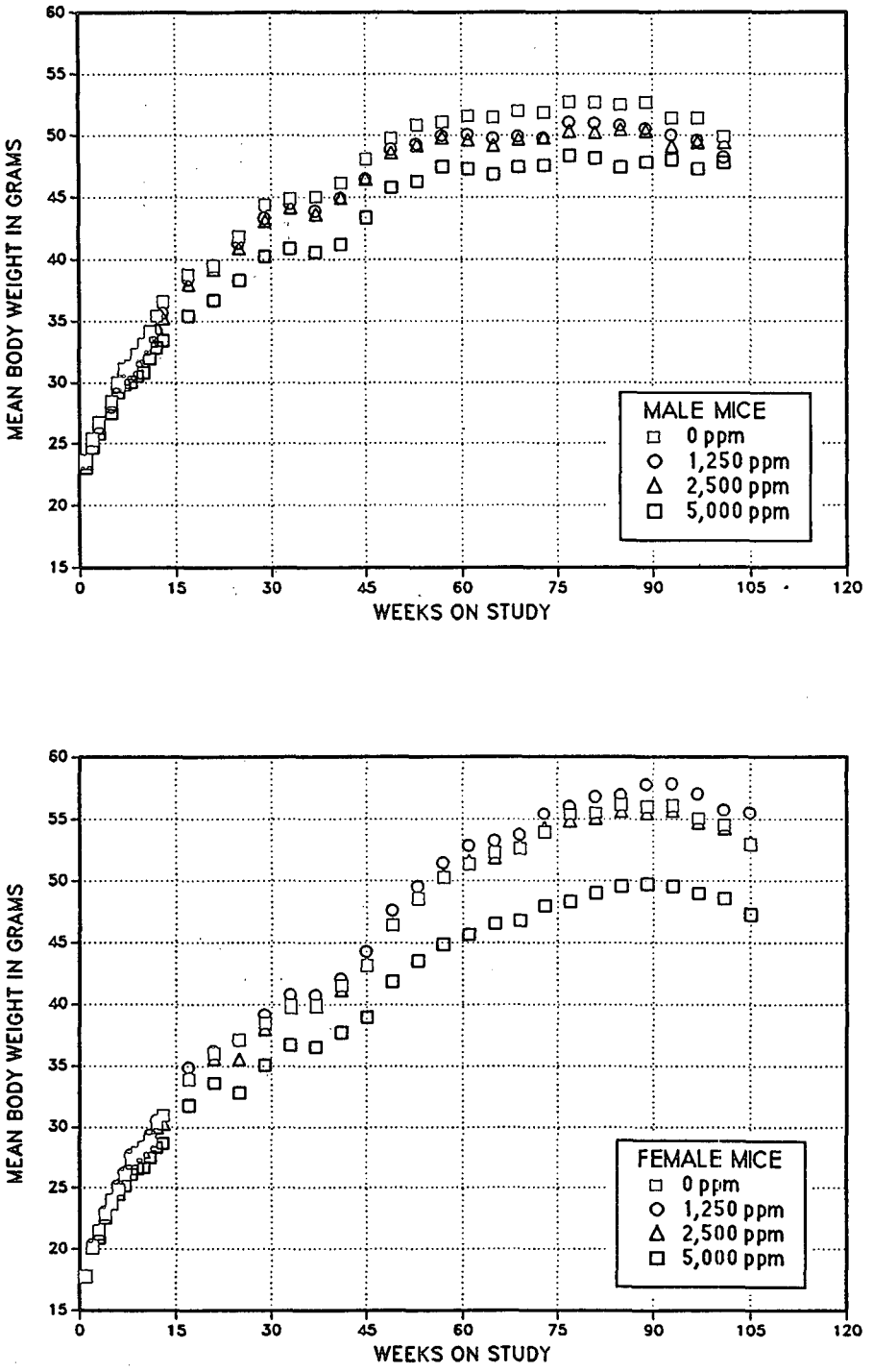


FIGURE 4
Growth Curves for Male and Female Mice Administered *t*-Butylhydroquinone in Feed for 2 Years

TABLE 16
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	1,250 ppm Av. Wt. (g)	1,250 ppm Wt. (% of controls)	1,250 ppm No. of Survivors	2,500 ppm Av. Wt. (g)	2,500 ppm Wt. (% of controls)	2,500 ppm No. of Survivors	5,000 ppm Av. Wt. (g)	5,000 ppm Wt. (% of controls)	5,000 ppm No. of Survivors
1	23.7	60	23.5	99	60	23.4	99	60	23.0	97	60
2	25.4	60	25.3	100	60	25.3	100	60	24.7	97	60
3	26.7	60	26.3	99	60	26.3	99	60	25.8	97	60
5	28.4	60	28.0	99	60	28.2	99	60	27.5	97	60
6	30.0	60	29.6	99	60	29.7	99	60	29.2	97	60
7	31.1	60	30.7	99	60	30.3	97	60	29.8	96	60
8	31.3	60	31.0	99	60	30.7	98	60	30.0	96	60
9	32.3	60	32.1	99	60	31.7	98	60	30.5	94	60
10	33.1	60	32.9	99	60	32.8	99	60	30.8	93	60
11	34.2	60	33.6	98	60	33.4	98	60	31.9	93	60
12	35.4	60	34.2	97	60	34.5	98	60	32.8	93	60
13	36.6	60	35.6	97	60	35.2	96	60	33.4	91	60
17	38.8	60	38.3	99	60	38.0	98	60	35.4	91	60
21	39.4	60	39.6	101	60	39.2	100	60	36.7	93	60
25	41.9	60	41.3	99	60	40.9	98	60	38.3	91	60
29	44.4	60	43.3	98	60	43.1	97	60	40.2	91	59
33	44.9	60	44.4	99	60	44.2	98	60	40.9	91	59
37	45.0	60	43.9	98	60	43.6	97	60	40.6	90	59
41	46.1	60	44.9	97	60	45.0	98	60	41.2	89	59
45	48.1	60	46.5	97	60	46.5	97	60	43.4	90	59
49	49.7	60	48.8	98	60	48.6	98	60	45.8	92	59
53	50.8	60	49.3	97	60	49.2	97	60	46.3	91	59
57	51.1	60	50.0	98	60	49.8	98	60	47.5	93	59
61	51.5	60	50.1	97	60	49.6	96	59	47.3	92	59
65	51.5	60	49.8	97	60	49.2	96	59	46.9	91	59
69[a]	51.9	50	49.9	96	50	49.7	96	50	47.4	91	50
73	51.8	50	49.8	96	50	49.8	96	50	47.6	92	50
77	52.7	50	51.0	97	50	50.3	95	49	48.4	92	50
81	52.6	49	51.0	97	50	50.2	95	47	48.1	91	50
85	52.4	49	50.8	97	50	50.5	96	47	47.4	91	49
89	52.6	47	50.5	96	49	50.3	96	46	47.8	91	46
93	51.4	46	50.0	97	48	49.1	96	46	48.0	93	44
97	51.4	43	49.6	97	47	49.4	96	41	47.3	92	44
101	49.9	41	48.2	97	47	49.4	99	40	47.8	96	42
Mean for weeks											
1-13	30.7		30.2	98		30.1	98		29.1	95	
14-52	44.3		43.4	98		43.2	98		40.3	91	
53-101	51.7		50.0	97		49.7	96		47.5	92	

[a] Interim evaluation occurred during week 66.

TABLE 17
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone

Weeks on Study	0 ppm		1,250 ppm			2,500 ppm			5,000 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	17.7	60	17.9	101	60	17.8	101	60	17.8	101	60
2	20.1	60	20.4	102	60	20.2	101	60	20.1	100	60
3	21.5	60	21.6	101	60	21.3	99	60	20.9	97	60
4	22.8	60	23.1	101	60	22.9	100	60	22.6	99	60
5	24.0	60	24.1	100	60	23.9	100	60	23.7	99	60
6	24.9	60	25.2	101	60	25.0	100	60	24.5	98	60
7	26.0	60	26.3	101	60	26.2	101	60	25.2	97	60
8	27.4	60	27.7	101	60	27.4	100	60	26.1	95	60
9	27.9	60	27.9	100	60	27.5	99	60	26.6	95	60
10	28.3	60	28.5	101	60	28.0	99	60	26.7	94	60
11	28.9	60	29.3	101	60	28.8	100	60	27.5	95	60
12	30.3	60	30.5	101	60	30.0	99	60	28.3	93	60
13	30.9	60	30.9	100	60	30.3	98	60	28.7	93	59
17	33.9	60	34.9	103	60	34.1	101	60	31.8	94	59
21	36.0	60	36.2	101	60	35.6	99	60	33.6	93	59
25	37.1	60	37.1	100	60	35.6	96	60	32.8	88	59
29	38.5	60	39.2	102	60	38.0	99	60	35.1	91	59
33	39.9	60	40.8	102	60	39.8	100	60	36.7	92	59
37	39.9	60	40.8	102	60	39.9	100	60	36.5	92	59
41	41.5	60	42.1	101	60	41.2	99	60	37.7	91	59
45	43.2	60	44.3	103	60	43.4	101	59	39.0	90	58
49	46.4	60	47.6	103	60	46.5	100	59	41.9	90	58
53	48.5	59	49.5	102	59	48.7	100	59	43.5	90	58
57	50.2	59	51.4	102	59	50.5	101	59	44.9	89	58
61	51.3	59	52.9	103	58	51.6	101	59	45.6	89	57
65	52.3	59	53.2	102	58	51.9	99	59	46.6	89	56
69[a]	52.6	49	53.7	102	49	52.7	100	49	46.8	89	50
73	53.9	49	55.4	103	47	54.3	101	49	47.9	89	50
77	55.4	49	56.0	101	47	54.9	99	49	48.3	87	50
81	55.5	48	56.8	102	46	55.1	99	47	49.0	88	49
85	56.2	46	56.9	101	46	55.7	99	47	49.6	88	49
89	56.0	44	57.8	103	44	55.5	99	46	49.7	89	49
93	56.1	42	57.9	103	42	55.7	99	46	49.6	88	48
97	55.1	40	57.0	103	40	54.7	99	44	49.0	89	48
101	54.5	39	55.8	102	39	54.2	99	43	48.6	89	47
Mean for weeks											
1-13	25.4		25.6	101		25.3	100		24.5	96	
14-52	39.6		40.3	102		39.3	99		36.1	91	
53-101	53.7		54.9	102		53.5	100		47.6	89	

[a] Interim evaluation occurred during week 66.

Pathology and Statistical Analyses

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

Liver: The absolute liver weights of all exposed groups of males were greater than that of the controls (Table F4), although the differences were not statistically significant. Absolute liver weights of exposed groups of females were similar to that of the controls. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) in females administered 1,250 ppm were significantly greater than those in the control group (Tables 18 and D3), although the incidence of hepatocellular neoplasms occurred with a significant negative trend. Incidences of hepatocellular neoplasms in exposed groups of males generally decreased with increasing exposure concentration (Tables 18 and C3). The incidences of hepatocellular adenoma or carcinoma (combined) in control and exposed groups of males and females were within the historical control range for mice from NTP 2-year feed studies (males, 10%-68%; females, 3%-56%; Tables 18, C4a, and D4a). Incidences of nonneoplastic lesions of the liver observed in exposed groups of males and females were similar to the incidences observed in the control groups (Tables 18, C5 and D5). There is a high rate of spontaneously occurring liver neoplasms in mice (particularly in males), and a positive correlation with body weights has been demonstrated (Seilkop, 1995).

Thyroid gland: The incidences of follicular cell adenoma in exposed groups of females were greater than that in the controls (0 ppm, 1/51; 1,250 ppm, 3/51; 2,500 ppm, 2/50; 5,000 ppm, 5/54; Table D3); however, the differences were not statistically significant, and the incidences did not exceed the historical control range for 2-year NTP feed studies (0% to 9%; Table D4b). Incidences of follicular cell hyperplasia in exposed groups of females were greater than those in controls at the end of the 2-year study (12/51, 19/51, 24/50, 24/54; Table D5), although, the severity of the hyperplasia in exposed groups was similar to that in the controls. This lesion was not observed at the 15-month interim evaluation. Additionally, significant increases of thyroid follicular cell proliferative lesions did not occur in female mice at the end of the 2-year study. Therefore, these marginal increases were not considered related to *t*-butylhydroquinone exposure.

TABLE 18
Incidences of Hepatocellular Neoplasms in Mice in the 2-Year Feed Study of t-Butylhydroquinone

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
15-Month Interim Evaluation				
Adenoma				
Overall rate[a]	1/10 (10%)	1/10 (10%)	1/9 (11%)	0/9 (0%)
Carcinoma				
Overall rate	0/10 (0%)	0/10 (0%)	0/9 (0%)	1/9 (11%)
2-Year Study				
Number Examined Microscopically	50	50	51	51
Basophilic Focus[b]	3	2	2	5
Clear Cell Focus	6	7	7	4
Eosinophilic Focus	8	5	5	4
Mixed Cell Focus	5	8	4	7
Adenoma				
Overall rate	28/50 (56%)	22/50 (44%)	22/51 (43%)	14/51 (27%)
Adjusted rate[c]	60.6%	47.8%	53.2%	31.7%
Terminal rate[d]	21/39 (54%)	22/46 (48%)	19/38 (50%)	12/42 (29%)
First incidence (days)	595	727 (T)	409	630
Logistic regression test[e]	P=0.004N	P=0.144N	P=0.147N	P=0.004N
Carcinoma				
Overall rate	8/50 (16%)	11/50 (22%)	12/51 (24%)	8/51 (16%)
Adjusted rate	19.1%	22.8%	26.0%	17.6%
Terminal rate	6/39 (15%)	9/46 (20%)	6/38 (16%)	5/42 (12%)
First incidence (days)	619	619	409	615
Logistic regression test	P=0.370N	P=0.248	P=0.342	P=0.585N
Adenoma or Carcinoma[f]				
Overall rate	31/50 (62%)	28/50 (56%)	29/51 (57%)	17/51 (33%)
Adjusted rate	65.8%	58.3%	63.8%	37.7%
Terminal rate	23/39 (59%)	26/46 (57%)	22/38 (58%)	14/42 (33%)
First incidence (days)	595	619	409	615
Logistic regression test	P=0.002N	P=0.369N	P=0.341N	P=0.004N

(continued)

TABLE 18
Incidences of Hepatocellular Neoplasms in Mice in the 2-Year Feed Study of t-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Female				
15-Month Interim Evaluation				
Adenoma				
Overall rate	0/9 (0%)	0/8 (0%)	1/9 (11%)	0/6 (0%)
Carcinoma				
Overall rate	0/9 (0%)	1/8 (13%)	0/9 (0%)	0/6 (0%)
2-Year Study				
Number Examined Microscopically	51	52	51	54
Basophilic Focus	2	1	1	0
Clear Cell Focus	0	0	2	2
Eosinophilic Focus	7	14	10	12
Mixed Cell Focus	1	3	2	1
Adenoma				
Overall rate	9/51 (18%)	20/52 (38%)	16/51 (31%)	5/54 (9%)
Adjusted rate	22.7%	51.0%	37.1%	11.6%
Terminal rate	8/38 (21%)	16/35 (46%)	13/40 (33%)	5/43 (12%)
First incidence (days)	582	598	555	734 (T)
Logistic regression test	P=0.027N	P=0.011	P=0.096	P=0.146N
Carcinoma				
Overall rate	8/51 (16%)	8/52 (15%)	8/51 (16%)	5/54 (9%)
Adjusted rate	18.4%	19.2%	17.6%	11.6%
Terminal rate	4/38 (11%)	4/35 (11%)	4/40 (10%)	5/43 (12%)
First incidence (days)	461	469	548	734 (T)
Logistic regression test	P=0.357N	P=0.559N	P=0.592	P=0.240N
Adenoma or Carcinoma[g]				
Overall rate	17/51 (33%)	28/52 (54%)	23/51 (45%)	10/54 (19%)
Adjusted rate	38.9%	64.7%	48.8%	23.3%
Terminal rate	12/38 (32%)	20/35 (57%)	16/40 (40%)	10/43 (23%)
First incidence (days)	461	469	548	734 (T)
Logistic regression test	P=0.010N	P=0.025	P=0.155	P=0.064N

(T) Terminal sacrifice
[a] Number of animals with neoplasm per number of animals with liver examined microscopically
[b] Number of animals with lesion
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[f] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 509/1,316 (38.7% ± 13.9%); range, 10%-68%
[g] Historical incidence: 260/1,312 (19.8% ± 12.8%); range, 3%-56%

GENETIC TOXICOLOGY

t-Butylhydroquinone (3 to 3,333 μg/plate) was tested for induction of mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA102 with and without induced rat or hamster liver S9 (Zeiger *et al.*, 1992; Table E1). No mutagenicity was detected in any of the strain/activation combinations. No induction of sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3) was noted in cultured Chinese hamster ovary cells treated with *t*-butylhydroquinone in the absence of S9 activation. However, in the presence of S9, positive dose-related responses were obtained in both these *in vitro* cytogenetic assays. The response obtained in the chromosomal aberrations test was particularly strong, and up to 90% of treated cells showed multiple chromosomal aberrations at the higher doses (200 to 249 μg/mL). These positive results in cultured Chinese hamster ovary cells may have resulted from the generation of superoxide and H_2O_2 within the cell from the autooxidation of *t*-butylhydroquinone to *t*-butylquinone and the further generation of oxidative byproducts, thereby indirectly producing chromosome breakage (Phillips *et al.*, 1989). In contrast to the positive results obtained in the *in vitro* assays for chromosome damage, results of an *in vivo* bone marrow micronucleus test were clearly negative (Table E4). No significant increase in the number of micronucleated erythrocytes was observed in male mice treated with three intraperitoneal injections of up to 300 mg *t*-butylhydroquinone/kg body weight.

DISCUSSION AND CONCLUSIONS

t-Butylhydroquinone, a white to light tan crystalline solid, is primarily used as an antioxidant in fats, oils, and foods containing high fat concentrations, and in a large number of cosmetic preparations (CIR, 1986).

t-Butylhydroquinone was nominated for toxicity and carcinogenicity testing by the Food and Drug Administration because of the potential for its increased use, its structural relationship to carcinogenic chemicals such as hydroquinone, butylated hydroxytoluene, and butylated hydroxyanisole, and because of the lack of adequate *t*-butylhydroquinone carcinogenicity studies. Toxicology and carcinogenicity studies were conducted in F344/N rats and B6C3F$_1$ mice. Mice were exposed to the chemical in the feed for 13 weeks or 2 years. In the 13-week and long-term rat studies, dams were exposed to *t*-butylhydroquinone in feed beginning 2 weeks prior to cohabitation through weaning. Following weaning, pups selected for study were given dosed feed for 13 weeks or for 127 weeks (males) or 133 weeks (females). The oral route of administration was used because human exposure to the food additive occurs predominantly via this route. In addition, perinatal exposure was studied because butylated hydroxytoluene (a structurally related chemical) induced hepatocellular neoplasms in rats exposed in this manner.

Three chemicals structurally related to *t*-butylhydroquinone (hydroquinone, butylated hydroxytoluene, and butylated hydroxyanisole) were found to be carcinogenic to rats and/or mice. Hydroquinone (25 or 50 mg/kg body weight) given by gavage for 2 years was carcinogenic to F344 rats, causing increased incidences of renal tubule cell adenomas in males and mononuclear cell leukemia in females. Hydroquinone (50 or 100 mg/kg) administered similarly was carcinogenic to female mice, causing an increased incidence of hepatocellular neoplasms (Kari *et al.*, 1992). Butylated hydroxytoluene administered in feed for up to 2 years at concentrations up to 10,000 ppm was not carcinogenic to rats and mice (NCI, 1979; Hirose *et al.*, 1981; Shirai *et al.*, 1982). However, *in utero* exposure to butylated hydroxytoluene induced hepatocellular neoplasms in rats (Olsen *et al.*, 1983). Feeding butylated hydroxyanisole to male F344 rats at a concentration of 2% for 13 weeks caused proliferation of the forestomach epithelium, which was a reversible effect following removal of the chemical from their diet (Iverson, *et al.*, 1985). Butylated hydroxyanisole administered in feed at concentrations of up to 2% for 2 years caused an increase in the incidence of squamous cell carcinoma of the forestomach in male and female F344 rats (Ito *et al.*, 1982).

Exposure concentrations greater than 10,000 ppm were not used in the 13-week rat study because dams exposed to 20,000 or 40,000 ppm did not litter. The inability to litter was likely due to lower mean body weights of the dams. Additionally, the average number of surviving pups per litter was less in dams exposed to 10,000 ppm than in control dams, and pups born to dams exposed to 5,000 or 10,000 ppm had lower mean body weights than pups born to control dams. These results were similar to those observed in an earlier reproductive study that examined three generations of Sprague-Dawley rats exposed to 5,000 ppm *t*-butylhydroquinone in feed (Terhaar and Krasavage, 1968b; Krasavage and Terhaar, 1970; Krasavage, 1977). There was a slight increase in pup mortality and a decrease in feed consumption, with a subsequent decrease in the pup body weight.

All male and female F$_1$ rats exposed to 0, 2,500, 5,000, or 10,000 ppm *t*-butylhydroquinone in feed for 13 weeks survived to the end of the study. Decreased feed consumption might account for lower mean body weight gains of male rats exposed to 10,000 ppm and lower final mean body weights of F$_1$ male and female rats exposed to 5,000 or 10,000 ppm. As in the present 13-week study, Astill *et al.* (1975) reported that 10,000 ppm *t*-butylhydroquinone given to rats for 22 days caused a decrease in mean body weights, but had no effect on survival.

At various time points there were increases in serum bile acid levels and serum alanine aminotransferase activity levels in male and female rats exposed to *t*-butylhydroquinone. Such increases are generally associated with liver toxicity. However, because the increases observed in these two parameters were marginal, and since histopathologic evaluation did not reveal any evidence of liver toxicity, these marginal increases were not considered to be biologically significant. No biologically significant changes in clinical chemistry parameters were observed in Sprague-Dawley rats exposed to 10,000 ppm *t*-butylhydroquinone in feed for 3 weeks or to 5,000 ppm *t*-butylhydroquinone in feed for 20 months (Terhaar and Krasavage, 1968a; Astill *et al.*, 1975).

The effect of *t*-butylhydroquinone on reproductive parameters in rats included significantly lower mean spermatid counts, spermatid heads per testis, and spermatid heads per gram of testis only in males exposed to 5,000 ppm (the mid-dose). The estrous cycles of females exposed to 2,500 or 5,000 ppm were significantly longer than that of the control. The number of females with estrous cycles that were of unclear duration or were longer than 12 days was increased in the 10,000 ppm group. Together, these data suggest that *t*-butylhydroquinone has an as yet undefined effect on the female reproductive system.

Histopathologic changes observed in rats exposed to 5,000 or 10,000 ppm *t*-butylhydroquinone in the 13-week study included increased incidences of nasal respiratory epithelial hyperplasia, nasal exudate (males only), splenic pigmentation, splenic atrophy of the red pulp (females only), and kidney mineralization (females only). Since there was no other evidence of anemia, the cause for the observed splenic changes is not clear. In previous studies, the noses of rats exposed to 5,000 ppm *t*-butylhydroquinone for as long as 20 months were not examined (Astill *et al.*, 1975). However, the authors did examine the spleen and bone marrow in addition to other organs and did not find any chemical-related changes. Administration of hydroquinone (50 mg/kg body weight per day, 5 days per week, for 13 weeks) caused a regenerative anemia and myelotoxicity in female rats (NTP, 1989). Hydroquinone caused a decrease in hematocrit levels, hemoglobin concentrations, and erythrocyte counts.

In the 13-week mouse study, there were no chemical-related deaths. Although feed consumption data indicate that consumption by exposed groups was similar to that by control male and female mice, excessive scatter of feed by mice in the 10,000, 20,000, and 40,000 ppm groups was observed. This in turn may have contributed to the lower mean body weights of mice in these exposure groups.

The effect of *t*-butylhydroquinone on reproductive parameters in mice included generally lower caudal, epididymis, and testis weights in males exposed to 10,000 or 40,000 ppm than in controls. The estrous cycle of female mice exposed to 40,000 ppm was significantly longer than that of the controls. Reproductive organ weight and estrous cycle data were different only in exposure groups that had corresponding significantly lower mean body weights. Based on previous studies (Chapin *et al.*, 1993), the body weight differences can account for these reproductive effects. This is also supported by the lack of difference in spermatogenesis efficiency.

Chemical-related histopathologic effects were generally observed in the nose and skin (inflammation) and the forestomach (hyperplasia of mucosal epithelium) of 10,000, 20,000, and 40,000 ppm mice. The effects were attributed to the direct irritating action of *t*-butylhydroquinone on these tissues. Increased segmented neutrophil counts in these exposure groups may have been a response to these inflammatory effects. Proliferative forestomach lesions have not been reported in other studies of *t*-butylhydroquinone in mice. However, proliferative forestomach lesions have been reported in mice exposed to hydroquinone and rats exposed to *t*-butylhydroquinone and butylated hydroxyanisole. Epithelial hyperplasia of the forestomach occurred in mice dosed with 400 mg hydroquinone/kg body weight per day, 5 days per week for 13 weeks (NTP, 1989). Hyperplasia of the forestomach was reported in male F344 rats exposed to 2,000 ppm butylated hydroxyanisole (a structurally related chemical) in feed for 13 weeks (Iverson *et al.*, 1985) and Fischer rats exposed to 1,000 ppm *t*-butylhydroquinone in feed for 28 days (Nera *et al.*, 1984). Similar lesions were observed in Wistar rats exposed to 2,000 ppm *t*-butylhydroquinone in feed for 28 days (Altmann *et al.*, 1985).

Although hyperplasia of the pulmonary pneumocytes was observed in mice treated with butylated hydroxytoluene (a structurally related chemical) (Marino and Mitchell, 1972; Witschi and Saheb, 1974; Saheb and Witschi, 1975), no chemical-related lesions were observed in the lungs of rats or mice in the present 13-week studies. Mizutani *et al.* (1982) have demonstrated the possibility that phenolic antioxidants can only exert toxic effects if the hydroxyl group of the antioxidants is hindered by a methyl group at the 4-position and an ortho-alkyl group on the phenolic ring. Since *t*-butylhydroquinone does not have the methyl group at the 4-position, it would not be expected to undergo metabolic transformation to an active lung toxicant, which may explain the lack of lung lesions in the present studies.

Based on lower final mean body weights, increased incidences of inflammation of the nose and skin, increased incidences of forestomach epithelial hyperplasia, and increased severity of nonneoplastic lesions observed in mice exposed to 10,000, 20,000, or 40,000 ppm, the exposure concentrations selected for the 2-year mouse study were 1,250, 2,500, and 5,000 ppm.

In the long-term (rats) and 2-year (mice) studies, rats and mice were exposed to 1,250, 2,500, or 5,000 ppm *t*-butylhydroquinone in feed. Based on the lower mean body weights in male and female rats and mice exposed to 5,000 ppm and on the presence of chemical-related kidney lesions in rats, the doses selected for the long-term and 2-year studies were considered adequate for evaluating the carcinogenic potential of *t*-butylhydroquinone.

In the long-term rat study, *t*-butylhydroquinone was not carcinogenic to male or female rats exposed to 1,250, 2,500, or 5,000 ppm in feed, as evidenced by the absence of chemical-related increased neoplasm incidences at any site. However, the incidence of mammary gland neoplasms in exposed groups of male and female rats and of pituitary gland neoplasms in exposed groups of males were decreased. The decreased incidences of these neoplasms may be related to mean body weight decreases of exposed groups of rats. This observation is supported by Seilkop (1995), who found positive relationships between body weight and pituitary gland neoplasms in male and female rats and mammary gland neoplasms in female rats.

Nonneoplastic lesions observed in male rats exposed to *t*-butylhydroquinone included increased incidences of cysts and suppurative inflammation in the kidney. These increased incidences in rats were probably related to *t*-butylhydroquinone exposure. Hydroquinone was nephrotoxic to rats administered 25 or 50 mg/kg body weight for up to 2 years; the chemical caused increased severities of nonneoplastic renal lesions in males and females and increased incidences of nonneoplastic cortical lesions in males (Kari *et al.*, 1992).

Mild regenerative anemia was observed in female rats administered 50 mg hydroquinone/kg body weight per day, 5 days per week for as long as 2 years. This anemia was characterized by decreases in hematocrit levels, hemoglobin concentrations, and erythrocyte counts (Kari, *et al.*, 1992).

In the 2-year mouse study, *t*-butylhydroquinone did not cause carcinogenic effects in male or female mice exposed to 1,250, 2,500, or 5,000 ppm, nor did the chemical cause increased incidences of nonneoplastic lesions.

CONCLUSIONS

Under the conditions of this long-term feed study, there was *no evidence of carcinogenic activity** of *t*-butylhydroquinone in male or female F344/N rats exposed to 1,250, 2,500, or 5,000 ppm. Under the conditions of this 2-year feed study, there was *no evidence of carcinogenic activity* of *t*-butylhydroquinone in male or female B6C3F$_1$ mice exposed to 1,250, 2,500, or 5,000 ppm.

Exposure of rats to *t*-butylhydroquinone in feed resulted in decreased incidences of mammary gland neoplasms in males and females.

---

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

REFERENCES

Altmann, H.J., Wester, P.W., Matthiaschk, G., Grunow, W., and Van der Heijden, C.A. (1985). Induction of early lesions in the forestomach of rats by 3-tert-butyl-4-hydroxyanisole (BHA). *Food Chem. Toxicol.* 23, 723-731.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Armstrong, K.E., and Wattenberg, L.W. (1985). Metabolism of 3-*tert*-butyl-4-hydroxyanisole to 3-*tert*-butyl-4,5-dihydroxyanisole by rat liver microsome. *Cancer Res.* 45, 1507-1510.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* 257, 229-306.

Astill, B.D., and Mulligan, L.T. (1977). Phenolic antioxidants and the inhibition of hepatotoxicity from *N*-dimethylnitrosamine formed *in situ* in the rat stomach. *Food Cosmet. Toxicol.* 15, 167-171.

Astill, B.D., and Roudabush, R.L. (1973). Monotertiary butyl hydroquinone (TBHQ): Biochemical behavior in rats, dogs and humans. *Fed. Proc.* 32, 734a.

Astill, B.D., Mills, J., Fassett, D.W., Roudabush, R.L., and Terhaar, C.J. (1962). Fate of butylated hydroxyanisole in man and dog. *Agric. Food Chem.* 10, 315-322.

Astill, B.D., Terhaar, C.J., Krasavage, W.J., Wolf, G.L., Roudabush, R.L., and Fassett, D.W. (1975). Safety evaluation and biochemical behavior of monotertiarybutylhydroquinone. *J. Am. Oil Chem. Soc.* 52, 53-58.

Bergmann, B., Dohrmann, J.K., and Kahl, R. (1992). Formation of the semiquinone anion radical from *tert*-butylquinone and from *tert*-butylhydroquinone in rat liver microsome. *Toxicology* 74, 127-133.

Boehme, M.A., and Branen, A.L. (1977). Effects of food antioxidants on prostaglandin biosynthesis. *J. Food Sci.* 42, 1243-1246.

Bonin, A.M., and Baker, R.S.U. (1980). Mutagenicity testing of some approved food additives with the *Salmonella*/microsome assay. *Food Technol. Aust. U.A.* 32, 608-611.

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

Burnett, C., Goldenthal, E.I., Harris, S.B., Wazeter, F.X., Strausburg, J., Kapp, R., and Voelker, R. (1976). Teratology and percutaneous toxicity studies on hair dyes. *J. Toxicol. Environ. Health* 1, 1027-1040.

Calnan, C.D. (1981). Monotertiary butyl hydroquinone in lipstick. *Contact Dermatitis* 7, 280-281.

Chapin, R.E., Gulati, D.K., Fail, P.A., Hope, E., Russell, S.R., Heindel, J.J., George, J.D., Grizzle, T.B., Teague, J.L. (1993). The effects of feed restriction on reproductive function in Swiss CD-1 mice. *Fundam. Appl. Toxicol.* 20, 15-22.

Code of Federal Regulations (CFR) 21, Part 58

Code of Federal Regulations (CFR) 21, § 172.185

Code of Federal Regulations (CFR) **21**, § 177.2420

Cosmetic Ingredient Review (CIR) (1986). Final Report on the Safety Assessment of *t*-Butyl Hydroquinone. *J. Am. Coll. Toxicol.* **5**, 329-351.

Cosmetic Ingredient Review (CIR) (1991). Final Report on the Safety Assessment of *t*-Butyl Hydroquinone. *J. Am. Coll. Toxicol.* **10**, 1-7.

Cox, D.R. (1972). Regression models and life-tables. *J. R. Stat. Soc.* **B34**, 187-220.

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology*: *Mechanisms and Toxicity of Chemical Carcinogens and Mutagens* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co. Inc., Princeton, NJ.

De Long, M.J., Prochaska, H.J., and Talalay, P. (1985). Tissue-specific induction patterns of cancer-protective enzymes in mice by *tert*-butyl-4-hydroxy-anisole and related substituted phenols. *Cancer Res.* **45**, 546-551.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumor prevalence data. *Appl. Statist.* **32**, 236-248.

Dixon, W.J., and Massey, F.J., Jr. (1951). *Introduction to Statistical Analysis*, 1st ed., pp. 145-147. McGraw-Hill Book Company, Inc., New York.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

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

El-Rashidy, R., and Niazi, S. (1983). A new metabolite of butylated hydroxyanisole in man. *Biopharm. Drug Dispos.* **4**, 389-396.

Epstein, S.S., Saporoschetz, I.B., and Hutner, S.H. (1967). Toxicity of antioxidants to *Tetrahymena pyriformis*. *J. Protozool.* **14**, 238-244.

Flamm, W.G., Weisburger, E., Clayson, D., Witschi, H., Conning, D., and Kawachi, T. (1982). Report of the Working Group on the Toxicology and Metabolism of Antioxidants. Unpublished section of the Four Nation Working Group Report. Food and Drug Administration, Washington, DC.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* **10** (Suppl. 10), 1-175.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *J. Natl. Cancer Inst.* **62**, 957-974.

Giri, A.K., Sen, S., Talukder, G., Sharma, A., and Banerjee, T.S. (1984). Mutachromosomal effects of *tert*-butylhydroquinone in bone-marrow cells of mice. *Food Chem. Toxicol.* **22**, 459-460.

Hageman, G.J., Verhage, H., and Kleinjans, J.C.S. (1988). Butylated hydroxyanisole, butylated hydroxy-toluene and *tert*-butylhydroquinone are not mutagenic in the Salmonella/microsome assay using new tester strains. *Mutat. Res.* **208**, 207-211.

Hasegawa, R., Tiwawech, D., Hirose, M., Takaba, K., Hoshiya, T., Shirai, T., and Ito, N. (1992). Suppression of diethylnitrosamine-initiated preneoplastic foci development in the rat liver by combined administration of four antioxidants at low doses. *Jpn. J. Cancer Res.* **83**, 431-437.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* 58, 385-392.

Hirose, M., Shibata, M., Hagiwara, A., Imaida, K., and Ito, N. (1981). Chronic toxicity of butylated hydroxytoluene in Wistar rats. *Food Cosmet. Toxicol.* 19, 147-151.

Hirose, M., Masuda, A., Fukushima, S., and Ito, N. (1988). Effects of subsequent antioxidant treatment on 7,12-dimethylbenz[*a*]anthracene-initiated carcinogenesis of the mammary gland, ear duct and forestomach in Sprague-Dawley rats. *Carcinogenesis* 9, 101-104.

Hirose, M., Yada, H., Hakoi, K., Takahashi, S., and Ito, N. (1993). Modification of carcinogenesis by α-tocopherol, t-butylhydroquinone, propyl gallate and butylated hydroxytoluene in a rat multi-organ carcinogenesis model. *Carcinogenesis* 14, 2359-2364.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Ito, N., Hagiwara, A., Shibata, M., Ogiso, T., and Fukushima, S. (1982). Induction of squamous cell carcinoma in the forestomach of F344 rats treated with butylated hydroxyanisole. *Gann* 73, 332-334.

Iverson, F., Lok, E., Nera, E., Karpinski, K., and Clayson, D.B. (1985). A 13-week feeding study of butylated hydroxyanisole: The subsequent regression of the induced lesions in male Fischer 344 rat forestomach epithelium. *Toxicology* 35, 1-11.

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

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

Kari, F.W., Bucher, J., Eustis, S.L., Haseman, J.K., and Huff, J.E. (1992). Toxicity and carcinogenicity of hydroquinone in F344/N rats and B6C3F$_1$ mice. *Food Chem. Toxicol.*, 30, 737-747.

Kawabe, M., Takaba, K., Yoshida, Y., and Hirose, M. (1994). Effects of combined treatment with phenolic compounds and sodium nitrite on two-stage carcinogenesis and cell proliferation in the rat stomach. *Jpn. J. Cancer Res.* 85, 17-25.

Kawano, S., Nakao, T., and Hiraga, K. (1981). Induction of hepatic microsomal monooxygenases in female rats given various substituted phenols and hydroquinones. *Jpn. J. Pharmacol.* 31, 459-462.

Kirk-Othmer Encyclopedia of Chemical Technology (1981). 3rd ed., Vol. 13, p. 60. John Wiley and Sons, New York.

Krasavage, W.J. (1977). Evaluation of the teratogenic potential of tertiary butylhydroquinone (TBHQ) in the rat. *Teratology* 16, 31-34.

Krasavage, W.J. (1984). The lack of effect of tertiary butylhydroquinone on prothrombin time in male rats. *Drug Chem. Toxicol.* 7, 329-334.

Krasavage, W.J., and O'Donohue, J.L. (1984). Lack of lung damage in mice following administration of tertiary butylhydroquinone. *Drug Chem. Toxicol.* 7, 335-343.

Krasavage, W.J., and Terhaar, C.J. (1970). The reproductive performance of rats fed monotertiary butylhydroquinone: A single generation study. Unpublished report from the Toxicology Laboratory, Eastman Kodak, submitted to the World Health Organization by Eastman Chemical Products, Inc.

Li, Y., and Trush, M.A. (1994). Reactive oxygen-dependent DNA damage resulting from the oxidation of phenolic compounds by a copper-redox cycle mechanism. *Cancer Res.* 54 (Suppl. 7), 1895s-1898s.

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

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* 79, 639-648.

Margolin, B.H., Risko, K.J., Frome, E.L., and Tice, R.R. (1990). A general purpose statistical analysis program for micronucleus assay data. Appendix 2: Micronucleus data management and analysis version 1.4a. Integrated Laboratory Systems, Research Triangle Park, NC.

Marino, A.A., and Mitchell, J.T. (1972). Lung damage in mice following intraperitoneal injection of butylated hydroxytoluene. *Proc. Soc. Exp. Biol. Med.* **140**, 122-125.

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

Matsuoka, A., Matsui, M., Miyata, N., Sofuni, T., and Ishidate, M., Jr. (1990). Mutagenicity of 3-*tert*-butyl-4-hydroxyanisole (BHA) and its metabolites in short-term tests *in vitro*. *Mutat. Res.* **241**, 125-132.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Mizuno, M., Toda, M., Danno, G., Kanazawa, K., and Natake, M. (1988). Desmutagenic effects of sulfhydryl compounds on a mutagen formed from butylated hydroxyanisole reacted with sodium nitrite. *Agric. Biol. Chem.* **52**, 2843-2849.

Mizutani, T., Ishida, I., Yamamoto, K., and Tajima, K. (1982). Pulmonary toxicity of butylated hydroxytoluene and related alkylphenols: Structural requirements for toxic potency in mice. *Toxicol. Appl. Pharmacol.* **62**, 273-281.

Morimoto, K., Tsuji, K., Iio, T., Miyata, N., Uchida, A., Osawa, R., Kitsutaka, H., and Takahashi, A. (1991). DNA damage in forestomach epithelium from male F344 rats following oral administration of *tert*-butylquinone, one of the forestomach metabolites of 3-BHA. *Carcinogenesis* **12**, 703-708.

Morrison, D.F. (1976). *Multivariate Statistical Methods*, 2nd ed., pp. 170-179. McGraw-Hill Book Company, New York.

Mukherjee, A., Talukder, G., and Sharma, A. (1989). Sister chromatid exchanges induced by tertiary butyl hydroquinone in bone marrow cells of mice. *Environ. Mol. Mutagen.* **13**, 234-237.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1979). Bioassay of Butylated Hydroxytoluene (BHT) for Possible Carcinogenicity (CAS No. 128-37-0). Technical Report Series No. 150. NIH Publication No. 79-1706. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH) (1990). National Occupational Exposure Survey (1981-1983), unpublished provisional data as of July 1, 1990. NIOSH, Cincinnati, OH.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Toxicology Program (NTP) (1987). Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluations in Toxicity Testing for Rats and Mice, 10/31/82 version (updated December 1987). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989). Toxicology and Carcinogenesis Studies of Hydroquinone (CAS No. 123-31-9) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 366. NIH Publication No. 90-2821. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nera, E.A., Lok, E., Iverson, F., Ormsby, E., Karpinski, K.F., and Clayson, D.B. (1984). Short-term pathological and proliferative effects of butylated hydroxyanisole and other phenolic antioxidants in the forestomach of Fischer 344 rats *Toxicology* 32, 197-213.

Olsen, P., Bille, N., and Meyer, O. (1983). Hepatocellular neoplasms in rats induced by butylated hydroxytoluene (BHT). *Acta Pharmacol. Toxicol.* 53, 433-434.

Phillips, B.J., Carroll, P.A., Tee, A.C., and Anderson, D. (1989). Microsome-mediated clastogenicity of butylated hydroxyanisol (BHA) in cultured Chinese hamster ovary cells: The possible role of reactive oxygen species. *Mutat. Res.* 214, 105-114.

Rahimthula, A.D., Jernstrom, B., Dock, L., and Moldeus, P. (1982). Effects of dietary and in vitro 2(3)-*t*-butyl-4-hydroxyanisole and other phenols on hepatic enzyme activities in mice. *Br. J. Cancer* 45, 935-944.

RTECS [database online] (1983). National Institute for Occupational Safety and Health: 1971-. Updated quarterly. Available from: National Library of Medicine, Bethesda, MD.

Rogers, C.G., Boyes, B.G., Matula, T.I., and Stapley, R. (1992). Evaluation of genotoxicity of *tert*-butylhydroquinone in an hepatocyte-mediated assay with V79 Chinese hamster lung cells and in strain D7 of *Saccharomyces cerevisiae*. *Mutat. Res.* 280, 17-27.

Sadtler Standard Spectra. IR No. 46130; UV No. 24724; NMR No. 21464. Sadtler Research Laboratories, Philadelphia, PA.

Saheb, W., and Witschi, H. (1975). Lung growth in mice after a single dose of butylated hydroxytoluene. *Toxicol. Appl. Pharmacol.* 33, 309-319.

Schilderman, P.A.E.L., van Maanen, J.M.S., ten Vaarwerk, F.J., Lafleur, M.V.M., Westmijze, E.J., ten Hoor, F., and Kleinjans, J.C.S. (1993). The role of prostaglandin H synthase-mediated metabolism in the induction of oxidative DNA damage by BHA metabolites. *Carcinogenesis* 14, 1297-1302.

Seilkop, S.K. (1995). The effect of body weight on tumor incidence and carcinogenicity testing in B6C3F$_1$ mice and F344 rats. *Fundam. Appl. Toxicol.* 24, 247-259.

Shirai, T., Hagiwara, A., Kurata, Y., Shibata, M., Fukushima, S., and Ito, N. (1982). Lack of carcinogenicity of butylated hydroxytoluene on long-term administration to B6C3F$_1$ mice. *Food Chem. Toxicol.* 20, 861-865.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* 33, 386-389.

Sims, R.J., and Fioriti, J.A. (1980). Antioxidants as stabilizers for fats, oils, and lipid-containing foods. In *CRC Handbook of Food Additives* (T.E. Furia, Ed.), 2nd ed., Vol. II, pp. 13-56. CRC Press, Inc., Boca Raton, FL.

Snedecor, G.W., and Cochran, W.G., Eds. (1980). *Statistical Methods*, 7th ed., pp. 215-237, 252-254, 295. Iowa State University Press, Ames, IA.

Sokal, R.R., and Rohlf, F.J., Eds. (1981). *Biometry*, 7th Ed., pp. 403-405, 429-432. W.H. Freeman and Co., San Francisco.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233-241.

Takahashi, O., and Hiraga, K. (1978). Dose-response study of hemorrhagic death by dietary butylated hydroxytoluene (BHT) in male rats. *Toxicol. Appl. Pharmacol.* **43**, 399-406.

Tamano, S., Fukushima, S., Shirai, T., Hirose, M., and Ito, N. (1987). Modification by α-tocopherol, propyl gallate and tertiary butylhydroquinone of urinary bladder carcinogenesis in Fischer 344 rats pretreated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. *Cancer Lett.* **35**, 39-46.

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

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* **236**, 933-941.

Terhaar, C.J., and Krasavage, W.J. (1968a). Dietary feeding of TBHQ and related compounds to rats and dogs: The response of liver processing enzymes and liver glucose-6-phosphatase activity. Unpublished report from the Biochemistry Laboratory, Eastman Kodak, submitted to the World Health Organization by Eastman Chemical Products, Inc.

Terhaar, C.J., and Krasavage, W.J. (1968b). The reproductive performance of rats fed monotertiary butylhydroquinone. Unpublished report from the Toxicology Laboratory, Eastman Kodak, submitted to the World Health Organization by Eastman Chemical Products, Inc.

U.S. Environmental Protection Agency (USEPA) (1985). Chemicals in Commerce Information System, Public File, U.S. Environmental Protection Agency, Washington, DC.

U.S. International Trade Commission (USITC) (1984). U.S. Government Printing Office, Washington, DC.

Verhagen, H., Thijssen, H.H.W., ten Hoor, F., and Kleinjans, J.C.S. (1989). Disposition of single oral doses of butylated hydroxyanisole in man and rat. *Food Chem. Toxicol.* **27**, 151-158.

White, I.R., Lovell, C.R., and Cronin, E. (1984). Antioxidants in cosmetics. *Contact Dermatitis* **11**, 265-267.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Witschi, H., and Saheb, W. (1974). Stimulation of DNA synthesis in mouse lung following intraperitoneal injection of butylated hydroxytoluene. *Proc. Soc. Exp. Biol. Med.* **147**, 690-693.

Yoshida, Y., Hirose, M., Takaba, K., Kimura, J., and Ito, N. (1994). Induction and promotion of forestomach tumors by sodium nitrite in combination with ascorbic acid or sodium ascorbate in rats with or without *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine pretreatment. *Int. J. Cancer* **56**, 124-128.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1992). *Salmonella* mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ. Mol. Mutagen.* **19** (Suppl. 21), 2-141.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE LONG-TERM FEED STUDY OF *t*-BUTYLHYDROQUINONE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	48	51	50	42
Natural deaths	4	2	7	4
Survivors				
Terminal sacrifice	8	7	1	14
Missexed	0	0	2	0
Animals examined microscopically	70	70	68	70
Systems Examined At 3 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
Long-Term Study				
Alimentary System				
Intestine large, colon	(58)	(58)	(58)	(60)
Leiomyosarcoma		1 (2%)		
Intestine large, rectum	(59)	(60)	(58)	(59)
Carcinoma			1 (2%)	
Intestine large, cecum	(60)	(58)	(58)	(60)
Intestine small, duodenum	(60)	(60)	(58)	(60)
Intestine small, jejunum	(60)	(60)	(57)	(60)
Carcinoma			1 (2%)	
Intestine small, ileum	(60)	(59)	(58)	(59)
Leiomyoma		1 (2%)		
Liver	(60)	(60)	(58)	(60)
Hepatocellular carcinoma				2 (3%)
Hepatocellular adenoma	4 (7%)	4 (7%)		3 (5%)
Histiocytic sarcoma	1 (2%)			
Leiomyosarcoma, metastatic, intestine large, colon		1 (2%)		
Osteosarcoma, metastatic, mesentery			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Alimentary System (continued)				
Mesentery	(20)	(11)	(7)	(16)
Histiocytic sarcoma	1 (5%)			
Leiomyosarcoma, metastatic, intestine large, colon		1 (9%)		
Osteosarcoma			1 (14%)	
Schwannoma malignant	1 (5%)			
Oral mucosa	(1)	(2)	(2)	
Squamous cell carcinoma	1 (100%)	1 (50%)	2 (100%)	
Squamous cell papilloma		1 (50%)		
Pancreas	(60)	(59)	(58)	(60)
Leiomyosarcoma, metastatic, intestine large, colon		1 (2%)		
Acinus, adenoma	3 (5%)		1 (2%)	
Salivary glands	(60)	(60)	(58)	(60)
Carcinoma			1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)	
Stomach, forestomach	(60)	(60)	(58)	(59)
Squamous cell papilloma			1 (2%)	1 (2%)
Stomach, glandular	(60)	(60)	(58)	(60)
Tongue	(1)	(2)	(1)	(4)
Squamous cell carcinoma	1 (100%)			
Squamous cell papilloma				2 (50%)
Tooth	(1)		(2)	(1)
Odontoma			1 (50%)	
Cardiovascular System				
Heart	(60)	(60)	(58)	(60)
Schwannoma malignant	1 (2%)			
Endocrine System				
Adrenal cortex	(60)	(60)	(58)	(60)
Adenoma	1 (2%)			1 (2%)
Adrenal medulla	(60)	(60)	(58)	(60)
Pheochromocytoma malignant	1 (2%)	3 (5%)	1 (2%)	3 (5%)
Pheochromocytoma benign	13 (22%)	16 (27%)	11 (19%)	11 (18%)
Pheochromocytoma benign, multiple	1 (2%)	4 (7%)	4 (7%)	1 (2%)
Islets, pancreatic	(60)	(59)	(58)	(60)
Adenoma	5 (8%)	2 (3%)	1 (2%)	3 (5%)
Carcinoma	1 (2%)			
Pituitary gland	(60)	(58)	(57)	(60)
Pars distalis, adenoma	19 (32%)	16 (28%)	17 (30%)	6 (10%)
Pars distalis, carcinoma		1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(60)	(60)	(58)	(60)
C-cell, adenoma	5 (8%)	2 (3%)	2 (3%)	4 (7%)
C-cell, carcinoma		1 (2%)		2 (3%)
Follicular cell, adenoma		1 (2%)	1 (2%)	
Follicular cell, carcinoma				3 (5%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
General Body System				
Peritoneum	(1)		(1)	(3)
Genital System				
Preputial gland	(60)	(60)	(58)	(60)
Adenoma	5 (8%)	3 (5%)	6 (10%)	3 (5%)
Carcinoma	2 (3%)	2 (3%)	1 (2%)	5 (8%)
Carcinoma, multiple			1 (2%)	
Prostate	(60)	(60)	(58)	(60)
Adenoma	2 (3%)	2 (3%)	1 (2%)	1 (2%)
Seminal vesicle	(60)	(60)	(58)	(60)
Leiomyosarcoma, metastatic, intestine large, colon		1 (2%)		
Testes	(60)	(60)	(57)	(60)
Bilateral, interstitial cell, adenoma	42 (70%)	40 (67%)	45 (79%)	50 (83%)
Interstitial cell, adenoma	13 (22%)	9 (15%)	11 (19%)	9 (15%)
Hematopoietic System				
Bone marrow	(60)	(60)	(58)	(60)
Lymph node	(33)	(36)	(34)	(35)
Mediastinal, osteosarcoma, metastatic, mesentery			1 (3%)	
Lymph node, mandibular	(60)	(60)	(58)	(60)
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Fibrosarcoma, metastatic, skin			1 (2%)	
Lymph node, mesenteric	(60)	(58)	(57)	(60)
Hemangioma				1 (2%)
Spleen	(60)	(60)	(58)	(60)
Fibroma	2 (3%)	1 (2%)		
Histiocytic sarcoma	1 (2%)			
Leiomyosarcoma, metastatic, intestine large, colon		1 (2%)		
Osteosarcoma, metastatic, mesentery			1 (2%)	
Sarcoma	1 (2%)		1 (2%)	1 (2%)
Thymus	(58)	(55)	(54)	(56)
Thymoma malignant				1 (2%)
Integumentary System				
Mammary gland	(57)	(57)	(56)	(58)
Adenoma	1 (2%)		1 (2%)	
Fibroadenoma	9 (16%)	4 (7%)	4 (7%)	6 (10%)
Fibroadenoma, multiple	1 (2%)			1 (2%)
Skin	(60)	(60)	(57)	(60)
Basal cell carcinoma	1 (2%)			
Keratoacanthoma	3 (5%)	4 (7%)	4 (7%)	4 (7%)
Keratoacanthoma, multiple	1 (2%)			
Squamous cell papilloma	2 (3%)	1 (2%)		2 (3%)
Squamous cell papilloma, multiple		1 (2%)		
Trichoepithelioma	2 (3%)	1 (2%)		1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Integumentary System (continued)				
Skin (continued)	(60)	(60)	(57)	(60)
Sebaceous gland, adenoma	1 (2%)	1 (2%)		
Subcutaneous tissue, fibroma	3 (5%)	8 (13%)	6 (11%)	6 (10%)
Subcutaneous tissue, fibroma, multiple	1 (2%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, hemangioma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, schwannoma benign	1 (2%)			
Subcutaneous tissue, schwannoma malignant			1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(60)	(60)	(58)	(60)
Osteosarcoma			1 (2%)	
Skeletal muscle		(2)	(2)	
Leiomyosarcoma, metastatic, intestine large, colon		1 (50%)		
Osteosarcoma, metastatic, mesentery			1 (50%)	
Nervous System				
Brain	(60)	(60)	(58)	(60)
Astrocytoma malignant	1 (2%)	1 (2%)		
Oligodendroglioma malignant	1 (2%)			
Spinal cord	(2)	(3)	(1)	(1)
Respiratory System				
Lung	(60)	(60)	(58)	(60)
Alveolar/bronchiolar adenoma	3 (5%)	2 (3%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma				1 (2%)
Carcinoma, metastatic, salivary glands			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Squamous cell carcinoma, metastatic, oral mucosa			1 (2%)	
Nose	(60)	(60)	(58)	(60)
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma	1 (2%)			
Pleura			(1)	
Special Senses System				
Ear		(1)	(1)	
Squamous cell papilloma		1 (100%)		
Eye	(4)	(2)	(1)	(2)
Carcinoma, metastatic, salivary glands			1 (100%)	
Zymbal's gland	(2)	(1)	(3)	(4)
Adenoma				1 (25%)
Carcinoma	2 (100%)	1 (100%)	3 (100%)	3 (75%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Urinary System				
Kidney	(60)	(60)	(58)	(60)
Lipoma	1 (2%)			
Osteosarcoma, metastatic, mesentery			1 (2%)	
Renal tubule, adenoma	2 (3%)		1 (2%)	1 (2%)
Transitional epithelium, carcinoma	1 (2%)			
Urinary bladder	(60)	(60)	(58)	(60)
Papilloma			1 (2%)	1 (2%)
Systemic Lesions				
Multiple organs[b]	(60)	(60)	(58)	(60)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	39 (65%)	47 (78%)	40 (69%)	32 (53%)
Lymphoma malignant	1 (2%)			
Mesothelioma malignant	1 (2%)		1 (2%)	3 (5%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	60	59	57	60
Total primary neoplasms	207	185	178	179
Total animals with benign neoplasms	60	56	56	59
Total benign neoplasms	148	125	120	120
Total animals with malignant neoplasms	51	53	50	47
Total malignant neoplasms	59	60	58	59
Total animals with metastatic neoplasms		1	5	2
Total metastatic neoplasms		6	11	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 A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of t-Butylhydroquinone: 0 ppm

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

+: 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 Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	704	705	708	710	711	729	730	733	736	738	750	752	752	757	758	759	761	774	774	785	786	788	796	796	796	805	807	808
Carcass ID Number	03434	04499	04140	04410	04747	05255	05266	05256	05199	05232	05323	05236	05363	05241	05310	05303	05388	05131	05414	05221	05229	05233	05351	05312	05322	05350	05408	05408
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X		X					
Histiocytic sarcoma																												
Mesentery	+			+	+	+																	+					
Histiocytic sarcoma																												
Schwannoma malignant																												
Oral mucosa																												
Squamous cell carcinoma																												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																		+										
Squamous cell carcinoma																		X										
Tooth																												
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																												
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant				X																								
Pheochromocytoma benign	X			X	X			X					X						X					X	X	X		
Pheochromocytoma benign, multiple																												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X					X					
Carcinoma																												
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Pars distalis, adenoma						X	X					X	X			X			X		X	X	X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
C-cell, adenoma							X			X					X										X	X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	8 2 4	8 3 1	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	0 5 3	0 0 4	0 1 1	0 1 2	0 1 3	0 3 9	0 4 0	0 4 2	0 4 5	0 5 7	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular adenoma							X				4
Histiocytic sarcoma											1
Mesentery	+	+	+						+		20
Histiocytic sarcoma											1
Schwannoma malignant											1
Oral mucosa											1
Squamous cell carcinoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Acinus, adenoma			X		X				X		3
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue											1
Squamous cell carcinoma											1
Tooth											1
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Schwannoma malignant											1
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma malignant											1
Pheochromocytoma benign		X	X								13
Pheochromocytoma benign, multiple									X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma		X								X	5
Carcinoma					X						1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	55
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma	X						X			X	19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma											5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	3 8 1	4 8 9	4 9 9	5 0 0	5 2 8	5 3 4	5 4 4	5 5 6	5 6 3	6 1 8	6 1 8	6 2 2	6 2 6	6 4 2	6 5 9	6 6 7	6 6 8	6 7 3	7 7 4	7 7 4	7 7 4	7 8 7	8 8 7	9 4
Carcass ID Number	0 5 9	0 2 4	0 1 6	0 6 0	0 4 8	0 4 4	0 4 6	0 2 0	0 3 7	0 1 7	0 2 5	0 4 6	0 4 3	0 4 1	0 0 7	0 3 5	0 5 0	0 2 8	0 1 5	0 1 8	0 2 7	0 5 8	0 0 5	0 0 9	0 2 2
General Body System																								
Peritoneum																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																		X	
Carcinoma	X									X														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X		X	X			X		X	X	X		X	X	X		X	
Interstitial cell, adenoma		X	X	X		X		X			X			X				X				X		X
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+						+	+	+	+		+			+	+	+		+		+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Histiocytic sarcoma									X															
Sarcoma																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+
Adenoma																	X							
Fibroadenoma	X																							
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																								
Keratoacanthoma																X								
Keratoacanthoma, multiple																							X	
Squamous cell papilloma																								
Trichoepithelioma																								
Sebaceous gland, adenoma																	X							
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, fibroma, multiple																								
Subcutaneous tissue, fibrosarcoma																								
Subcutaneous tissue, hemangioma																								
Subcutaneous tissue, hemangiosarcoma													X											
Subcutaneous tissue, schwannoma benign																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	7 0 4	7 0 5	7 0 8	7 1 0	7 1 9	7 2 9	7 3 0	7 3 6	7 3 8	7 5 0	7 5 2	7 5 2	7 5 7	7 5 8	7 5 9	7 6 1	7 7 4	7 7 4	7 8 5	7 8 6	7 8 6	7 8 6	7 9 5	8 0 7	8 0 8
Carcass ID Number	0 3 4	0 4 9	0 1 4	0 1 0	0 4 7	0 5 5	0 2 6	0 5 6	0 1 9	0 3 2	0 2 3	0 3 6	0 4 1	0 3 0	0 3 3	0 3 8	0 3 1	0 5 4	0 2 1	0 2 9	0 3 3	0 5 1	0 5 2	0 0 2	0 0 8
General Body System																									
Peritoneum																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
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							X				X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+		+	+		+	+	+				+	+	+	+		+	+			+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
Histiocytic sarcoma																									
Sarcoma										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma							X														X		X		X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																X									
Keratoacanthoma																									
Keratoacanthoma, multiple																									
Squamous cell papilloma																							X		
Trichoepithelioma															X								X		
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																X									
Subcutaneous tissue, fibroma, multiple																	X								
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, schwannoma benign																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	8 2 4	8 3 1	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	0 5 3	0 0 4	0 1 1	0 1 2	0 1 3	0 3 9	0 4 0	0 4 2	0 4 5	0 5 7	Total Tissues/ Tumors
General Body System											
Peritoneum										+	1
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Preputial gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma						X			X		5
Carcinoma											2
Prostate	+	+	+	+	+	+	+	+	+	+	60
Adenoma			X			X					2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	60
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	42
Interstitial cell, adenoma											13
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+			+				+	+	33
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	60
Spleen	+	+	+	+	+	+	+	+	+	+	60
Fibroma									X		2
Histiocytic sarcoma											1
Sarcoma											1
Thymus	+	+	+	M	+	+	+	+	+	+	58
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	57
Adenoma											1
Fibroadenoma					X		X	X	X		9
Fibroadenoma, multiple						X					1
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell carcinoma											1
Keratoacanthoma			X	X							3
Keratoacanthoma, multiple											1
Squamous cell papilloma										X	2
Trichoepithelioma											2
Sebaceous gland, adenoma											1
Subcutaneous tissue, fibroma		X						X			3
Subcutaneous tissue, fibroma, multiple											1
Subcutaneous tissue, fibrosarcoma				X							1
Subcutaneous tissue, hemangioma							X				1
Subcutaneous tissue, hemangiosarcoma											1
Subcutaneous tissue, schwannoma benign											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	3 8 1	4 8 9	4 9 9	5 0 0	5 0 8	5 3 4	5 4 4	5 5 6	5 6 3	6 1 8	6 1 8	6 2 2	6 2 6	6 4 2	6 5 9	6 6 7	6 6 8	6 7 3	7 7 4	7 7 4	7 7 4	7 8 7	8 9 7	9 4
Carcass ID Number	0 5 9	0 2 4	0 1 6	0 6 0	0 4 8	0 4 4	0 4 6	0 2 0	0 3 7	0 1 7	0 2 5	0 0 6	0 4 3	0 0 1	0 3 7	0 3 5	0 5 0	0 2 8	0 1 5	0 1 8	0 2 7	0 5 8	0 0 5	0 0 9	0 2 2
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant								X																
Oligodendroglioma malignant																								
Peripheral nerve																								
Spinal cord																								
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X							X							
Histiocytic sarcoma									X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye		+												+										
Zymbal's gland				+																				
Carcinoma				X																				
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma					X																			
Renal tubule, adenoma																								X
Transitional epithelium, carcinoma				X																				
Urethra		+																						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Leukemia mononuclear						X	X					X		X	X	X	X	X	X	X	X	X	X	X
Lymphoma malignant																								
Mesothelioma malignant																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	704	705	708	710	711	729	730	736	738	750	752	752	757	758	759	761	774	774	785	786	786	786	795	807	808
Carcass ID Number	00334	00449	00141	00110	00447	00555	00226	00556	00191	00332	00223	00336	00441	00330	00388	00331	00354	00521	00229	00333	00551	00552	00022	00028	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Oligodendroglioma malignant					X																				
Peripheral nerve											+										+				
Spinal cord											+										+				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																							+		
Carcinoma																							X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Renal tubule, adenoma	X																								
Transitional epithelium, carcinoma																									
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear	X		X	X	X	X		X	X	X	X			X	X	X	X	X	X	X	X	X	X		X
Lymphoma malignant																									
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of t-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	8 2 4	8 3 1	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	0 5 3	0 0 4	0 1 1	0 1 2	0 1 3	0 3 9	0 4 0	0 4 2	0 4 5	0 5 7	Total Tissues/ Tumors
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Astrocytoma malignant											1
Oligodendroglioma malignant											1
Peripheral nerve											2
Spinal cord											2
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											3
Histiocytic sarcoma											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Squamous cell papilloma											1
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Eye			+	+							4
Zymbal's gland											2
Carcinoma											2
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Lipoma											1
Renal tubule, adenoma											2
Transitional epithelium, carcinoma											1
Urethra											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Leukemia mononuclear					X		X	X	X		39
Lymphoma malignant		X									1
Mesothelioma malignant										X	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	8 3 1	8 5 2	8 5 2	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	1 1 1 6	1 1 4	1 3 0	0 7 1	0 7 6	0 7 7	0 8 0	0 8 3	0 9 1	1 0 5	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	59
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Leiomyosarcoma		X									1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	59
Leiomyoma							X				1
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular adenoma					X						4
Leiomyosarcoma, metastatic, intestine large, colon		X									1
Mesentery		+									11
Leiomyosarcoma, metastatic, intestine large, colon		X									1
Oral mucosa											2
Squamous cell carcinoma											1
Squamous cell papilloma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Leiomyosarcoma, metastatic, intestine large, colon		X									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue											2
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma malignant				X							3
Pheochromocytoma benign				X	X	X			X		16
Pheochromocytoma benign, multiple	X									X	4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											2
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	54
Pituitary gland	+	+	+	+	+	+	+	+	+	M	58
Pars distalis, adenoma		X			X		X	X	X		16
Pars distalis, carcinoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma	X								X		2
C-cell, carcinoma											1
Follicular cell, adenoma					X						1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	2 8 9	3 7 3	3 9 4	4 6 7	5 3 5	5 3 5	5 4 7	5 5 4	5 6 2	5 6 4	5 8 3	6 1 9	6 3 4	6 4 7	6 5 5	6 5 6	6 6 2	6 6 6	6 6 7	6 6 8	6 7 7	6 8 2	6 8 4	6 8 4	6 9 7
Carcass ID Number	0 9 5	0 7 4	0 9 0	1 1 0	1 0 2	1 2 2	1 0 7	1 1 9	1 1 5	0 8 9	1 2 3	1 0 9	1 2 7	1 2 5	1 2 4	1 2 0	1 2 8	1 1 8	1 2 1	0 7 5	0 9 9	1 0 3	0 8 7	0 9 3	0 7 3
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma				X																					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine large, colon																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X			X	X				X		X	X	X	X	X	X
Interstitial cell, adenoma					X	X	X	X			X	X			X	X									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+	+	+	+			+		+	+	+		+	+	+	+	+	+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma										X															
Leiomyosarcoma, metastatic, intestine large, colon																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma													X												
Squamous cell papilloma																									
Squamous cell papilloma, multiple																									
Trichoepithelioma																									
Sebaceous gland, adenoma										X															
Subcutaneous tissue, fibroma												X													X
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Leiomyosarcoma, metastatic, intestine large, colon																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant										X															
Peripheral nerve		+	+															+							
Spinal cord		+	+															+							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	6 9 7	6 9 7	7 0 2	7 0 8	7 0 8	7 2 2	7 2 2	7 2 5	7 2 9	7 3 0	7 3 0	7 3 0	7 4 4	7 4 4	7 4 5	7 6 1	7 6 5	7 6 6	7 6 8	7 7 3	7 8 6	8 0 6	8 1 8	8 3 0
Carcass ID Number	1 0 4	1 1 3	0 9 4	0 8 1	0 8 5	0 7 9	1 1 2	1 0 8	0 7 8	0 8 6	0 8 8	1 0 6	0 7 2	0 9 2	0 8 4	0 8 2	1 1 7	1 0 0	1 1 1	1 2 6	0 9 6	0 9 7	1 2 9	1 0 1	1 0 9
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X	X				
Carcinoma																					X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine large, colon																								
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																
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+	+	+	+		+			+		+	+		+			+	+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Leiomyosarcoma, metastatic, intestine large, colon																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+
Integumentary System																								
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																					X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X								X				X	
Squamous cell papilloma																								
Squamous cell papilloma, multiple																								
Trichoepithelioma																				X				
Sebaceous gland, adenoma																								
Subcutaneous tissue, fibroma	X								X															
Subcutaneous tissue, fibrosarcoma										X														
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								
Leiomyosarcoma, metastatic, intestine large, colon																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																								
Peripheral nerve																								
Spinal cord																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	8 3 1	8 5 2	8 5 2	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	1 1 6	1 1 4	1 3 0	0 7 1	0 7 6	0 7 7	0 8 0	0 8 3	0 9 1	1 0 5	Total Tissues/ Tumors
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Preputial gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma	X										3
Carcinoma											2
Prostate	+	+	+	+	+	+	+	+	+	+	60
Adenoma				X							2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Leiomyosarcoma, metastatic, intestine large, colon		X									1
Testes	+	+	+	+	+	+	+	+	+	+	60
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma											9
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+		+					+	36
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	58
Spleen	+	+	+	+	+	+	+	+	+	+	60
Fibroma											1
Leiomyosarcoma, metastatic, intestine large, colon		X									1
Thymus	M	+	+	+	+	+	+	+	+	+	55
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	57
Fibroadenoma		X		X				X			4
Skin	+	+	+	+	+	+	+	+	+	+	60
Keratoacanthoma											4
Squamous cell papilloma								X			1
Squamous cell papilloma, multiple				X							1
Trichoepithelioma											1
Sebaceous gland, adenoma											1
Subcutaneous tissue, fibroma				X	X			X	X		8
Subcutaneous tissue, fibrosarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle		+									2
Leiomyosarcoma, metastatic, intestine large, colon		X									1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Astrocytoma malignant											1
Peripheral nerve											3
Spinal cord											3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	2 8 9	3 7 3	3 9 4	4 6 7	5 3 5	5 3 5	5 4 7	5 5 4	5 6 2	5 6 4	5 8 3	6 1 9	6 3 4	6 4 7	6 5 5	6 5 6	6 6 2	6 6 6	6 6 7	6 6 8	6 7 7	6 8 2	6 8 4	6 8 4	6 9 7
Carcass ID Number	0 9 5	0 7 4	0 9 0	1 1 0	1 0 2	1 2 2	1 0 7	1 1 9	1 1 5	0 1 9	1 8 3	1 2 9	1 0 7	1 2 5	1 2 4	1 2 0	1 2 8	1 1 8	1 2 1	0 7 5	0 9 9	1 0 3	0 8 7	0 9 3	0 7 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Squamous cell papilloma																									
Eye	+																								
Zymbal's gland								+																	
Carcinoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra												+													
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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	6 9 7	6 9 7	7 0 2	7 0 8	7 0 8	7 2 2	7 2 2	7 2 5	7 2 9	7 3 0	7 3 0	7 3 0	7 4 4	7 4 4	7 4 5	7 6 1	7 6 5	7 6 6	7 6 8	7 7 3	7 8 6	8 0 6	8 1 4	8 3 0
Carcass ID Number	1 0 4	1 1 3	0 9 4	0 8 1	0 8 5	0 7 9	1 1 2	1 0 8	0 7 8	0 8 6	0 8 8	1 0 6	0 7 2	0 9 2	0 8 4	0 8 2	1 1 7	1 0 0	1 1 1	1 2 6	0 9 6	0 9 7	1 2 9	0 0 1	0 9 8
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X												X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																			+					
Squamous cell papilloma																			X					
Eye							+																	
Zymbal's gland																								
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																								
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	X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	8	8	8	8	8	8	8	8	8	8	
	3	5	5	5	5	5	5	5	5	5	
	1	2	2	7	7	7	7	7	7	7	
Carcass ID Number	1	1	1	0	0	0	0	0	0	1	Total
	1	1	3	7	7	7	8	8	9	0	Tissues/
	6	4	0	1	6	7	0	3	1	5	Tumors
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											2
Nose	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma											1
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear											1
Squamous cell papilloma											1
Eye											2
Zymbal's gland											1
Carcinoma											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Urethra											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X			X	X	X	X	X	X		47

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	6 7 3	6 7 4	6 7 7	6 8 2	6 9 1	6 9 4	6 9 5	6 9 5	7 1 0	7 2 5	7 2 9	7 2 9	7 3 0	7 3 8	7 4 4	7 5 7	7 5 7	7 6 1	7 6 6	7 6 7	7 7 3	7 7 7	7 8 6	7 9 2	7 9 5
Carcass ID Number	1 4 3	1 7 5	1 9 4	1 7 3	2 0 0	1 0 0	1 7 6	1 9 5	1 8 4	1 9 7	1 4 7	1 6 8	1 8 5	1 8 4 2	1 6 7	1 8 6	1 8 8	1 4 6	1 6 3	1 4 1	1 6 0	1 5 3	1 7 7	1 4 9	1 6 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X													
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, mesentery																									
Mesentery											+		+					+							
Osteosarcoma																									
Oral mucosa													+												
Squamous cell carcinoma													X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibrosarcoma, metastatic, skin																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth		+														+									
Odontoma																X									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant														X											
Pheochromocytoma benign					X			X			X		X				X					X			X
Pheochromocytoma benign, multiple																							X	X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X			X						X	X	X		X		X					
Pars distalis, carcinoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X																X				
Follicular cell, adenoma																									
General Body System																									
Peritoneum																		+							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	8 0 6	8 1 0	8 1 5	8 4 5	8 5 2	8 5 2	8 5 2	8 5 7	
Carcass ID Number	1 4 5	1 6 4	1 5 6	1 5 4	1 5 9	1 6 5	1 8 1	1 6 9	Total Tissues/ Tumors
Alimentary System									
Esophagus	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	58
Intestine large, rectum	+	+	+	+	+	+	+	+	58
Carcinoma									1
Intestine large, cecum	+	+	+	+	+	+	+	+	58
Intestine small, duodenum	+	+	+	+	+	+	+	+	58
Intestine small, jejunum	+	+	+	+	+	+	+	+	57
Carcinoma									1
Intestine small, ileum	+	+	+	+	+	+	+	+	58
Liver	+	+	+	+	+	+	+	+	58
Osteosarcoma, metastatic, mesentery									1
Mesentery									7
Osteosarcoma									1
Oral mucosa									2
Squamous cell carcinoma									2
Pancreas	+	+	+	+	+	+	+	+	58
Acinus, adenoma							X		1
Salivary glands	+	+	+	+	+	+	+	+	58
Carcinoma									1
Fibrosarcoma, metastatic, skin									1
Stomach, forestomach	+	+	+	+	+	+	+	+	58
Squamous cell papilloma									1
Stomach, glandular	+	+	+	+	+	+	+	+	58
Tongue					+				1
Tooth									2
Odontoma									1
Cardiovascular System									
Blood vessel	+	+	+	+	+	+	+	+	58
Heart	+	+	+	+	+	+	+	+	58
Endocrine System									
Adrenal cortex	+	+	+	+	+	+	+	+	58
Adrenal medulla	+	+	+	+	+	+	+	+	58
Pheochromocytoma malignant									1
Pheochromocytoma benign	X	X				X			11
Pheochromocytoma benign, multiple				X				X	4
Islets, pancreatic	+	+	+	+	+	+	+	+	58
Adenoma									1
Parathyroid gland	M	+	+	+	+	+	+	+	55
Pituitary gland	+	+	+	+	+	+	+	+	57
Pars distalis, adenoma			X	X				X	17
Pars distalis, carcinoma									1
Thyroid gland	+	+	+	+	+	+	+	+	58
C-cell, adenoma									2
Follicular cell, adenoma	X								1
General Body System									
Peritoneum									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	4 0 8	4 6 4	4 7 3	4 9 3	5 0 1	5 2 6	5 3 5	5 3 5	5 5 2	5 6 2	5 6 2	5 7 0	5 7 8	5 9 1	5 9 1	5 9 1	6 0 4	6 1 4	6 1 8	6 1 9	6 2 5	6 4 0	6 4 2	6 5 5	6 6 1
Carcass ID Number	1 7 8	1 5 8	1 9 8	1 9 3	1 7 4	1 7 1	1 4 8	1 5 5	1 8 9	1 5 7	1 7 9	1 8 2	1 7 0	1 6 6	1 7 2	1 8 3	1 5 2	1 9 0	1 6 7	1 8 2	1 5 1	1 9 1	1 5 0	1 4 4	1 9 2
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X											X						X		
Carcinoma																	X								
Carcinoma, multiple																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
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
Interstitial cell, adenoma		X			X		X							X							X			X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+		+		+	+					+	+			+	+		+	+	+		+
Mediastinal, osteosarcoma, metastatic, mesentery																		X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin											X														
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, mesentery																		X							
Sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma							X																		
Subcutaneous tissue, fibroma																				X	X		X		
Subcutaneous tissue, fibrosarcoma											X														
Subcutaneous tissue, schwannoma malignant												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma					X																				
Skeletal muscle																		+							
Mesothelioma malignant, metastatic, peritoneum																									
Osteosarcoma, metastatic, mesentery																		X							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord									+																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of t-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	8 0 6	8 1 0	8 1 5	8 4 5	8 5 2	8 5 2	8 5 2	8 5 7	
Carcass ID Number	1 4 5	1 6 4	1 5 6	1 5 4	1 5 9	1 6 5	1 8 1	1 6 9	Total Tissues/ Tumors
Genital System									
Epididymis	+	+	+	+	+	+	+	+	57
Preputial gland	+	+	+	+	+	+	+	+	58
Adenoma				X				X	6
Carcinoma									1
Carcinoma, multiple									1
Prostate	+	+	+	+	+	+	+	+	58
Adenoma									1
Seminal vesicle	+	+	+	+	+	+	+	+	58
Testes	+	+	+	+	+	+	+	+	57
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	45
Interstitial cell, adenoma			X						11
Hematopoietic System									
Bone marrow	+	+	+	+	+	+	+	+	58
Lymph node	+	+	+	+	+	+			34
Mediastinal, osteosarcoma, metastatic, mesentery									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	58
Fibrosarcoma, metastatic, skin									1
Lymph node, mesenteric	+	+	+	+	I	+	+	+	57
Spleen	+	+	+	+	+	+	+	+	58
Osteosarcoma, metastatic, mesentery									1
Sarcoma									1
Thymus	+	+	+	I	+	M	M	+	54
Integumentary System									
Mammary gland	+	+	+	+	+	+	+	+	56
Adenoma						X			1
Fibroadenoma									4
Skin	+	+	+	+	+	+	+	+	57
Keratoacanthoma	X	X					X		4
Subcutaneous tissue, fibroma									6
Subcutaneous tissue, fibrosarcoma									1
Subcutaneous tissue, schwannoma malignant									1
Musculoskeletal System									
Bone	+	+	+	+	+	+	+	+	58
Osteosarcoma									1
Skeletal muscle									2
Mesothelioma malignant, metastatic, peritoneum									1
Osteosarcoma, metastatic, mesentery									1
Nervous System									
Brain	+	+	+	+	+	+	+	+	58
Peripheral nerve									1
Spinal cord									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of t-Butylhydroquinone: 2,500 ppm (continued)

Number of Days on Study	4 0 8	4 6 4	4 7 3	4 9 3	5 0 1	5 2 6	5 3 5	5 3 5	5 5 2	5 6 2	5 6 2	5 7 0	5 7 8	5 9 1	5 9 1	5 9 1	6 0 4	6 1 4	6 1 8	6 1 9	6 2 5	6 4 0	6 4 2	6 5 5	6 6 1
Carcass ID Number	1 7 8	1 5 8	1 9 8	1 9 3	1 7 4	1 7 1	1 4 8	1 5 5	1 8 9	1 5 7	1 7 9	1 8 2	1 7 0	1 6 6	1 7 2	1 8 3	1 5 2	1 9 0	1 8 7	1 6 2	1 5 1	1 9 1	1 5 0	1 4 4	1 9 2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Carcinoma, metastatic, salivary glands																						X			
Squamous cell carcinoma, metastatic, oral mucosa																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear									+																
Eye																						+			
Carcinoma, metastatic, salivary glands																						X			
Zymbal's gland																							+		
Carcinoma																							X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, mesentery																		X							
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								X	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X	X	X	X	X	X					X	X	X			X		X				X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	6 7 3	6 7 4	6 7 7	6 8 2	6 9 1	6 9 4	6 9 5	6 9 5	7 1 0	7 2 5	7 2 9	7 2 9	7 3 0	7 3 8	7 4 4	7 5 7	7 5 7	7 6 1	7 6 6	7 6 7	7 7 3	7 7 7	7 8 6	7 9 2	7 9 5
Carcass ID Number	1 4 3	1 7 5	1 9 4	1 7 3	2 0 0	1 8 0	1 7 6	1 9 5	1 8 4	1 9 7	1 4 7	1 6 8	1 8 5	1 4 2	1 6 7	1 8 6	1 8 8	1 4 6	1 6 3	1 4 1	1 6 0	1 5 3	1 7 7	1 4 9	1 6 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, salivary glands																									
Squamous cell carcinoma, metastatic, oral mucosa																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																		+							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Carcinoma, metastatic, salivary glands																									
Zymbal's gland		+																							+
Carcinoma		X																							X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, mesentery																									
Renal tubule, adenoma																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
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	X			X
Mesothelioma malignant																		X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	8 0 6	8 1 0	8 1 5	8 4 5	8 5 2	8 5 2	8 5 2	8 5 7	
Carcass ID Number	1 4 5	1 6 4	1 5 6	1 5 4	1 5 9	1 6 5	1 8 1	1 6 9	Total Tissues/ Tumors
Respiratory System									
Lung	+	+	+	+	+	+	+	+	58
Alveolar/bronchiolar adenoma									1
Carcinoma, metastatic, salivary glands									1
Squamous cell carcinoma, metastatic, oral mucosa									1
Nose	+	+	+	+	+	+	+	+	58
Pleura									1
Trachea	+	+	+	+	+	+	+	+	58
Special Senses System									
Ear									1
Eye									1
Carcinoma, metastatic, salivary glands									1
Zymbal's gland									3
Carcinoma									3
Urinary System									
Kidney	+	+	+	+	+	+	+	+	58
Osteosarcoma, metastatic, mesentery									1
Renal tubule, adenoma									1
Urinary bladder	+	+	+	+	+	+	+	+	58
Papilloma									1
Systemic Lesions									
Multiple organs	+	+	+	+	+	+	+	+	58
Leukemia mononuclear	X	X				X	X	X	40
Mesothelioma malignant									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	2 1 8	2 1 9	2 2 2	2 2 6	2 3 3	2 4 1	2 4 8	2 4 9	2 5 5	2 6 6	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	59
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma											2
Hepatocellular adenoma			X								3
Mesothelioma malignant, metastatic, peritoneum											1
Mesentery					+						16
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Squamous cell papilloma											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue										+	4
Squamous cell papilloma										X	2
Tooth											1
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma malignant		X					X				3
Pheochromocytoma benign	X	X					X				11
Pheochromocytoma benign, multiple						X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma				X							3
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	58
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma						X			X		6
Pars distalis, carcinoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma						X					4
C-cell, carcinoma							X				2
Follicular cell, carcinoma									X		3
General Body System											
Peritoneum											3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	4 2 3	4 8 7	4 8 7	5 0 8	5 2 0	5 3 7	5 5 1	5 8 9	6 0 3	6 2 1	6 2 6	6 2 6	6 2 6	6 2 7	6 3 2	6 4 2	6 4 7	6 4 7	6 4 7	6 5 5	6 6 8	6 7 5	6 8 2	6 9 1	7 0 2
Carcass ID Number	2 4 2	2 4 5	2 6 4	2 5 7	2 3 0	2 7 0	2 5 8	2 1 7	2 3 5	2 6 3	2 2 4	2 4 6	2 5 3	2 5 4	2 3 6	2 2 9	2 3 9	2 4 4	2 5 0	2 6 8	2 5 1	2 6 5	2 2 5	2 6 7	2 4 0
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma					X				X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
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	X	X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+		+		+	+		+	+	+			+		+	+	+	+		+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland		X																							
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma													X												
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																	X								
Squamous cell papilloma																									X
Trichoepithelioma													X												
Subcutaneous tissue, fibroma																X									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	7 0 2	7 0 2	7 1 2	7 3 2	7 3 2	7 3 2	7 3 2	7 4 2	7 4 2	7 5 2	7 5 2	7 6 2	7 6 2	7 7 2	7 7 2	7 8 2	7 8 2	8 0 2	8 0 2	8 0 2	8 1 2	8 3 2	8 5 2	8 5 2	8 5 2
Carcass ID Number	2 4 7	2 1 1	2 5 1	2 2 1	2 4 3	2 5 6	2 6 2	2 2 7	2 2 8	2 3 2	2 5 2	2 3 1	2 3 4	2 6 9	2 2 0	2 3 7	2 2 3	2 3 8	2 6 0	2 6 1	2 1 3	2 1 2	2 1 4	2 1 5	2 1 6
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X							X		
Carcinoma			X																X						X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X
Interstitial cell, adenoma				X															X		X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+		+	+	+			+	+		+	+		+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Thymoma malignant														X											
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibroadenoma		X										X													
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma			X								X														
Squamous cell papilloma																									X
Trichoepithelioma																									
Subcutaneous tissue, fibroma											X		X		X										
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, schwannoma malignant																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																						+			
Spinal cord																						+			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm (continued)

Number of Days on Study	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	2 1 8	2 1 9	2 2 2	2 2 6	2 3 3	2 4 1	2 4 8	2 4 9	2 5 5	2 6 6	Total Tissues/ Tumors
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Preputial gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma									X		3
Carcinoma											5
Prostate	+	+	+	+	+	+	+	+	+	+	60
Adenoma								X			1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	60
Bilateral, interstitial cell, adenoma	X	X	X		X	X	X	X		X	50
Interstitial cell, adenoma				X					X		9
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node			+					+	+		35
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, Zymbal's gland											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	60
Hemangioma									X		1
Spleen	+	+	+	+	+	+	+	+	+	+	60
Sarcoma											1
Thymus	+	+	M	M	M	+	+	+	+	+	56
Thymoma malignant											1
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	58
Fibroadenoma	X		X			X				X	6
Fibroadenoma, multiple				X							1
Skin	+	+	+	+	+	+	+	+	+	+	60
Keratoacanthoma	X										4
Squamous cell papilloma											2
Trichoepithelioma											1
Subcutaneous tissue, fibroma			X						X		6
Subcutaneous tissue, fibrosarcoma											1
Subcutaneous tissue, schwannoma malignant											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Peripheral nerve											1
Spinal cord											1
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											1
Alveolar/bronchiolar carcinoma											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	4 2 3	4 8 7	4 8 7	5 0 8	5 2 0	5 3 7	5 5 1	5 8 9	6 0 3	6 2 1	6 2 6	6 2 6	6 2 6	6 2 7	6 3 2	6 4 2	6 4 7	6 4 7	6 4 7	6 5 5	6 6 8	6 7 5	6 8 2	6 9 1	7 0 2
Carcass ID Number	2 4 2	2 4 5	2 6 4	2 5 7	2 3 0	2 7 0	2 5 8	2 1 7	2 3 5	2 6 3	2 2 4	2 4 6	2 5 3	2 5 4	2 3 6	2 2 9	2 3 9	2 4 4	2 5 0	2 6 8	2 5 1	2 6 5	2 2 5	2 6 7	2 4 0
Special Senses System																									
Eye								+																	
Harderian gland																									
Zymbal's gland		+																			+				+
Adenoma																									X
Carcinoma		X																			X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	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 Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	7 0 2	7 0 2	7 1 2	7 3 2	7 3 2	7 3 2	7 3 2	7 4 2	7 4 2	7 5 2	7 6 2	7 6 2	7 7 2	7 7 2	7 8 2	7 8 2	8 0 2	8 0 2	8 0 2	8 1 2	8 3 2	8 5 2	8 5 2	8 5 2
Carcass ID Number	2 4 7	2 1 1	2 5 9	2 2 1	2 4 3	2 5 6	2 6 2	2 2 7	2 2 8	2 3 2	2 5 2	2 3 1	2 3 4	2 6 9	2 2 0	2 3 7	2 2 3	2 3 8	2 6 0	2 6 1	2 1 3	2 1 2	2 1 4	2 1 5	2 1 6
Special Senses System																								
Eye				+																				
Harderian gland																								
Zymbal's gland										+														
Adenoma																								
Carcinoma										X														
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																	X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	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 Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	8 5 7	
Carcass ID Number	2 1 8	2 1 9	2 2 2	2 2 6	2 3 3	2 4 1	2 4 8	2 4 9	2 5 5	2 6 6	Total Tissues/ Tumors
Special Senses System											
Eye											2
Harderian gland		+									1
Zymbal's gland											4
Adenoma											1
Carcinoma											3
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Renal tubule, adenoma											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Papilloma						X					1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear			X		X			X	X		32
Mesothelioma malignant											3

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	14/60 (23%)	20/60 (33%)	15/58 (26%)	12/60 (20%)
Adjusted rate[b]	59.8%	85.5%	100.0%	49.8%
Terminal rate[c]	2/8 (25%)	5/7 (71%)	1/1 (100%)	5/14 (36%)
First incidence (days)	667	655	473	487
Life table test[d]	P=0.071N	P=0.148	P=0.090	P=0.193N
Logistic regression test[d]	P=0.161N	P=0.123	P=0.224	P=0.351N
Cochran-Armitage test[d]	P=0.223N			
Fisher exact test[d]		P=0.156	P=0.458	P=0.412N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/60 (2%)	3/60 (5%)	1/58 (2%)	3/60 (5%)
Adjusted rate	3.1%	23.8%	5.0%	21.4%
Terminal rate	0/8 (0%)	1/7 (14%)	0/1 (0%)	3/14 (21%)
First incidence (days)	710	702	738	857 (T)
Life table test	P=0.496	P=0.302	P=0.698	P=0.465
Logistic regression test	P=0.390	P=0.296	P=0.738	P=0.394
Cochran-Armitage test	P=0.313			
Fisher exact test		P=0.309	P=0.744	P=0.309
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	14/60 (23%)	21/60 (35%)	16/58 (28%)	13/60 (22%)
Adjusted rate	59.8%	85.9%	100.0%	55.4%
Terminal rate	2/8 (25%)	5/7 (71%)	1/1 (100%)	6/14 (43%)
First incidence (days)	667	655	473	487
Life table test	P=0.090N	P=0.113	P=0.062	P=0.239N
Logistic regression test	P=0.210N	P=0.087	P=0.159	P=0.431N
Cochran-Armitage test	P=0.282N			
Fisher exact test		P=0.114	P=0.375	P=0.500N
Liver: Hepatocellular Adenoma				
Overall rate	4/60 (7%)	4/60 (7%)	0/58 (0%)	3/60 (5%)
Adjusted rate	25.1%	23.7%	0.0%	12.7%
Terminal rate	1/8 (13%)	1/7 (14%)	0/1 (0%)	1/14 (7%)
First incidence (days)	642	697	—[e]	708
Life table test	P=0.223N	P=0.615	P=0.170N	P=0.370N
Logistic regression test	P=0.291N	P=0.631	P=0.096N	P=0.463N
Cochran-Armitage test	P=0.322N			
Fisher exact test		P=0.641N	P=0.064N	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	4/60 (7%)	4/60 (7%)	0/58 (0%)	5/60 (8%)
Adjusted rate	25.1%	23.7%	0.0%	21.0%
Terminal rate	1/8 (13%)	1/7 (14%)	0/1 (0%)	1/14 (7%)
First incidence (days)	642	697	—	708
Life table test	P=0.504N	P=0.615	P=0.170N	P=0.611N
Logistic regression test	P=0.526	P=0.631	P=0.096N	P=0.548
Cochran-Armitage test	P=0.479			
Fisher exact test		P=0.641N	P=0.064N	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of t-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/60 (5%)	2/60 (3%)	1/58 (2%)	1/60 (2%)
Adjusted rate	10.2%	8.2%	2.4%	4.3%
Terminal rate	0/8 (0%)	0/7 (0%)	0/1 (0%)	0/14 (0%)
First incidence (days)	618	708	604	773
Life table test	P=0.187N	P=0.518N	P=0.409N	P=0.276N
Logistic regression test	P=0.201N	P=0.502N	P=0.294N	P=0.306N
Cochran-Armitage test	P=0.202N			
Fisher exact test		P=0.500N	P=0.322N	P=0.309N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/60 (5%)	2/60 (3%)	1/58 (2%)	2/60 (3%)
Adjusted rate	10.2%	8.2%	2.4%	11.2%
Terminal rate	0/8 (0%)	0/7 (0%)	0/1 (0%)	1/14 (7%)
First incidence (days)	618	708	604	773
Life table test	P=0.342N	P=0.518N	P=0.409N	P=0.418N
Logistic regression test	P=0.399N	P=0.502N	P=0.294N	P=0.488N
Cochran-Armitage test	P=0.406N			
Fisher exact test		P=0.500N	P=0.322N	P=0.500N
Mammary Gland: Fibroadenoma				
Overall rate	10/60 (17%)	4/60 (7%)	4/58 (7%)	7/60 (12%)
Adjusted rate	72.0%	40.7%	24.8%	40.2%
Terminal rate	5/8 (63%)	2/7 (29%)	0/1 (0%)	5/14 (36%)
First incidence (days)	381	786	619	708
Life table test	P=0.100N	P=0.085N	P=0.526N	P=0.059N
Logistic regression test	P=0.195N	P=0.033N	P=0.183N	P=0.107N
Cochran-Armitage test	P=0.350N			
Fisher exact test		P=0.077N	P=0.087N	P=0.301N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	11/60 (18%)	4/60 (7%)	5/58 (9%)	7/60 (12%)
Adjusted rate	72.6%	40.7%	43.6%	40.2%
Terminal rate	5/8 (63%)	2/7 (29%)	0/1 (0%)	5/14 (36%)
First incidence (days)	381	786	619	708
Life table test	P=0.072N	P=0.055N	P=0.580N	P=0.039N
Logistic regression test	P=0.145N	P=0.022N	P=0.213N	P=0.076N
Cochran-Armitage test	P=0.282N			
Fisher exact test		P=0.048N	P=0.101N	P=0.222N
Pancreas: Adenoma				
Overall rate	3/60 (5%)	0/59 (0%)	1/58 (2%)	0/60 (0%)
Adjusted rate	37.5%	0.0%	25.0%	0.0%
Terminal rate	3/8 (38%)	0/7 (0%)	0/1 (0%)	0/14 (0%)
First incidence (days)	857 (T)	—	852	—
Life table test	P=0.050N	P=0.130N	P=0.599	P=0.038N
Logistic regression test	P=0.044N	P=0.130N	P=0.728N	P=0.038N
Cochran-Armitage test	P=0.087N			
Fisher exact test		P=0.125N	P=0.322N	P=0.122N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Pancreatic Islets: Adenoma				
Overall rate	5/60 (8%)	2/59 (3%)	1/58 (2%)	3/60 (5%)
Adjusted rate	32.5%	7.6%	5.3%	15.9%
Terminal rate	1/8 (13%)	0/7 (0%)	0/1 (0%)	1/14 (7%)
First incidence (days)	667	697	744	708
Life table test	P=0.220N	P=0.246N	P=0.297N	P=0.208N
Logistic regression test	P=0.280N	P=0.230N	P=0.173N	P=0.287N
Cochran-Armitage test	P=0.319N			
Fisher exact test		P=0.226N	P=0.111N	P=0.359N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	6/60 (10%)	2/59 (3%)	1/58 (2%)	3/60 (5%)
Adjusted rate	42.1%	7.6%	5.3%	15.9%
Terminal rate	2/8 (25%)	0/7 (0%)	0/1 (0%)	1/14 (7%)
First incidence (days)	667	697	744	708
Life table test	P=0.130N	P=0.163N	P=0.269N	P=0.112N
Logistic regression test	P=0.175N	P=0.142N	P=0.117N	P=0.170N
Cochran-Armitage test	P=0.212N			
Fisher exact test		P=0.142N	P=0.062N	P=0.245N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	19/60 (32%)	16/58 (28%)	17/57 (30%)	6/60 (10%)
Adjusted rate	63.8%	80.0%	100.0%	30.2%
Terminal rate	2/8 (25%)	4/6 (67%)	1/1 (100%)	3/14 (21%)
First incidence (days)	528	562	562	668
Life table test	P=0.002N	P=0.468N	P=0.241	P=0.002N
Logistic regression test	P=0.003N	P=0.410N	P=0.573	P=0.002N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.389N	P=0.494N	P=0.003N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	19/60 (32%)	17/58 (29%)	18/57 (32%)	7/60 (12%)
Adjusted rate	63.8%	81.1%	100.0%	31.6%
Terminal rate	2/8 (25%)	4/6 (67%)	1/1 (100%)	3/14 (21%)
First incidence (days)	528	562	562	627
Life table test	P=0.004N	P=0.539N	P=0.188	P=0.004N
Logistic regression test	P=0.005N	P=0.494N	P=0.487	P=0.006N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.469N	P=0.575N	P=0.007N
Preputial Gland: Adenoma				
Overall rate	5/60 (8%)	3/60 (5%)	6/58 (10%)	3/60 (5%)
Adjusted rate	31.1%	20.0%	100.0%	18.4%
Terminal rate	2/8 (25%)	0/7 (0%)	1/1 (100%)	2/14 (14%)
First incidence (days)	528	766	526	786
Life table test	P=0.228N	P=0.401N	P=0.133	P=0.205N
Logistic regression test	P=0.358N	P=0.369N	P=0.436	P=0.312N
Cochran-Armitage test	P=0.386N			
Fisher exact test		P=0.359N	P=0.476	P=0.359N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Preputial Gland: Carcinoma				
Overall rate	2/60 (3%)	2/60 (3%)	2/58 (3%)	5/60 (8%)
Adjusted rate	3.6%	7.9%	6.0%	18.4%
Terminal rate	0/8 (0%)	0/7 (0%)	0/1 (0%)	1/14 (7%)
First incidence (days)	381	467	604	520
Life table test	P=0.169	P=0.667	P=0.625	P=0.287
Logistic regression test	P=0.098	P=0.614N	P=0.622N	P=0.200
Cochran-Armitage test	P=0.115			
Fisher exact test		P=0.691N	P=0.678	P=0.219
Preputial Gland: Adenoma or Carcinoma				
Overall rate	7/60 (12%)	5/60 (8%)	7/58 (12%)	8/60 (13%)
Adjusted rate	33.6%	26.3%	100.0%	34.2%
Terminal rate	2/8 (25%)	0/7 (0%)	1/1 (100%)	3/14 (21%)
First incidence (days)	381	467	526	520
Life table test	P=0.541N	P=0.435N	P=0.228	P=0.529N
Logistic regression test	P=0.355	P=0.373N	P=0.609	P=0.556
Cochran-Armitage test	P=0.350			
Fisher exact test		P=0.381N	P=0.585	P=0.500
Skin: Keratoacanthoma				
Overall rate	4/60 (7%)	4/60 (7%)	4/58 (7%)	4/60 (7%)
Adjusted rate	28.6%	18.8%	44.8%	15.5%
Terminal rate	2/8 (25%)	0/7 (0%)	0/1 (0%)	1/14 (7%)
First incidence (days)	667	634	535	647
Life table test	P=0.406N	P=0.612	P=0.268	P=0.516N
Logistic regression test	P=0.538N	P=0.632	P=0.517	P=0.616N
Cochran-Armitage test	P=0.567			
Fisher exact test		P=0.641N	P=0.622	P=0.641N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	6/60 (10%)	6/60 (10%)	4/58 (7%)	6/60 (10%)
Adjusted rate	45.1%	42.0%	44.8%	24.2%
Terminal rate	3/8 (38%)	2/7 (29%)	0/1 (0%)	2/14 (14%)
First incidence (days)	667	634	535	647
Life table test	P=0.297N	P=0.573	P=0.424	P=0.423N
Logistic regression test	P=0.468N	P=0.606	P=0.543N	P=0.566N
Cochran-Armitage test	P=0.533N			
Fisher exact test		P=0.619N	P=0.393N	P=0.619N
Skin: Trichoepithelioma or Basal Cell Carcinoma				
Overall rate	3/60 (5%)	1/60 (2%)	0/58 (0%)	1/60 (2%)
Adjusted rate	16.5%	6.3%	0.0%	2.0%
Terminal rate	0/8 (0%)	0/7 (0%)	0/1 (0%)	0/14 (0%)
First incidence (days)	759	773	—	626
Life table test	P=0.171N	P=0.328N	P=0.179N	P=0.240N
Logistic regression test	P=0.197N	P=0.313N	P=0.168N	P=0.298N
Cochran-Armitage test	P=0.202N			
Fisher exact test		P=0.309N	P=0.128N	P=0.309N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Carcinoma				
Overall rate	8/60 (13%)	7/60 (12%)	4/58 (7%)	7/60 (12%)
Adjusted rate	50.3%	45.6%	44.8%	25.7%
Terminal rate	3/8 (38%)	2/7 (29%)	0/1 (0%)	2/14 (14%)
First incidence (days)	667	634	535	626
Life table test	P=0.216N	P=0.556N	P=0.599N	P=0.308N
Logistic regression test	P=0.363N	P=0.521N	P=0.320N	P=0.454N
Cochran-Armitage test	P=0.420N			
Fisher exact test		P=0.500N	P=0.198N	P=0.500N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/60 (7%)	8/60 (13%)	6/58 (10%)	6/60 (10%)
Adjusted rate	30.0%	61.8%	26.7%	26.7%
Terminal rate	1/8 (13%)	4/7 (57%)	0/1 (0%)	2/14 (14%)
First incidence (days)	761	619	619	642
Life table test	P=0.434N	P=0.146	P=0.143	P=0.574
Logistic regression test	P=0.491	P=0.161	P=0.274	P=0.448
Cochran-Armitage test	P=0.439			
Fisher exact test		P=0.181	P=0.350	P=0.372
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	5/60 (8%)	9/60 (15%)	7/58 (12%)	7/60 (12%)
Adjusted rate	40.0%	63.3%	28.2%	29.3%
Terminal rate	2/8 (25%)	4/7 (57%)	0/1 (0%)	2/14 (14%)
First incidence (days)	761	619	562	642
Life table test	P=0.412N	P=0.151	P=0.106	P=0.605
Logistic regression test	P=0.491	P=0.173	P=0.282	P=0.470
Cochran-Armitage test	P=0.443			
Fisher exact test		P=0.197	P=0.357	P=0.381
Testes: Adenoma				
Overall rate	55/60 (92%)	49/60 (82%)	56/57 (98%)	59/60 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	8/8 (100%)	7/7 (100%)	1/1 (100%)	14/14 (100%)
First incidence (days)	489	535	464	487
Life table test	P=0.346N	P=0.399N	P=0.019	P=0.306N
Logistic regression test	P=0.009	P=0.116N	P=0.054	P=0.104
Cochran-Armitage test	P=0.013			
Fisher exact test		P=0.089N	P=0.116	P=0.103
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/60 (8%)	2/60 (3%)	2/58 (3%)	4/60 (7%)
Adjusted rate	25.2%	22.9%	10.9%	17.6%
Terminal rate	0/8 (0%)	1/7 (14%)	0/1 (0%)	2/14 (14%)
First incidence (days)	730	831	691	603
Life table test	P=0.357N	P=0.246N	P=0.382N	P=0.355N
Logistic regression test	P=0.478N	P=0.221N	P=0.311N	P=0.473N
Cochran-Armitage test	P=0.521N			
Fisher exact test		P=0.219N	P=0.234N	P=0.500N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/60 (8%)	3/60 (5%)	2/58 (3%)	6/60 (10%)
Adjusted rate	25.2%	24.7%	10.9%	26.5%
Terminal rate	0/8 (0%)	1/7 (14%)	0/1 (0%)	3/14 (21%)
First incidence (days)	730	667	691	603
Life table test	P=0.545	P=0.391N	P=0.382N	P=0.575N
Logistic regression test	P=0.404	P=0.368N	P=0.311N	P=0.536
Cochran-Armitage test	P=0.361			
Fisher exact test		P=0.359N	P=0.234N	P=0.500
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	0/60 (0%)	0/60 (0%)	0/58 (0%)	3/60 (5%)
Adjusted rate	0.0%	0.0%	0.0%	18.8%
Terminal rate	0/8 (0%)	0/7 (0%)	0/1 (0%)	1/14 (7%)
First incidence (days)	—	—	—	810
Life table test	P=0.053	—	—	P=0.237
Logistic regression test	P=0.031	—	—	P=0.179
Cochran-Armitage test	P=0.012			
Fisher exact test		—	—	P=0.122
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	0/60 (0%)	1/60 (2%)	1/58 (2%)	3/60 (5%)
Adjusted rate	0.0%	14.3%	12.5%	18.8%
Terminal rate	0/8 (0%)	1/7 (14%)	0/1 (0%)	1/14 (7%)
First incidence (days)	—	857 (T)	806	810
Life table test	P=0.174	P=0.473	P=0.419	P=0.237
Logistic regression test	P=0.113	P=0.473	P=0.423	P=0.179
Cochran-Armitage test	P=0.055			
Fisher exact test		P=0.500	P=0.492	P=0.122
Zymbal's Gland: Carcinoma				
Overall rate	2/60 (3%)	1/60 (2%)	3/58 (5%)	3/60 (5%)
Adjusted rate	9.9%	1.9%	16.3%	7.8%
Terminal rate	0/8 (0%)	0/7 (0%)	0/1 (0%)	0/14 (0%)
First incidence (days)	500	554	642	487
Life table test	P=0.339	P=0.493N	P=0.369	P=0.527
Logistic regression test	P=0.284	P=0.462N	P=0.495	P=0.483
Cochran-Armitage test	P=0.302			
Fisher exact test		P=0.500N	P=0.484	P=0.500
Zymbal's Gland: Adenoma or Carcinoma				
Overall rate	2/60 (3%)	1/60 (2%)	3/58 (5%)	4/60 (7%)
Adjusted rate	9.9%	1.9%	16.3%	10.4%
Terminal rate	0/8 (0%)	0/7 (0%)	0/1 (0%)	0/14 (0%)
First incidence (days)	500	554	642	487
Life table test	P=0.197	P=0.493N	P=0.369	P=0.366
Logistic regression test	P=0.149	P=0.462N	P=0.495	P=0.321
Cochran-Armitage test	P=0.163			
Fisher exact test		P=0.500N	P=0.484	P=0.340

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	39/60 (65%)	47/60 (78%)	40/58 (69%)	32/60 (53%)
Adjusted rate	87.2%	97.2%	100.0%	75.2%
Terminal rate	4/8 (50%)	6/7 (86%)	1/1 (100%)	6/14 (43%)
First incidence (days)	534	394	464	423
Life table test	P=0.035N	P=0.148	P=0.053	P=0.085N
Logistic regression test	P=0.034N	P=0.039	P=0.347	P=0.168N
Cochran-Armitage test	P=0.031N			
Fisher exact test		P=0.078	P=0.397	P=0.133N
All Organs: Malignant Mesothelioma				
Overall rate	1/60 (2%)	0/60 (0%)	1/58 (2%)	3/60 (5%)
Adjusted rate	12.5%	0.0%	6.3%	7.2%
Terminal rate	1/8 (13%)	0/7 (0%)	0/1 (0%)	0/14 (0%)
First incidence (days)	857 (T)	—	761	626
Life table test	P=0.151	P=0.527N	P=0.538	P=0.366
Logistic regression test	P=0.103	P=0.527N	P=0.676	P=0.306
Cochran-Armitage test	P=0.097			
Fisher exact test		P=0.500N	P=0.744	P=0.309
All Organs: Benign Neoplasms				
Overall rate	60/60 (100%)	56/60 (93%)	56/58 (97%)	59/60 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	8/8 (100%)	7/7 (100%)	1/1 (100%)	14/14 (100%)
First incidence (days)	381	535	464	487
Life table test	P=0.149N	P=0.492N	P=0.056	P=0.154N
Logistic regression test	P=0.450N	P=0.100N	P=0.282N	P=0.354N
Cochran-Armitage test	P=0.578			
Fisher exact test		P=0.059N	P=0.239N	P=0.500N
All Organs: Malignant Neoplasms				
Overall rate	51/60 (85%)	53/60 (88%)	50/58 (86%)	47/60 (78%)
Adjusted rate	95.5%	97.8%	100.0%	91.2%
Terminal rate	6/8 (75%)	6/7 (86%)	1/1 (100%)	10/14 (71%)
First incidence (days)	381	289	464	423
Life table test	P=0.092N	P=0.363	P=0.054	P=0.123N
Logistic regression test	P=0.150N	P=0.394	P=0.565N	P=0.249N
Cochran-Armitage test	P=0.131N			
Fisher exact test		P=0.395	P=0.530	P=0.240N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	60/60 (100%)	59/60 (98%)	57/58 (98%)	60/60 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	8/8 (100%)	7/7 (100%)	1/1 (100%)	14/14 (100%)
First incidence (days)	381	289	464	423
Life table test	P=0.155N	P=0.467	P=0.046	P=0.180N
Logistic regression test	P=0.673N	P=0.773N	P=0.404N	—[f]
Cochran-Armitage test	P=0.595			
Fisher exact test		P=0.500N	P=0.492N	P=1.000N

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	48	51	50	42
Natural deaths	4	2	7	4
Survivors				
Terminal sacrifice	8	7	1	14
Missexed	0	0	2	0
Animals examined microscopically	70	70	68	70
3-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)			
Intestine small, ileum	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid		1 (10%)		
Liver	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule		1 (10%)		
Inflammation, subacute	1 (10%)		1 (10%)	2 (20%)
Bile duct, hyperplasia				1 (10%)
Pancreas	(10)	(10)	(10)	(10)
Atrophy	1 (10%)			2 (20%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)		
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	2 (20%)	4 (40%)	2 (20%)	2 (20%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)			1 (10%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)		
Pituitary gland	(10)	(10)	(9)	(10)
Pars intermedia, cyst			1 (11%)	
Thyroid gland	(10)	(10)	(10)	(10)
Ectopic thymus	1 (10%)			
Ultimobranchial cyst	1 (10%)	1 (10%)		3 (30%)

[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 Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
3-Month Interim Evaluation (continued)				
Genital System				
Prostate	(10)	(10)	(10)	(10)
Inflammation, suppurative		2 (20%)	1 (10%)	
Testes	(10)	(10)	(10)	(10)
Seminiferous tubule, atrophy		1 (10%)		
Hematopoietic System				
Lymph node		(1)	(2)	
Mediastinal, hemorrhage		1 (100%)		
Mediastinal, hyperplasia, lymphoid		1 (100%)		
Renal, hemorrhage			2 (100%)	
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)		
Spleen	(10)	(10)	(10)	(10)
Pigmentation, hemosiderin			3 (30%)	5 (50%)
Thymus	(10)	(10)	(10)	(10)
Hemorrhage			3 (30%)	1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, subacute	4 (40%)	5 (50%)	7 (70%)	7 (70%)
Alveolar epithelium, hyperplasia	3 (30%)	1 (10%)	1 (10%)	3 (30%)
Nose	(10)	(10)	(10)	(10)
Goblet cell, hyperplasia				7 (70%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	1 (10%)	1 (10%)		
Nephropathy	5 (50%)	5 (50%)	4 (40%)	6 (60%)
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Long-Term Study				
Alimentary System				
Intestine large, colon	(58)	(58)	(58)	(60)
Edema			1 (2%)	1 (2%)
Parasite metazoan	7 (12%)	6 (10%)	3 (5%)	2 (3%)
Intestine large, rectum	(59)	(60)	(58)	(59)
Edema	2 (3%)		1 (2%)	1 (2%)
Hemorrhage				1 (2%)
Parasite metazoan	5 (8%)		1 (2%)	8 (14%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Alimentary System (continued)				
Intestine large, cecum	(60)	(58)	(58)	(60)
Edema	3 (5%)	2 (3%)	3 (5%)	3 (5%)
Parasite metazoan	1 (2%)	2 (3%)		3 (5%)
Intestine small, duodenum	(60)	(60)	(58)	(60)
Epithelium, hyperplasia	2 (3%)			4 (7%)
Intestine small, jejunum	(60)	(60)	(57)	(60)
Metaplasia, osseous			1 (2%)	
Epithelium, hyperplasia	1 (2%)			1 (2%)
Intestine small, ileum	(60)	(59)	(58)	(59)
Ulcer			1 (2%)	
Liver	(60)	(60)	(58)	(60)
Angiectasis	10 (17%)	1 (2%)	4 (7%)	7 (12%)
Basophilic focus	7 (12%)	3 (5%)	2 (3%)	7 (12%)
Clear cell focus	1 (2%)	3 (5%)	1 (2%)	5 (8%)
Degeneration, cystic	23 (38%)	16 (27%)	11 (19%)	5 (8%)
Eosinophilic focus	10 (17%)	4 (7%)	1 (2%)	4 (7%)
Eosinophilic focus, multiple	1 (2%)			
Fibrosis	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hemorrhage			1 (2%)	
Hepatodiaphragmatic nodule	7 (12%)	7 (12%)	4 (7%)	8 (13%)
Inflammation, subacute		1 (2%)		
Mixed cell focus	2 (3%)			2 (3%)
Necrosis, focal	8 (13%)	6 (10%)	3 (5%)	2 (3%)
Thrombosis	1 (2%)	3 (5%)		1 (2%)
Bile duct, cyst	2 (3%)			
Bile duct, hyperplasia	52 (87%)	49 (82%)	43 (74%)	25 (42%)
Centrilobular, atrophy		1 (2%)		
Centrilobular, fibrosis				1 (2%)
Centrilobular, necrosis	2 (3%)	1 (2%)		2 (3%)
Hepatocyte, vacuolization cytoplasmic	6 (10%)	4 (7%)	7 (12%)	3 (5%)
Kupffer cell, hyperplasia		1 (2%)		
Kupffer cell, pigmentation	11 (18%)	18 (30%)	8 (14%)	10 (17%)
Mesentery	(20)	(11)	(7)	(16)
Accessory spleen	1 (5%)	3 (27%)		4 (25%)
Fat, necrosis	16 (80%)	7 (64%)	6 (86%)	13 (81%)
Pancreas	(60)	(59)	(58)	(60)
Atrophy	15 (25%)	19 (32%)	12 (21%)	15 (25%)
Acinus, cytoplasmic alteration	3 (5%)	1 (2%)	1 (2%)	4 (7%)
Acinus, hyperplasia, focal	2 (3%)	3 (5%)	2 (3%)	2 (3%)
Salivary glands	(60)	(60)	(58)	(60)
Atrophy		1 (2%)		
Stomach, forestomach	(60)	(60)	(58)	(59)
Edema	9 (15%)	4 (7%)	5 (9%)	6 (10%)
Erosion		2 (3%)		
Hyperplasia	8 (13%)	6 (10%)	9 (16%)	12 (20%)
Ulcer	8 (13%)	1 (2%)	3 (5%)	7 (12%)
Mucosa, hyperplasia	1 (2%)	1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Alimentary System (continued)				
Stomach, glandular	(60)	(60)	(58)	(60)
Edema	1 (2%)	1 (2%)	3 (5%)	3 (5%)
Erosion	1 (2%)	3 (5%)	2 (3%)	1 (2%)
Mineralization	1 (2%)	2 (3%)	5 (9%)	
Ulcer	3 (5%)	3 (5%)	3 (5%)	
Tongue	(1)	(2)	(1)	(4)
Epithelium, hyperplasia		2 (100%)	1 (100%)	2 (50%)
Cardiovascular System				
Blood vessel	(60)	(60)	(58)	(60)
Hypertrophy	1 (2%)	3 (5%)	1 (2%)	4 (7%)
Inflammation, subacute	1 (2%)	1 (2%)	1 (2%)	
Mineralization		1 (2%)	1 (2%)	
Thrombosis			1 (2%)	
Heart	(60)	(60)	(58)	(60)
Cardiomyopathy	40 (67%)	39 (65%)	35 (60%)	37 (62%)
Mineralization		1 (2%)		
Necrosis	1 (2%)			
Thrombosis	6 (10%)	8 (13%)	4 (7%)	
Endocardium, hyperplasia	1 (2%)			
Schwann cell, hyperplasia		1 (2%)		
Endocrine System				
Adrenal cortex	(60)	(60)	(58)	(60)
Accessory adrenal cortical nodule	17 (28%)	10 (17%)	12 (21%)	13 (22%)
Degeneration, cystic		1 (2%)		
Degeneration, fatty	9 (15%)	10 (17%)	8 (14%)	7 (12%)
Hemorrhage	1 (2%)			2 (3%)
Hyperplasia, focal	4 (7%)	2 (3%)	2 (3%)	3 (5%)
Hypertrophy, focal	6 (10%)	5 (8%)	2 (3%)	2 (3%)
Necrosis	1 (2%)			
Adrenal medulla	(60)	(60)	(58)	(60)
Hyperplasia	26 (43%)	22 (37%)	15 (26%)	12 (20%)
Islets, pancreatic	(60)	(59)	(58)	(60)
Hyperplasia	3 (5%)		2 (3%)	1 (2%)
Parathyroid gland	(55)	(54)	(55)	(58)
Hyperplasia	6 (11%)	8 (15%)	7 (13%)	9 (16%)
Pituitary gland	(60)	(58)	(57)	(60)
Nuclear alteration				1 (2%)
Pars distalis, angiectasis	4 (7%)	2 (3%)	1 (2%)	
Pars distalis, cyst	6 (10%)	3 (5%)	4 (7%)	7 (12%)
Pars distalis, cyst, hemorrhagic	1 (2%)		1 (2%)	
Pars distalis, hyperplasia, focal	10 (17%)	8 (14%)	8 (14%)	14 (23%)
Pars intermedia, angiectasis		1 (2%)	2 (4%)	1 (2%)
Pars intermedia, cyst	1 (2%)	6 (10%)	4 (7%)	2 (3%)
Thyroid gland	(60)	(60)	(58)	(60)
Ultimobranchial cyst	1 (2%)	1 (2%)	1 (2%)	5 (8%)
C-cell, hyperplasia	9 (15%)	8 (13%)	9 (16%)	7 (12%)
Follicle, cyst	1 (2%)	3 (5%)	1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
General Body System				
None				
Genital System				
Epididymis	(60)	(60)	(57)	(60)
Atypia cellular	27 (45%)	26 (43%)	28 (49%)	25 (42%)
Granuloma sperm				1 (2%)
Preputial gland	(60)	(60)	(58)	(60)
Cyst	3 (5%)	3 (5%)	4 (7%)	4 (7%)
Hyperplasia	3 (5%)	2 (3%)	4 (7%)	2 (3%)
Inflammation, chronic	26 (43%)	16 (27%)	18 (31%)	12 (20%)
Inflammation, suppurative	3 (5%)	7 (12%)	3 (5%)	5 (8%)
Prostate	(60)	(60)	(58)	(60)
Cyst	1 (2%)			
Fibrosis	3 (5%)	1 (2%)		
Inflammation, chronic	5 (8%)	1 (2%)		
Inflammation, suppurative	36 (60%)	39 (65%)	40 (69%)	23 (38%)
Epithelium, hyperplasia	11 (18%)	10 (17%)	6 (10%)	8 (13%)
Testes	(60)	(60)	(57)	(60)
Interstitial cell, hyperplasia	4 (7%)	7 (12%)	6 (11%)	3 (5%)
Seminiferous tubule, atrophy	7 (12%)	5 (8%)	2 (4%)	5 (8%)
Hematopoietic System				
Bone marrow	(60)	(60)	(58)	(60)
Hyperplasia	6 (10%)	5 (8%)	2 (3%)	7 (12%)
Infiltration cellular, histiocyte				2 (3%)
Myelofibrosis	4 (7%)	8 (13%)		2 (3%)
Lymph node	(33)	(36)	(34)	(35)
Deep cervical, hyperplasia, lymphoid		1 (3%)		
Iliac, hemorrhage	1 (3%)			
Inguinal, hyperplasia, lymphoid	2 (6%)			1 (3%)
Mediastinal, congestion				2 (6%)
Mediastinal, hemorrhage	3 (9%)	2 (6%)	3 (9%)	3 (9%)
Mediastinal, hyperplasia, lymphoid	1 (3%)	1 (3%)	1 (3%)	2 (6%)
Mediastinal, pigmentation	13 (39%)	14 (39%)	17 (50%)	16 (46%)
Pancreatic, ectasia		1 (3%)		
Pancreatic, hyperplasia, plasma cell				1 (3%)
Pancreatic, pigmentation	9 (27%)	3 (8%)	4 (12%)	3 (9%)
Renal, ectasia				2 (6%)
Renal, hemorrhage	1 (3%)	1 (3%)	1 (3%)	2 (6%)
Renal, hyperplasia, lymphoid			1 (3%)	
Renal, pigmentation	8 (24%)	8 (22%)	8 (24%)	7 (20%)
Lymph node, mandibular	(60)	(60)	(58)	(60)
Ectasia	3 (5%)	8 (13%)	7 (12%)	6 (10%)
Hemorrhage	2 (3%)		2 (3%)	3 (5%)
Hyperplasia, lymphoid	11 (18%)	7 (12%)	10 (17%)	17 (28%)
Hyperplasia, plasma cell		1 (2%)	1 (2%)	
Pigmentation	6 (10%)	3 (5%)	7 (12%)	5 (8%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(60)	(58)	(57)	(60)
Ectasia	7 (12%)	1 (2%)	7 (12%)	10 (17%)
Hemorrhage	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Hyperplasia, lymphoid	3 (5%)	1 (2%)	10 (18%)	6 (10%)
Pigmentation		1 (2%)		
Spleen	(60)	(60)	(58)	(60)
Congestion	1 (2%)			
Fibrosis	21 (35%)	20 (33%)	9 (16%)	13 (22%)
Hematopoietic cell proliferation	7 (12%)	6 (10%)	3 (5%)	8 (13%)
Metaplasia, lipocyte	1 (2%)			
Necrosis	2 (3%)	2 (3%)	3 (5%)	
Pigmentation, hemosiderin	13 (22%)	9 (15%)	11 (19%)	12 (20%)
Lymphoid follicle, atrophy	1 (2%)			
Red pulp, atrophy		1 (2%)		
Thymus	(58)	(55)	(54)	(56)
Ectopic parathyroid gland		1 (2%)	2 (4%)	
Integumentary System				
Mammary gland	(57)	(57)	(56)	(58)
Dilatation	23 (40%)	24 (42%)	17 (30%)	10 (17%)
Galactocele	5 (9%)	4 (7%)	1 (2%)	2 (3%)
Hyperplasia	7 (12%)	4 (7%)	5 (9%)	6 (10%)
Skin	(60)	(60)	(57)	(60)
Cyst epithelial inclusion	2 (3%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage				1 (2%)
Hyperkeratosis		1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic		1 (2%)	2 (4%)	
Ulcer		1 (2%)	1 (2%)	
Epidermis, hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, thrombosis				1 (2%)
Musculoskeletal System				
Bone	(60)	(60)	(58)	(60)
Fibrous osteodystrophy	6 (10%)	5 (8%)	5 (9%)	7 (12%)
Hyperostosis	1 (2%)		1 (2%)	
Femur, osteopetrosis	1 (2%)	2 (3%)	1 (2%)	
Nervous System				
Brain	(60)	(60)	(58)	(60)
Atrophy	12 (20%)	8 (13%)	8 (14%)	3 (5%)
Gliosis			1 (2%)	
Hemorrhage	2 (3%)	1 (2%)	1 (2%)	1 (2%)
Hydrocephalus	4 (7%)	3 (5%)	4 (7%)	
Necrosis	1 (2%)			1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Respiratory System				
Lung	(60)	(60)	(58)	(60)
Congestion	2 (3%)			
Edema	1 (2%)			1 (2%)
Hemorrhage	3 (5%)	5 (8%)	2 (3%)	2 (3%)
Infiltration cellular, histiocyte	19 (32%)	21 (35%)	10 (17%)	14 (23%)
Inflammation, subacute		2 (3%)		1 (2%)
Metaplasia, osseous	1 (2%)			
Mineralization		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	4 (7%)	9 (15%)	5 (9%)	7 (12%)
Nose	(60)	(60)	(58)	(60)
Foreign body	6 (10%)	8 (13%)	2 (3%)	2 (3%)
Inflammation, suppurative	17 (28%)	22 (37%)	15 (26%)	11 (18%)
Goblet cell, hyperplasia	5 (8%)	3 (5%)	9 (16%)	13 (22%)
Mucosa, hyperplasia	14 (23%)	18 (30%)	13 (22%)	10 (17%)
Mucosa, metaplasia, squamous	8 (13%)	13 (22%)	8 (14%)	7 (12%)
Special Senses System				
Eye	(4)	(2)	(1)	(2)
Atrophy	2 (50%)			1 (50%)
Cataract	1 (25%)			1 (50%)
Inflammation, chronic		1 (50%)		
Retina, degeneration	1 (25%)			1 (50%)
Urinary System				
Kidney	(60)	(60)	(58)	(60)
Cyst	2 (3%)	3 (5%)	7 (12%)	11 (18%)
Developmental malformation		1 (2%)		
Inflammation, suppurative	9 (15%)	8 (13%)	9 (16%)	20 (33%)
Mineralization	12 (20%)	3 (5%)	2 (3%)	1 (2%)
Nephropathy	60 (100%)	60 (100%)	58 (100%)	60 (100%)
Renal tubule, accumulation, hyaline droplet	1 (2%)	1 (2%)	2 (3%)	1 (2%)
Renal tubule, atrophy				1 (2%)
Renal tubule, hyperplasia, focal			1 (2%)	
Renal tubule, necrosis	3 (5%)	1 (2%)	1 (2%)	
Renal tubule, pigmentation	18 (30%)	26 (43%)	17 (29%)	15 (25%)
Transitional epithelium, hyperplasia	13 (22%)	12 (20%)	11 (19%)	21 (35%)
Urinary bladder	(60)	(60)	(58)	(60)
Hemorrhage	1 (2%)			
Inflammation, suppurative	1 (2%)			
Transitional epithelium, hyperplasia	2 (3%)			

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE LONG-TERM FEED STUDY OF *t*-BUTYLHYDROQUINONE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	40	41	33	36
Natural deaths	10	8	9	7
Survivors				
Terminal sacrifice	10	11	16	17
Missexed	0	0	2	0
Animals examined microscopically	70	70	68	70
Systems Examined At 3 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
Long-Term Study				
Alimentary System				
Intestine large, colon	(60)	(59)	(56)	(59)
Intestine large, rectum	(59)	(59)	(57)	(59)
Intestine large, cecum	(60)	(60)	(57)	(60)
Intestine small, duodenum	(59)	(60)	(57)	(60)
Carcinoma			1 (2%)	
Intestine small, jejunum	(59)	(59)	(56)	(60)
Carcinoma			1 (2%)	
Intestine small, ileum	(60)	(58)	(57)	(58)
Leiomyosarcoma			1 (2%)	
Liver	(60)	(60)	(58)	(60)
Hepatocellular adenoma		1 (2%)	2 (3%)	1 (2%)
Hepatocellular adenoma, multiple				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Mesentery	(11)	(13)	(10)	(7)
Sarcoma stromal, metastatic, uterus	1 (9%)			
Oral mucosa			(1)	
Squamous cell carcinoma			1 (100%)	
Pancreas	(60)	(60)	(57)	(59)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Salivary glands	(60)	(60)	(58)	(60)
Stomach, forestomach	(60)	(60)	(57)	(60)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(60)	(60)	(57)	(60)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Alimentary System (continued)				
Tongue	(1)	(1)	(4)	(1)
Squamous cell carcinoma			1 (25%)	
Squamous cell papilloma	1 (100%)	1 (100%)	1 (25%)	
Cardiovascular System				
Heart	(60)	(60)	(58)	(60)
Schwannoma benign		1 (2%)		1 (2%)
Endocrine System				
Adrenal cortex	(60)	(60)	(58)	(60)
Adenoma	4 (7%)	1 (2%)		
Adrenal medulla	(60)	(60)	(58)	(60)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	2 (3%)	2 (3%)	1 (2%)	3 (5%)
Islets, pancreatic	(60)	(59)	(57)	(59)
Adenoma	2 (3%)	1 (2%)	3 (5%)	2 (3%)
Carcinoma			1 (2%)	
Parathyroid gland	(52)	(55)	(53)	(54)
Adenoma	2 (4%)			1 (2%)
Carcinoma, metastatic, thyroid gland				1 (2%)
Pituitary gland	(60)	(60)	(57)	(60)
Pars distalis, adenoma	26 (43%)	27 (45%)	34 (60%)	28 (47%)
Pars distalis, carcinoma	2 (3%)	1 (2%)	1 (2%)	3 (5%)
Thyroid gland	(60)	(60)	(57)	(60)
C-cell, adenoma	7 (12%)	7 (12%)	7 (12%)	6 (10%)
C-cell, carcinoma	1 (2%)		2 (4%)	1 (2%)
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma	1 (2%)		1 (2%)	2 (3%)
General Body System				
Peritoneum	(1)			
Genital System				
Clitoral gland	(58)	(59)	(58)	(60)
Adenoma	6 (10%)	6 (10%)	5 (9%)	6 (10%)
Adenoma, multiple				1 (2%)
Carcinoma	6 (10%)	4 (7%)	5 (9%)	8 (13%)
Ovary	(60)	(60)	(57)	(60)
Carcinoma			1 (2%)	
Granulosa cell tumor malignant		1 (2%)		
Granulosa cell tumor benign	1 (2%)	1 (2%)		1 (2%)
Uterus	(60)	(60)	(58)	(60)
Adenoma			1 (2%)	1 (2%)
Carcinoma				1 (2%)
Leiomyoma	1 (2%)	1 (2%)	1 (2%)	
Polyp stromal	6 (10%)	12 (20%)	5 (9%)	9 (15%)
Polyp stromal, multiple	1 (2%)			
Sarcoma stromal	2 (3%)	1 (2%)	1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Hematopoietic System				
Bone marrow	(60)	(60)	(57)	(60)
Lymph node	(20)	(24)	(19)	(18)
Pancreatic, carcinoma, metastatic, ovary			1 (5%)	
Lymph node, mandibular	(59)	(60)	(55)	(60)
Lymph node, mesenteric	(58)	(60)	(55)	(60)
Carcinoma, metastatic, ovary			1 (2%)	
Spleen	(60)	(60)	(57)	(60)
Hemangiosarcoma	1 (2%)			
Osteosarcoma, metastatic, bone			1 (2%)	
Thymus	(56)	(60)	(57)	(57)
Thymoma malignant			1 (2%)	
Integumentary System				
Mammary gland	(60)	(59)	(58)	(60)
Adenoma	3 (5%)		1 (2%)	2 (3%)
Carcinoma	8 (13%)	6 (10%)	2 (3%)	3 (5%)
Carcinoma, multiple				1 (2%)
Fibroadenoma	28 (47%)	16 (27%)	25 (43%)	20 (33%)
Fibroadenoma, multiple	15 (25%)	17 (29%)	9 (16%)	7 (12%)
Skin	(60)	(60)	(58)	(60)
Basal cell carcinoma	1 (2%)	1 (2%)		
Keratoacanthoma			1 (2%)	
Squamous cell papilloma				2 (3%)
Subcutaneous tissue, fibroma	3 (5%)	2 (3%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibroma, multiple		1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Subcutaneous tissue, lipoma	1 (2%)			
Subcutaneous tissue, sarcoma				1 (2%)
Subcutaneous tissue, schwannoma malignant				1 (2%)
Musculoskeletal System				
Bone	(60)	(59)	(58)	(60)
Osteosarcoma			1 (2%)	
Skeletal muscle	(1)	(1)	(1)	(1)
Sarcoma				1 (100%)
Sarcoma stromal, metastatic, uterus	1 (100%)			
Nervous System				
Brain	(60)	(60)	(58)	(60)
Carcinoma, metastatic, mammary gland				1 (2%)
Carcinoma, metastatic, pituitary gland				1 (2%)
Oligodendroglioma malignant	1 (2%)			
Spinal cord	(2)	(2)	(3)	(4)
Astrocytoma malignant				1 (25%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Long-Term Feed Study of t-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Respiratory System				
Lung	(60)	(60)	(58)	(60)
Alveolar/bronchiolar adenoma	2 (3%)	2 (3%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		
Carcinoma, metastatic, ovary			1 (2%)	
Carcinoma, metastatic, thyroid gland				1 (2%)
Nose	(60)	(60)	(58)	(60)
Special Senses System				
Zymbal's gland			(1)	
Carcinoma			1 (100%)	
Urinary System				
Kidney	(60)	(60)	(57)	(60)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Renal tubule, adenoma	1 (2%)			
Urinary bladder	(59)	(60)	(58)	(59)
Papilloma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(60)	(60)	(58)	(60)
Leukemia mononuclear	27 (45%)	33 (55%)	22 (38%)	27 (45%)
Mesothelioma malignant	1 (2%)			
Neoplasm Summary				
Total animals with primary neoplasms[c]	59	59	56	59
Total primary neoplasms	164	147	145	148
Total animals with benign neoplasms	52	51	49	50
Total benign neoplasms	112	99	100	95
Total animals with malignant neoplasms	41	39	38	38
Total malignant neoplasms	52	48	45	53
Total animals with metastatic neoplasms	2		2	4
Total metastatic neoplasms	5		5	4

[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 Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	3 5 2	3 7 0	3 8 2	3 9 1	3 9 8	4 0 1	4 0 2	4 0 6	4 0 7	4 0 9	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, jejunum	+	+	M	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Liver	+	+	+	+	+	+	+	+	+	+	60
Mesentery											11
Sarcoma stromal, metastatic, uterus											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Sarcoma stromal, metastatic, uterus											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue	+										1
Squamous cell papilloma	X										1
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma								X			4
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma benign									X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma											2
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	52
Adenoma											2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma	X	X				X			X	X	26
Pars distalis, carcinoma											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma			X				X	X		X	7
C-cell, carcinoma				X							1
Follicular cell, carcinoma		X									1
General Body System											
Peritoneum											1
Genital System											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	58
Adenoma	X								X	X	6
Carcinoma		X				X	X	X			6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of t-Butylhydroquinone: 0 ppm
(continued)

Number of Days on Study	2 9 7	3 0 2	3 8 0	4 1 8	4 2 1	4 9 7	5 4 0	5 4 0	5 4 6	5 7 8	5 7 9	6 1 3	6 2 7	6 2 8	6 3 8	6 4 0	6 4 9	6 6 1	6 9 0	6 9 4	7 0 4	7 1 2	7 2 2	7 2 4	7 3 3
Carcass ID Number	3 5 5	3 5 7	3 9 9	3 7 9	3 8 0	3 9 5	3 6 1	3 8 1	3 7 6	3 5 1	3 5 9	3 6 4	3 6 9	3 5 6	3 7 4	3 8 5	3 5 4	3 9 2	3 5 8	3 9 3	3 7 8	3 6 2	3 7 3	3 6 7	3 7 5
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Polyp stromal																	X					X			
Polyp stromal, multiple																									
Sarcoma stromal		X																							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+		+					+						+	+	+	+	+			+	+	
Mediastinal, mesothelioma malignant, metastatic, peritoneum			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X				X									
Carcinoma								X								X									X
Fibroadenoma							X			X				X	X		X	X	X		X		X	X	X
Fibroadenoma, multiple				X							X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																X									
Subcutaneous tissue, fibroma								X											X						
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
Sarcoma stromal, metastatic, uterus		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant																									
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm
(continued)

Number of Days on Study	7 3 3	7 3 6	7 5 8	7 6 1	7 6 5	7 6 5	7 6 6	7 7 7	7 7 8	7 8 5	7 8 9	7 9 5	7 9 5	7 9 6	7 9 9	8 0 2	8 0 8	8 3 0	8 3 1	8 5 4	8 5 5	8 5 6	8 7 9	8 8 0	8 8 8
Carcass ID Number	4 0 4	3 7 1	3 8 3	3 6 8	3 8 6	3 9 0	3 7 2	3 8 8	3 6 0	3 9 7	4 1 0	3 8 9	3 9 4	3 6 6	3 8 7	3 6 5	3 0 7	3 7 0	3 8 7	3 6 4	4 0 3	4 0 5	4 0 8	3 9 6	3 5 3
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																								X	
Polyp stromal	X											X											X		
Polyp stromal, multiple					X																				
Sarcoma stromal																						X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+						+							+		+				+
Mediastinal, mesothelioma malignant, metastatic, peritoneum																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	I	I	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma							X		X				X					X							
Fibroadenoma	X	X	X	X		X			X	X						X	X	X		X			X		X
Fibroadenoma, multiple					X						X			X	X				X		X	X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																						X			
Subcutaneous tissue, lipoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Sarcoma stromal, metastatic, uterus																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant																									
Peripheral nerve		+																			+				
Spinal cord		+																			+				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	3 5 2	3 7 0	3 8 2	3 9 1	3 9 8	4 0 1	4 0 2	4 0 6	4 0 7	4 0 9	Total Tissues/ Tumors
Genital System (continued)											
Ovary	+	+	+	+	+	+	+	+	+	+	60
Granulosa cell tumor benign											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Leiomyoma											1
Polyp stromal		X									6
Polyp stromal, multiple											1
Sarcoma stromal											2
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node		+						+		+	20
Mediastinal, mesothelioma malignant, metastatic, peritoneum											1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	59
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	58
Spleen	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma					X						1
Thymus	+	+	+	+	+	+	+	+	+	+	56
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma											3
Carcinoma					X						8
Fibroadenoma	X	X		X			X				28
Fibroadenoma, multiple			X		X	X		X	X	X	15
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell carcinoma											1
Subcutaneous tissue, fibroma										X	3
Subcutaneous tissue, fibrosarcoma											1
Subcutaneous tissue, lipoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Sarcoma stromal, metastatic, uterus											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Oligodendroglioma malignant				X							1
Peripheral nerve											2
Spinal cord											2
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma									X		2
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm
(continued)

Number of Days on Study	2 9 7	3 0 2	3 8 0	4 1 8	4 2 1	4 9 7	5 4 0	5 4 0	5 4 6	5 7 8	5 7 9	6 1 3	6 2 7	6 2 8	6 3 8	6 4 0	6 4 9	6 6 1	6 9 0	6 9 4	7 0 4	7 1 2	7 2 2	7 2 4	7 3 3
Carcass ID Number	3 5 5	3 5 7	3 9 9	3 7 9	3 8 0	3 9 5	3 6 1	3 8 1	3 7 6	3 5 1	3 5 9	3 6 4	3 6 9	3 5 6	3 7 4	3 8 5	3 5 4	3 9 2	3 5 8	3 9 3	3 7 8	3 6 2	3 7 3	3 6 7	3 7 5
Special Senses System																									
Ear																									
Eye													+											+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus		X																							
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X			X	X			X				X		X	X		X		X	X
Mesothelioma malignant			X																						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm
(continued)

Number of Days on Study	7 3 3	7 3 6	7 5 8	7 6 1	7 6 5	7 6 5	7 6 6	7 7 7	7 7 8	7 8 5	7 8 9	7 9 5	7 9 5	7 9 6	7 9 9	8 0 2	8 0 8	8 3 0	8 3 1	8 5 4	8 5 5	8 5 6	8 7 9	8 8 0	8 8 8
Carcass ID Number	4 0 4	3 7 1	3 8 3	3 6 8	3 8 6	3 9 0	3 7 2	3 8 8	3 6 0	3 9 7	4 1 0	3 8 9	3 9 4	3 6 6	3 8 7	4 6 5	3 0 0	3 7 7	3 8 4	4 6 3	4 0 3	4 0 5	4 0 8	3 9 6	3 5 3
Special Senses System																									
Ear		+																							
Eye						+										+									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X	X			X	X	X	X			X			X						X
Mesothelioma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 0 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	3 5 2	3 7 0	3 8 2	3 9 1	3 9 8	4 0 1	4 0 2	4 0 6	4 0 7	4 0 9	Total Tissues/ Tumors
Special Senses System											
Ear											1
Eye											4
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Sarcoma stromal, metastatic, uterus											1
Renal tubule, adenoma					X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X		X					X	X	X	27
Mesothelioma malignant											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of t-Butylhydroquinone: 1,250 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	4 2 7	4 3 4	4 4 4	4 5 1	4 5 2	4 5 3	4 5 5	4 5 6	4 6 5	4 7 3	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	+	+	+	I	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	58
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular adenoma											1
Mesentery		+	+						+		13
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue											1
Squamous cell papilloma											1
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Schwannoma benign											1
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma benign									X	X	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	55
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma	X		X	X						X	27
Pars distalis, carcinoma		X									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma											7
General Body System											
None											
Genital System											
Clitoral gland	+	+	+	+	M	+	+	+	+	+	59
Adenoma											6
Carcinoma										X	4
Ovary	+	+	+	+	+	+	+	+	+	+	60
Granulosa cell tumor malignant											1
Granulosa cell tumor benign											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Leiomyoma											1
Polyp stromal						X					12
Sarcoma stromal											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	737	746	761	774	781	788	799	799	799	800	800	800	801	803	803	803	804	805	806	806	807	809	809	809	809
Carcass ID Number	44050	44066	44131	44147	44229	44667	44758	44853	44926	44022	44066	44577	44669	44772	44141	44716	44343	44525	44559	44654	44362	44464	44777	44868	44202
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+				+	+				+				+		+				+	+		+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X				X								X
Fibroadenoma					X					X		X	X	X			X		X						X
Fibroadenoma, multiple			X			X		X	X						X	X		X		X	X			X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma												X													
Subcutaneous tissue, fibroma																									X
Subcutaneous tissue, fibroma, multiple				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																						+			
Spinal cord																						+			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear															+										
Eye															+										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X			X	X				X	X	X		X	X	X		X		X	X	X	X	X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	4 2 7	4 3 4	4 4 4	4 5 1	4 5 2	4 5 3	4 5 5	4 5 6	4 6 5	4 7 3	Total Tissues/ Tumors
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node			+			+					24
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	60
Spleen	+	+	+	+	+	+	+	+	+	+	60
Thymus	+	+	+	+	+	+	+	+	+	+	60
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	59
Carcinoma			X			X					6
Fibroadenoma			X	X		X					16
Fibroadenoma, multiple	X	X			X		X	X		X	17
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell carcinoma											1
Subcutaneous tissue, fibroma											2
Subcutaneous tissue, fibroma, multiple											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	59
Skeletal muscle											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Peripheral nerve											1
Spinal cord											2
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma				X				X			2
Alveolar/bronchiolar carcinoma											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear											1
Eye											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear			X			X				X	33

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of t-Butylhydroquinone: 2,500 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	778	788	789	799	801	816	817	817	845	856	860	883	883	888	909	901	914	918	918	918	918	928	928	928	928
Carcass ID Number	54 13	51 18	51 19	53 92	53 29	53 35	49 06	50 67	49 04	50 02	53 01	53 33	54 05	55 50	51 02	54 17	51 44	49 47	49 78	49 89	50 06	50 68	51 00	51 10	51 13
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma									X																
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X												
Osteosarcoma, metastatic, bone	X																								
Mesentery		+	+									+		+											
Oral mucosa																									
Squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X																				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																+									+
Squamous cell carcinoma																									
Squamous cell papilloma																									X
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign			X																						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X									X									X	
Carcinoma																				X					
Parathyroid gland	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X			X	X						X	X	X		X	X	X	X	X	X	X		X	X	X
Pars distalis, carcinoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X	X													
C-cell, carcinoma																		X							
Follicular cell, adenoma														X											
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	5 2 1	5 2 2	5 2 3	5 2 4	5 2 5	5 3 6	5 3 7	5 4 6	Total Tissues/ Tumors
Alimentary System									
Esophagus	+	+	+	+	+	+	+	+	57
Intestine large, colon	+	+	+	+	+	+	+	+	56
Intestine large, rectum	+	+	+	+	+	+	+	+	57
Intestine large, cecum	+	+	+	+	+	+	+	+	57
Intestine small, duodenum	+	+	+	+	+	+	+	+	57
Carcinoma				X					1
Intestine small, jejunum	+	+	+	+	+	+	+	+	56
Carcinoma									1
Intestine small, ileum	+	+	+	+	+	+	+	+	57
Leiomyosarcoma									1
Liver	+	+	+	+	+	+	+	+	58
Hepatocellular adenoma		X							2
Osteosarcoma, metastatic, bone									1
Mesentery									10
Oral mucosa									1
Squamous cell carcinoma									1
Pancreas	+	+	+	+	+	+	+	+	57
Salivary glands	+	+	+	+	+	+	+	+	58
Stomach, forestomach	+	+	+	+	+	+	+	+	57
Squamous cell papilloma									1
Stomach, glandular	+	+	+	+	+	+	+	+	57
Tongue							+		4
Squamous cell carcinoma									1
Squamous cell papilloma									1
Cardiovascular System									
Blood vessel	+	+	+	+	+	+	+	+	58
Heart	+	+	+	+	+	+	+	+	58
Endocrine System									
Adrenal cortex	+	+	+	+	+	+	+	+	58
Adrenal medulla	+	+	+	+	+	+	+	+	58
Pheochromocytoma benign									1
Islets, pancreatic	+	+	+	+	+	+	+	+	57
Adenoma									3
Carcinoma									1
Parathyroid gland	+	+	+	+	+	+	+	+	53
Pituitary gland	+	+	+	+	+	+	+	+	57
Pars distalis, adenoma		X	X	X	X	X		X	34
Pars distalis, carcinoma									1
Thyroid gland	+	+	+	+	+	+	+	+	57
C-cell, adenoma						X			7
C-cell, carcinoma			X						2
Follicular cell, adenoma									1
Follicular cell, carcinoma							X		1
General Body System									
None									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	1	4	4	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	9	2	9	7	0	1	3	4	5	5	6	6	6	8	0	2	3	5	5	6	6	7	7	7	7
	7	5	8	8	0	3	2	9	7	8	1	6	7	2	3	1	8	7	8	7	7	2	2	4	4
Carcass ID Number	5	5	5	5	4	5	5	5	5	5	5	4	5	4	5	5	5	5	5	5	5	4	5	5	5
	4	0	2	3	9	0	3	2	4	4	2	9	2	9	1	4	0	0	0	1	1	9	4	0	4
	1	4	9	4	2	3	8	6	0	2	0	3	7	5	5	8	5	9	1	6	7	1	9	0	4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X		X												
Carcinoma																					X				
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leiomyoma																									
Polyp stromal		X																							
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+		+		+	+	+				+						+	+		+			
Pancreatic, carcinoma, metastatic, ovary																			X						
Lymph node, mandibular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, ovary																			X						
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Carcinoma																									
Fibroadenoma					X				X					X		X			X	X				X	X
Fibroadenoma, multiple																					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma															X										
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+																		
Spinal cord							+																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, ovary																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of t-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	7 8 8	7 8 9	7 8 9	7 9 9	8 0 1	8 1 6	8 1 7	8 1 7	8 4 5	8 5 6	8 6 0	8 8 3	8 8 3	8 8 8	8 9 0	8 9 1	8 9 4	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8
Carcass ID Number	5 4 3	5 1 8	5 1 9	5 3 2	5 3 9	5 3 5	4 9 6	5 0 7	4 9 0 4	5 0 2	5 3 1	5 3 3	5 4 5	5 5 0	5 1 2	5 4 7	5 1 4	4 9 7	4 9 8	4 9 9	5 0 6	5 0 8	5 1 0	5 1 1	5 1 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X			X	
Carcinoma							X	X			X						X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																							
Leiomyoma													X												
Polyp stromal					X					X						X	X								
Sarcoma stromal																								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+		+				+							+					+			+		
Pancreatic, carcinoma, metastatic, ovary																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, ovary																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone	X																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant															X										
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma															X		X								
Fibroadenoma	X	X	X	X	X	X			X		X	X			X			X		X			X	X	
Fibroadenoma, multiple							X	X								X	X		X		X	X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma						X																			
Subcutaneous tissue, fibrosarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma	X																								
Skeletal muscle															+										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve															+	+									
Spinal cord															+	+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Carcinoma, metastatic, ovary																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	8 8 8 8 8 8 8 8 9 9 9 9 9 9 9 9 8 8 8 8 8 8 8 8	
Carcass ID Number	5 5 5 5 5 5 5 5 2 2 2 2 2 3 3 4 1 2 3 4 5 6 7 6	Total Tissues/ Tumors
Genital System		
Clitoral gland	+ + + + + + + +	58
Adenoma	X	5
Carcinoma		5
Ovary	+ + + + + + + +	57
Carcinoma		1
Uterus	+ + + + + + + +	58
Adenoma		1
Leiomyoma		1
Polyp stromal		5
Sarcoma stromal		1
Hematopoietic System		
Bone marrow	+ + + + + + + +	57
Lymph node	+	19
Pancreatic, carcinoma, metastatic, ovary		1
Lymph node, mandibular	+ + + + + + + +	55
Lymph node, mesenteric	+ + + + + + + +	55
Carcinoma, metastatic, ovary		1
Spleen	+ + + + + + + +	57
Osteosarcoma, metastatic, bone		1
Thymus	+ + + + + + + +	57
Thymoma malignant		1
Integumentary System		
Mammary gland	+ + + + + + + +	58
Adenoma		1
Carcinoma		2
Fibroadenoma	X X X	25
Fibroadenoma, multiple	X	9
Skin	+ + + + + + + +	58
Keratoacanthoma		1
Subcutaneous tissue, fibroma		1
Subcutaneous tissue, fibrosarcoma		1
Musculoskeletal System		
Bone	+ + + + + + + +	58
Osteosarcoma		1
Skeletal muscle		1
Nervous System		
Brain	+ + + + + + + +	58
Peripheral nerve		3
Spinal cord		3
Respiratory System		
Lung	+ + + + + + + +	58
Alveolar/bronchiolar adenoma		1
Carcinoma, metastatic, ovary		1
Nose	+ + + + + + + +	58
Trachea	+ + + + + + + +	58

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 2,500 ppm (continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	5 2 1	5 2 2	5 2 3	5 2 4	5 2 5	5 3 6	5 3 7	5 4 6	Total Tissues/ Tumors
Special Senses System									
Ear									1
Eye		+							3
Zymbal's gland							+		1
Carcinoma							X		1
Urinary System									
Kidney	+	+	+	+	+	+	+	+	57
Urinary bladder	+	+	+	+	+	+	+	+	58
Systemic Lesions									
Multiple organs	+	+	+	+	+	+	+	+	58
Leukemia mononuclear								X	22

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	5 9 3	5 9 4	5 9 5	6 0 4	6 0 9	6 1 1	6 1 2	6 1 3	6 1 4	6 2 0	Total Tissues/ Tumors
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	58
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular adenoma											1
Hepatocellular adenoma, multiple											1
Mesentery											7
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue											1
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Schwannoma benign											1
Endocrine System											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma malignant											1
Pheochromocytoma benign			X								3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	54
Adenoma											1
Carcinoma, metastatic, thyroid gland											1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma	X			X	X			X			28
Pars distalis, carcinoma											3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma										X	6
C-cell, carcinoma											1
Follicular cell, carcinoma								X			2
General Body System											
None											
Genital System											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma	X										6
Adenoma, multiple											1
Carcinoma											8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm (continued)

Number of Days on Study	5 0 1	5 7 2	5 9 1	5 9 6	6 0 0	6 1 3	6 2 8	6 2 8	6 3 3	6 4 0	6 5 9	6 6 6	6 7 3	6 7 3	6 9 0	6 9 1	7 0 5	7 1 2	7 5 0	7 5 2	7 7 4	7 7 7	7 8 9	7 8 9	7 8 9
Carcass ID Number	6 0 8	5 8 8	5 9 7	5 8 6	6 1 7	5 6 8	5 8 1	5 9 1	5 6 6	5 7 0	6 0 7	5 8 5	5 6 1	5 7 9	5 9 6	6 1 8	6 0 0	6 6 3	6 6 9	5 8 2	6 1 5	6 0 2	6 6 2	5 9 0	6 0 5
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma																									
Polyp stromal			X			X				X							X				X	X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+	+					+				+	+	+		+		+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																				X					
Carcinoma, multiple															X										
Fibroadenoma				X	X		X	X								X						X			
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma																									
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																				X					
Carcinoma, metastatic, pituitary gland																									
Peripheral nerve											+														
Spinal cord											+														
Astrocytoma malignant											X														
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	8 0 7	8 1 0	8 3 0	8 3 1	8 3 1	8 3 9	8 4 1	8 4 5	8 5 6	8 5 8	8 6 2	8 6 9	8 7 9	8 8 8	8 9 1	8 9 1	8 9 4	8 9 7	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8
Carcass ID Number	5 7 6	5 6 4	6 0 3	6 0 1	6 1 6	6 1 9	5 9 8	5 8 4	5 6 5	5 8 9	5 9 2	5 7 1	5 7 5	5 6 7	5 6 6	6 1 0	5 7 7	5 9 9	5 7 2	5 7 3	5 7 4	5 7 8	5 8 0	5 8 3	5 8 7
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																				X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Polyp stromal		X																				X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+	+					+					+			+				+		+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																								
Carcinoma			X			X																			
Carcinoma, multiple																									
Fibroadenoma	X		X		X			X	X	X					X					X	X		X	X
Fibroadenoma, multiple											X	X	X	X				X	X			X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X																
Subcutaneous tissue, fibroma												X													
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma							X																		
Subcutaneous tissue, sarcoma																									
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								+	
Sarcoma																								X	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Carcinoma, metastatic, pituitary gland																						X			
Peripheral nerve						+							+			+									
Spinal cord						+							+			+									
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	8 9 8	
Carcass ID Number	5 9 3	5 9 4	5 9 5	6 0 4	6 0 9	6 1 1	6 1 2	6 1 3	6 1 4	6 2 0	Total Tissues/ Tumors
Genital System (continued)											
Ovary	+	+	+	+	+	+	+	+	+	+	60
Granulosa cell tumor benign											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Carcinoma									X		1
Polyp stromal						X					9
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node											18
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	60
Spleen	+	+	+	+	+	+	+	+	+	+	60
Thymus	+	+	+	+	M	+	+	+	+	+	57
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma	X										2
Carcinoma											3
Carcinoma, multiple											1
Fibroadenoma	X			X	X						20
Fibroadenoma, multiple											7
Skin	+	+	+	+	+	+	+	+	+	+	60
Squamous cell papilloma		X									2
Subcutaneous tissue, fibroma											1
Subcutaneous tissue, fibrosarcoma								X			1
Subcutaneous tissue, hemangiosarcoma											1
Subcutaneous tissue, sarcoma					X						1
Subcutaneous tissue, schwannoma malignant									X		1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Sarcoma											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, mammary gland											1
Carcinoma, metastatic, pituitary gland											1
Peripheral nerve											4
Spinal cord											4
Astrocytoma malignant											1
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma			X								1
Carcinoma, metastatic, thyroid gland											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	0	1	3	3	3	3	4	4	5	5	6	6	7	8	9	9	9	9	9	9	9	9	9	9	9
	7	0	0	1	1	9	1	5	6	8	2	9	9	8	1	1	4	7	8	8	8	8	8	8	8
Carcass ID Number	5	5	6	6	6	6	5	5	5	5	5	5	5	5	6	6	5	5	5	5	5	5	5	5	5
	7	6	0	0	1	1	9	8	6	8	9	7	7	6	0	1	7	9	7	7	7	7	8	8	8
	6	4	3	1	6	9	8	4	5	9	2	1	5	7	6	0	7	9	2	3	4	8	0	3	7
Special Senses System																									
Ear																+									
Eye														+											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
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 Long-Term Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	8	8	8	8	8	8	8	8	8	8	
	9	9	9	9	9	9	9	9	9	9	
	8	8	8	8	8	8	8	8	8	8	
Carcass ID Number	5	5	5	6	6	6	6	6	6	6	Total
	9	9	9	0	0	1	1	1	1	2	Tissues/
	3	4	5	4	9	1	2	3	4	0	Tumors
Special Senses System											
Ear											1
Eye											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Papilloma					X						1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear			X		X			X		X	27

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	4/60 (7%)	1/60 (2%)	0/58 (0%)	0/60 (0%)
Adjusted rate[b]	25.9%	3.6%	0.0%	0.0%
Terminal rate[c]	1/10 (10%)	0/11 (0%)	0/16 (0%)	0/17 (0%)
First incidence (days)	795	795	—[e]	—
Life table test[d]	P=0.007N	P=0.146N	P=0.025N	P=0.019N
Logistic regression test[d]	P=0.010N	P=0.143N	P=0.030N	P=0.024N
Cochran-Armitage test[d]	P=0.020N			
Fisher exact test[d]		P=0.182N	P=0.064N	P=0.059N
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	2/60 (3%)	2/60 (3%)	1/58 (2%)	3/60 (5%)
Adjusted rate	16.4%	18.2%	3.1%	12.3%
Terminal rate	1/10 (10%)	2/11 (18%)	0/16 (0%)	1/17 (6%)
First incidence (days)	856	898 (T)	789	750
Life table test	P=0.567N	P=0.649N	P=0.358N	P=0.630N
Logistic regression test	P=0.568	P=0.632N	P=0.410N	P=0.673
Cochran-Armitage test	P=0.403			
Fisher exact test		P=0.691N	P=0.513N	P=0.500
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	2/60 (3%)	2/60 (3%)	1/58 (2%)	4/60 (7%)
Adjusted rate	16.4%	18.2%	3.1%	16.9%
Terminal rate	1/10 (10%)	2/11 (18%)	0/16 (0%)	1/17 (6%)
First incidence (days)	856	898 (T)	789	750
Life table test	P=0.445	P=0.649N	P=0.358N	P=0.601
Logistic regression test	P=0.387	P=0.632N	P=0.410N	P=0.539
Cochran-Armitage test	P=0.227			
Fisher exact test		P=0.691N	P=0.513N	P=0.340
Clitoral Gland: Adenoma				
Overall rate	6/58 (10%)	6/59 (10%)	5/58 (9%)	7/60 (12%)
Adjusted rate	38.3%	23.5%	22.2%	27.0%
Terminal rate	3/10 (30%)	0/10 (0%)	3/16 (19%)	2/17 (12%)
First incidence (days)	579	649	661	628
Life table test	P=0.323N	P=0.515N	P=0.275N	P=0.375N
Logistic regression test	P=0.490N	P=0.549N	P=0.380N	P=0.513N
Cochran-Armitage test	P=0.464			
Fisher exact test		P=0.607N	P=0.500N	P=0.526
Clitoral Gland: Carcinoma				
Overall rate	6/58 (10%)	4/59 (7%)	5/58 (9%)	8/60 (13%)
Adjusted rate	43.2%	16.0%	18.8%	29.0%
Terminal rate	4/10 (40%)	1/10 (10%)	0/16 (0%)	2/17 (12%)
First incidence (days)	649	666	767	750
Life table test	P=0.547N	P=0.349N	P=0.244N	P=0.465N
Logistic regression test	P=0.403	P=0.316N	P=0.332N	P=0.579N
Cochran-Armitage test	P=0.258			
Fisher exact test		P=0.361N	P=0.500N	P=0.415

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	12/58 (21%)	10/59 (17%)	10/58 (17%)	14/60 (23%)
Adjusted rate	74.9%	35.8%	36.8%	47.4%
Terminal rate	7/10 (70%)	1/10 (10%)	3/16 (19%)	4/17 (24%)
First incidence (days)	579	649	661	628
Life table test	P=0.288N	P=0.320N	P=0.116N	P=0.248N
Logistic regression test	P=0.519N	P=0.309N	P=0.210N	P=0.402N
Cochran-Armitage test	P=0.338			
Fisher exact test		P=0.389N	P=0.407N	P=0.451
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/60 (3%)	3/60 (5%)	1/58 (2%)	1/60 (2%)
Adjusted rate	14.5%	21.9%	4.5%	5.9%
Terminal rate	1/10 (10%)	2/11 (18%)	0/16 (0%)	1/17 (6%)
First incidence (days)	802	831	883	898 (T)
Life table test	P=0.124N	P=0.574	P=0.331N	P=0.316N
Logistic regression test	P=0.144N	P=0.569	P=0.389N	P=0.350N
Cochran-Armitage test	P=0.282N			
Fisher exact test		P=0.500	P=0.513N	P=0.500N
Mammary Gland: Fibroadenoma				
Overall rate	43/60 (72%)	33/60 (55%)	34/58 (59%)	27/60 (45%)
Adjusted rate	100.0%	96.6%	86.0%	74.4%
Terminal rate	10/10 (100%)	10/11 (91%)	11/16 (69%)	9/17 (53%)
First incidence (days)	418	537	600	596
Life table test	P<0.001N	P=0.034N	P=0.004N	P<0.001N
Logistic regression test	P<0.001N	P=0.006N	P=0.009N	P<0.001N
Cochran-Armitage test	P=0.005N			
Fisher exact test		P=0.044N	P=0.098N	P=0.003N
Mammary Gland: Adenoma				
Overall rate	3/60 (5%)	0/60 (0%)	1/58 (2%)	2/60 (3%)
Adjusted rate	9.9%	0.0%	2.9%	8.6%
Terminal rate	0/10 (0%)	0/11 (0%)	0/16 (0%)	1/17 (6%)
First incidence (days)	613	—	774	807
Life table test	P=0.417N	P=0.099N	P=0.240N	P=0.326N
Logistic regression test	P=0.562N	P=0.133N	P=0.345N	P=0.503N
Cochran-Armitage test	P=0.557N			
Fisher exact test		P=0.122N	P=0.322N	P=0.500N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	45/60 (75%)	33/60 (55%)	34/58 (59%)	27/60 (45%)
Adjusted rate	100.0%	96.6%	86.0%	74.4%
Terminal rate	10/10 (100%)	10/11 (91%)	11/16 (69%)	9/17 (53%)
First incidence (days)	418	537	600	596
Life table test	P<0.001N	P=0.019N	P=0.002N	P<0.001N
Logistic regression test	P<0.001N	P=0.002N	P=0.003N	P<0.001N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.017N	P=0.045N	P<0.001N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Mammary Gland: Carcinoma				
Overall rate	8/60 (13%)	6/60 (10%)	2/58 (3%)	4/60 (7%)
Adjusted rate	29.3%	35.4%	10.8%	10.5%
Terminal rate	1/10 (10%)	3/11 (27%)	0/16 (0%)	0/17 (0%)
First incidence (days)	540	640	890	690
Life table test	P=0.029N	P=0.308N	P=0.019N	P=0.070N
Logistic regression test	P=0.073N	P=0.345N	P=0.042N	P=0.177N
Cochran-Armitage test	P=0.105N			
Fisher exact test		P=0.389N	P=0.053N	P=0.181N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	10/60 (17%)	6/60 (10%)	3/58 (5%)	6/60 (10%)
Adjusted rate	34.9%	35.4%	13.4%	18.2%
Terminal rate	1/10 (10%)	3/11 (27%)	0/16 (0%)	1/17 (6%)
First incidence (days)	540	640	774	690
Life table test	P=0.045N	P=0.153N	P=0.014N	P=0.064N
Logistic regression test	P=0.123N	P=0.180N	P=0.036N	P=0.193N
Cochran-Armitage test	P=0.170N			
Fisher exact test		P=0.211N	P=0.043N	P=0.211N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	48/60 (80%)	34/60 (57%)	34/58 (59%)	30/60 (50%)
Adjusted rate	100.0%	96.6%	86.0%	76.3%
Terminal rate	10/10 (100%)	10/11 (91%)	11/16 (69%)	9/17 (53%)
First incidence (days)	418	537	600	596
Life table test	P<0.001N	P=0.011N	P<0.001N	P<0.001N
Logistic regression test	P<0.001N	P<0.001N	P<0.001N	P<0.001N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.005N	P=0.010N	P<0.001N
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/60 (2%)	1/60 (2%)	3/58 (5%)	0/60 (0%)
Adjusted rate	10.0%	6.7%	9.6%	0.0%
Terminal rate	1/10 (10%)	0/11 (0%)	1/16 (6%)	0/17 (0%)
First incidence (days)	898 (T)	873	425	—
Life table test	P=0.296N	P=0.734N	P=0.403	P=0.394N
Logistic regression test	P=0.435N	P=0.725N	P=0.258	P=0.394N
Cochran-Armitage test	P=0.411N			
Fisher exact test		P=0.752N	P=0.297	P=0.500N
Pancreatic Islets: Adenoma				
Overall rate	2/60 (3%)	1/59 (2%)	3/57 (5%)	2/59 (3%)
Adjusted rate	11.2%	1.8%	14.4%	9.8%
Terminal rate	0/10 (0%)	0/11 (0%)	1/16 (6%)	1/17 (6%)
First incidence (days)	661	537	816	869
Life table test	P=0.487N	P=0.458N	P=0.660N	P=0.509N
Logistic regression test	P=0.561	P=0.537N	P=0.585	P=0.609N
Cochran-Armitage test	P=0.493			
Fisher exact test		P=0.506N	P=0.476	P=0.684

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	2/60 (3%)	1/59 (2%)	4/57 (7%)	2/59 (3%)
Adjusted rate	11.2%	1.8%	20.1%	9.8%
Terminal rate	0/10 (0%)	0/11 (0%)	2/16 (13%)	1/17 (6%)
First incidence (days)	661	537	816	869
Life table test	P=0.483N	P=0.458N	P=0.556	P=0.509N
Logistic regression test	P=0.561	P=0.537N	P=0.445	P=0.609N
Cochran-Armitage test	P=0.469			
Fisher exact test		P=0.506N	P=0.315	P=0.684
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	26/60 (43%)	27/60 (45%)	34/57 (60%)	28/60 (47%)
Adjusted rate	80.9%	75.2%	90.7%	69.8%
Terminal rate	5/10 (50%)	5/11 (45%)	13/16 (81%)	7/17 (41%)
First incidence (days)	540	480	600	501
Life table test	P=0.083N	P=0.408N	P=0.410N	P=0.103N
Logistic regression test	P=0.492N	P=0.550N	P=0.207	P=0.481N
Cochran-Armitage test	P=0.328			
Fisher exact test		P=0.500	P=0.057	P=0.427
Pituitary Gland (Pars Distalis): Carcinoma				
Overall rate	2/60 (3%)	1/60 (2%)	1/57 (2%)	3/60 (5%)
Adjusted rate	5.0%	9.1%	6.3%	10.1%
Terminal rate	0/10 (0%)	1/11 (9%)	1/16 (6%)	1/17 (6%)
First incidence (days)	540	898 (T)	898 (T)	666
Life table test	P=0.457	P=0.483N	P=0.418N	P=0.609
Logistic regression test	P=0.334	P=0.504N	P=0.535N	P=0.441
Cochran-Armitage test	P=0.324			
Fisher exact test		P=0.500N	P=0.519N	P=0.500
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	28/60 (47%)	28/60 (47%)	35/57 (61%)	31/60 (52%)
Adjusted rate	81.9%	79.3%	93.8%	74.0%
Terminal rate	5/10 (50%)	6/11 (55%)	14/16 (88%)	8/17 (47%)
First incidence (days)	540	480	600	501
Life table test	P=0.103N	P=0.352N	P=0.337N	P=0.124N
Logistic regression test	P=0.484	P=0.474N	P=0.256	P=0.573
Cochran-Armitage test	P=0.245			
Fisher exact test		P=0.573N	P=0.079	P=0.358
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/60 (5%)	3/60 (5%)	1/58 (2%)	1/60 (2%)
Adjusted rate	13.8%	13.5%	3.6%	4.2%
Terminal rate	1/10 (10%)	1/11 (9%)	0/16 (0%)	0/17 (0%)
First incidence (days)	540	498	816	869
Life table test	P=0.090N	P=0.628N	P=0.227N	P=0.200N
Logistic regression test	P=0.178N	P=0.643	P=0.329N	P=0.313N
Cochran-Armitage test	P=0.167N			
Fisher exact test		P=0.660N	P=0.322N	P=0.309N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	4/60 (7%)	3/60 (5%)	2/58 (3%)	3/60 (5%)
Adjusted rate	19.9%	13.5%	6.6%	15.4%
Terminal rate	1/10 (10%)	1/11 (9%)	0/16 (0%)	2/17 (12%)
First incidence (days)	540	498	789	869
Life table test	P=0.228N	P=0.450N	P=0.219N	P=0.279N
Logistic regression test	P=0.382N	P=0.505N	P=0.337N	P=0.410N
Cochran-Armitage test	P=0.423N			
Fisher exact test		P=0.500N	P=0.356N	P=0.500N
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/60 (12%)	7/60 (12%)	7/57 (12%)	6/60 (10%)
Adjusted rate	44.9%	28.1%	21.8%	24.2%
Terminal rate	4/10 (40%)	0/11 (0%)	1/16 (6%)	3/17 (18%)
First incidence (days)	540	669	649	633
Life table test	P=0.156N	P=0.504N	P=0.348N	P=0.208N
Logistic regression test	P=0.320N	P=0.550N	P=0.566N	P=0.351N
Cochran-Armitage test	P=0.436N			
Fisher exact test		P=0.611N	P=0.571	P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/60 (13%)	7/60 (12%)	9/57 (16%)	7/60 (12%)
Adjusted rate	54.1%	28.1%	32.2%	27.6%
Terminal rate	5/10 (50%)	0/11 (0%)	3/16 (19%)	3/17 (18%)
First incidence (days)	540	669	649	633
Life table test	P=0.160N	P=0.393N	P=0.387N	P=0.174N
Logistic regression test	P=0.325N	P=0.427N	P=0.605N	P=0.309N
Cochran-Armitage test	P=0.492N			
Fisher exact test		P=0.500N	P=0.454	P=0.500N
Uterus: Stromal Polyp				
Overall rate	7/60 (12%)	12/60 (20%)	5/58 (9%)	9/60 (15%)
Adjusted rate	28.7%	38.8%	19.2%	24.8%
Terminal rate	1/10 (10%)	1/11 (9%)	0/16 (0%)	2/17 (12%)
First incidence (days)	649	576	425	591
Life table test	P=0.267N	P=0.257	P=0.195N	P=0.554N
Logistic regression test	P=0.503	P=0.167	P=0.363N	P=0.388
Cochran-Armitage test	P=0.534			
Fisher exact test		P=0.159	P=0.405N	P=0.395
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	9/60 (15%)	13/60 (22%)	6/58 (10%)	9/60 (15%)
Adjusted rate	34.9%	40.2%	24.2%	24.8%
Terminal rate	1/10 (10%)	1/11 (9%)	1/16 (6%)	2/17 (12%)
First incidence (days)	302	576	425	591
Life table test	P=0.132N	P=0.360	P=0.123N	P=0.332N
Logistic regression test	P=0.431N	P=0.227	P=0.304N	P=0.536
Cochran-Armitage test	P=0.374N			
Fisher exact test		P=0.240	P=0.316N	P=0.601N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/60 (45%)	33/60 (55%)	22/58 (38%)	27/60 (45%)
Adjusted rate	76.5%	79.3%	51.6%	63.2%
Terminal rate	5/10 (50%)	4/11 (36%)	2/16 (13%)	5/17 (29%)
First incidence (days)	421	481	197	501
Life table test	P=0.039N	P=0.430	P=0.064N	P=0.106N
Logistic regression test	P=0.355N	P=0.217	P=0.313N	P=0.529N
Cochran-Armitage test	P=0.346N			
Fisher exact test		P=0.181	P=0.277N	P=0.573N
All Organs: Benign Neoplasms				
Overall rate	52/60 (87%)	51/60 (85%)	49/58 (84%)	50/60 (83%)
Adjusted rate	100.0%	100.0%	96.0%	95.8%
Terminal rate	10/10 (100%)	11/11 (100%)	14/16 (88%)	15/17 (88%)
First incidence (days)	418	480	425	501
Life table test	P=0.005N	P=0.251N	P=0.021N	P=0.009N
Logistic regression test	P=0.079N	P=0.225N	P=0.099N	P=0.085N
Cochran-Armitage test	P=0.354N			
Fisher exact test		P=0.500N	P=0.470N	P=0.399N
All Organs: Malignant Neoplasms				
Overall rate	41/60 (68%)	39/60 (65%)	38/58 (66%)	39/60 (65%)
Adjusted rate	100.0%	84.9%	82.2%	82.8%
Terminal rate	10/10 (100%)	5/11 (45%)	9/16 (56%)	10/17 (59%)
First incidence (days)	302	481	197	501
Life table test	P=0.020N	P=0.246N	P=0.049N	P=0.024N
Logistic regression test	P=0.360N	P=0.374N	P=0.439N	P=0.343N
Cochran-Armitage test	P=0.412N			
Fisher exact test		P=0.423N	P=0.448N	P=0.423N
All Organs: Benign or Malignant Neoplasms				
Overall rate	59/60 (98%)	59/60 (98%)	56/58 (97%)	59/60 (98%)
Adjusted rate	100.0%	100.0%	98.2%	98.3%
Terminal rate	10/10 (100%)	11/11 (100%)	15/16 (94%)	16/17 (94%)
First incidence (days)	302	480	197	501
Life table test	P=0.009N	P=0.283N	P=0.026N	P=0.016N
Logistic regression test	P=0.508N	P=0.639N	P=0.392N	P=0.624N
Cochran-Armitage test	P=0.589N			
Fisher exact test		P=0.752N	P=0.487N	P=0.752N

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
3-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	40	41	33	36
Natural deaths	10	8	9	7
Survivors				
Terminal sacrifice	10	11	16	17
Missexed	0	0	2	0
Animals examined microscopically	70	70	68	70
3-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)
Liver	(10)	(10)	(10)	(10)
Angiectasis				1 (10%)
Hepatodiaphragmatic nodule	2 (20%)		1 (10%)	1 (10%)
Pancreas	(10)	(10)	(10)	(10)
Atrophy		1 (10%)	1 (10%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	3 (30%)			1 (10%)
Hyperplasia, focal	1 (10%)	1 (10%)		
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, cyst	2 (20%)	1 (10%)		
Thyroid gland	(10)	(10)	(10)	(10)
Ectopic thymus	1 (10%)		1 (10%)	
Ultimobranchial cyst	2 (20%)		3 (30%)	1 (10%)
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Inflammation, chronic	1 (10%)			
Ovary	(10)	(10)	(10)	(10)
Cyst			1 (10%)	1 (10%)
Uterus	(10)	(10)	(10)	(10)
Hydrometra	1 (10%)	5 (50%)	1 (10%)	2 (20%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Inflammation, granulomatous			1 (10%)	
Lymph node, mandibular	(10)	(10)	(10)	(10)
Hemorrhage	2 (20%)	1 (10%)	2 (20%)	2 (20%)
Spleen	(10)	(10)	(10)	(10)
Pigmentation, hemosiderin	5 (50%)	7 (70%)	8 (80%)	10 (100%)

[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 Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
3-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Infiltration cellular, histiocyte		1 (10%)		
Inflammation, subacute	4 (40%)	1 (10%)	3 (30%)	2 (20%)
Alveolar epithelium, hyperplasia	1 (10%)	1 (10%)		1 (10%)
Nose	(10)	(10)	(10)	(10)
Inflammation, suppurative		1 (10%)		
Goblet cell, hyperplasia				1 (10%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Cyst				1 (10%)
Mineralization	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Long-Term Study				
Alimentary System				
Esophagus	(58)	(60)	(57)	(60)
Epithelium, hyperplasia		1 (2%)		
Intestine large, colon	(60)	(59)	(56)	(59)
Edema				1 (2%)
Parasite metazoan	6 (10%)	4 (7%)	4 (7%)	5 (8%)
Ulcer				1 (2%)
Intestine large, rectum	(59)	(59)	(57)	(59)
Edema	1 (2%)			
Parasite metazoan	2 (3%)	2 (3%)	6 (11%)	8 (14%)
Intestine large, cecum	(60)	(60)	(57)	(60)
Edema		2 (3%)	1 (2%)	2 (3%)
Parasite metazoan	2 (3%)	1 (2%)	3 (5%)	1 (2%)
Intestine small, duodenum	(59)	(60)	(57)	(60)
Erosion		1 (2%)		
Epithelium, hyperplasia		1 (2%)	1 (2%)	
Intestine small, ileum	(60)	(58)	(57)	(58)
Inflammation, chronic active			1 (2%)	
Epithelium, hyperplasia			1 (2%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Long-Term Feed Study of t-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Alimentary System (continued)				
Liver	(60)	(60)	(58)	(60)
Angiectasis	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Basophilic focus	26 (43%)	31 (52%)	31 (53%)	29 (48%)
Clear cell focus	2 (3%)		4 (7%)	5 (8%)
Degeneration, cystic	1 (2%)			1 (2%)
Eosinophilic focus	10 (17%)	13 (22%)	12 (21%)	17 (28%)
Eosinophilic focus, multiple				1 (2%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	2 (3%)
Hemorrhage			4 (7%)	
Hepatodiaphragmatic nodule	12 (20%)	10 (17%)	8 (14%)	18 (30%)
Inflammation, granulomatous	12 (20%)	9 (15%)	9 (16%)	10 (17%)
Mixed cell focus	2 (3%)	6 (10%)	8 (14%)	7 (12%)
Necrosis, focal	6 (10%)	3 (5%)	5 (9%)	3 (5%)
Bile duct, cyst			1 (2%)	1 (2%)
Bile duct, hyperplasia	17 (28%)	20 (33%)	18 (31%)	24 (40%)
Centrilobular, necrosis				1 (2%)
Hepatocyte, vacuolization cytoplasmic	14 (23%)	14 (23%)	9 (16%)	3 (5%)
Kupffer cell, pigmentation	12 (20%)	14 (23%)	7 (12%)	9 (15%)
Mesentery	(11)	(13)	(10)	(7)
Accessory spleen	1 (9%)	1 (8%)		2 (29%)
Fat, necrosis	9 (82%)	12 (92%)	8 (80%)	5 (71%)
Pancreas	(60)	(60)	(57)	(59)
Atrophy	20 (33%)	21 (35%)	13 (23%)	13 (22%)
Metaplasia, hepatocyte	1 (2%)			
Acinus, cytoplasmic alteration		1 (2%)		1 (2%)
Acinus, hyperplasia, focal		1 (2%)	2 (4%)	
Salivary glands	(60)	(60)	(58)	(60)
Atrophy	2 (3%)		1 (2%)	
Stomach, forestomach	(60)	(60)	(57)	(60)
Edema	4 (7%)	3 (5%)	4 (7%)	
Erosion	1 (2%)			1 (2%)
Hyperplasia			1 (2%)	1 (2%)
Ulcer	2 (3%)	4 (7%)	3 (5%)	2 (3%)
Mucosa, hyperplasia	5 (8%)	9 (15%)	8 (14%)	5 (8%)
Stomach, glandular	(60)	(60)	(57)	(60)
Edema	1 (2%)	1 (2%)	2 (4%)	
Erosion	3 (5%)	2 (3%)	6 (11%)	2 (3%)
Ulcer	2 (3%)	4 (7%)	1 (2%)	
Tongue	(1)	(1)	(4)	(1)
Epithelium, hyperplasia			2 (50%)	1 (100%)
Cardiovascular System				
Heart	(60)	(60)	(58)	(60)
Cardiomyopathy	28 (47%)	32 (53%)	26 (45%)	28 (47%)
Thrombosis	3 (5%)	3 (5%)		
Valve, inflammation, chronic	1 (2%)			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Endocrine System				
Adrenal cortex	(60)	(60)	(58)	(60)
Accessory adrenal cortical nodule	11 (18%)	14 (23%)	9 (16%)	9 (15%)
Atrophy	1 (2%)			
Degeneration, fatty	9 (15%)	16 (27%)	17 (29%)	12 (20%)
Hemorrhage	1 (2%)		2 (3%)	1 (2%)
Hyperplasia, diffuse	3 (5%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	3 (5%)	6 (10%)	4 (7%)	2 (3%)
Hypertrophy, focal	9 (15%)	6 (10%)	4 (7%)	7 (12%)
Metaplasia, osseous			1 (2%)	
Necrosis		2 (3%)	1 (2%)	
Adrenal medulla	(60)	(60)	(58)	(60)
Hyperplasia	5 (8%)	11 (18%)	7 (12%)	7 (12%)
Islets, pancreatic	(60)	(59)	(57)	(59)
Hyperplasia	1 (2%)			
Parathyroid gland	(52)	(55)	(53)	(54)
Hyperplasia	1 (2%)		1 (2%)	1 (2%)
Pituitary gland	(60)	(60)	(57)	(60)
Pars distalis, angiectasis	8 (13%)	3 (5%)	6 (11%)	7 (12%)
Pars distalis, cyst	14 (23%)	24 (40%)	17 (30%)	19 (32%)
Pars distalis, hyperplasia, focal	9 (15%)	15 (25%)	1 (2%)	9 (15%)
Pars intermedia, angiectasis		2 (3%)		
Pars intermedia, cyst	2 (3%)	5 (8%)	4 (7%)	3 (5%)
Thyroid gland	(60)	(60)	(57)	(60)
Ultimobranchial cyst	2 (3%)		1 (2%)	1 (2%)
C-cell, hyperplasia	8 (13%)	9 (15%)	3 (5%)	8 (13%)
Follicle, cyst	1 (2%)		2 (4%)	1 (2%)
Follicular cell, hyperplasia				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(58)	(59)	(58)	(60)
Cyst	2 (3%)	7 (12%)	6 (10%)	5 (8%)
Cyst, multiple	1 (2%)			
Hyperplasia	3 (5%)	6 (10%)	3 (5%)	4 (7%)
Inflammation, chronic	2 (3%)	2 (3%)	2 (3%)	2 (3%)
Inflammation, suppurative	2 (3%)	3 (5%)	3 (5%)	1 (2%)
Ovary	(60)	(60)	(57)	(60)
Cyst	17 (28%)	11 (18%)	18 (32%)	17 (28%)
Uterus	(60)	(60)	(58)	(60)
Hydrometra	3 (5%)	5 (8%)	3 (5%)	7 (12%)
Hyperplasia, cystic	4 (7%)	5 (8%)	2 (3%)	3 (5%)
Cervix, hypertrophy			1 (2%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Long-Term Feed Study of t-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Hematopoietic System				
Bone marrow	(60)	(60)	(57)	(60)
Depletion cellular	1 (2%)		1 (2%)	
Fibrosis				1 (2%)
Hyperplasia	1 (2%)			
Infiltration cellular, histiocyte			1 (2%)	
Myelofibrosis	2 (3%)	4 (7%)	1 (2%)	3 (5%)
Lymph node	(20)	(24)	(19)	(18)
Hyperplasia, lymphoid		1 (4%)		
Inguinal, ectasia			1 (5%)	
Inguinal, hemorrhage			1 (5%)	
Inguinal, hyperplasia, lymphoid			1 (5%)	
Mediastinal, ectasia	1 (5%)			
Mediastinal, hemorrhage	3 (15%)	1 (4%)	7 (37%)	
Mediastinal, hyperplasia, lymphoid	1 (5%)			
Mediastinal, pigmentation	14 (70%)	9 (38%)	11 (58%)	6 (33%)
Pancreatic, hemorrhage			1 (5%)	
Pancreatic, pigmentation	1 (5%)	6 (25%)	4 (21%)	4 (22%)
Renal, hemorrhage				2 (11%)
Renal, pigmentation	1 (5%)	2 (8%)		7 (39%)
Lymph node, mandibular	(59)	(60)	(55)	(60)
Ectasia	2 (3%)	2 (3%)	4 (7%)	1 (2%)
Hemorrhage	3 (5%)	2 (3%)	3 (5%)	
Hyperplasia, lymphoid	13 (22%)	9 (15%)	14 (25%)	7 (12%)
Hyperplasia, plasma cell	1 (2%)			1 (2%)
Pigmentation	20 (34%)	19 (32%)	26 (47%)	25 (42%)
Lymph node, mesenteric	(58)	(60)	(55)	(60)
Ectasia	2 (3%)	2 (3%)	2 (4%)	2 (3%)
Hemorrhage		1 (2%)	9 (16%)	7 (12%)
Hyperplasia, lymphoid	2 (3%)	2 (3%)	3 (5%)	4 (7%)
Pigmentation			1 (2%)	1 (2%)
Spleen	(60)	(60)	(57)	(60)
Fibrosis	3 (5%)	5 (8%)	3 (5%)	3 (5%)
Hematopoietic cell proliferation	15 (25%)	12 (20%)	17 (30%)	11 (18%)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid				1 (2%)
Metaplasia, lipocyte				1 (2%)
Necrosis		2 (3%)	2 (4%)	1 (2%)
Pigmentation, hemosiderin	24 (40%)	27 (45%)	33 (58%)	41 (68%)
Lymphoid follicle, atrophy	1 (2%)	1 (2%)		
Red pulp, atrophy	1 (2%)			1 (2%)
Integumentary System				
Mammary gland	(60)	(59)	(58)	(60)
Dilatation	37 (62%)	48 (81%)	39 (67%)	34 (57%)
Galactocele	5 (8%)	4 (7%)	1 (2%)	5 (8%)
Hyperplasia	12 (20%)	6 (10%)	11 (19%)	15 (25%)
Inflammation, suppurative				1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Integumentary System (continued)				
Skin	(60)	(60)	(58)	(60)
Cyst epithelial inclusion	1 (2%)			1 (2%)
Hyperkeratosis	1 (2%)			
Inflammation, chronic	1 (2%)			
Ulcer		1 (2%)	1 (2%)	2 (3%)
Epidermis, hyperplasia	1 (2%)		2 (3%)	2 (3%)
Musculoskeletal System				
Bone	(60)	(59)	(58)	(60)
Fibrous osteodystrophy			1 (2%)	1 (2%)
Hyperostosis				1 (2%)
Cranium, osteopetrosis	8 (13%)	9 (15%)	6 (10%)	9 (15%)
Femur, osteopetrosis	9 (15%)	10 (17%)	6 (10%)	5 (8%)
Skeletal muscle	(1)	(1)	(1)	(1)
Hemorrhage		1 (100%)		
Nervous System				
Brain	(60)	(60)	(58)	(60)
Atrophy	19 (32%)	20 (33%)	25 (43%)	22 (37%)
Hemorrhage				1 (2%)
Hydrocephalus	4 (7%)	1 (2%)	3 (5%)	8 (13%)
Necrosis		1 (2%)	1 (2%)	
Respiratory System				
Lung	(60)	(60)	(58)	(60)
Congestion	1 (2%)			
Edema		1 (2%)		
Hemorrhage	2 (3%)	1 (2%)	1 (2%)	2 (3%)
Infiltration cellular, histiocyte	28 (47%)	23 (38%)	30 (52%)	23 (38%)
Inflammation, subacute	3 (5%)			
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	4 (7%)	4 (7%)	2 (3%)	4 (7%)
Nose	(60)	(60)	(58)	(60)
Foreign body	3 (5%)		3 (5%)	
Inflammation, suppurative	5 (8%)	1 (2%)	11 (19%)	3 (5%)
Goblet cell, hyperplasia	10 (17%)	2 (3%)	3 (5%)	6 (10%)
Mucosa, hyperplasia	5 (8%)	1 (2%)	12 (21%)	1 (2%)
Mucosa, metaplasia, squamous	3 (5%)		4 (7%)	
Special Senses System				
Eye	(4)	(1)	(3)	(1)
Cataract	3 (75%)	1 (100%)	3 (100%)	1 (100%)
Hemorrhage	1 (25%)		1 (33%)	
Inflammation, chronic			1 (33%)	
Retina, degeneration	4 (100%)	1 (100%)	3 (100%)	1 (100%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Long-Term Study (continued)				
Urinary System				
Kidney	(60)	(60)	(57)	(60)
Cyst		1 (2%)		2 (3%)
Hydronephrosis		1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	3 (5%)	5 (8%)
Inflammation, suppurative	2 (3%)	1 (2%)		
Mineralization	57 (95%)	56 (93%)	44 (77%)	48 (80%)
Nephropathy	37 (62%)	38 (63%)	37 (65%)	39 (65%)
Renal tubule, atrophy	1 (2%)	4 (7%)		5 (8%)
Renal tubule, cytoplasmic alteration	5 (8%)	3 (5%)	4 (7%)	2 (3%)
Renal tubule, dilatation			1 (2%)	1 (2%)
Renal tubule, necrosis	2 (3%)	1 (2%)	1 (2%)	2 (3%)
Renal tubule, pigmentation	15 (25%)	16 (27%)	11 (19%)	16 (27%)
Transitional epithelium, hyperplasia	2 (3%)	2 (3%)	6 (11%)	3 (5%)
Urinary bladder	(59)	(60)	(58)	(59)
Transitional epithelium, hyperplasia		1 (2%)	1 (2%)	2 (3%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF *t*-BUTYLHYDROQUINONE

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	9
Early deaths				
Accidental death	1			
Moribund	6	3	7	7
Natural deaths	4	1	6	2
Survivors				
Terminal sacrifice	39	46	38	42
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine small, jejunum	(10)	(10)	(9)	(9)
Liver	(10)	(10)	(9)	(9)
Hepatocellular carcinoma				1 (11%)
Hepatocellular adenoma	1 (10%)	1 (10%)	1 (11%)	
Endocrine System				
Thyroid gland	(10)	(10)	(9)	(9)
Follicular cell, adenoma			1 (11%)	
Respiratory System				
Lung	(10)	(10)	(9)	(9)
Alveolar/bronchiolar adenoma		1 (10%)	2 (22%)	1 (11%)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(9)	(9)
Lymphoma malignant				1 (11%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study				
Alimentary System				
Intestine small, jejunum	(50)	(50)	(48)	(50)
Carcinoma		1 (2%)	3 (6%)	
Intestine small, ileum	(49)	(49)	(49)	(49)
Carcinoma	1 (2%)			
Liver	(50)	(50)	(51)	(51)
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hemangiosarcoma, multiple	2 (4%)			1 (2%)
Hepatocellular carcinoma	5 (10%)	9 (18%)	8 (16%)	7 (14%)
Hepatocellular carcinoma, multiple	3 (6%)	2 (4%)	4 (8%)	1 (2%)
Hepatocellular adenoma	21 (42%)	14 (28%)	17 (33%)	11 (22%)
Hepatocellular adenoma, multiple	7 (14%)	8 (16%)	5 (10%)	3 (6%)
Histiocytic sarcoma			2 (4%)	
Mesentery	(2)	(7)	(14)	(1)
Histiocytic sarcoma		1 (14%)	2 (14%)	
Pancreas	(49)	(50)	(51)	(51)
Histiocytic sarcoma		1 (2%)		
Stomach, forestomach	(49)	(50)	(51)	(51)
Squamous cell papilloma		1 (2%)	1 (2%)	2 (4%)
Stomach, glandular	(49)	(50)	(51)	(50)
Carcinoid tumor benign		1 (2%)		
Cardiovascular System				
Heart	(50)	(50)	(51)	(51)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(51)
Subcapsular, adenoma	1 (2%)	4 (8%)	1 (2%)	2 (4%)
Islets, pancreatic	(50)	(50)	(51)	(51)
Adenoma	1 (2%)	1 (2%)		2 (4%)
Parathyroid gland	(49)	(46)	(50)	(44)
Adenoma				1 (2%)
Pituitary gland	(46)	(42)	(45)	(49)
Pars distalis, adenoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(51)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	
Follicular cell, carcinoma				1 (2%)
General Body System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(51)	(50)
Hemangioma	1 (2%)			
Preputial gland	(50)	(49)	(50)	(51)
Histiocytic sarcoma			1 (2%)	
Testes	(50)	(50)	(51)	(51)
Interstitial cell, adenoma				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(51)	(51)
Hemangiosarcoma		1 (2%)		1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymph node	(3)	(3)	(6)	(3)
Iliac, histiocytic sarcoma			2 (33%)	
Inguinal, histiocytic sarcoma		1 (33%)		
Mediastinal, histiocytic sarcoma		1 (33%)	1 (17%)	
Pancreatic, histiocytic sarcoma			1 (17%)	
Renal, histiocytic sarcoma		1 (33%)	1 (17%)	
Lymph node, mandibular	(48)	(48)	(49)	(51)
Histiocytic sarcoma			1 (2%)	
Lymph node, mesenteric	(50)	(48)	(51)	(51)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Spleen	(50)	(50)	(51)	(51)
Hemangioma			1 (2%)	
Hemangiosarcoma	4 (8%)	1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)	
Thymus	(44)	(38)	(43)	(42)
Integumentary System				
Skin	(50)	(50)	(51)	(51)
Basal cell carcinoma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)	
Subcutaneous tissue, lipoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle	(2)		(1)	(1)
Hemangiosarcoma, multiple	1 (50%)			
Histiocytic sarcoma			1 (100%)	
Nervous System				
None				
Respiratory System				
Lung	(50)	(48)	(51)	(51)
Alveolar/bronchiolar adenoma	11 (22%)	8 (17%)	8 (16%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	2 (4%)	1 (2%)	
Alveolar/bronchiolar carcinoma	3 (6%)	3 (6%)	2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple		2 (4%)	1 (2%)	2 (4%)
Hepatocellular carcinoma, metastatic, liver	4 (8%)	1 (2%)	2 (4%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Special Senses System				
Ear				(1)
External ear, histiocytic sarcoma				1 (100%)
Harderian gland	(3)	(9)	(6)	(3)
Adenoma	2 (67%)	8 (89%)	4 (67%)	3 (100%)
Carcinoma			2 (33%)	
Bilateral, adenoma	1 (33%)			
Urinary System				
Kidney	(50)	(50)	(51)	(51)
Histiocytic sarcoma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(51)	(51)
Histiocytic sarcoma		1 (2%)	2 (4%)	1 (2%)
Lymphoma malignant	4 (8%)	2 (4%)	6 (12%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	2	3	3
2-Year study	39	44	42	36
Total primary neoplasms				
15-Month interim evaluation	1	2	4	3
2-Year study	78	72	69	56
Total animals with benign neoplasms				
15-Month interim evaluation	1	2	3	1
2-Year study	33	37	31	26
Total benign neoplasms				
15-Month interim evaluation	1	2	4	1
2-Year study	50	48	39	34
Total animals with malignant neoplasms				
15-Month interim evaluation				2
2-Year study	21	23	25	19
Total malignant neoplasms				
15-Month interim evaluation				2
2-Year study	28	24	30	22
Total animals with metastatic neoplasms				
2-Year study	5	1	2	1
Total metastatic neoplasms				
2-Year study	5	1	2	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 C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 0 ppm

Number of Days on Study	5 3 9	5 9 5	6 1 9	6 4 7	6 5 1	6 5 1	6 7 3	6 8 0	7 0 5	7 1 2	7 2 3	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 7	7 2 7	7 2 7	7 2 7	7 2 8
Carcass ID Number	0 3 7	0 3 9	0 3 3	0 3 6	0 3 6	0 4 7	0 4 1	0 2 4	0 0 5	0 1 7	0 6 0	0 0 1	0 0 7	0 1 0	0 1 8	0 3 0	0 3 3	0 4 4	0 4 5	0 4 8	0 5 5	0 5 6	0 5 8	0 5 9	0 0 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma		X																							
Hemangiosarcoma, multiple															X										
Hepatocellular carcinoma			X						X			X												X	
Hepatocellular carcinoma, multiple													X	X											X
Hepatocellular adenoma		X	X		X	X	X				X	X	X			X			X			X			
Hepatocellular adenoma, multiple								X										X		X				X	
Mesentery																									+
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+					+	+	+		+	+		+					+	+	+	+		+		+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X														
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 *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	00004	00048	00049	00111	00112	00125	00227	00228	00229	00250	00252	00253	00254	00311	00315	00316	00319	00320	00322	00323	00331	00332	00334	00345	00340	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																									X	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma						X																				1
Hemangiosarcoma																										1
Hemangiosarcoma, multiple															X											2
Hepatocellular carcinoma																				X						5
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma			X	X			X	X		X					X	X	X						X	X		21
Hepatocellular adenoma, multiple													X							X					X	7
Mesentery															+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+		+		+		+	+			+	+		+		+		+		+	+	+	+	+		28
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X											1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma																X										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	46
Pars distalis, adenoma																										1
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 *t*-Butylhydroquinone: 0 ppm (continued)

Number of Days on Study	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	9	1	4	5	5	7	8	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	9	5	9	7	1	1	3	0	5	2	3	7	7	7	7	7	7	7	7	7	7	7	7	8
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	3	3	0	3	4	4	2	0	1	6	0	0	1	1	3	4	4	4	4	5	5	5	0
	7	9	3	6	6	7	1	4	5	7	0	1	7	0	8	0	3	4	5	8	5	6	8	9	3
Genital System																								
Coagulating gland											+											+		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																	+							
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X											X									
Thymus	+	+	+	+	+	+	M	+	M	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																			X					
Subcutaneous tissue, hemangiosarcoma			X																					
Subcutaneous tissue, lipoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+				+																		
Hemangiosarcoma, multiple		X																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+																		
Spinal cord						+																		
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X			X	X									X			X		X		
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma					X				X															
Hepatocellular carcinoma, metastatic, liver									X			X	X	X										
Hepatocholangiocarcinoma, metastatic, liver			X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 0 4	0 0 8	0 0 9	0 1 1	0 1 2	0 2 5	0 2 7	0 2 8	0 2 9	0 5 0	0 5 2	0 5 3	0 5 4	0 1 4	0 1 5	0 1 6	0 1 9	0 2 0	0 2 2	0 2 3	0 3 1	0 3 2	0 3 4	0 3 5	0 4 0	Total Tissues/ Tumors
Genital System																										
Coagulating gland					+					+																4
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																		X								1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+												+								3
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X							X										4
Thymus	+	+	+	I	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Subcutaneous tissue, hemangiosarcoma									X																	2
Subcutaneous tissue, lipoma															X											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Hemangiosarcoma, multiple																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X							X			X	X					X				11
Alveolar/bronchiolar adenoma, multiple																								X		1
Alveolar/bronchiolar carcinoma								X																		3
Hepatocellular carcinoma, metastatic, liver																										4
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	00004	00048	00049	00111	00112	00125	00227	00228	00229	00250	00252	00253	00254	00144	00115	00116	00119	00220	00223	00231	00232	00234	00235	00240	Total Tissues/ Tumors
Special Senses System																											
Harderian gland													+					+									3
Adenoma													X					X									2
Bilateral, adenoma																											1
Zymbal's gland								+																			1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant					X													X									4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 9 3	0 9 4	0 9 5	0 9 6	1 2 0	0 7 3	0 7 4	0 7 7	0 7 8	0 7 9	0 8 1	0 8 4	0 8 7	0 8 8	0 8 9	0 9 0	0 9 3	1 0 4	1 0 6	1 0 7	1 0 9	1 1 0	1 1 2	1 1 3	1 1 4	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
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma							X		X			X		X				X								9
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X	X			X	X		X					X	X	X			X							14
Hepatocellular adenoma, multiple				X	X					X	X														X	8
Mesentery													+							+						7
Histiocytic sarcoma																				X						1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor benign														X												1
Tooth	+		+	+	+			+		+	+		+	+		+	+		+	+				+	+	26
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma											X								X			X				4
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	42
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm (continued)

Number of Days on Study	6 1 9	6 3 0	6 5 4	7 1 0	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 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
Carcass ID Number	0 9 1	0 8 2	0 9 9	0 7 2	0 6 2	0 6 7	0 7 5	0 8 0	0 9 7	0 9 8	1 0 0	1 0 2	1 0 5	1 0 8	1 1 6	1 1 7	1 1 9	0 6 1	0 6 4	0 6 5	0 6 6	0 6 8	0 7 0	0 8 6	0 9 2
Genital System																									
Coagulating gland							+		+					+											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Histiocytic sarcoma																									
Lymph node														+											
Inguinal, histiocytic sarcoma																									
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Histiocytic sarcoma																									
Thymus	M	+	+	I	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	+	M	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Alveolar/bronchiolar adenoma	X					X				X						X									
Alveolar/bronchiolar adenoma, multiple																									X
Alveolar/bronchiolar carcinoma														X							X				
Alveolar/bronchiolar carcinoma, multiple			X																						
Hepatocellular carcinoma, metastatic, liver					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland										+	+		+	+							+		+		
Adenoma											X		X	X							X		X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 9 3	0 9 4	0 9 5	0 9 6	1 2 0	0 7 3	0 7 4	0 7 7	0 7 8	0 7 9	0 8 1	0 8 4	0 8 7	0 8 8	0 8 9	0 9 0	1 0 3	1 0 4	1 0 6	1 0 7	1 0 9	1 1 0	1 1 2	1 1 3	1 1 4	Total Tissues/ Tumors
Genital System																										
Coagulating gland														+					+						+	6
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																				X						1
Lymph node																				+	+					3
Inguinal, histiocytic sarcoma																				X						1
Mediastinal, histiocytic sarcoma																				X						1
Renal, histiocytic sarcoma																				X						1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																				X						1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																				X						1
Thymus	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	I	M	38
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	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
Alveolar/bronchiolar adenoma					X				X			X					X									8
Alveolar/bronchiolar adenoma, multiple													X													2
Alveolar/bronchiolar carcinoma																					X					3
Alveolar/bronchiolar carcinoma, multiple						X																				2
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																		+	+			+				9
Adenoma																		X	X			X				8

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of t-Butylhydroquinone: 1,250 ppm (continued)

Number of Days on Study	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	09 93	09 94	09 95	09 96	12 60	07 03	07 04	07 07	07 08	07 09	08 01	08 04	08 07	08 08	08 09	09 00	10 03	10 04	10 06	10 07	10 09	11 00	11 02	11 03	11 04	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Lymphoma malignant																						X				2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm (continued)

Number of Days on Study	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 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	1 1 6 9	1 2 3	1 3 7	1 3 9	1 4 0	1 4 4	1 4 7	1 4 8	1 5 0	1 5 5	1 5 7	1 5 9	1 6 2	1 7 3	1 7 4	1 2 7	1 2 8	1 2 9	1 3 0	1 3 6	1 7 5	1 7 6	1 7 7	1 7 8	1 7 9	1 8 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Carcinoma											X																3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Hepatocellular carcinoma								X		X					X			X									8
Hepatocellular carcinoma, multiple				X																							4
Hepatocellular adenoma				X		X		X			X			X			X		X					X		X	X	17
Hepatocellular adenoma, multiple							X					X								X								5
Histiocytic sarcoma																											2
Mesentery	+			+		+					+			+				+							+		14
Histiocytic sarcoma																											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																					X						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth	+								+	+	+			+	+	+								+		+	18
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Endocrine System																											
Adrenal cortex	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcapsular, adenoma																			X								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	I	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																											1
General Body System																											
Peritoneum																		+									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm (continued)

Number of Days on Study	4 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	0 2 4 5 1 5 5 6 6 7 8 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2
	9 0 9 0 9 4 7 6 9 3 0 0 4 7 7 7 7 7 7 7 7 7 7 7 7 7
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	5 7 6 7 3 3 2 2 4 4 5 4 6 2 3 3 4 5 5 6 6 6 6 6 6 6
	1 1 1 0 4 1 1 6 2 5 4 9 0 5 3 8 6 2 3 3 4 5 6 7 8
Genital System	
Coagulating gland	+
Epididymis	+ +
Preputial gland	+ + + + + + + + + + + + + + + + + + + M + + + +
Histiocytic sarcoma	X
Prostate	+ +
Seminal vesicle	+ +
Testes	+ +
Hematopoietic System	
Bone marrow	+ +
Histiocytic sarcoma	X
Lymph node	+ + + + + + +
Iliac, histiocytic sarcoma	X X
Mediastinal, histiocytic sarcoma	X
Pancreatic, histiocytic sarcoma	X
Renal, histiocytic sarcoma	X
Lymph node, mandibular	+ M +
Histiocytic sarcoma	X
Lymph node, mesenteric	+ +
Histiocytic sarcoma	X
Spleen	+ +
Hemangioma	
Histiocytic sarcoma	X
Thymus	+ M + + + + + + + + M + M + + + I + + I + + + + +
Integumentary System	
Mammary gland	M M + M M M M M M M M M M M M M M M M M M M M M M
Skin	+ +
Subcutaneous tissue, hemangiosarcoma	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Histiocytic sarcoma	X
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X
Alveolar/bronchiolar adenoma, multiple	X
Alveolar/bronchiolar carcinoma	X
Alveolar/bronchiolar carcinoma, multiple	X
Hepatocellular carcinoma, metastatic, liver	X X
Nose	+ +
Trachea	+ + + + + + M + + + + + + + + + + + + + + + + + +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm (continued)

Number of Days on Study	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	16 9	16 2	16 3	16 3	16 4	16 4	16 4	16 4	16 5	16 5	16 5	16 5	16 6	16 7	16 7	16 2	16 2	16 2	16 3	16 3	16 7	16 7	16 7	16 7	16 7	Total Tissues/ Tumors
Genital System																										
Coagulating gland									+																	2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Lymph node																									+	6
Iliac, histiocytic sarcoma																										2
Mediastinal, histiocytic sarcoma																										1
Pancreatic, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangioma					X																					1
Histiocytic sarcoma																										1
Thymus	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	43
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																										1
Histiocytic sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma										X		X							X			X			X	8
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																	X									2
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm (continued)

Number of Days on Study	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 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	1 6 9	1 2 3	1 3 7	1 3 9	1 4 0	1 4 4	1 4 7	1 4 8	1 5 0	1 5 5	1 5 7	1 5 9	1 6 2	1 7 3	1 7 4	1 7 7	1 8 8	1 8 9	1 9 0	1 3 6	1 7 5	1 7 6	1 7 7	1 7 8	1 7 9	1 8 0	Total Tissues/ Tumors
Special Senses System																											
Harderian gland			+	+					+	+																	6
Adenoma									X	X																	4
Carcinoma			X	X																							2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											2
Lymphoma malignant											X		X										X			X	6

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm (continued)

Number of Days on Study	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 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 4 0	1 8 0	1 9 0	1 9 2	1 9 5	1 9 6	1 9 8	2 1 7	2 1 8	2 2 0	2 2 1	2 2 2	2 2 5	2 2 6	2 2 7	2 1 1	2 1 2	2 1 4	2 1 5	2 1 6	2 2 9	2 3 0	2 3 6	2 3 7	2 3 8	2 3 9	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																										X	1
Hemangiosarcoma, multiple																											1
Hepatocellular carcinoma					X												X			X			X		X	7
Hepatocellular carcinoma, multiple																											1
Hepatocellular adenoma	X				X			X				X	X				X										11
Hepatocellular adenoma, multiple															X					X		X					3
Mesentery																			+								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																											2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth		+	+	+		+	+			+				+	+	+		+	+		+				+		26
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcapsular, adenoma																											2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma	X																										2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	44
Adenoma												X															1
Pituitary gland	+	+	+	+	I	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, carcinoma																X											1
General Body System																											
Tissue NOS																											3
Genital System																											
Coagulating gland																									+		1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Interstitial cell, adenoma										X																	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm (continued)

Number of Days on Study	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 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 4 0	1 8 8	1 9 0	1 9 2	1 9 5	1 9 6	1 9 8	2 1 7	2 1 8	2 2 0	2 2 1	2 2 2	2 2 5	2 2 6	2 2 7	2 1 1	2 1 2	2 1 4	2 1 5	2 1 6	2 2 9	2 3 0	2 3 6	2 3 7	2 3 8	2 3 9	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Lymph node																	+										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	42
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma							X							X				X								X	9
Alveolar/bronchiolar carcinoma		X							X									X									4
Alveolar/bronchiolar carcinoma, multiple																					X						2
Hepatocellular carcinoma, metastatic, liver					X																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Ear																											1
External ear, histiocytic sarcoma																											1
Harderian gland	+																								+		3
Adenoma	X																								X		3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Lymphoma malignant																	X										3

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	1/50 (2%)	4/50 (8%)	1/50 (2%)	2/51 (4%)
Adjusted rate[b]	2.6%	8.7%	2.7%	4.8%
Terminal rate[c]	1/39 (3%)	4/46 (9%)	1/37 (3%)	2/42 (5%)
First incidence (days)	727 (T)	727 (T)	727 (T)	727 (T)
Life table test[d]	P=0.592N	P=0.233	P=0.750	P=0.526
Logistic regression test[d]	P=0.592N	P=0.233	P=0.750	P=0.526
Cochran-Armitage test[d]	P=0.588N			
Fisher exact test[d]		P=0.181	P=0.753N	P=0.508
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	8/50 (16%)	4/51 (8%)	3/51 (6%)
Adjusted rate	7.7%	17.4%	10.5%	7.0%
Terminal rate	3/39 (8%)	8/46 (17%)	4/38 (11%)	2/42 (5%)
First incidence (days)	727 (T)	727 (T)	727 (T)	688
Life table test	P=0.331N	P=0.159	P=0.486	P=0.631N
Logistic regression test	P=0.351N	P=0.159	P=0.486	P=0.661N
Cochran-Armitage test	P=0.325N			
Fisher exact test		P=0.100	P=0.511	P=0.652N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	8/50 (16%)	6/51 (12%)	3/51 (6%)
Adjusted rate	7.7%	17.4%	15.8%	7.0%
Terminal rate	3/39 (8%)	8/46 (17%)	6/38 (16%)	2/42 (5%)
First incidence (days)	727 (T)	727 (T)	727 (T)	688
Life table test	P=0.367N	P=0.159	P=0.228	P=0.631N
Logistic regression test	P=0.389N	P=0.159	P=0.228	P=0.661N
Cochran-Armitage test	P=0.360N			
Fisher exact test		P=0.100	P=0.254	P=0.652N
Intestine, Small (Jejunum): Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/51 (6%)	0/51 (0%)
Adjusted rate	0.0%	2.2%	7.3%	0.0%
Terminal rate	0/39 (0%)	1/46 (2%)	2/38 (5%)	0/42 (0%)
First incidence (days)	—[e]	727 (T)	654	—
Life table test	P=0.632N	P=0.533	P=0.123	—
Logistic regression test	P=0.628N	P=0.533	P=0.124	—
Cochran-Armitage test	P=0.627N			
Fisher exact test		P=0.500	P=0.125	—
Liver: Hepatocellular Adenoma				
Overall rate	28/50 (56%)	22/50 (44%)	22/51 (43%)	14/51 (27%)
Adjusted rate	60.6%	47.8%	53.2%	31.7%
Terminal rate	21/39 (54%)	22/46 (48%)	19/38 (50%)	12/42 (29%)
First incidence (days)	595	727 (T)	409	630
Life table test	P=0.005N	P=0.050N	P=0.208N	P=0.004N
Logistic regression test	P=0.004N	P=0.144N	P=0.147N	P=0.004N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.159N	P=0.137N	P=0.003N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	8/50 (16%)	11/50 (22%)	12/51 (24%)	8/51 (16%)
Adjusted rate	19.1%	22.8%	26.0%	17.6%
Terminal rate	6/39 (15%)	9/46 (20%)	6/38 (16%)	5/42 (12%)
First incidence (days)	619	619	409	615
Life table test	P=0.490N	P=0.437	P=0.225	P=0.566N
Logistic regression test	P=0.370N	P=0.248	P=0.342	P=0.585N
Cochran-Armitage test	P=0.465N			
Fisher exact test		P=0.306	P=0.243	P=0.590N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	31/50 (62%)	28/50 (56%)	29/51 (57%)	17/51 (33%)
Adjusted rate	65.8%	58.3%	63.8%	37.7%
Terminal rate	23/39 (59%)	26/46 (57%)	22/38 (58%)	14/42 (33%)
First incidence (days)	595	619	409	615
Life table test	P=0.006N	P=0.126N	P=0.480N	P=0.005N
Logistic regression test	P=0.002N	P=0.369N	P=0.341N	P=0.004N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.342N	P=0.373N	P=0.003N
Liver: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/51 (2%)	2/51 (4%)
Adjusted rate	7.1%	2.2%	2.6%	4.3%
Terminal rate	2/39 (5%)	1/46 (2%)	1/38 (3%)	1/42 (2%)
First incidence (days)	595	727 (T)	727 (T)	589
Life table test	P=0.471N	P=0.262N	P=0.317N	P=0.478N
Logistic regression test	P=0.423N	P=0.379N	P=0.278N	P=0.446N
Cochran-Armitage test	P=0.465N			
Fisher exact test		P=0.309N	P=0.301N	P=0.491N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/50 (24%)	10/48 (21%)	9/51 (18%)	9/51 (18%)
Adjusted rate	28.1%	22.0%	22.1%	20.1%
Terminal rate	9/39 (23%)	9/44 (20%)	7/38 (18%)	7/42 (17%)
First incidence (days)	647	619	619	589
Life table test	P=0.266N	P=0.304N	P=0.344N	P=0.272N
Logistic regression test	P=0.250N	P=0.466N	P=0.312N	P=0.295N
Cochran-Armitage test	P=0.245N			
Fisher exact test		P=0.447N	P=0.294N	P=0.294N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/50 (6%)	5/48 (10%)	3/51 (6%)	6/51 (12%)
Adjusted rate	7.0%	11.0%	7.2%	13.3%
Terminal rate	1/39 (3%)	4/44 (9%)	1/38 (3%)	4/42 (10%)
First incidence (days)	651	654	666	595
Life table test	P=0.242	P=0.418	P=0.648	P=0.266
Logistic regression test	P=0.279	P=0.279	P=0.630N	P=0.271
Cochran-Armitage test	P=0.252			
Fisher exact test		P=0.335	P=0.652N	P=0.254

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	15/48 (31%)	11/51 (22%)	14/51 (27%)
Adjusted rate	33.7%	32.4%	26.3%	30.0%
Terminal rate	10/39 (26%)	13/44 (30%)	8/38 (21%)	10/42 (24%)
First incidence (days)	647	619	619	589
Life table test	P=0.394N	P=0.450N	P=0.286N	P=0.445N
Logistic regression test	P=0.371N	P=0.483	P=0.237N	P=0.459N
Cochran-Armitage test	P=0.361N			
Fisher exact test		P=0.534	P=0.229N	P=0.475N
Spleen: Hemangiosarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	0/51 (0%)	0/51 (0%)
Adjusted rate	9.7%	2.2%	0.0%	0.0%
Terminal rate	3/39 (8%)	1/46 (2%)	0/38 (0%)	0/42 (0%)
First incidence (days)	647	727 (T)	—	—
Life table test	P=0.020N	P=0.144N	P=0.068N	P=0.060N
Logistic regression test	P=0.019N	P=0.190N	P=0.060N	P=0.060N
Cochran-Armitage test	P=0.019N			
Fisher exact test		P=0.181N	P=0.056N	P=0.056N
All Organs: Hemangiosarcoma				
Overall rate	7/50 (14%)	3/50 (6%)	2/51 (4%)	2/51 (4%)
Adjusted rate	15.8%	6.5%	5.3%	4.3%
Terminal rate	4/39 (10%)	3/46 (7%)	2/38 (5%)	1/42 (2%)
First incidence (days)	595	727 (T)	727 (T)	589
Life table test	P=0.058N	P=0.120N	P=0.093N	P=0.081N
Logistic regression test	P=0.040N	P=0.242N	P=0.061N	P=0.055N
Cochran-Armitage test	P=0.052N			
Fisher exact test		P=0.159N	P=0.075N	P=0.075N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	9/50 (18%)	3/50 (6%)	3/51 (6%)	2/51 (4%)
Adjusted rate	20.6%	6.5%	7.9%	4.3%
Terminal rate	6/39 (15%)	3/46 (7%)	3/38 (8%)	1/42 (2%)
First incidence (days)	595	727 (T)	727 (T)	589
Life table test	P=0.023N	P=0.041N	P=0.073N	P=0.027N
Logistic regression test	P=0.017N	P=0.095N	P=0.052N	P=0.019N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.061N	P=0.056N	P=0.024N
All Organs: Malignant Lymphoma (NOS)				
Overall rate	4/50 (8%)	2/50 (4%)	6/51 (12%)	3/51 (6%)
Adjusted rate	10.3%	4.3%	14.9%	7.1%
Terminal rate	4/39 (10%)	2/46 (4%)	4/38 (11%)	3/42 (7%)
First incidence (days)	727 (T)	727 (T)	673	727 (T)
Life table test	P=0.547N	P=0.264N	P=0.356	P=0.459N
Logistic regression test	P=0.568N	P=0.264N	P=0.353	P=0.459N
Cochran-Armitage test	P=0.541N			
Fisher exact test		P=0.339N	P=0.383	P=0.489N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Benign Neoplasms				
Overall rate	33/50 (66%)	38/50 (76%)	32/51 (63%)	27/51 (53%)
Adjusted rate	70.0%	79.1%	74.1%	57.4%
Terminal rate	25/39 (64%)	36/46 (78%)	27/38 (71%)	22/42 (52%)
First incidence (days)	595	619	409	589
Life table test	P=0.063N	P=0.550N	P=0.557N	P=0.122N
Logistic regression test	P=0.049N	P=0.209	P=0.482N	P=0.140N
Cochran-Armitage test	P=0.036N			
Fisher exact test		P=0.189	P=0.447N	P=0.128N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	23/50 (46%)	25/51 (49%)	20/51 (39%)
Adjusted rate	47.1%	46.9%	49.9%	41.4%
Terminal rate	16/39 (41%)	20/46 (43%)	13/38 (34%)	14/42 (33%)
First incidence (days)	595	619	409	589
Life table test	P=0.439N	P=0.488N	P=0.279	P=0.427N
Logistic regression test	P=0.324N	P=0.337	P=0.380	P=0.450N
Cochran-Armitage test	P=0.392N			
Fisher exact test		P=0.420	P=0.306	P=0.467N
All Organs: Benign or Malignant Neoplasms				
Overall rate	39/50 (78%)	45/50 (90%)	43/51 (84%)	37/51 (73%)
Adjusted rate	81.2%	90.0%	86.0%	75.5%
Terminal rate	30/39 (77%)	41/46 (89%)	31/38 (82%)	30/42 (71%)
First incidence (days)	595	619	409	589
Life table test	P=0.253N	P=0.557N	P=0.248	P=0.288N
Logistic regression test	P=0.158N	P=0.089	P=0.293	P=0.378N
Cochran-Armitage test	P=0.136N			
Fisher exact test		P=0.086	P=0.289	P=0.343N

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

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

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	344/1,316 (26.1%)	220/1,316 (16.7%)	509/1,316 (38.7%)
Standard deviation	13.2%	7.2%	13.9%
Range	4%-60%	3%-29%	10%-68%

[a] Data as of 17 June 1994

TABLE C4b
Historical Incidence of Spleen Hemangiosarcoma in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls
Overall Historical Incidence	
Total	28/1,302 (2.2%)
Standard deviation	2.7%
Range	0%-8%

[a] Data as of 17 June 1994

TABLE C4c
Historical Incidence of Hemangioma and Hemangiosarcoma in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Overall Historical Incidence			
Total	7/1,324 (0.5%)	68/1,324 (5.1%)	75/1,324 (5.7%)
Standard deviation	1.1%	4.1%	3.9%
Range	0%-3%	0%-16%	0%-16%

[a] Data as of 17 June 1994

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	9
Early deaths				
Accidental death	1			
Moribund	6	3	7	7
Natural deaths	4	1	6	2
Survivors				
Terminal sacrifice	39	46	38	42
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(9)
Basophilic focus	2 (20%)			
Clear cell focus			2 (22%)	
Fatty change, focal	1 (10%)		1 (11%)	
Hematopoietic cell proliferation				1 (11%)
Mixed cell focus				1 (11%)
Necrosis, focal	1 (10%)			
Mesentery			(1)	
Fat, necrosis			1 (100%)	
Pancreas	(10)	(10)	(9)	(9)
Atrophy, focal			1 (11%)	
Tooth	(1)	(1)		(2)
Incisor, dysplasia	1 (100%)	1 (100%)		2 (100%)
Endocrine System				
Adrenal cortex	(10)	(10)	(9)	(9)
Cyst	1 (10%)			
Subcapsular, hyperplasia		1 (10%)		2 (22%)
Islets, pancreatic	(10)	(10)	(9)	(9)
Cyst			1 (11%)	
Parathyroid gland	(10)	(10)	(8)	(9)
Cyst		1 (10%)		
Pituitary gland	(9)	(10)	(8)	(8)
Cyst			1 (13%)	
Thyroid gland	(10)	(10)	(9)	(9)
Degeneration, cystic, focal	1 (10%)			
Fibrosis, focal	1 (10%)			
Genital System				
Preputial gland	(10)	(10)	(9)	(8)
Degeneration, cystic		2 (20%)	1 (11%)	
Seminal vesicle	(10)	(10)	(9)	(9)
Inflammation, chronic		1 (10%)		
Testes	(10)	(10)	(9)	(9)
Granuloma sperm	1 (10%)			

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Spleen	(10)	(10)	(9)	(9)
Hematopoietic cell proliferation				2 (22%)
Thymus	(9)	(10)	(9)	(9)
Cyst			1 (11%)	
Integumentary System				
Skin	(10)	(10)	(9)	(9)
Alopecia				1 (11%)
Respiratory System				
Lung	(10)	(10)	(9)	(9)
Alveolar epithelium, hyperplasia	1 (10%)		1 (11%)	
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine small, jejunum	(50)	(50)	(48)	(50)
Perforation			1 (2%)	
Peyer's patch, hyperplasia, lymphoid		2 (4%)	1 (2%)	1 (2%)
Intestine small, ileum	(49)	(49)	(49)	(49)
Peyer's patch, hyperplasia, lymphoid				1 (2%)
Liver	(50)	(50)	(51)	(51)
Angiectasis	2 (4%)	1 (2%)		1 (2%)
Basophilic focus	3 (6%)	2 (4%)	2 (4%)	5 (10%)
Clear cell focus	4 (8%)	3 (6%)	5 (10%)	3 (6%)
Clear cell focus, multiple	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Cyst				1 (2%)
Eosinophilic focus	7 (14%)	4 (8%)	4 (8%)	3 (6%)
Eosinophilic focus, multiple	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Fatty change	1 (2%)			
Fatty change, focal	6 (12%)	8 (16%)	5 (10%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)			
Hepatodiaphragmatic nodule		1 (2%)		
Infiltration cellular, mixed cell	1 (2%)			
Inflammation, focal	2 (4%)		1 (2%)	
Mixed cell focus	5 (10%)	8 (16%)	4 (8%)	4 (8%)
Mixed cell focus, multiple				3 (6%)
Necrosis, focal	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Pigmentation, focal	1 (2%)			
Thrombosis	1 (2%)			

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver (continued)	(50)	(50)	(51)	(51)
Bile duct, hyperplasia		1 (2%)		
Centrilobular, necrosis			1 (2%)	
Oval cell, hyperplasia			1 (2%)	
Mesentery	(2)	(7)	(14)	(1)
Inflammation, chronic		1 (14%)	3 (21%)	
Artery, inflammation, chronic	1 (50%)		1 (7%)	
Fat, necrosis		5 (71%)	6 (43%)	1 (100%)
Pancreas	(49)	(50)	(51)	(51)
Atrophy, diffuse	1 (2%)	1 (2%)		
Atrophy, focal			1 (2%)	
Duct, cyst	1 (2%)	2 (4%)		
Stomach, forestomach	(49)	(50)	(51)	(51)
Edema			1 (2%)	
Erosion	1 (2%)		1 (2%)	
Inflammation, chronic	3 (6%)	2 (4%)	1 (2%)	
Epithelium, hyperplasia	4 (8%)	2 (4%)	1 (2%)	
Stomach, glandular	(49)	(50)	(51)	(50)
Edema			1 (2%)	
Erosion	1 (2%)		1 (2%)	
Mineralization	1 (2%)		1 (2%)	
Pigmentation, focal			1 (2%)	
Epithelium, hyperplasia, cystic		1 (2%)		
Tooth	(28)	(26)	(18)	(26)
Incisor, dysplasia	28 (100%)	26 (100%)	18 (100%)	26 (100%)
Cardiovascular System				
Heart	(50)	(50)	(51)	(51)
Inflammation, chronic, focal	2 (4%)			
Artery, degeneration				1 (2%)
Artery, inflammation, chronic				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(51)
Accessory adrenal cortical nodule	3 (6%)	1 (2%)		2 (4%)
Cyst			1 (2%)	
Cytoplasmic alteration, focal	1 (2%)	3 (6%)	2 (4%)	
Fibrosis	1 (2%)	1 (2%)		
Subcapsular, hyperplasia, focal	5 (10%)	4 (8%)	6 (12%)	8 (16%)
Islets, pancreatic	(50)	(50)	(51)	(51)
Hyperplasia			1 (2%)	1 (2%)
Parathyroid gland	(49)	(46)	(50)	(44)
Cyst	2 (4%)	1 (2%)		
Pituitary gland	(46)	(42)	(45)	(49)
Angiectasis		1 (2%)		
Cyst	1 (2%)	2 (5%)	2 (4%)	3 (6%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(51)
Degeneration, cystic, focal	6 (12%)	5 (10%)	6 (12%)	6 (12%)
C-cell, hyperplasia	1 (2%)			
Follicle, hypertrophy, focal		1 (2%)		
Follicular cell, hyperplasia	6 (12%)	12 (24%)	6 (12%)	6 (12%)
General Body System				
Tissue NOS				(3)
Pelvic, inflammation, chronic				2 (67%)
Genital System				
Coagulating gland	(4)	(6)	(2)	(1)
Inflammation, chronic				1 (100%)
Epididymis	(50)	(50)	(51)	(50)
Spermatocele				1 (2%)
Preputial gland	(50)	(49)	(50)	(51)
Degeneration, cystic	22 (44%)	28 (57%)	32 (64%)	29 (57%)
Inflammation, chronic	8 (16%)	5 (10%)	8 (16%)	5 (10%)
Prostate	(49)	(50)	(51)	(51)
Inflammation, chronic, focal			1 (2%)	
Epithelium, hyperplasia, focal	1 (2%)		2 (4%)	1 (2%)
Seminal vesicle	(50)	(50)	(51)	(51)
Inflammation, chronic				1 (2%)
Testes	(50)	(50)	(51)	(51)
Fibrosis				1 (2%)
Mineralization, focal		1 (2%)		1 (2%)
Thrombosis				1 (2%)
Artery, inflammation, chronic				1 (2%)
Germinal epithelium, degeneration		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(51)	(51)
Angiectasis	1 (2%)			
Hyperplasia		1 (2%)		
Myelofibrosis	1 (2%)			
Lymph node	(3)	(3)	(6)	(3)
Bronchial, hyperplasia			1 (17%)	
Iliac, hemorrhage			1 (17%)	
Inguinal, hyperplasia	2 (67%)	1 (33%)		
Inguinal, hyperplasia, lymphoid		1 (33%)	1 (17%)	
Inguinal, pigmentation		1 (33%)		
Mediastinal, hyperplasia		1 (33%)		
Mediastinal, hyperplasia, lymphoid	1 (33%)			
Renal, hemorrhage			1 (17%)	
Lymph node, mandibular	(48)	(48)	(49)	(51)
Hyperplasia, lymphoid		1 (2%)		1 (2%)

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(48)	(51)	(51)
Ectasia	2 (4%)			
Hematopoietic cell proliferation	1 (2%)	2 (4%)	2 (4%)	
Hemorrhage	12 (24%)	11 (23%)	9 (18%)	9 (18%)
Hyperplasia			1 (2%)	
Hyperplasia, histiocytic		1 (2%)		1 (2%)
Hyperplasia, lymphoid	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Spleen	(50)	(50)	(51)	(51)
Accessory spleen	1 (2%)			
Hematopoietic cell proliferation	8 (16%)	12 (24%)	17 (33%)	9 (18%)
Hyperplasia, lymphoid		2 (4%)	1 (2%)	1 (2%)
Thymus	(44)	(38)	(43)	(42)
Cyst	4 (9%)	8 (21%)	4 (9%)	4 (10%)
Integumentary System				
Skin	(50)	(50)	(51)	(51)
Alopecia	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic, focal	2 (4%)			
Ulcer	1 (2%)			
Epidermis, hyperplasia, focal	1 (2%)			
Subcutaneous tissue, edema			2 (4%)	1 (2%)
Subcutaneous tissue, mineralization, focal		1 (2%)		1 (2%)
Subcutaneous tissue, necrosis, focal		1 (2%)		
Musculoskeletal System				
Skeletal muscle	(2)		(1)	(1)
Mineralization, focal	1 (50%)			
Nervous System				
Brain	(50)	(50)	(51)	(51)
Atrophy, focal	1 (2%)			
Respiratory System				
Lung	(50)	(48)	(51)	(51)
Congestion		1 (2%)	1 (2%)	
Hemorrhage		2 (4%)		
Hyperplasia, histiocytic	2 (4%)	4 (8%)	1 (2%)	1 (2%)
Inflammation, chronic, focal		1 (2%)	1 (2%)	1 (2%)
Thrombosis, multiple			1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	5 (10%)	3 (6%)	9 (18%)
Interstitium, edema				1 (2%)
Mediastinum, edema			1 (2%)	
Nose	(50)	(50)	(51)	(51)
Inflammation, suppurative	2 (4%)	2 (4%)		
Mucosa, cyst				1 (2%)
Mucosa, polyp, inflammatory		1 (2%)		
Mucosa, glands, dilatation, focal	9 (18%)	18 (36%)	10 (20%)	9 (18%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *t*-Butylhydroquinone
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Special Senses System				
Harderian gland	(3)	(9)	(6)	(3)
Hyperplasia, focal		1 (11%)		
Urinary System				
Kidney	(50)	(50)	(51)	(51)
Cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Fibrosis, focal	1 (2%)			
Hydronephrosis		1 (2%)		1 (2%)
Hyperplasia, focal				1 (2%)
Necrosis, focal	1 (2%)			
Nephropathy	50 (100%)	47 (94%)	48 (94%)	50 (98%)
Pelvis, inflammation, suppurative				1 (2%)
Renal tubule, dilatation, diffuse	1 (2%)			
Renal tubule, dilatation, focal		1 (2%)		1 (2%)
Renal tubule, hyperplasia, focal	1 (2%)	1 (2%)		
Urinary bladder	(50)	(50)	(51)	(51)
Calculus microscopic observation only		1 (2%)		
Transitional epithelium, hyperplasia		1 (2%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF *t*-BUTYLHYDROQUINONE

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	8	9	6
Early deaths				
Moribund sacrifice	11	7	6	6
Natural death	2	10	5	5
Survivors				
Died last week of study	1			1
Terminal sacrifice	37	35	40	42
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(8)	(9)	(6)
Hepatocellular carcinoma		1 (13%)		
Hepatocellular adenoma			1 (11%)	
Genital System				
Ovary	(9)	(8)	(9)	(6)
Cystadenoma			1 (11%)	
Respiratory System				
Lung	(9)	(8)	(9)	(6)
Alveolar/bronchiolar adenoma	1 (11%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(50)	(50)	(47)	(54)
Intestine large, cecum	(51)	(50)	(48)	(53)
Intestine small, duodenum	(51)	(51)	(48)	(53)
Leiomyosarcoma				1 (2%)
Intestine small, jejunum	(51)	(51)	(48)	(53)
Intestine small, ileum	(51)	(51)	(47)	(53)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(51)	(52)	(51)	(54)
Hemangioma		1 (2%)		
Hemangiosarcoma	1 (2%)			1 (2%)
Hepatoblastoma			1 (2%)	
Hepatocellular carcinoma	7 (14%)	8 (15%)	7 (14%)	4 (7%)
Hepatocellular carcinoma, multiple	1 (2%)		1 (2%)	1 (2%)
Hepatocellular adenoma	8 (16%)	11 (21%)	11 (22%)	4 (7%)
Hepatocellular adenoma, multiple	1 (2%)	9 (17%)	5 (10%)	1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Mesentery	(10)	(13)	(7)	(8)
Hepatocellular carcinoma, metastatic, liver			1 (14%)	
Histiocytic sarcoma			1 (14%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (8%)		
Pancreas	(51)	(52)	(49)	(54)
Carcinoma		1 (2%)		
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Salivary glands	(51)	(52)	(51)	(53)
Sarcoma		1 (2%)		
Sarcoma, metastatic, skin		1 (2%)		
Stomach, forestomach	(51)	(52)	(51)	(54)
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma	1 (2%)			2 (4%)
Stomach, glandular	(51)	(52)	(49)	(54)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(51)	(51)	(50)	(54)
Capsule, hepatocellular carcinoma, metastatic, liver			1 (2%)	
Adrenal medulla	(51)	(51)	(51)	(54)
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign	1 (2%)	1 (2%)		
Islets, pancreatic	(51)	(52)	(48)	(54)
Adenoma	1 (2%)		1 (2%)	
Pituitary gland	(49)	(44)	(46)	(49)
Pars distalis, adenoma	5 (10%)	5 (11%)	5 (11%)	4 (8%)
Pars distalis, carcinoma		1 (2%)		
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(51)	(51)	(50)	(54)
Follicular cell, adenoma	1 (2%)	3 (6%)	2 (4%)	5 (9%)
General Body System				
Tissue NOS		(2)	(1)	
Pelvic, hemangiosarcoma, multiple			1 (100%)	

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Genital System				
Clitoral gland	(51)	(52)	(50)	(54)
Ovary	(50)	(49)	(47)	(50)
Cystadenoma	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Granulosa cell tumor malignant			1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	
Luteoma	1 (2%)			
Teratoma NOS				1 (2%)
Uterus	(51)	(52)	(50)	(54)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Leiomyosarcoma				1 (2%)
Endometrium, adenoma	1 (2%)		1 (2%)	
Endometrium, carcinoma	1 (2%)			
Endometrium, polyp stromal			3 (6%)	1 (2%)
Hematopoietic System				
Bone marrow	(51)	(52)	(51)	(54)
Lymph node	(7)	(8)	(12)	(9)
Iliac, histiocytic sarcoma	1 (14%)		1 (8%)	
Inguinal, histiocytic sarcoma		1 (13%)		
Mediastinal, hepatocellular carcinoma, metastatic, liver			1 (8%)	
Mediastinal, histiocytic sarcoma			1 (8%)	
Renal, histiocytic sarcoma	1 (14%)		1 (8%)	
Lymph node, mandibular	(48)	(52)	(50)	(52)
Lymph node, mesenteric	(50)	(48)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)		1 (2%)	2 (4%)
Spleen	(51)	(52)	(50)	(54)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)		
Thymus	(45)	(51)	(47)	(48)
Histiocytic sarcoma				1 (2%)
Integumentary System				
Mammary gland	(51)	(51)	(51)	(54)
Carcinoma				1 (2%)
Myoepithelioma			1 (2%)	
Skin	(51)	(52)	(51)	(54)
Basal cell carcinoma	1 (2%)			
Squamous cell papilloma				1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma	2 (4%)	2 (4%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(51)	(52)	(51)	(54)
Osteosarcoma				1 (2%)
Skeletal muscle	(1)	(1)	(2)	
Hepatocellular carcinoma, metastatic, liver			1 (50%)	
Nervous System				
None				
Respiratory System				
Lung	(51)	(52)	(51)	(54)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	4 (8%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)	
Basal cell carcinoma, metastatic, skin	1 (2%)			
Hepatoblastoma, metastatic, liver			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Mediastinum, squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Special Senses System				
Harderian gland		(1)	(6)	(1)
Adenoma			6 (100%)	1 (100%)
Carcinoma		1 (100%)		
Urinary System				
Kidney	(51)	(52)	(50)	(53)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach		1 (2%)		
Urinary bladder	(51)	(51)	(50)	(53)
Histiocytic sarcoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(51)	(52)	(51)	(54)
Histiocytic sarcoma	2 (4%)	2 (4%)	3 (6%)	4 (7%)
Lymphoma malignant	3 (6%)	9 (17%)	10 (20%)	8 (15%)
Lymphoma malignant mixed		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	1	2	
2-Year study	32	41	36	33
Total primary neoplasms				
15-Month interim evaluation	1	1	2	
2-Year study	46	61	71	49
Total animals with benign neoplasms				
15-Month interim evaluation	1		2	
2-Year study	22	26	25	19
Total benign neoplasms				
15-Month interim evaluation	1		2	
2-Year study	25	34	42	25
Total animals with malignant neoplasms				
15-Month interim evaluation		1		
2-Year study	18	22	22	22
Total malignant neoplasms				
15-Month interim evaluation		1		
2-Year study	21	27	29	23
Total animals with metastatic neoplasms				
2-Year study	2	3	6	3
Total metastatic neoplasms				
2-Year study	2	6	12	3
Total animals with uncertain neoplasms — benign or malignant				
2-Year study				1
Total uncertain neoplasms				
2-Year study				1

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 0 ppm

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

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

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

Number of Days on Study	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 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 9 8	2 4 3	2 4 4	2 4 6	2 4 7	2 4 9	2 5 0	2 5 1	2 8 5	2 8 8	2 9 1	2 9 5	2 9 6	3 0 0	2 5 9	2 6 2	2 6 4	2 6 5	2 7 0	2 7 3	2 7 4	2 7 5	2 7 6	2 7 9	2 8 0	2 8 2	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Hepatocellular carcinoma							X						X	X													7
Hepatocellular carcinoma, multiple																		X									1
Hepatocellular adenoma	X							X	X																		8
Hepatocellular adenoma, multiple												X															1
Histiocytic sarcoma																											1
Mesentery		+							+				+									+					10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																		X									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																											1
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																			X						X		5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma																											1
General Body System																											
None																											

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

Number of Days on Study	3 6 4	4 6 1	5 5 0	5 6 7	5 8 2	6 1 7	6 1 8	6 1 9	6 2 2	6 6 7	6 7 3	6 7 7	7 2 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
Carcass ID Number	2 7 2	2 6 3	2 8 7	2 6 1	2 4 8	2 6 9	2 8 6	2 4 1	2 6 8	2 7 7	2 5 2	2 7 1	2 8 4	2 4 5	2 5 4	2 5 5	2 5 6	2 5 7	2 5 8	2 6 6	2 6 8 1	2 8 9 0	2 9 9 3	2 9 9 4	2 9 9 7
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																					X				
Histiocytic sarcoma											X														
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma											X														
Endometrium, adenoma																									
Endometrium, carcinoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+		+			+	+		+			+							+		
Iliac, histiocytic sarcoma											X														
Renal, histiocytic sarcoma											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Thymus	+	+	+	I	M	M	M	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma													X												
Subcutaneous tissue, histiocytic sarcoma																									
Subcutaneous tissue, sarcoma																					X			X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord				+				+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma																	X						X		
Basal cell carcinoma, metastatic, skin													X												
Hepatocellular carcinoma, metastatic, liver		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	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 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 9 8	2 4 3	2 4 4	2 4 6	2 4 7	2 4 9	2 5 0	2 5 1	2 5 5	2 8 8	2 8 8	2 9 1	2 9 5	2 9 6	3 0 0	2 5 9	2 6 2	2 6 4	2 6 5	2 7 0	2 7 3	2 7 4	2 7 5	2 7 6	2 7 9	2 8 0	2 8 2	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																		X									2
Histiocytic sarcoma																											1
Luteoma					X																						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																X											1
Histiocytic sarcoma																											1
Endometrium, adenoma																	X										1
Endometrium, carcinoma													X														1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node																											7
Iliac, histiocytic sarcoma																											1
Renal, histiocytic sarcoma																											1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell carcinoma																											1
Subcutaneous tissue, histiocytic sarcoma							X																				1
Subcutaneous tissue, sarcoma																											2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma							X												X								2
Alveolar/bronchiolar adenoma, multiple																											1
Alveolar/bronchiolar carcinoma																											2
Basal cell carcinoma, metastatic, skin																											1
Hepatocellular carcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

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

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

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

Number of Days on Study	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 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 9 8	2 4 3	2 4 4	2 4 6	2 4 7	2 4 9	2 5 0	2 5 1	2 8 5	2 8 8	2 9 1	2 9 5	2 9 6	3 0 0	2 5 9	2 6 2	2 6 4	2 6 5	2 7 0	2 7 3	2 7 4	2 7 5	2 7 6	2 7 9	2 8 0	2 8 2	Total Tissues/ Tumors
Special Senses System																											
Ear																											1
Lacrimal gland																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma							X																				2
Lymphoma malignant										X																	3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 5 1	3 5 5	3 5 6	3 5 8	3 5 9	3 0 2	3 1 3	3 1 4	3 1 6	3 1 7	3 2 8	3 3 2	3 3 3	3 3 4	3 3 5	3 4 9	3 5 2	3 2 0	3 2 1	3 2 3	3 2 5	3 2 6	3 3 9	3 4 0	3 4 1	3 4 4	3 4 7	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangioma																												1
Hepatocellular carcinoma															X													8
Hepatocellular adenoma					X		X	X			X		X										X		X			11
Hepatocellular adenoma, multiple		X							X			X				X										X	X	9
Histiocytic sarcoma																												1
Mesentery							+				+					+			+									13
Squamous cell carcinoma, metastatic, stomach, forestomach																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma														X														1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma																												1
Sarcoma, metastatic, skin																												1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma																												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tooth																												2
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign												X																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	44
Pars distalis, adenoma	X	X						X				X																5
Pars distalis, carcinoma																												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma			X																									3
General Body System																												
Tissue NOS					+							+																2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	3 6 5	3 9 9	4 6 9	4 9 4	5 0 3	5 6 2	5 9 8	6 1 2	6 2 3	6 2 3	6 5 4	6 6 8	6 9 7	7 0 6	7 1 0	7 2 5	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 4 4	7 4 4	7 3 4
Carcass ID Number	3 5 3	3 3 0	3 4 4	3 4 2	3 5 4	3 0 4	3 1 8	3 6 0	3 2 9	3 3 6	3 5 0	3 3 1	3 1 0	3 1 5	3 4 5	3 2 4	3 4 6	3 0 1	3 0 3	3 0 6	3 0 8	3 0 9	3 1 1	3 2 2	3 3 8
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma											X							X							
Histiocytic sarcoma																			X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+				+	+			+			+						
Inguinal, histiocytic sarcoma																			X						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal		+																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma						X													X						
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+										+								
Spinal cord		+					+										+								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X								X			
Hepatocellular carcinoma, metastatic, liver										X															
Histiocytic sarcoma																			X						
Squamous cell carcinoma, metastatic, stomach, forestomach				X																					
Mediastinum, squamous cell carcinoma, metastatic, stomach, forestomach				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 5 1	3 5 5	3 5 6	3 5 8	3 5 9	3 0 2	3 1 3	3 1 4	3 1 6	3 1 7	3 2 8	3 2 3	3 3 3	3 3 4	3 3 5	3 4 9	3 5 2	3 2 0	3 2 1	3 2 3	3 2 5	3 2 6	3 3 9	3 4 0	3 4 1	3 4 3	3 4 7	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Ovary	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																											2
Histiocytic sarcoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node							+				+																8
Inguinal, histiocytic sarcoma																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lymph node, mediastinal																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Subcutaneous tissue, histiocytic sarcoma																											2
Subcutaneous tissue, sarcoma															X												2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Peripheral nerve																											2
Spinal cord																											3
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma																											2
Hepatocellular carcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Squamous cell carcinoma, metastatic, stomach, forestomach																											1
Mediastinum, squamous cell carcinoma, metastatic, stomach, forestomach																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 1,250 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 5 1	3 5 5	3 5 6	3 5 8	3 5 9	3 5 0 2	3 5 1 3	3 5 1 4	3 5 1 6	3 5 1 7	3 5 2 8	3 5 3 2	3 5 3 3	3 5 3 4	3 5 3 5	3 5 4 9	3 5 5 2	3 5 2 0	3 5 2 1	3 5 2 3	3 5 2 5	3 5 2 6	3 5 3 9	3 5 4 0	3 5 4 1	3 5 4 3	3 5 4 7	Total Tissues/ Tumors
Special Senses System																											
Harderian gland															+												1
Carcinoma															X												1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																											1
Squamous cell carcinoma, metastatic, stomach, forestomach																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																											2
Lymphoma malignant						X	X				X							X									9
Lymphoma malignant mixed																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm

Number of Days on Study	2 8 8	4 5 6	5 4 8	5 5 5	6 1 8	6 5 1	6 6 4	6 7 6	7 1 8	7 2 3	7 2 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
Carcass ID Number	3 9 2	3 8 3	4 1 4	4 0 3	3 8 9	4 0 2	4 1 7	4 1 3	3 9 0	4 0 0	3 8 4	3 6 1	3 6 2	3 6 3	3 6 5	3 6 7	3 6 8	3 6 9	3 7 0	3 7 2	3 7 8	3 9 6	4 0 7	4 1 6	3 7 4
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	A	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatocellular carcinoma			X				X	X												X					X
Hepatocellular carcinoma, multiple						X																			
Hepatocellular adenoma				X						X	X		X										X		
Hepatocellular adenoma, multiple																	X								
Histiocytic sarcoma					X																				
Mesentery	+	+			+		+														+				
Hepatocellular carcinoma, metastatic, liver							X																		
Histiocytic sarcoma					X																				
Oral mucosa																							+		
Pancreas	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver							X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth														+					+					+	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, hepatocellular carcinoma, metastatic, liver							X																		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant											X														
Islets, pancreatic	+	A	+		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Pars distalis, adenoma																X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																		X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 7 5	3 7 6	3 7 7	3 7 8	3 7 9	3 8 2	4 0 5	4 0 6	4 1 5	4 1 9	4 2 0	3 8 5	3 8 6	3 8 7	3 9 3	3 9 4	3 9 5	3 9 7	3 9 8	3 9 9	4 0 1	4 0 4	4 0 9	4 1 0	4 1 1	4 1 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatoblastoma													X													1
Hepatocellular carcinoma		X																				X				7
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma									X				X	X	X				X				X			11
Hepatocellular adenoma, multiple							X					X										X			X	5
Histiocytic sarcoma																										1
Mesentery								+															+			7
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																			+							4
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, hepatocellular carcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma												X														1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma				X			X															X	X			5
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma				X																						2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	2 4 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 8 5 4 5 1 5 6 7 1 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 8 6 8 5 8 1 4 6 8 3 4 4 4 4 4 4 4 4 4 4 4 4 5
Carcass ID Number	3 3 4 4 3 4 4 4 3 4 3 3 3 3 3 3 3 3 3 3 3 4 4 3 9 8 1 0 8 0 1 1 9 0 8 6 6 6 6 6 6 6 7 7 8 9 0 1 7 2 3 4 3 9 2 7 3 0 0 4 1 2 3 5 7 8 9 0 2 0 6 7 6 4
General Body System	
Tissue NOS	+
Pelvic, hemangiosarcoma, multiple	X
Genital System	
Clitoral gland	+ + + + + + + M + + + + + + + + + + + + + + + + +
Ovary	+ + + + + A + + M + + + + + + + + M + + + + + + +
Cystadenoma	
Granulosa cell tumor malignant	X
Histiocytic sarcoma	X
Uterus	+ + + + + A + + + + + + + + + + + + + + + + + + +
Histiocytic sarcoma	X
Endometrium, adenoma	
Endometrium, polyp stromal	X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + + + + + + + + + + + + + + +
Iliac, histiocytic sarcoma	X
Mediastinal, hepatocellular carcinoma, metastatic, liver	X
Mediastinal, histiocytic sarcoma	X
Renal, histiocytic sarcoma	X
Lymph node, mandibular	+ + + + + A + + + + + + + + + + + + + + + + + + +
Lymph node, mesenteric	+ + + + + A + + + + + + + + + + + + + + M + + + +
Hepatocellular carcinoma, metastatic, liver	X
Histiocytic sarcoma	X
Lymph node, mediastinal	+ +
Spleen	+ + + + + A + + + + + + + + + + + + + + + + + + +
Hemangiosarcoma	X
Thymus	+ + + M + A + + + + + + + + + + + M + + + + + + +
Integumentary System	
Mammary gland	+ +
Myoepithelioma	
Skin	+ +
Subcutaneous tissue, fibrosarcoma	X
Subcutaneous tissue, histiocytic sarcoma	X
Subcutaneous tissue, sarcoma	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+ +
Hepatocellular carcinoma, metastatic, liver	X
Nervous System	
Brain	+ +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 7 5	3 7 6	3 7 7	3 7 8	3 7 9	3 8 2	4 0 5	4 0 6	4 1 5	4 1 9	4 2 0	3 8 5	3 8 6	3 8 7	3 9 3	3 9 4	3 9 5	3 9 7	3 9 8	3 9 9	4 0 1	4 0 4	4 0 9	4 1 0	4 1 1	4 1 2	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Pelvic, hemangiosarcoma, multiple																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma		X												X										X		3
Granulosa cell tumor malignant																										1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						2
Endometrium, adenoma														X												1
Endometrium, polyp stromal			X					X																		3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node								+														+				12
Iliac, histiocytic sarcoma																										1
Mediastinal, hepatocellular carcinoma, metastatic, liver																										1
Mediastinal, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Lymph node, mediastinal																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Myoepithelioma																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																										2
Hepatocellular carcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	2 8 8	4 5 6	5 4 8	5 5 5	6 1 8	6 5 1	6 6 4	6 7 6	7 1 8	7 2 3	7 2 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
Carcass ID Number	3 9 2	3 8 3	4 1 4	4 0 3	3 8 9	4 0 2	4 1 7	4 1 3	3 9 0	4 0 0	3 8 4	3 6 1	3 6 2	3 6 3	3 6 5	3 6 7	3 6 8	3 6 9	3 7 0	3 7 2	3 8 0	3 9 6	4 0 7	4 1 6	3 7 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Hepatoblastoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver						X	X																		X
Histiocytic sarcoma					X																				
Sarcoma, metastatic, skin																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland												+													
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X					X															
Lymphoma malignant									X				X				X	X	X	X				X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 2,500 ppm
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 7 5	3 7 6	3 7 7	3 7 8	3 7 9	3 8 2	4 0 5	4 0 6	4 1 5	4 1 9	4 2 0	3 8 5	3 8 6	3 8 7	3 9 3	3 9 4	3 9 5	3 9 7	3 9 8	3 9 9	4 0 1	4 0 4	4 0 9	4 1 0	4 1 1	4 1 2	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma	X	X																				X			X	4
Alveolar/bronchiolar carcinoma								X																		1
Hepatoblastoma, metastatic, liver													X													1
Hepatocellular carcinoma, metastatic, liver																							X			4
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye															+											1
Harderian gland												+	+		+				+					+		6
Adenoma												X	X		X				X					X		6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																				X						3
Lymphoma malignant		X						X														X				10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 6 7	4 6 8	4 7 6	4 2 1	4 2 2	4 3 2	4 3 5	4 3 7	4 5 3	4 5 4	4 5 5	4 5 6	4 7 0	4 7 1	4 7 3	4 7 4	4 7 7	4 3 9	4 4 2	4 4 4	4 4 7	4 4 9	4 5 0	4 5 8	4 6 0	4 6 1	4 6 2	4 7 5	4 8 0	Total Tissues/ Tumors
Alimentary System																														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leiomyosarcoma																														1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Hemangiosarcoma																														1
Hepatocellular carcinoma																			X								X			4
Hepatocellular carcinoma, multiple							X																							1
Hepatocellular adenoma																	X						X							4
Hepatocellular adenoma, multiple																														1
Histiocytic sarcoma																														2
Mesentery			+									+																		8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Squamous cell papilloma				X																						X				2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Tooth		+																												1
Cardiovascular System																														
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+		M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Pars distalis, adenoma				X														X												4
Pars intermedia, adenoma																														1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Follicular cell, adenoma																		X									X			5
General Body System																														
None																														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	0 8 2	2 9 6	4 1 8	4 2 9	5 3 8	6 2 9	7 0 1	7 0 3	7 2 2	7 2 3	7 2 8	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 4 3	4 3 8	4 6 5	4 3 6	4 4 5	4 4 8	4 7 8	4 5 9	4 7 9	4 4 0	4 5 1	4 2 4	4 2 5	4 2 6	4 2 7	4 2 8	4 2 9	4 3 0	4 3 1	4 3 3	4 4 6	4 5 7	4 6 3	4 6 4	4 6 6
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	M	+	+	+
Cystadenoma																								
Teratoma NOS	X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Leiomyosarcoma																					X			
Endometrium, polyp stromal															X									
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+		+		+		+			+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		X						
Subcutaneous tissue, fibrosarcoma								X																
Subcutaneous tissue, histiocytic sarcoma									X															
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma						X																		
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord				+																				
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X			X			
Hepatocellular carcinoma, metastatic, liver																			X					
Histiocytic sarcoma			X																					
Osteosarcoma, metastatic, bone						X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 6 7	4 6 8	4 6 6	4 7 1	4 7 2	4 8 2	4 8 5	4 8 7	4 9 3	4 9 4	4 9 5	4 9 5	4 9 6	4 9 0	4 9 1	4 9 3	4 9 4	4 9 7	4 9 9	4 0 2	4 0 4	4 0 7	4 1 9	4 2 0	4 2 8	4 3 0	4 3 1	4 3 2	4 3 5	4 3 0	Total Tissues/ Tumors
Genital System																														
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Ovary	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma											X				X															2
Teratoma NOS																														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Histiocytic sarcoma																														1
Leiomyosarcoma																														1
Endometrium, polyp stromal																														1
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node				+							+												+							9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	52
Lymph node, mesenteric	+		+	+	+	I	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																		X												2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	48
Histiocytic sarcoma																														1
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma									X																					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Squamous cell papilloma																														1
Subcutaneous tissue, fibrosarcoma																														1
Subcutaneous tissue, histiocytic sarcoma																														1
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Osteosarcoma																														1
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Spinal cord																				+										2
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Alveolar/bronchiolar adenoma	X																													3
Hepatocellular carcinoma, metastatic, liver																											X			2
Histiocytic sarcoma																														1
Osteosarcoma, metastatic, bone																														1
Nose	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone: 5,000 ppm
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of t-Butylhydroquinone: 5,000 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 6 7	4 6 8	4 7 6	4 2 1	4 2 2	4 3 2	4 3 5	4 3 7	4 5 3	4 5 4	4 5 5	4 5 6	4 7 0	4 7 1	4 7 3	4 7 4	4 7 7	4 3 9	4 4 2	4 4 4	4 4 7	4 4 9	4 5 0	4 5 8	4 6 0	4 6 1	4 6 2	4 7 5	4 8 0	Total Tissues/ Tumors
Special Senses System																														
Harderian gland																														1
Adenoma																														1
Urinary System																														
Kidney	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	53
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Histiocytic sarcoma																		X												4
Lymphoma malignant			X	X								X										X								8

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Harderian Gland: Adenoma				
Overall rate[a]	0/51 (0%)	0/52 (0%)	6/51 (12%)	1/54 (2%)
Adjusted rate[b]	0.0%	0.0%	15.0%	2.3%
Terminal rate[c]	0/38 (0%)	0/35 (0%)	6/40 (15%)	1/43 (2%)
First incidence (days)	—[e]	—	734 (T)	734 (T)
Life table test[d]	P=0.294	—	P=0.020	P=0.525
Logistic regression test[d]	P=0.294	—	P=0.020	P=0.525
Cochran-Armitage test[d]	P=0.255			
Fisher exact test[d]		—	P=0.013	P=0.514
Harderian Gland: Adenoma or Carcinoma				
Overall rate	0/51 (0%)	1/52 (2%)	6/51 (12%)	1/54 (2%)
Adjusted rate	0.0%	2.9%	15.0%	2.3%
Terminal rate	0/38 (0%)	1/35 (3%)	6/40 (15%)	1/43 (2%)
First incidence (days)	—	734 (T)	734 (T)	734 (T)
Life table test	P=0.379	P=0.484	P=0.020	P=0.525
Logistic regression test	P=0.379	P=0.484	P=0.020	P=0.525
Cochran-Armitage test	P=0.334			
Fisher exact test		P=0.505	P=0.013	P=0.514
Liver: Hepatocellular Adenoma				
Overall rate	9/51 (18%)	20/52 (38%)	16/51 (31%)	5/54 (9%)
Adjusted rate	22.7%	51.0%	37.1%	11.6%
Terminal rate	8/38 (21%)	16/35 (46%)	13/40 (33%)	5/43 (12%)
First incidence (days)	582	598	555	734 (T)
Life table test	P=0.023N	P=0.008	P=0.111	P=0.135N
Logistic regression test	P=0.027N	P=0.011	P=0.096	P=0.146N
Cochran-Armitage test	P=0.041N			
Fisher exact test		P=0.016	P=0.083	P=0.165N
Liver: Hepatocellular Carcinoma				
Overall rate	8/51 (16%)	8/52 (15%)	8/51 (16%)	5/54 (9%)
Adjusted rate	18.4%	19.2%	17.6%	11.6%
Terminal rate	4/38 (11%)	4/35 (11%)	4/40 (10%)	5/43 (12%)
First incidence (days)	461	469	548	734 (T)
Life table test	P=0.155N	P=0.566	P=0.561N	P=0.216N
Logistic regression test	P=0.357N	P=0.559N	P=0.592	P=0.240N
Cochran-Armitage test	P=0.188N			
Fisher exact test		P=0.590N	P=0.607N	P=0.241N
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma				
Overall rate	17/51 (33%)	28/52 (54%)	23/51 (45%)	10/54 (19%)
Adjusted rate	38.9%	64.7%	48.8%	23.3%
Terminal rate	12/38 (32%)	20/35 (57%)	16/40 (40%)	10/43 (23%)
First incidence (days)	461	469	548	734 (T)
Life table test	P=0.007N	P=0.021	P=0.233	P=0.050N
Logistic regression test	P=0.010N	P=0.025	P=0.155	P=0.064N
Cochran-Armitage test	P=0.011N			
Fisher exact test		P=0.028	P=0.155	P=0.065N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	8/51 (16%)	8/52 (15%)	9/51 (18%)	5/54 (9%)
Adjusted rate	18.4%	19.2%	19.9%	11.6%
Terminal rate	4/38 (11%)	4/35 (11%)	5/40 (13%)	5/43 (12%)
First incidence (days)	461	469	548	734 (T)
Life table test	P=0.163N	P=0.566	P=0.543	P=0.216N
Logistic regression test	P=0.197N	P=0.559N	P=0.484	P=0.240N
Cochran-Armitage test	P=0.200N			
Fisher exact test		P=0.590N	P=0.500	P=0.241N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	17/51 (33%)	28/52 (54%)	23/51 (45%)	10/54 (19%)
Adjusted rate	38.9%	64.7%	48.8%	23.3%
Terminal rate	12/38 (32%)	20/35 (57%)	16/40 (40%)	10/43 (23%)
First incidence (days)	461	469	548	734 (T)
Life table test	P=0.007N	P=0.021	P=0.233	P=0.050N
Logistic regression test	P=0.010N	P=0.025	P=0.155	P=0.064N
Cochran-Armitage test	P=0.011N			
Fisher exact test		P=0.028	P=0.155	P=0.065N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/51 (6%)	2/52 (4%)	4/51 (8%)	3/54 (6%)
Adjusted rate	7.9%	5.3%	10.0%	7.0%
Terminal rate	3/38 (8%)	1/35 (3%)	4/40 (10%)	3/43 (7%)
First incidence (days)	734 (T)	706	734 (T)	734 (T)
Life table test	P=0.571N	P=0.530N	P=0.528	P=0.605N
Logistic regression test	P=0.567N	P=0.509N	P=0.528	P=0.605N
Cochran-Armitage test	P=0.528			
Fisher exact test		P=0.491N	P=0.500	P=0.633N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/51 (10%)	2/52 (4%)	5/51 (10%)	3/54 (6%)
Adjusted rate	13.2%	5.3%	12.5%	7.0%
Terminal rate	5/38 (13%)	1/35 (3%)	5/40 (13%)	3/43 (7%)
First incidence (days)	734 (T)	706	734 (T)	734 (T)
Life table test	P=0.321N	P=0.247N	P=0.599N	P=0.290N
Logistic regression test	P=0.311N	P=0.223N	P=0.599N	P=0.290N
Cochran-Armitage test	P=0.381N			
Fisher exact test		P=0.210N	P=0.630N	P=0.326N
Ovary: Cystadenoma				
Overall rate	2/50 (4%)	2/49 (4%)	3/47 (6%)	2/50 (4%)
Adjusted rate	5.4%	5.3%	7.9%	5.1%
Terminal rate	2/37 (5%)	1/34 (3%)	3/38 (8%)	2/39 (5%)
First incidence (days)	734 (T)	654	734 (T)	734 (T)
Life table test	P=0.571N	P=0.671	P=0.512	P=0.676N
Logistic regression test	P=0.586N	P=0.679	P=0.512	P=0.676N
Cochran-Armitage test	P=0.568			
Fisher exact test		P=0.684	P=0.470	P=0.691N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	5/49 (10%)	5/44 (11%)	5/46 (11%)	4/49 (8%)
Adjusted rate	12.3%	16.1%	13.2%	10.5%
Terminal rate	3/36 (8%)	5/31 (16%)	5/38 (13%)	4/38 (11%)
First incidence (days)	567	734 (T)	734 (T)	734 (T)
Life table test	P=0.351N	P=0.550	P=0.600N	P=0.465N
Logistic regression test	P=0.382N	P=0.554	P=0.593	P=0.502N
Cochran-Armitage test	P=0.401N			
Fisher exact test		P=0.559	P=0.589	P=0.500N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	5/49 (10%)	6/44 (14%)	5/46 (11%)	4/49 (8%)
Adjusted rate	12.3%	18.0%	13.2%	10.5%
Terminal rate	3/36 (8%)	5/31 (16%)	5/38 (13%)	4/38 (11%)
First incidence (days)	567	598	734 (T)	734 (T)
Life table test	P=0.310N	P=0.423	P=0.600N	P=0.465N
Logistic regression test	P=0.350N	P=0.423	P=0.593	P=0.502N
Cochran-Armitage test	P=0.358N			
Fisher exact test		P=0.423	P=0.589	P=0.500N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/51 (2%)	3/51 (6%)	2/50 (4%)	5/54 (9%)
Adjusted rate	2.6%	8.0%	5.1%	11.4%
Terminal rate	1/38 (3%)	2/34 (6%)	2/39 (5%)	4/43 (9%)
First incidence (days)	734 (T)	612	734 (T)	728
Life table test	P=0.120	P=0.276	P=0.509	P=0.137
Logistic regression test	P=0.103	P=0.300	P=0.509	P=0.142
Cochran-Armitage test	P=0.092			
Fisher exact test		P=0.309	P=0.492	P=0.116
Uterus: Stromal Polyp				
Overall rate	0/51 (0%)	0/52 (0%)	3/51 (6%)	1/54 (2%)
Adjusted rate	0.0%	0.0%	7.5%	2.3%
Terminal rate	0/38 (0%)	0/35 (0%)	3/40 (8%)	1/43 (2%)
First incidence (days)	—	—	734 (T)	734 (T)
Life table test	P=0.291	—	P=0.130	P=0.525
Logistic regression test	P=0.291	—	P=0.130	P=0.525
Cochran-Armitage test	P=0.262			
Fisher exact test		—	P=0.121	P=0.514
All Organs: Histiocytic Sarcoma				
Overall rate	2/51 (4%)	2/52 (4%)	3/51 (6%)	4/54 (7%)
Adjusted rate	5.0%	4.9%	6.8%	8.5%
Terminal rate	1/38 (3%)	1/35 (3%)	1/40 (3%)	2/43 (5%)
First incidence (days)	673	562	618	418
Life table test	P=0.279	P=0.673	P=0.526	P=0.397
Logistic regression test	P=0.246	P=0.679N	P=0.498	P=0.376
Cochran-Armitage test	P=0.238			
Fisher exact test		P=0.684N	P=0.500	P=0.367

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Malignant Lymphoma (Mixed or NOS)				
Overall rate	3/51 (6%)	9/52 (17%)	10/51 (20%)	8/54 (15%)
Adjusted rate	7.1%	22.7%	24.3%	18.2%
Terminal rate	1/38 (3%)	5/35 (14%)	9/40 (23%)	7/43 (16%)
First incidence (days)	582	668	718	728
Life table test	P=0.271	P=0.061	P=0.050	P=0.150
Logistic regression test	P=0.217	P=0.063	P=0.041	P=0.122
Cochran-Armitage test	P=0.190			
Fisher exact test		P=0.065	P=0.036	P=0.119
All Organs: Benign Neoplasms				
Overall rate	23/51 (45%)	26/52 (50%)	27/51 (53%)	19/54 (35%)
Adjusted rate	54.3%	63.1%	59.7%	43.2%
Terminal rate	19/38 (50%)	20/35 (57%)	22/40 (55%)	18/43 (42%)
First incidence (days)	567	598	288	728
Life table test	P=0.060N	P=0.244	P=0.367	P=0.137N
Logistic regression test	P=0.106N	P=0.326	P=0.289	P=0.168N
Cochran-Armitage test	P=0.131N			
Fisher exact test		P=0.382	P=0.276	P=0.201N
All Organs: Malignant Neoplasms				
Overall rate	18/51 (35%)	22/52 (42%)	22/51 (43%)	22/54 (41%)
Adjusted rate	39.6%	47.2%	45.8%	44.8%
Terminal rate	11/38 (29%)	11/35 (31%)	14/40 (35%)	16/43 (37%)
First incidence (days)	461	469	548	418
Life table test	P=0.531N	P=0.249	P=0.366	P=0.460
Logistic regression test	P=0.152	P=0.279	P=0.269	P=0.352
Cochran-Armitage test	P=0.367			
Fisher exact test		P=0.299	P=0.272	P=0.355
All Organs: Benign or Malignant Neoplasms				
Overall rate	33/51 (65%)	41/52 (79%)	37/51 (73%)	33/54 (61%)
Adjusted rate	68.7%	83.7%	74.0%	65.9%
Terminal rate	23/38 (61%)	27/35 (77%)	27/40 (68%)	26/43 (60%)
First incidence (days)	461	469	288	82
Life table test	P=0.110N	P=0.074	P=0.419	P=0.312N
Logistic regression test	P=0.206N	P=0.055	P=0.258	P=0.432N
Cochran-Armitage test	P=0.206N			
Fisher exact test		P=0.084	P=0.261	P=0.429N

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

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

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	194/1,312 (14.8%)	90/1,312 (6.9%)	260/1,312 (19.8%)
Standard deviation	10.5%	6.1%	12.8%
Range	2%-50%	0%-20%	3%-56%

[a] Data as of 17 June 1994

TABLE D4b
Historical Incidence of Thyroid Gland (Follicular Cell) Adenoma in Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls
Overall Historical Incidence	
Total	27/1,301 (2.1%)
Standard deviation	2.8%
Range	0%-9%

[a] Data as of 17 June 1994

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	8	9	6
Early deaths				
Moribund	11	7	6	6
Natural deaths	2	10	5	5
Survivors				
Died last week of study	1			1
Terminal sacrifice	37	35	40	42
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(8)	(9)	(6)
Mixed cell focus		1 (13%)	1 (11%)	
Vacuolization cytoplasmic, focal	1 (11%)			
Mesentery				(1)
Fat, necrosis				1 (100%)
Pancreas	(9)	(8)	(9)	(6)
Atrophy, focal	1 (11%)			
Endocrine System				
Adrenal cortex	(9)	(8)	(9)	(6)
Accessory adrenal cortical nodule			1 (11%)	
Parathyroid gland	(9)	(7)	(9)	(6)
Hyperplasia		1 (14%)		
Thyroid gland	(9)	(8)	(9)	(6)
Degeneration, cystic, focal				1 (17%)
Genital System				
Ovary	(9)	(8)	(9)	(6)
Cyst	4 (44%)		1 (11%)	1 (17%)
Uterus	(9)	(8)	(9)	(6)
Hydrometra	4 (44%)	1 (13%)	1 (11%)	2 (33%)
Inflammation, suppurative	1 (11%)	2 (25%)		
Endometrium, hyperplasia, cystic	9 (100%)	8 (100%)	8 (89%)	6 (100%)
Hematopoietic System				
Lymph node, mandibular	(9)	(8)	(9)	(5)
Hyperplasia, lymphoid	1 (11%)			
Spleen	(9)	(8)	(9)	(6)
Fibrosis, focal		1 (13%)		
Integumentary System				
Skin	(9)	(8)	(9)	(6)
Alopecia, focal			1 (11%)	

[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 *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(9)	(8)	(9)	(6)
Alveolar epithelium, hyperplasia			1 (11%)	
Urinary System				
Kidney	(9)	(8)	(9)	(6)
Renal tubule, dilatation, focal			1 (11%)	
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Gallbladder	(50)	(50)	(47)	(54)
Cyst			1 (2%)	
Intestine small, duodenum	(51)	(51)	(48)	(53)
Erosion	1 (2%)			
Inflammation, chronic, focal	1 (2%)			
Intestine small, jejunum	(51)	(51)	(48)	(53)
Perforation, chronic			1 (2%)	
Peyer's patch, hyperplasia, lymphoid			1 (2%)	
Intestine small, ileum	(51)	(51)	(47)	(53)
Peyer's patch, hyperplasia, lymphoid			1 (2%)	1 (2%)
Liver	(51)	(52)	(51)	(54)
Angiectasis	2 (4%)			1 (2%)
Basophilic focus	2 (4%)	1 (2%)	1 (2%)	
Clear cell focus			2 (4%)	2 (4%)
Eosinophilic focus	4 (8%)	9 (17%)	9 (18%)	11 (20%)
Eosinophilic focus, multiple	3 (6%)	5 (10%)	1 (2%)	1 (2%)
Fatty change	4 (8%)	1 (2%)		
Fatty change, focal	2 (4%)		1 (2%)	
Hematopoietic cell proliferation	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Hemorrhage, focal				1 (2%)
Hyperplasia, focal, lymphoid				1 (2%)
Infarct	1 (2%)		1 (2%)	
Infiltration cellular, mixed cell	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Inflammation, focal	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Mineralization, focal			1 (2%)	
Mixed cell focus	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Mixed cell focus, multiple			1 (2%)	
Necrosis, focal	1 (2%)	1 (2%)		2 (4%)
Thrombosis	1 (2%)			
Bile duct, cyst	1 (2%)		1 (2%)	
Centrilobular, necrosis	1 (2%)		1 (2%)	1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(10)	(13)	(7)	(8)
Hemorrhage		1 (8%)		
Inflammation, chronic	1 (10%)	1 (8%)	3 (43%)	4 (50%)
Fat, necrosis	8 (80%)	5 (38%)	1 (14%)	1 (13%)
Pancreas	(51)	(52)	(49)	(54)
Atrophy, focal		1 (2%)	2 (4%)	
Duct, cyst	1 (2%)			
Salivary glands	(51)	(52)	(51)	(53)
Vacuolization cytoplasmic			1 (2%)	
Stomach, forestomach	(51)	(52)	(51)	(54)
Erosion	3 (6%)		1 (2%)	
Inflammation, chronic	5 (10%)		1 (2%)	3 (6%)
Pigmentation, focal				1 (2%)
Ulcer	1 (2%)			2 (4%)
Epithelium, hyperplasia	5 (10%)		1 (2%)	4 (7%)
Stomach, glandular	(51)	(52)	(49)	(54)
Erosion	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic				1 (2%)
Pigmentation, focal		1 (2%)		
Ulcer				1 (2%)
Glands, degeneration, cystic, focal			1 (2%)	
Tooth		(2)	(4)	(1)
Incisor, dysplasia		2 (100%)	4 (100%)	1 (100%)
Cardiovascular System				
Blood vessel	(50)	(52)	(51)	(54)
Mesenteric artery, inflammation, chronic			1 (2%)	
Heart	(51)	(52)	(51)	(54)
Inflammation, chronic, focal			1 (2%)	
Thrombosis			1 (2%)	
Artery, inflammation, chronic			2 (4%)	
Myocardium, mineralization, focal				1 (2%)
Endocrine System				
Adrenal cortex	(51)	(51)	(50)	(54)
Accessory adrenal cortical nodule	2 (4%)	4 (8%)		1 (2%)
Cytoplasmic alteration, focal	1 (2%)			
Hematopoietic cell proliferation	1 (2%)			
Capsule, hyperplasia	1 (2%)			
Subcapsular, hyperplasia, focal				2 (4%)
Adrenal medulla	(51)	(51)	(51)	(54)
Hyperplasia	1 (2%)			4 (7%)
Islets, pancreatic	(51)	(52)	(48)	(54)
Hyperplasia				1 (2%)
Parathyroid gland	(46)	(49)	(49)	(49)
Cyst		1 (2%)		

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(49)	(44)	(46)	(49)
Angiectasis	2 (4%)		2 (4%)	1 (2%)
Cyst			1 (2%)	
Pars distalis, angiectasis	1 (2%)			
Pars distalis, cytoplasmic alteration, focal	2 (4%)	3 (7%)	2 (4%)	1 (2%)
Pars distalis, hyperplasia, focal	3 (6%)	3 (7%)	2 (4%)	1 (2%)
Pars intermedia, hyperplasia, focal		1 (2%)		
Thyroid gland	(51)	(51)	(50)	(54)
Degeneration, cystic, focal	1 (2%)			
Inflammation			1 (2%)	
Inflammation, chronic, focal	1 (2%)			2 (4%)
C-cell, hyperplasia	2 (4%)		1 (2%)	
Follicular cell, hyperplasia	12 (24%)	19 (37%)	24 (48%)	24 (44%)
General Body System				
None				
Genital System				
Clitoral gland	(51)	(52)	(50)	(54)
Degeneration, cystic		4 (8%)	2 (4%)	3 (6%)
Ovary	(50)	(49)	(47)	(50)
Angiectasis	2 (4%)	2 (4%)		3 (6%)
Cyst	15 (30%)	10 (20%)	10 (21%)	11 (22%)
Hemorrhage	1 (2%)			
Hyperplasia, tubular				1 (2%)
Inflammation, suppurative	2 (4%)	2 (4%)	2 (4%)	5 (10%)
Thrombosis				1 (2%)
Interstitial cell, hyperplasia		1 (2%)		
Uterus	(51)	(52)	(50)	(54)
Cyst		1 (2%)		1 (2%)
Hemorrhage		1 (2%)		
Hydrometra	13 (25%)	11 (21%)	12 (24%)	14 (26%)
Hyperplasia, focal, histiocytic		1 (2%)		
Inflammation, suppurative	3 (6%)			3 (6%)
Endometrium, hyperplasia, cystic	50 (98%)	52 (100%)	50 (100%)	51 (94%)
Hematopoietic System				
Bone marrow	(51)	(52)	(51)	(54)
Hyperplasia	2 (4%)			
Hyperplasia, focal, histiocytic	1 (2%)			
Myelofibrosis	1 (2%)			
Lymph node	(7)	(8)	(12)	(9)
Hyperplasia, cystic	1 (14%)			
Iliac, hemorrhage	1 (14%)			
Iliac, hyperplasia	2 (29%)	1 (13%)		1 (11%)
Inguinal, hyperplasia			2 (17%)	
Lumbar, hyperplasia				1 (11%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph Node (continued)	(7)	(8)	(12)	(9)
Mediastinal, hyperplasia	1 (14%)	1 (13%)	2 (17%)	1 (11%)
Mediastinal, hyperplasia, lymphoid	1 (14%)			1 (11%)
Mediastinal, inflammation, focal, suppurative				1 (11%)
Renal, hemorrhage	1 (14%)			
Renal, hyperplasia	2 (29%)	2 (25%)	1 (8%)	3 (33%)
Lymph node, mandibular	(48)	(52)	(50)	(52)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)	
Lymph node, mesenteric	(50)	(48)	(49)	(50)
Amyloid deposition	1 (2%)			
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia	1 (2%)	2 (4%)		1 (2%)
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	6 (12%)	3 (6%)	3 (6%)	1 (2%)
Spleen	(51)	(52)	(50)	(54)
Angiectasis				1 (2%)
Congestion		1 (2%)		
Fibrosis, focal				1 (2%)
Hematopoietic cell proliferation	14 (27%)	14 (27%)	13 (26%)	13 (24%)
Hemorrhage			1 (2%)	
Hyperplasia, lymphoid	3 (6%)	8 (15%)	7 (14%)	7 (13%)
Necrosis, focal	1 (2%)			
Thymus	(45)	(51)	(47)	(48)
Cyst		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	
Integumentary System				
Mammary gland	(51)	(51)	(51)	(54)
Ectasia	3 (6%)	1 (2%)		
Hyperplasia		1 (2%)		
Skin	(51)	(52)	(51)	(54)
Alopecia, focal				1 (2%)
Inflammation, chronic, focal			1 (2%)	
Ulcer			1 (2%)	
Epidermis, hyperplasia, focal				1 (2%)
Subcutaneous tissue, edema		1 (2%)		
Subcutaneous tissue, inflammation, chronic, focal		1 (2%)		1 (2%)
Musculoskeletal System				
Skeletal muscle	(1)	(1)	(2)	
Inflammation, suppurative	1 (100%)	1 (100%)	1 (50%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *t*-Butylhydroquinone
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Nervous System				
Brain	(51)	(52)	(51)	(54)
Atrophy, focal	3 (6%)	4 (8%)	1 (2%)	1 (2%)
Artery, meninges, inflammation, chronic			1 (2%)	
Meninges, cyst			1 (2%)	
Respiratory System				
Lung	(51)	(52)	(51)	(54)
Congestion	1 (2%)			
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, mixed cell			1 (2%)	2 (4%)
Inflammation, chronic, focal				1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)		1 (2%)	2 (4%)
Interstitium, inflammation, suppurative	2 (4%)			1 (2%)
Mediastinum, inflammation, chronic				1 (2%)
Pleura, mediastinum, inflammation, chronic			1 (2%)	1 (2%)
Nose	(51)	(52)	(49)	(53)
Inflammation, suppurative		1 (2%)		1 (2%)
Mucosa, glands, dilatation, focal	16 (31%)	27 (52%)	16 (33%)	26 (49%)
Nasolacrimal duct, cyst		1 (2%)		
Trachea	(51)	(52)	(50)	(54)
Artery, peritracheal tissue, inflammation, chronic			1 (2%)	
Special Senses System				
Eye			(1)	
Cornea, inflammation, chronic			1 (100%)	
Urinary System				
Kidney	(51)	(52)	(50)	(53)
Congestion		2 (4%)		
Cyst				1 (2%)
Hydronephrosis	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Inflammation, chronic	2 (4%)			1 (2%)
Metaplasia, focal, osseous			1 (2%)	
Nephropathy	30 (59%)	32 (62%)	35 (70%)	28 (53%)
Artery, inflammation, chronic			1 (2%)	
Renal tubule, casts				1 (2%)
Renal tubule, dilatation, focal			1 (2%)	
Renal tubule, pigmentation			1 (2%)	
Renal tubule, pigmentation, hemoglobin				1 (2%)
Urinary bladder	(51)	(51)	(50)	(53)
Angiectasis	1 (2%)			
Hyperplasia, lymphoid			2 (4%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). *t*-Butylhydroquinone was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA102 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor® 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following 2 days incubation at 37° C. All tests were repeated using either the same or different S9 concentrations.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of *t*-butylhydroquinone. The high dose was limited by toxicity. All assays 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 which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold-increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

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

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 25.5 hours with *t*-butylhydroquinone in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 25.5 hours, the medium containing *t*-butylhydroquinone 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 *t*-butylhydroquinone, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no *t*-butylhydroquinone, and incubation proceeded for an additional 25.5 hours, with Colcemid® present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was observed in the presence of S9, incubation time in the second trial with S9 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 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 *t*-butylhydroquinone for 8 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 *t*-butylhydroquinone and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for an additional 18 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, the incubation period was extended beyond the normal 10 to 12 hour period.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level in the trial without S9. Because large numbers of aberrations were observed in the cells treated in the presence of S9, fewer cells were scored per dose level. Cells with large numbers of aberrations are difficult to score, and the process is extremely arduous. Because so many aberrations were observed in almost 100% of the cells, use of a smaller sample size does not affect the validity of the statistical analysis of the data. Classes of aberrations scored included "simple" (breaks and terminal deletions), "complex" (rearrangements and translocations), and "other" (pulverized cells, despiralized chromosomes, and cells containing ten or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose-response curve and individual dose points. For a single trial, a statistically significant ($P < 0.05$) difference for one dose point and a significant trend ($P < 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend in the absence of a statistically significant increase at any one dose point led to an equivocal call. 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

Selection of doses was based upon published LD_{50} information; no preliminary range-finding studies were required. Male $B6C3F_1$ mice received three intraperitoneal injections of *t*-butylhydroquinone dissolved in corn oil at 24-hour intervals. Up to five mice were treated per exposure group and the highest dose administered was 400 mg/kg. Solvent control animals received corn oil only, and the positive control mice received injections of 25 mg/kg cyclophosphamide. The mice were killed 24 hours after the final injection and slides were prepared from bone marrow smears obtained from the femurs. Slides were air-dried, fixed, and stained. Two thousand polychromatic erythrocytes (PCEs) were scored per animal for frequency of micronucleated cells. No animals survived in the 400 mg/kg group and only one mouse survived in the 300 mg/kg dose group.

The results were tabulated as the mean of the pooled results from all animals within an exposure 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 exposure groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the

control group (Margolin *et al.*, 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 ≤0.025 or the P value for any single exposure group is ≤0.025/n where n = the number of exposure 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, reproducibility of any effects observed, and the magnitudes of those effects.

RESULTS

t-Butylhydroquinone (3 to 3,333 μg/plate) was tested for induction of mutations in *S. typhimurium* strains TA97, TA98, TA100, and TA102 with and without induced rat or hamster liver S9 (Zeiger *et al.*, 1992; Table E1). No mutagenicity was detected in any of the strain/activation combinations. No induction of SCEs (Table E2) or Abs (Table E3) was noted in cultured CHO cells treated with *t*-butylhydroquinone in the absence of S9 activation. However, in the presence of S9, positive dose-related responses were obtained in both these *in vitro* cytogenetic assays. The response obtained in the Abs test was particularly strong, and up to 90% of treated cells showed multiple Abs at the higher doses (200 to 249 μg/mL). These positive results in cultured CHO cells may have resulted from the generation of superoxide and H_2O_2 within the cell from the autooxidation of *t*-butylhydroquinone to *t*-butylquinone and the further generation of oxidative byproducts, thereby indirectly producing chromosome breakage (Phillips *et al.*, 1989). In contrast to the positive results obtained in the *in vitro* assays for chromosome damage, results of an *in vivo* bone marrow micronucleus test were clearly negative. No significant increase in micronucleated erythrocytes was observed in male mice treated with three intraperitoneal injections of up to 300 mg/kg *t*-butylhydroquinone (Table E4).

TABLE E1
Mutagenicity of *t*-Butylhydroquinone in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	Revertants/plate[b] -S9 Trial 2
TA102	0	309 ± 25.5	202 ± 12.4
	3	319 ± 18.6	213 ± 5.8
	10	323 ± 9.8	187 ± 9.2
	33	267 ± 25.5	166 ± 3.6
	100	234 ± 12.3	180 ± 7.1
	166		191 ± 10.0
	333	128 ± 21.4[c]	
Trial summary		Negative	Negative
Positive control[d]		1,433 ± 26.6	565 ± 18.7

Strain	Dose (μg/plate)	Revertants/plate +hamster S9 10%	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 10%	+rat S9 30%
TA102 (continued)							
	0	249 ± 11.0	122 ± 2.6	331 ± 25.3	233 ± 7.1	189 ± 3.1	342 ± 18.5
	3		135 ± 13.0			185 ± 7.2	
	10		127 ± 4.0			175 ± 16.3	
	33	227 ± 18.5	135 ± 10.6	372 ± 27.1	279 ± 19.7	145 ± 6.7	370 ± 40.1
	100	224 ± 10.8	129 ± 4.8	348 ± 10.8	238 ± 16.5	143 ± 4.5	363 ± 25.4
	333	188 ± 13.5	150 ± 8.7	328 ± 12.0	169 ± 11.5	167 ± 6.8	363 ± 21.1
	666						
	1,000	63 ± 11.5		200 ± 10.5	58 ± 9.1		277 ± 12.7
	1,666	0 ± 0.00			31 ± 4.3		
	3,333			0 ± 0.0[c]			22 ± 3.2[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		604 ± 165.4	332 ± 29.4	2,127 ± 104.3	1,239 ± 25.6	939 ± 10.5	2,633 ± 58.1

TABLE E1
Mutagenicity of *t*-Butylhydroquinone in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	Trial 2	Trial 3
TA100	0	143 ± 6.0	95 ± 11.0	121 ± 10.3
	3		83 ± 3.3	111 ± 11.6
	10	129 ± 11.3	98 ± 7.5	112 ± 5.1
	33	115 ± 1.2	90 ± 4.8	113 ± 7.9
	100	145 ± 2.5	85 ± 3.2	119 ± 11.2
	166		79 ± 4.4	106 ± 3.8
	333	Toxic		
	666	Toxic		
Trial summary		Negative	Negative	Negative
Positive control		317 ± 9.3	394 ± 24.4	450 ± 20.9

	Revertants/plate +hamster S9 10%	10%	+rat S9 10%	30%
TA100 (continued)				
0	118 ± 11.0	172 ± 1.2	108 ± 4.0	141 ± 10.7
33	115 ± 4.7	127 ± 16.2	134 ± 3.5	150 ± 13.2
100	111 ± 7.8	153 ± 3.4	140 ± 10.7	111 ± 14.8
333	101 ± 7.7	128 ± 8.2	131 ± 2.2	145 ± 12.5
1,000	103 ± 11.3	85 ± 10.7	103 ± 7.5	141 ± 8.5
1,666	81 ± 3.0[c]		61 ± 6.4	
3,333		0 ± 0.0[c]		106 ± 10.5
Trial summary	Negative	Negative	Negative	Negative
Positive control	691 ± 48.0	645 ± 37.1	553 ± 18.8	627 ± 22.6

TABLE E1
Mutagenicity of *t*-Butylhydroquinone in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	Trial 2	Trial 3	Trial 4
TA98	0	32 ± 2.6	22 ± 1.2	27 ± 0.9	20 ± 2.3
	3		19 ± 1.9	25 ± 0.3	19 ± 1.0
	10	26 ± 0.7	25 ± 4.9	27 ± 0.7	21 ± 2.3
	33	24 ± 3.8	21 ± 2.5	87 ± 5.5	16 ± 4.9
	100	24 ± 1.9	20 ± 0.6	11 ± 1.2[c]	14 ± 3.1
	166		30 ± 4.5	0 ± 0.0[c]	4 ± 2.3[c]
	333	Toxic			
	666	Toxic			
Trial summary		Negative	Negative	Equivocal	Negative
Positive control		474 ± 22.1	505 ± 19.5	487 ± 44.2	537 ± 36.4

Strain	Dose (μg/plate)	Revertants/plate +hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA98 (continued)					
	0	35 ± 7.8	30 ± 1.2	38 ± 3.8	38 ± 1.9
	33	33 ± 3.8	25 ± 3.2	36 ± 2.0	40 ± 2.6
	100	35 ± 2.0	42 ± 6.0	36 ± 3.3	34 ± 5.2
	333	26 ± 2.3	37 ± 2.5	36 ± 4.2	31 ± 3.2
	1,000	23 ± 1.8	26 ± 5.5	27 ± 0.7	15 ± 3.5
	1,666	4 ± 0.9[c]		14 ± 3.2[c]	
	3,333		0 ± 0.0[c]		Toxic
Trial summary		Negative	Negative	Negative	Negative
Positive control		725 ± 35.2	489 ± 16.0	197 ± 20.1	192 ± 3.2

TABLE E1
Mutagenicity of *t*-Butylhydroquinone in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA97	0	127 ± 6.7	151 ± 6.6	154 ± 3.4	163 ± 15.2	176 ± 18.3	223 ± 8.1
	3	155 ± 18.8	141 ± 5.9				
	10	155 ± 4.9	163 ± 8.5				
	33	167 ± 8.6	157 ± 3.3	158 ± 6.7	228 ± 3.8	192 ± 7.1	198 ± 6.4
	100	171 ± 4.0	163 ± 7.1	167 ± 15.8	218 ± 19.8	202 ± 12.2	176 ± 6.8
	166		124 ± 11.0				
	333	0 ± 0.0[c]		170 ± 12.5	150 ± 6.1	181 ± 7.1	146 ± 23.0
	666						
	1,000			140 ± 7.6	160 ± 10.3	152 ± 9.7	154 ± 15.4
	1,666			55 ± 35.2[c]		72 ± 6.2[c]	
	3,333				0 ± 0.0[c]		0 ± 0.0[c]
Trial summary		Equivocal	Negative	Negative	Equivocal	Negative	Negative
Positive control		415 ± 11.2	388 ± 27.1	620 ± 34.7	368 ± 24.9	617 ± 4.7	454 ± 25.6

[a] Study performed at SRI International. The detailed protocol and these data are presented in Zeiger *et al.* (1992).
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100), 9-aminoacridine (TA97), 4-nitro-*o*-phenylenediamine (TA98), and mitomycin C (TA102). The positive control for metabolic activation with all strains was 2-aminoanthracene, except 2-aminoanthracene/sterigmatocystin was used for TA102.

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

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Summary: Negative								
Dimethylsulfoxide		50	1,014	477	0.47	9.5	25.5	
Mitomycin-C	0.001	50	996	566	0.56	11.3	25.5	20.80
	0.010	5	100	138	1.38	27.6	25.5	193.36
t-Butylhydroquinone	0.5	50	1,024	441	0.43	8.8	25.5	-8.45
	1.7	50	1,020	566	0.55	11.3	25.5	17.96
	5.0	50	1,029	490	0.47	9.8	25.5	1.23
	16.7	0						
					P=0.062[c]			
+S9								
Trial 1								
Summary: Positive								
Dimethylsufoxide		50	1,029	409	0.39	8.2	25.5	
Cyclophosphamide	0.4	50	1,019	706	0.69	14.1	25.5	74.31
	2.0	5	105	210	2.00	42.0	25.5	403.18
t-Butylhydroquinone	5.0	50	1,031	494	0.47	9.9	25.5	20.55*
	16.7	50	1,016	598	0.58	12.0	25.5	48.08*
	50.0	50	1,033	603	0.58	12.1	25.5	46.86*
	166.7	0					25.5	
					P<0.001			
Trial 2								
Summary: Positive								
Dimethylsulfoxide		25	523	208	0.39	8.3	25.5	
Cyclophosphamide	0.4	25	517	278	0.53	11.1	25.5	35.20
	2.0	5	102	168	1.64	33.6	25.5	314.14
t-Butylhydroquinone	49.8	25	514	318	0.61	12.7	25.5	55.56*
	100.5	25	516	352	0.68	14.1	30.5[d]	71.53*
	150.0	25	521	359	0.68	14.4	30.5[d]	73.26*
					P<0.000			

* Positive (P<0.01)
[a] Study performed at Litton Bionetics, Inc. A detailed description of the protocol is presented in Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Significance of SCEs/chromosome tested by the linear regression trend test vs. log of the dose
[d] Because t-butylhydroquinone induced a delay in the cell division cycle, harvest time was extended to maximize the proportion of second-division cells available for analysis.

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

Dose (μg/mL)	Total Cells	No.of Abs	Abs/ Cell	Cells with Abs (%)
-S9				
Harvest time: 10.0 hours				
Summary: Negative				
Dimethylsulfoxide				
	200	5	0.03	2.5
Mitomycin-C				
0.25	200	37	0.19	16.0
0.75	25	13	0.52	32.0
t-Butylhydroquinone				
5.0	200	6	0.03	3.0
7.6	200	5	0.03	2.5
10.1	200	4	0.02	2.0
25.2	0			
				P=0.410[b]
+S9				
Trial 1				
Harvest time: 20.0 hours[c]				
Summary: Positive				
Dimethylsulfoxide				
	200	11	0.06	2.0
Cyclophosphamide				
6.25	200	43	0.22	20.0
12.5	25	22	0.88	40.0
t-Butylhydroquinone				
100.5	100	79	0.79	36.0*
150.0	20	53	2.65	75.0*
200.0	10	36	3.60	80.0*
				P<0.001
Trial 2				
Harvest time: 20.0 hours[c]				
Summary: Positive				
Dimethylsufoxide				
	100	3	0.03	2.0
Cyclophosphamide				
6.25	100	22	0.22	18.0
12.5	25	20	0.80	48.0
t-Butylhydroquinone				
149.4	25	22	0.88	44.0*
199.2	10	31	3.10	90.0*
249.0	10	39	3.90	90.0*
300.0	0			
				P<0.001

* Positive (P<0.05)
[a] Study performed at Litton Bionetics, Inc. The detailed protocol is presented in Galloway *et al.* (1987). Abs=aberrations.
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose
[c] Because significant chemical-induced cell cycle delay was anticipated, incubation time prior to addition of Colcemid® was lengthened to ensure sufficient metaphases for analysis.

TABLE E4
Frequency of Micronuclei in Bone Marrow Cells of Male Mice Treated with *t*-Butylhydroquinone by Intraperitoneal Injection[a]

Dose (mg/kg)	Number of Mice	Micronucleated PCEs/1,000 Cells[b]
Cyclophosphamide[c]		
25.00	5	17.6 ± 1.46
t-Butylhydroquinone		
0.00	5	0.8 ± 0.44
9.38	4	0.9 ± 0.43
18.75	5	1.7 ± 0.46
37.50	5	1.3 ± 0.41
75.00	5	1.0 ± 0.45
150.00	5	1.4 ± 0.19
300.00	1	1.0
		P=0.367[d]

[a] Study performed at Environmental Health Research and Testing, Inc. 0 mg/kg is the solvent (corn oil) control. Frequency of micronuclei was measured in 2,000 polychromatic erythrocytes (PCEs) per mouse.
[b] Data presented as mean ± standard error
[c] Positive control
[d] Trend test

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

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

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
n	10	10	10	10
Male				
Necropsy body wt	340 ± 7	339 ± 3	313 ± 7**	284 ± 6**
Heart				
Absolute	0.957 ± 0.019	0.940 ± 0.019	0.876 ± 0.017**	0.806 ± 0.016**
Relative	2.82 ± 0.04	2.77 ± 0.04	2.80 ± 0.04	2.84 ± 0.03
R. Kidney				
Absolute	1.181 ± 0.034	1.252 ± 0.019	1.205 ± 0.029	1.145 ± 0.024
Relative	3.47 ± 0.06	3.70 ± 0.06**	3.85 ± 0.05**	4.04 ± 0.04**
Liver				
Absolute	11.950 ± 0.327	14.411 ± 0.229**	12.670 ± 0.441	12.557 ± 0.338
Relative	35.16 ± 0.67	42.52 ± 0.49**	40.42 ± 0.80**	44.23 ± 0.62**
Lung				
Absolute	1.567 ± 0.060	1.274 ± 0.020**	1.246 ± 0.021**	1.212 ± 0.013**
Relative	4.62 ± 0.18	3.76 ± 0.06**	3.99 ± 0.07**	4.29 ± 0.10
R. Testis				
Absolute	1.399 ± 0.030	1.471 ± 0.017	1.407 ± 0.016	1.392 ± 0.017
Relative	4.12 ± 0.05	4.34 ± 0.04*	4.51 ± 0.08**	4.92 ± 0.09**
Thymus				
Absolute	0.263 ± 0.015	0.286 ± 0.009	0.276 ± 0.018	0.251 ± 0.012
Relative	0.78 ± 0.05	0.85 ± 0.03	0.88 ± 0.05	0.88 ± 0.04
Female				
Necropsy body wt	201 ± 5	199 ± 3	184 ± 2**	173 ± 3**
Heart				
Absolute	0.631 ± 0.013	0.619 ± 0.013	0.585 ± 0.014*	0.575 ± 0.011**
Relative	3.14 ± 0.06	3.11 ± 0.04	3.18 ± 0.05	3.33 ± 0.05*
R. Kidney				
Absolute	0.726 ± 0.014	0.717 ± 0.013	0.689 ± 0.012	0.675 ± 0.016*
Relative	3.61 ± 0.04	3.61 ± 0.05	3.75 ± 0.06	3.91 ± 0.07**
Liver				
Absolute	6.358 ± 0.210	6.781 ± 0.160	6.256 ± 0.096	6.743 ± 0.198
Relative	31.53 ± 0.50	34.12 ± 0.64*	34.10 ± 0.54*	39.08 ± 1.01**
Lung				
Absolute	1.033 ± 0.028	0.988 ± 0.015	0.988 ± 0.037	0.929 ± 0.017**
Relative	5.14 ± 0.12	4.98 ± 0.10	5.37 ± 0.17	5.39 ± 0.09
Thymus				
Absolute	0.260 ± 0.016	0.271 ± 0.008	0.259 ± 0.009	0.245 ± 0.006
Relative	1.29 ± 0.07	1.36 ± 0.04	1.41 ± 0.05	1.42 ± 0.04

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[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).

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the Long-Term Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
n	10	10	10	10
Male				
Necropsy body wt	355 ± 7	348 ± 4	338 ± 7	341 ± 6
R. Epididymis				
Absolute	0.472 ± 0.020	0.492 ± 0.016	0.474 ± 0.018	0.479 ± 0.014
Relative	1.33 ± 0.07	1.41 ± 0.05	1.40 ± 0.04	1.41 ± 0.04
R. Kidney				
Absolute	1.389 ± 0.038	1.351 ± 0.032	1.396 ± 0.038	1.385 ± 0.052
Relative	3.91 ± 0.06	3.88 ± 0.10	4.14 ± 0.08	4.06 ± 0.10
Liver				
Absolute	13.467 ± 0.435	13.527 ± 0.388	14.531 ± 0.572	14.420 ± 0.451
Relative	37.88 ± 0.62	38.90 ± 1.17	42.95 ± 1.15**	42.26 ± 0.86**
R. Testis				
Absolute	1.489 ± 0.022	1.463 ± 0.022	1.453 ± 0.031	1.485 ± 0.022
Relative	4.21 ± 0.11	4.21 ± 0.09	4.31 ± 0.06	4.36 ± 0.07
Female				
Necropsy body wt	199 ± 2	191 ± 2**	192 ± 3**	181 ± 2**
R. Kidney				
Absolute	0.749 ± 0.013	0.729 ± 0.012	0.728 ± 0.017	0.675 ± 0.015**
Relative	3.76 ± 0.07	3.82 ± 0.07	3.80 ± 0.05	3.73 ± 0.07
Liver				
Absolute	6.310 ± 0.150	6.625 ± 0.170	6.593 ± 0.162	6.255 ± 0.096
Relative	31.70 ± 0.80	34.67 ± 0.76**	34.40 ± 0.65*	34.61 ± 0.37*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[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).

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

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male						
n	10	9	9	10	9	8
Necropsy body wt	34.1 ± 0.7	31.9 ± 0.7*	32.3 ± 0.4*	30.1 ± 0.4**	27.6 ± 0.6**	23.7 ± 0.4**
Heart						
Absolute	0.143 ± 0.003	0.147 ± 0.005	0.151 ± 0.004	0.134 ± 0.003	0.127 ± 0.003**	0.113 ± 0.003**
Relative	4.20 ± 0.07	4.60 ± 0.15*	4.67 ± 0.07*	4.46 ± 0.10*	4.60 ± 0.14*	4.75 ± 0.10**
R. Kidney						
Absolute	0.286 ± 0.006	0.298 ± 0.007	0.310 ± 0.006	0.268 ± 0.007	0.236 ± 0.005**	0.195 ± 0.007**
Relative	8.41 ± 0.16	9.34 ± 0.18**	9.58 ± 0.15**	8.91 ± 0.16	8.54 ± 0.16	8.22 ± 0.18
Liver						
Absolute	1.334 ± 0.040	1.448 ± 0.033	1.559 ± 0.032**	1.313 ± 0.036	1.326 ± 0.057	1.318 ± 0.033
Relative	39.24 ± 1.19	45.45 ± 0.92**	48.19 ± 0.80**	43.68 ± 1.01**	47.89 ± 1.40**	55.59 ± 0.90**
Lung						
Absolute	0.180 ± 0.005[b]	0.177 ± 0.005	0.174 ± 0.005	0.175 ± 0.003	0.179 ± 0.008[c]	0.168 ± 0.007
Relative	5.27 ± 0.20[b]	5.55 ± 0.16	5.39 ± 0.12	5.84 ± 0.15*	6.48 ± 0.20**[c]	7.07 ± 0.27**
R. Testis						
Absolute	0.117 ± 0.002	0.119 ± 0.003	0.121 ± 0.001	0.115 ± 0.002	0.112 ± 0.003	0.105 ± 0.004**
Relative	3.44 ± 0.07	3.74 ± 0.07*	3.74 ± 0.04*	3.83 ± 0.06**	4.08 ± 0.09**	4.44 ± 0.17**
Thymus						
Absolute	0.038 ± 0.003	0.039 ± 0.004	0.034 ± 0.002[c]	0.030 ± 0.001*	0.031 ± 0.001*[c]	0.028 ± 0.003*
Relative	1.12 ± 0.08	1.22 ± 0.12	1.06 ± 0.05[c]	1.00 ± 0.06	1.12 ± 0.04[c]	1.17 ± 0.13
Female						
n	9	9	10	8	10	9
Necropsy body wt	30.7 ± 0.7	28.5 ± 1.0*	28.6 ± 0.7*	24.1 ± 0.4**	22.1 ± 0.4**	20.3 ± 0.5**
Heart						
Absolute	0.128 ± 0.004	0.126 ± 0.004	0.129 ± 0.003	0.115 ± 0.003*	0.105 ± 0.002**	0.103 ± 0.003**
Relative	4.17 ± 0.16	4.43 ± 0.16	4.53 ± 0.11	4.78 ± 0.11**	4.77 ± 0.11**	5.10 ± 0.12**
R. Kidney						
Absolute	0.218 ± 0.006	0.211 ± 0.006	0.212 ± 0.005	0.185 ± 0.005**	0.170 ± 0.005**	0.160 ± 0.004**
Relative	7.11 ± 0.26	7.44 ± 0.24	7.44 ± 0.18	7.69 ± 0.18	7.70 ± 0.14	7.91 ± 0.22*
Liver						
Absolute	1.203 ± 0.030	1.249 ± 0.038	1.293 ± 0.025	1.030 ± 0.027**	1.051 ± 0.039**	1.237 ± 0.032
Relative	39.22 ± 0.96	43.90 ± 1.00**	45.43 ± 1.06**	42.75 ± 0.54**	47.52 ± 0.93**	61.14 ± 1.73**
Lung						
Absolute	0.170 ± 0.008	0.166 ± 0.006	0.163 ± 0.006	0.169 ± 0.005	0.164 ± 0.005	0.150 ± 0.004
Relative	5.56 ± 0.32	5.82 ± 0.15	5.73 ± 0.25	7.02 ± 0.24**	7.42 ± 0.16**	7.41 ± 0.19**
Thymus						
Absolute	0.045 ± 0.002	0.048 ± 0.002[c]	0.044 ± 0.002	0.046 ± 0.002	0.037 ± 0.002*	0.028 ± 0.004**
Relative	1.49 ± 0.08	1.68 ± 0.05[c]	1.53 ± 0.07	1.92 ± 0.09*	1.65 ± 0.06	1.34 ± 0.16

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] n=8

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
n	10	10	9	9
Necropsy body wt	49.1 ± 1.0	50.3 ± 1.2	49.4 ± 1.0	45.4 ± 1.5
R. Epididymis				
Absolute	0.051 ± 0.002	0.052 ± 0.003	0.050 ± 0.002	0.048 ± 0.002
Relative	1.05 ± 0.05	1.04 ± 0.06	1.02 ± 0.03	1.06 ± 0.03
R. Kidney				
Absolute	0.422 ± 0.014	0.441 ± 0.022	0.439 ± 0.019	0.420 ± 0.018[b]
Relative	8.58 ± 0.14	8.76 ± 0.33	8.87 ± 0.21	9.29 ± 0.23[b]
Liver				
Absolute	2.042 ± 0.108[c]	2.257 ± 0.176	2.258 ± 0.155	2.401 ± 0.434
Relative	41.57 ± 1.39[c]	45.04 ± 3.74	45.42 ± 2.13	55.62 ± 13.39
R. Testis				
Absolute	0.118 ± 0.002	0.114 ± 0.002	0.116 ± 0.003	0.115 ± 0.004
Relative	2.42 ± 0.05	2.28 ± 0.06	2.36 ± 0.04	2.55 ± 0.09
Female				
n	9	8	9	6
Necropsy body wt	53.5 ± 1.8	53.6 ± 3.7	51.9 ± 1.8	44.8 ± 2.0
R. Kidney				
Absolute	0.279 ± 0.011	0.298 ± 0.014	0.287 ± 0.013	0.272 ± 0.009
Relative	5.24 ± 0.24	5.67 ± 0.33	5.53 ± 0.19	6.12 ± 0.37
Liver				
Absolute	1.696 ± 0.054	1.918 ± 0.153	1.820 ± 0.047	1.775 ± 0.029
Relative	31.73 ± 0.67	36.11 ± 2.20	35.26 ± 1.03	39.88 ± 1.46**

** Significantly different ($P \leq 0.01$) from the control group by Williams' test
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=8
[c] n=9

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)				
Day 5	41.1 ± 0.5	40.6 ± 0.5	41.5 ± 0.6	41.3 ± 0.4
Week 3	45.0 ± 0.7	44.6 ± 0.4	44.7 ± 0.8	42.4 ± 0.4**
Week 13	44.7 ± 1.0	45.0 ± 0.4	44.0 ± 0.8	44.6 ± 0.3
Hemoglobin (g/dL)				
Day 5	14.1 ± 0.2	14.0 ± 0.1	14.3 ± 0.2	14.2 ± 0.1
Week 3	15.2 ± 0.2	15.1 ± 0.1	15.0 ± 0.3	14.1 ± 0.1**
Week 13	15.3 ± 0.3	15.3 ± 0.2	14.9 ± 0.3	15.2 ± 0.1
Erythrocytes ($10^6/\mu L$)				
Day 5	7.15 ± 0.10	7.15 ± 0.08	7.35 ± 0.10	7.40 ± 0.07
Week 3	7.79 ± 0.12	7.77 ± 0.05	7.76 ± 0.16	7.34 ± 0.07**
Week 13	8.96 ± 0.20	9.04 ± 0.09	8.80 ± 0.16	8.87 ± 0.05
Reticulocytes ($10^6/\mu L$)				
Day 5	0.33 ± 0.04	0.44 ± 0.04	0.46 ± 0.05	0.44 ± 0.04
Week 3	0.21 ± 0.03	0.24 ± 0.03	0.28 ± 0.03	0.29 ± 0.03
Week 13	0.18 ± 0.02	0.19 ± 0.01	0.17 ± 0.03	0.17 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)				
Day 5	0.14 ± 0.04	0.09 ± 0.02	0.14 ± 0.03	0.11 ± 0.03
Week 3	0.12 ± 0.03	0.11 ± 0.03	0.17 ± 0.05	0.10 ± 0.03
Week 13	0.02 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.02 ± 0.01
Mean cell volume (fL)				
Day 5	57.5 ± 0.3	56.8 ± 0.2	56.4 ± 0.3**	55.9 ± 0.1**
Week 3	57.9 ± 0.4	57.3 ± 0.3	57.8 ± 0.4	57.7 ± 0.5
Week 13	50.0 ± 0.2	49.8 ± 0.3	50.1 ± 0.2	50.0 ± 0.2
Mean cell hemoglobin (pg)				
Day 5	19.7 ± 0.1	19.5 ± 0.1	19.5 ± 0.1*	19.2 ± 0.1**
Week 3	19.5 ± 0.2	19.4 ± 0.1	19.4 ± 0.1	19.3 ± 0.2
Week 13	17.1 ± 0.1	16.9 ± 0.1	16.9 ± 0.1	17.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)				
Day 5	34.4 ± 0.1	34.4 ± 0.2	34.4 ± 0.2	34.3 ± 0.1
Week 3	33.8 ± 0.4	33.8 ± 0.2	33.6 ± 0.2	33.4 ± 0.3
Week 13	34.2 ± 0.1	34.0 ± 0.1	33.8 ± 0.2	34.1 ± 0.1
Platelets ($10^3/\mu L$)				
Day 5	962.9 ± 9.6	938.6 ± 24.6	903.7 ± 26.1*	944.7 ± 16.2
Week 3	844.8 ± 38.0	828.9 ± 11.5	830.3 ± 17.0	909.7 ± 15.6**
Week 13	676.9 ± 23.2	655.7 ± 23.0	745.9 ± 54.6	688.1 ± 9.8
Leukocytes ($10^3/\mu L$)				
Day 5	9.02 ± 0.26	8.37 ± 0.31	8.58 ± 0.32	7.81 ± 0.36*
Week 3	9.03 ± 0.26	9.01 ± 0.11	8.84 ± 0.21	8.30 ± 0.28
Week 13	8.94 ± 0.45	8.96 ± 0.53	8.50 ± 0.63	9.44 ± 0.51
Segmented neutrophils ($10^3/\mu L$)				
Day 5	0.90 ± 0.06	0.87 ± 0.10	1.01 ± 0.11	0.80 ± 0.10
Week 3	1.06 ± 0.11	0.80 ± 0.09	0.96 ± 0.15	0.90 ± 0.07
Week 13	1.30 ± 0.17	1.11 ± 0.09	0.92 ± 0.13	1.38 ± 0.17
Lymphocytes ($10^3/\mu L$)				
Day 5	7.90 ± 0.32	7.36 ± 0.30	7.39 ± 0.37	6.89 ± 0.29
Week 3	7.76 ± 0.24	8.12 ± 0.12	7.69 ± 0.21	7.29 ± 0.30
Week 13	7.52 ± 0.36	7.72 ± 0.44	7.48 ± 0.58	7.95 ± 0.44
Monocytes ($10^3/\mu L$)				
Day 5	0.16 ± 0.05	0.10 ± 0.03	0.11 ± 0.02	0.08 ± 0.05
Week 3	0.15 ± 0.07	0.06 ± 0.02	0.09 ± 0.05	0.04 ± 0.02
Week 13	0.04 ± 0.02	0.02 ± 0.01	0.01 ± 0.01	0.00 ± 0.00

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male (continued)				
n	10	10	10	10
Hematology (continued)				
Eosinophils ($10^3/\mu L$)				
Day 5	0.03 ± 0.02	0.04 ± 0.03	0.05 ± 0.02	0.04 ± 0.02
Week 3	0.04 ± 0.02	0.02 ± 0.01	0.09 ± 0.02	0.07 ± 0.03
Week 13	0.10 ± 0.03	0.11 ± 0.05	0.10 ± 0.02	0.11 ± 0.04
Thromboplastin time (seconds)				
Week 13	10.63 ± 0.40[b]	10.29 ± 0.30[c]	10.96 ± 0.28[c]	10.21 ± 0.36[d]
Activated partial thromboplastin time (seconds)				
Week 13	19.95 ± 1.43[b]	19.40 ± 1.28[b]	18.29 ± 0.68[c]	19.84 ± 1.09[d]
Clinical Chemistry				
Blood urea nitrogen (mg/dL)				
Day 5	23.5 ± 0.7	22.8 ± 0.3	22.0 ± 0.4	21.9 ± 0.5
Week 3	21.1 ± 0.8	25.2 ± 0.6**	25.3 ± 0.7**	24.9 ± 0.6**
Week 13	22.9 ± 0.4	22.1 ± 0.6	22.2 ± 0.5	22.9 ± 0.3
Creatinine (mg/dL)				
Day 5	0.51 ± 0.02	0.48 ± 0.01	0.50 ± 0.03[d]	0.46 ± 0.02[b]
Week 3	0.58 ± 0.02	0.56 ± 0.03	0.58 ± 0.02	0.55 ± 0.01
Week 13	0.64 ± 0.02	0.63 ± 0.02	0.68 ± 0.02	0.67 ± 0.02
Total protein (g/dL)				
Day 5	6.3 ± 0.1	6.0 ± 0.1*	6.1 ± 0.1*	5.6 ± 0.1**
Week 3	6.3 ± 0.1	6.4 ± 0.1	6.4 ± 0.1	6.4 ± 0.1
Week 13	7.3 ± 0.1	7.3 ± 0.1	7.4 ± 0.1	7.5 ± 0.1
Albumin (g/dL)				
Day 5	3.7 ± 0.1	3.6 ± 0.1	3.5 ± 0.0	3.3 ± 0.1**
Week 3	3.7 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.8 ± 0.1
Week 13	4.0 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.3 ± 0.1*
Alanine aminotransferase (IU/L)				
Week 3	43 ± 1	48 ± 1*	48 ± 1*	48 ± 2*
Week 13	51 ± 2	63 ± 4*	44 ± 1	51 ± 1
Alkaline phosphatase (IU/L)				
Day 5	662 ± 17	603 ± 12	626 ± 20	611 ± 24
Week 3	498 ± 9	494 ± 8	504 ± 12	496 ± 9
Week 13	258 ± 9	243 ± 9	244 ± 3	253 ± 5
Creatine kinase (IU/L)				
Day 5	722 ± 98	635 ± 55	781 ± 50	800 ± 47
Week 3	973 ± 79	996 ± 108	925 ± 48	1,054 ± 100
Week 13	376 ± 47	492 ± 97	399 ± 44	428 ± 39
Sorbitol dehydrogenase (IU/L)				
Day 5	7 ± 0	8 ± 0	8 ± 0*	8 ± 0**
Week 3	9 ± 1	9 ± 1	10 ± 1	10 ± 0
Week 13	11 ± 1	12 ± 1	12 ± 1	10 ± 1
Bile acids (μmol/L)				
Day 5	21.6 ± 5.6[c]	19.2 ± 3.0[b]	43.7 ± 1.9**[b]	74.8 ± 10.6**[c]
Week 3	28.9 ± 2.8	30.8 ± 3.0	46.5 ± 5.1**	46.2 ± 4.1**
Week 13	22.1 ± 3.6	21.7 ± 2.3	31.4 ± 3.7*	42.0 ± 2.2**

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)				
Day 5	42.2 ± 0.5	42.0 ± 0.6	42.0 ± 0.4	42.3 ± 0.4
Week 3	46.2 ± 0.5	46.3 ± 0.6	45.5 ± 0.5	45.8 ± 0.5
Week 13	43.8 ± 0.4	43.4 ± 0.4	43.6 ± 0.3	42.7 ± 0.5[f]
Hemoglobin (g/dL)				
Day 5	14.7 ± 0.1	14.5 ± 0.2	14.3 ± 0.2	14.7 ± 0.1
Week 3	15.3 ± 0.2	15.3 ± 0.2	15.3 ± 0.2	15.2 ± 0.2
Week 13	14.6 ± 0.1	14.3 ± 0.1	14.4 ± 0.1	14.1 ± 0.2[f]
Erythrocytes ($10^6/\mu L$)				
Day 5	7.45 ± 0.10	7.42 ± 0.10	7.54 ± 0.07	7.68 ± 0.09
Week 3	7.78 ± 0.11	7.78 ± 0.08	7.73 ± 0.09	7.85 ± 0.08
Week 13	8.28 ± 0.06	8.16 ± 0.07	8.22 ± 0.07	8.03 ± 0.11[f]
Reticulocytes ($10^6/\mu L$)				
Day 5	0.30 ± 0.03	0.33 ± 0.02	0.28 ± 0.04	0.27 ± 0.03
Week 3	0.26 ± 0.03	0.26 ± 0.02	0.25 ± 0.03	0.21 ± 0.02
Week 13	0.19 ± 0.02	0.22 ± 0.03	0.23 ± 0.03	0.20 ± 0.03[f]
Nucleated erythrocytes ($10^3/\mu L$)				
Day 5	0.12 ± 0.05	0.07 ± 0.03	0.06 ± 0.03	0.07 ± 0.03
Week 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 13	0.04 ± 0.02	0.03 ± 0.02	0.06 ± 0.02	0.04 ± 0.04[f]
Mean cell volume (fL)				
Day 5	56.7 ± 0.3	56.6 ± 0.2	55.8 ± 0.3*	55.2 ± 0.1**
Week 3	59.4 ± 0.2	59.5 ± 0.3	58.9 ± 0.2	58.4 ± 0.3*
Week 13	52.9 ± 0.2	53.3 ± 0.2	53.1 ± 0.2	53.0 ± 0.2[f]
Mean cell hemoglobin (pg)				
Day 5	19.7 ± 0.1	19.6 ± 0.1	19.0 ± 0.3**	19.1 ± 0.1**
Week 3	19.7 ± 0.1	19.7 ± 0.1	19.8 ± 0.1	19.3 ± 0.2
Week 13	17.6 ± 0.1	17.6 ± 0.1	17.5 ± 0.1	17.6 ± 0.1[f]
Mean cell hemoglobin concentration (g/dL)				
Day 5	34.8 ± 0.1	34.7 ± 0.2	34.1 ± 0.5	34.7 ± 0.2
Week 3	33.1 ± 0.1	33.2 ± 0.2	33.6 ± 0.2	33.2 ± 0.2
Week 13	33.3 ± 0.2	33.0 ± 0.1	33.0 ± 0.2	33.1 ± 0.2[f]
Platelets ($10^3/\mu L$)				
Day 5	1,036.3 ± 44.7	1,009.3 ± 44.6	945.7 ± 44.5	923.4 ± 40.6
Week 3	901.6 ± 25.5	959.0 ± 38.5	962.2 ± 39.1	885.0 ± 31.4
Week 13	700.8 ± 5.8	737.4 ± 6.3	715.9 ± 23.1	744.2 ± 18.9[f]
Leukocytes ($10^3/\mu L$)				
Day 5	8.10 ± 0.28	8.45 ± 0.36	8.89 ± 0.29	7.84 ± 0.35
Week 3	8.02 ± 0.53	9.09 ± 0.23	8.81 ± 0.26	8.62 ± 0.48
Week 13	7.53 ± 0.60	7.09 ± 0.28	7.86 ± 0.32	8.34 ± 0.47[f]
Segmented neutrophils ($10^3/\mu L$)				
Day 5	0.71 ± 0.09	0.78 ± 0.07	0.77 ± 0.10	0.89 ± 0.09
Week 3	1.20 ± 0.12	1.10 ± 0.15	0.93 ± 0.11	0.89 ± 0.08
Week 13	1.36 ± 0.24	1.26 ± 0.14	1.23 ± 0.13	1.12 ± 0.11[f]
Lymphocytes ($10^3/\mu L$)				
Day 5	7.25 ± 0.26	7.56 ± 0.36	7.92 ± 0.27	6.80 ± 0.30
Week 3	6.33 ± 0.40	7.60 ± 0.25	7.48 ± 0.31	7.30 ± 0.41
Week 13	6.09 ± 0.42	5.71 ± 0.31	6.50 ± 0.26	7.03 ± 0.43[f]
Monocytes ($10^3/\mu L$)				
Day 5	0.10 ± 0.03	0.07 ± 0.02	0.07 ± 0.04	0.10 ± 0.04
Week 3	0.43 ± 0.10	0.37 ± 0.08	0.34 ± 0.08	0.39 ± 0.06
Week 13	0.05 ± 0.02	0.04 ± 0.02	0.08 ± 0.03	0.10 ± 0.04[f]

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female (continued)				
n	10	10	10	10
Hematology (continued)				
Eosinophils ($10^3/\mu L$)				
Day 5	0.08 ± 0.03	0.05 ± 0.02	0.15 ± 0.03	0.07 ± 0.03
Week 3	0.06 ± 0.02	0.06 ± 0.03	0.07 ± 0.03	0.06 ± 0.03
Week 13	0.05 ± 0.02	0.09 ± 0.02	0.07 ± 0.03	0.11 ± 0.03[f]
Thromboplastin time (seconds)				
Week 13	9.82 ± 0.33	9.83 ± 0.30[f]	10.24 ± 0.38	10.19 ± 0.37
Activated partial thromboplastin time (seconds)				
Week 13	20.13 ± 1.02	21.19 ± 1.61[f]	20.91 ± 0.91	20.12 ± 1.02
Clinical Chemistry				
Blood urea nitrogen (mg/dL)				
Day 5	22.7 ± 0.5	21.0 ± 0.6	21.9 ± 0.6	22.4 ± 0.7
Week 3	22.3 ± 0.8	25.2 ± 0.9*	26.4 ± 0.9**	26.4 ± 0.8**
Week 13	22.5 ± 0.6	23.4 ± 0.6	21.4 ± 0.8	20.0 ± 1.0
Creatinine (mg/dL)				
Day 5	0.54 ± 0.02	0.51 ± 0.02	0.55 ± 0.02	0.57 ± 0.03
Week 3	0.54 ± 0.02	0.51 ± 0.02	0.48 ± 0.02[f]	0.52 ± 0.02
Week 13	0.72 ± 0.01	0.78 ± 0.02*	0.78 ± 0.02	0.79 ± 0.02
Total protein (g/dL)				
Day 5	6.0 ± 0.1	5.8 ± 0.1	5.9 ± 0.1	5.8 ± 0.1
Week 3	6.0 ± 0.1	6.2 ± 0.1*	6.1 ± 0.1	6.2 ± 0.1*
Week 13	7.0 ± 0.1	7.0 ± 0.1	7.2 ± 0.1	7.0 ± 0.1
Albumin (g/dL)				
Day 5	4.0 ± 0.1	3.8 ± 0.1	3.9 ± 0.1	3.8 ± 0.1
Week 3	3.7 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	3.9 ± 0.1*
Week 13	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.2 ± 0.1
Alanine aminotransferase (IU/L)				
Day 5	47 ± 2[d]	49 ± 2	50 ± 3[f]	69 ± 2**[d]
Week 3	36 ± 1	43 ± 1**	39 ± 1*[f]	46 ± 1**[f]
Week 13	47 ± 3	46 ± 1	46 ± 3	45 ± 2
Alkaline phosphatase (IU/L)				
Day 5	598 ± 20	556 ± 12	535 ± 20	603 ± 17
Week 3	439 ± 11	440 ± 12	415 ± 8	460 ± 11
Week 13	254 ± 6	266 ± 9	267 ± 9	257 ± 7
Creatine kinase (IU/L)				
Day 5	1,030 ± 52	1,214 ± 67	1,248 ± 90	1,100 ± 92
Week 3	865 ± 94	802 ± 60	836 ± 132	692 ± 58
Week 13	261 ± 30	245 ± 19	240 ± 26	274 ± 34
Sorbitol dehydrogenase (IU/L)				
Day 5	7 ± 0	7 ± 0	7 ± 0*	8 ± 1**[f]
Week 3	9 ± 0	9 ± 0	8 ± 0	9 ± 0
Week 13	15 ± 1	14 ± 1	13 ± 1	14 ± 1
Bile acids (μmol/L)				
Day 5	18.6 ± 2.0	25.5 ± 2.5*	34.5 ± 3.9**	53.1 ± 3.5**[d]
Week 3	26.5 ± 3.4	31.5 ± 5.9	43.9 ± 5.2*[f]	46.9 ± 5.0**
Week 13	29.8 ± 3.9	38.4 ± 4.0	36.7 ± 4.1	49.4 ± 4.6**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=6 [c] n=7 [d] n=8 [e] n=4 [f] n=9

TABLE G2
Hematology Data for Rats at the 3-Month Interim Evaluation in the Long-Term Feed Study of t-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
n	10	10	10	10
Hematocrit (%)	46.4 ± 0.3	46.9 ± 0.5	46.6 ± 0.9	45.9 ± 0.5
Hemoglobin (g/dL)	15.3 ± 0.1	15.3 ± 0.1	15.2 ± 0.3	15.1 ± 0.1
Erythrocytes ($10^6/\mu L$)	9.03 ± 0.07	9.14 ± 0.07	9.04 ± 0.17	9.00 ± 0.11
Reticulocytes ($10^6/\mu L$)	0.16 ± 0.02	0.17 ± 0.02	0.17 ± 0.02	0.17 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.03	0.01 ± 0.01
Mean cell volume (fL)	51.4 ± 0.3	51.4 ± 0.4	51.6 ± 0.2	51.0 ± 0.3
Mean cell hemoglobin (pg)	16.9 ± 0.1	16.8 ± 0.1	16.8 ± 0.0	16.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.9 ± 0.2	32.6 ± 0.2	32.5 ± 0.1	32.9 ± 0.2
Platelets ($10^3/\mu L$)	797.3 ± 48.7	821.9 ± 12.7	817.1 ± 33.3	759.8 ± 26.3
Leukocytes ($10^3/\mu L$)	10.20 ± 0.84	10.66 ± 0.89	10.89 ± 1.06	10.74 ± 0.94
Segmented neutrophils ($10^3/\mu L$)	2.09 ± 0.22	1.93 ± 0.34	1.62 ± 0.25	1.71 ± 0.17
Lymphocytes ($10^3/\mu L$)	7.80 ± 0.74	8.28 ± 0.59	8.96 ± 0.83	8.64 ± 0.79
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.18 ± 0.05	0.31 ± 0.09	0.24 ± 0.06	0.28 ± 0.08
Eosinophils ($10^3/\mu L$)	0.13 ± 0.03	0.15 ± 0.05	0.06 ± 0.04	0.11 ± 0.03
Female				
n	9	10	10	10
Hematocrit (%)	44.8 ± 0.4	45.4 ± 0.5	44.5 ± 0.4	44.5 ± 0.4
Hemoglobin (g/dL)	15.0 ± 0.2	15.2 ± 0.1	15.1 ± 0.2	15.2 ± 0.1
Erythrocytes ($10^6/\mu L$)	8.41 ± 0.08	8.39 ± 0.06	8.39 ± 0.08	8.42 ± 0.05
Reticulocytes ($10^6/\mu L$)	0.15 ± 0.01	0.14 ± 0.02	0.13 ± 0.03	0.14 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.02	0.05 ± 0.02	0.04 ± 0.01	0.06 ± 0.02
Mean cell volume (fL)	53.3 ± 0.4	54.2 ± 0.7	53.0 ± 0.3	52.9 ± 0.4
Mean cell hemoglobin (pg)	17.8 ± 0.1	18.2 ± 0.1*	18.0 ± 0.1	18.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.3	33.6 ± 0.3	34.0 ± 0.2	34.1 ± 0.3
Platelets ($10^3/\mu L$)	763.8 ± 27.4	823.7 ± 21.4	819.8 ± 26.7	840.7 ± 15.5[b]
Leukocytes ($10^3/\mu L$)	7.35 ± 0.59	6.63 ± 0.59	7.35 ± 0.52	6.72 ± 0.43
Segmented neutrophils ($10^3/\mu L$)	1.15 ± 0.11	1.20 ± 0.24	1.24 ± 0.16	0.90 ± 0.13
Lymphocytes ($10^3/\mu L$)	6.04 ± 0.53	5.18 ± 0.36	5.95 ± 0.38	5.67 ± 0.38
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.12 ± 0.04	0.18 ± 0.03	0.13 ± 0.03	0.10 ± 0.02
Eosinophils ($10^3/\mu L$)	0.06 ± 0.02[c]	0.06 ± 0.02	0.04 ± 0.02	0.04 ± 0.02

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=8

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Study of t-Butylhydroquinone[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male						
n	10	10	10	9	10	10
Hematology						
Hematocrit (%)						
Day 5	45.0 ± 0.7	44.6 ± 0.8	45.9 ± 0.8	46.5 ± 1.0	45.5 ± 0.8	46.5 ± 1.2[c]
Week 3	48.6 ± 0.6	47.4 ± 0.5	47.2 ± 0.6	47.3 ± 0.5[b]	47.3 ± 0.7[c]	50.5 ± 1.3[b]
Week 13	47.7 ± 0.6[c]	47.7 ± 0.5	48.6 ± 0.5	48.3 ± 0.4[d]	47.9 ± 0.6	47.8 ± 0.9
Hemoglobin (g/dL)						
Day 5	15.2 ± 0.2	15.1 ± 0.3	15.1 ± 0.2	15.4 ± 0.3	15.1 ± 0.4	15.6 ± 0.3[c]
Week 3	16.5 ± 0.2	16.1 ± 0.2	16.1 ± 0.1	16.1 ± 0.2[b]	16.3 ± 0.2[c]	17.4 ± 0.5[b]
Week 13	16.0 ± 0.2[c]	15.7 ± 0.4	16.1 ± 0.1[c]	16.0 ± 0.2	16.1 ± 0.2[c]	15.9 ± 0.3[c]
Erythrocytes ($10^6/\mu L$)						
Day 5	9.05 ± 0.15	9.01 ± 0.18	9.22 ± 0.16	9.38 ± 0.20	9.21 ± 0.17	9.39 ± 0.23
Week 3	10.15 ± 0.15	9.92 ± 0.12	9.91 ± 0.12	9.94 ± 0.09[b]	10.08 ± 0.16[c]	10.92 ± 0.29[b]
Week 13	10.07 ± 0.12[c]	10.23 ± 0.12	10.24 ± 0.12[c]	10.16 ± 0.12	10.38 ± 0.12	10.38 ± 0.10[c]
Reticulocytes ($10^6/\mu L$)						
Day 5	0.51 ± 0.08[c]	0.45 ± 0.08	0.62 ± 0.17[b]	0.41 ± 0.08	0.59 ± 0.14[c]	0.68 ± 0.20[b]
Week 3	0.21 ± 0.02[c]	0.26 ± 0.02[c]	0.19 ± 0.01[c]	0.24 ± 0.02[e]	0.31 ± 0.04[c]	0.33 ± 0.04*[b]
Week 13	0.16 ± 0.06[f]	0.22 ± 0.03[g]	0.21 ± 0.02[h]	0.21 ± 0.04[i]	0.25 ± 0.04[e]	0.25 ± 0.03[i]
Mean cell volume (fL)						
Day 5	49.7 ± 0.3	49.6 ± 0.3	49.8 ± 0.4	49.4 ± 0.3	49.3 ± 0.3	49.6 ± 0.2[c]
Week 3	47.8 ± 0.3	47.7 ± 0.2	47.5 ± 0.2	47.4 ± 0.3[b]	47.0 ± 0.3[c]	46.1 ± 0.4**[b]
Week 13	47.4 ± 0.8[c]	46.6 ± 0.4	47.4 ± 0.5[c]	47.7 ± 0.6	46.1 ± 0.4	46.1 ± 0.7[c]
Mean cell hemoglobin (pg)						
Day 5	16.8 ± 0.1	16.7 ± 0.1	16.4 ± 0.1**	16.5 ± 0.1**	16.3 ± 0.1**	16.5 ± 0.1**[c]
Week 3	16.3 ± 0.1	16.3 ± 0.1	16.3 ± 0.1	16.2 ± 0.1[b]	16.2 ± 0.1[c]	15.9 ± 0.1**[b]
Week 13	15.9 ± 0.1[c]	15.3 ± 0.3*	15.7 ± 0.1[c]	15.8 ± 0.1	15.5 ± 0.1**[c]	15.3 ± 0.2**[c]
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.8 ± 0.1	33.7 ± 0.2	32.9 ± 0.2*	33.2 ± 0.2	33.1 ± 0.3	33.2 ± 0.2[b]
Week 3	34.1 ± 0.3	34.1 ± 0.1	34.2 ± 0.3	34.0 ± 0.2[b]	34.5 ± 0.3[c]	34.4 ± 0.1[b]
Week 13	33.5 ± 0.5[c]	32.8 ± 0.6	33.2 ± 0.4[c]	33.2 ± 0.4	33.5 ± 0.4[c]	33.3 ± 0.4[c]
Platelets ($10^3/\mu L$)						
Day 5	1,186 ± 63	1,128 ± 57	1,124 ± 61	1,224 ± 56	1,229 ± 87	1,245 ± 48
Week 3	937 ± 19	901 ± 34	956 ± 34	1,001 ± 19[b]	1,030 ± 47[c]	1,034 ± 20**[b]
Week 13	754 ± 58[c]	796 ± 39	834 ± 42[c]	887 ± 63	931 ± 50*	933 ± 53*[c]
Leukocytes ($10^3/\mu L$)						
Day 5	6.17 ± 0.29	5.75 ± 0.42	5.99 ± 0.33	6.59 ± 0.38	6.56 ± 0.28	7.77 ± 0.62*
Week 3	7.93 ± 0.38	8.36 ± 0.47	7.65 ± 0.60	9.11 ± 0.30*[b]	9.56 ± 0.60*[c]	8.74 ± 0.98[b]
Week 13	6.67 ± 0.61[c]	7.31 ± 0.50	7.71 ± 0.63[c]	9.82 ± 0.70*	8.30 ± 0.52	7.47 ± 0.69[c]
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.61 ± 0.10	0.43 ± 0.12	0.46 ± 0.07	0.71 ± 0.11	0.73 ± 0.11	1.00 ± 0.13
Week 3	1.10 ± 0.14	0.90 ± 0.15	0.91 ± 0.15	1.55 ± 0.14[b]	2.80 ± 0.42**[c]	2.91 ± 0.45**[b]
Week 13	0.94 ± 0.14[e]	0.77 ± 0.17[h]	1.09 ± 0.15[c]	1.51 ± 0.21	1.85 ± 0.44*	2.27 ± 0.41**[c]
Lymphocytes ($10^3/\mu L$)						
Day 5	5.53 ± 0.24	5.27 ± 0.36	5.49 ± 0.31	5.84 ± 0.33	5.77 ± 0.29	6.60 ± 0.56
Week 3	6.71 ± 0.29	7.41 ± 0.48	6.60 ± 0.52	7.45 ± 0.34[b]	6.57 ± 0.33[c]	5.70 ± 0.57[b]
Week 13	5.37 ± 0.67[e]	5.78 ± 0.31[h]	6.49 ± 0.64[c]	8.19 ± 0.55*	6.33 ± 0.18	5.11 ± 0.39[c]
Eosinophils ($10^3/\mu L$)						
Day 5	0.02 ± 0.01	0.05 ± 0.02	0.04 ± 0.02	0.07 ± 0.02	0.03 ± 0.02	0.16 ± 0.04**
Week 3	0.10 ± 0.04	0.07 ± 0.03	0.14 ± 0.03	0.15 ± 0.07[b]	0.18 ± 0.04[c]	0.13 ± 0.04[b]
Week 13	0.04 ± 0.02[e]	0.12 ± 0.03[h]	0.14 ± 0.04[c]	0.16 ± 0.05	0.13 ± 0.04	0.08 ± 0.03[c]
Thromboplastin time (seconds)						
Week 13	8.01 ± 0.18[c]	7.62 ± 0.17[c]	7.97 ± 0.20[e]	8.23 ± 0.31[h]	8.03 ± 0.23[b]	7.97 ± 0.35[e]
Activated partial thromboplastin time (seconds)						
Week 13	25.65 ± 0.25[j]	27.57 ± 1.17[f]	26.15 ± 1.25[j]	—[k]	—	—

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male (continued)						
n	8	10	8	8	9	9
Clinical Chemistry						
Blood urea nitrogen (mg/dL)						
Day 5	30.1 ± 1.1	27.2 ± 1.2	25.5 ± 1.4*	25.2 ± 1.0*	24.2 ± 1.3**	20.9 ± 1.3**^{e}
Week 3	27.1 ± 1.5	28.8 ± 1.5^{c}	25.4 ± 1.6^{d}	21.2 ± 1.0*	17.1 ± 0.7**^{b}	17.0 ± 0.6**^{i}
Week 13	27.5 ± 2.6^{e}	23.6 ± 1.7^{b}	25.1 ± 1.4^{e}	22.9 ± 0.6	19.1 ± 1.2**^{e}	20.3 ± 0.6**
Creatinine (mg/dL)						
Day 5	0.34 ± 0.05^{i}	0.38 ± 0.02^{h}	0.43 ± 0.04^{i}	0.34 ± 0.04^{g}	0.36 ± 0.02^{i}	0.33 ± 0.03^{f}
Week 3	0.35 ± 0.02^{i}	0.38 ± 0.02^{g}	0.36 ± 0.03^{e}	0.28 ± 0.02^{h}	0.33 ± 0.01^{h}	0.34 ± 0.02^{f}
Total protein (g/dL)						
Day 5	4.9 ± 0.1^{i}	4.9 ± 0.1^{h}	5.1 ± 0.1^{i}	5.1 ± 0.1^{g}	5.0 ± 0.1^{i}	5.2 ± 0.1^{f}
Albumin (g/dL)						
Day 5	2.8 ± 0.1^{g}	2.6 ± 0.1^{h}	2.8 ± 0.1^{g}	2.8 ± 0.1^{f}	2.9 ± 0.1^{i}	3.0 ± 0.1^{f}
Alanine aminotransferase (IU/L)						
Day 5	51 ± 6^{c}	43 ± 9	35 ± 5	29 ± 5**	38 ± 4^{b}	37 ± 6^{d}
Week 3	22 ± 2	24 ± 2^{c}	21 ± 2^{d}	18 ± 2	22 ± 4^{b}	16 ± 2^{h}
Week 13	83 ± 41^{f}	175 ± 93^{g}	111 ± 61^{i}	110 ± 49^{h}	118 ± 45^{i}	124 ± 22^{h}
Alkaline phosphatase (IU/L)						
Day 5	161 ± 6	158 ± 4	154 ± 6	153 ± 6	149 ± 5	139 ± 4^{e}
Week 3	118 ± 4^{g}	122 ± 7^{i}	122 ± 7^{g}	95 ± 2*^{e}	84 ± 6**^{h}	80 ± 6*^{j}
Creatine kinase (IU/L)						
Day 5	292 ± 75	161 ± 47	147 ± 30	141 ± 28	223 ± 53	150 ± 28
Sorbitol dehydrogenase (IU/L)						
Week 3	37 ± 3^{i}	46 ± 6^{h}	36 ± 2^{c}	37 ± 4	34 ± 3^{e}	42 ± 5^{f}
Week 13	30 ± 4^{j}	31 ± 2^{f}	34 ± 3^{j}	42 ± 16^{j}	27 ± 4^{f}	27^{l}
Bile acids (μmol/L)						
Week 3	10.7 ± 1.3^{c}	7.9 ± 0.5*	7.6 ± 0.4*^{d}	7.1 ± 0.6**	7.5 ± 0.7*^{b}	7.0 ± 0.9**^{h}
Week 13	21.2 ± 0.9^{i}	22.3 ± 0.8^{g}	22.0 ± 2.0^{h}	16.7 ± 2.5^{e}	19.8 ± 1.3^{i}	16.2 ± 1.3^{h}
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)						
Day 5	45.2 ± 0.3	44.6 ± 0.5	45.0 ± 0.6	45.7 ± 0.3	45.6 ± 1.2	47.9 ± 0.6**
Week 3	46.2 ± 1.4	49.5 ± 0.9	46.4 ± 0.6	46.9 ± 0.5	48.8 ± 1.5	46.9 ± 0.8^{c}
Week 13	47.4 ± 0.4	47.4 ± 0.4	48.0 ± 0.4	48.9 ± 1.4^{c}	47.4 ± 0.4	48.5 ± 1.0^{c}
Hemoglobin (g/dL)						
Day 5	15.0 ± 0.1	14.9 ± 0.2	15.1 ± 0.2	15.3 ± 0.1	15.4 ± 0.4	16.2 ± 0.2**
Week 3	15.6 ± 0.4	16.6 ± 0.3	15.7 ± 0.2	15.9 ± 0.2	16.9 ± 0.5^{c}	16.2 ± 0.2^{c}
Week 13	15.7 ± 0.2	15.6 ± 0.2	15.9 ± 0.1	16.2 ± 0.4^{c}	15.7 ± 0.2	16.3 ± 0.4^{c}
Erythrocytes (10^{6}/μL)						
Day 5	9.14 ± 0.12	9.04 ± 0.13	9.24 ± 0.15	9.51 ± 0.09*	9.55 ± 0.26	10.20 ± 0.16**
Week 3	9.40 ± 0.27	10.15 ± 0.17**	9.63 ± 0.09	9.98 ± 0.08*	10.60 ± 0.31**	10.29 ± 0.15**^{c}
Week 13	9.99 ± 0.11	10.07 ± 0.08	10.18 ± 0.09	10.50 ± 0.32^{c}	10.17 ± 0.07	10.58 ± 0.27^{c}
Reticulocytes (10^{6}/μL)						
Day 5	0.44 ± 0.05^{b}	0.42 ± 0.04^{c}	0.31 ± 0.04^{e}	0.42 ± 0.08	0.27 ± 0.04*	0.22 ± 0.04**
Week 3	0.14 ± 0.03^{h}	0.13 ± 0.02^{i}	0.15 ± 0.02^{h}	0.17 ± 0.03^{b}	0.24 ± 0.03^{i}	0.24 ± 0.04^{e}
Week 13	0.20 ± 0.02	0.19 ± 0.02^{b}	0.18 ± 0.02	0.21 ± 0.03^{c}	0.28 ± 0.03*	0.29 ± 0.04*^{b}

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Study of t-Butylhydroquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Female (continued)						
n	10	10	10	10	10	10
Hematology (continued)						
Mean cell volume (fL)						
Day 5	49.6 ± 0.5	49.4 ± 0.3	48.8 ± 0.4	48.0 ± 0.3*	47.7 ± 0.2**	47.2 ± 0.4**
Week 3	48.9 ± 0.2	48.9 ± 0.4	48.3 ± 0.3	47.0 ± 0.2**	45.9 ± 0.2**	45.6 ± 0.3**[c]
Week 13	47.5 ± 0.2	47.0 ± 0.2	47.1 ± 0.3	46.4 ± 0.2**[c]	46.6 ± 0.3**	46.0 ± 0.3**[c]
Mean cell hemoglobin (pg)						
Day 5	16.4 ± 0.2	16.5 ± 0.1	16.4 ± 0.1	16.1 ± 0.1	16.2 ± 0.1	15.9 ± 0.2
Week 3	16.6 ± 0.1	16.4 ± 0.1	16.3 ± 0.1*	15.9 ± 0.1**	15.7 ± 0.1**[c]	15.8 ± 0.1**[c]
Week 13	15.7 ± 0.1	15.5 ± 0.1	15.7 ± 0.1	15.4 ± 0.1[c]	15.5 ± 0.1	15.4 ± 0.1[c]
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.1 ± 0.2	33.4 ± 0.1	33.6 ± 0.2	33.5 ± 0.2	33.8 ± 0.2**	33.9 ± 0.2**
Week 3	33.9 ± 0.3	33.6 ± 0.2	33.8 ± 0.2	33.9 ± 0.3	34.2 ± 0.2[c]	34.6 ± 0.3[c]
Week 13	33.1 ± 0.2	32.9 ± 0.1	33.2 ± 0.2	33.1 ± 0.1[c]	33.2 ± 0.2	33.6 ± 0.2*[c]
Platelets ($10^3/\mu L$)						
Day 5	901.5 ± 21.6	900.0 ± 19.3	820.5 ± 38.6	915.0 ± 28.6	913.3 ± 34.3	914.5 ± 41.9
Week 3	788.8 ± 33.8	882.3 ± 29.6	814.6 ± 27.8[c]	938.9 ± 41.5**	1,040.8 ± 34.0**	1,158.2 ± 63.7**[c]
Week 13	853.4 ± 23.1	880.2 ± 42.5	867.9 ± 35.6	1,005.6 ± 31.0**[c]	966.7 ± 26.6**	1,141.9 ± 46.6**[c]
Leukocytes ($10^3/\mu L$)						
Day 5	6.91 ± 0.50	6.60 ± 0.45	6.44 ± 0.36	7.00 ± 0.50	6.85 ± 0.56	7.92 ± 0.70
Week 3	7.49 ± 0.37	7.85 ± 0.66	8.08 ± 0.39	8.23 ± 0.37	9.67 ± 1.01	10.64 ± 0.55**[c]
Week 13	5.67 ± 0.30	6.46 ± 0.41	5.66 ± 0.42	8.69 ± 0.65**[c]	8.88 ± 0.79**	8.11 ± 0.78**[c]
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.65 ± 0.10	0.65 ± 0.10	0.49 ± 0.06	0.83 ± 0.10	0.97 ± 0.24	2.12 ± 0.48**
Week 3	0.98 ± 0.17	1.11 ± 0.07	1.19 ± 0.14	1.61 ± 0.21**	1.76 ± 0.23**	3.78 ± 0.28**[c]
Week 13	0.82 ± 0.11	1.13 ± 0.13	0.87 ± 0.12	2.31 ± 0.56**[c]	2.14 ± 0.23**	2.74 ± 0.52**[c]
Lymphocytes ($10^3/\mu L$)						
Day 5	6.13 ± 0.47	5.92 ± 0.44	5.85 ± 0.32	6.06 ± 0.43	5.77 ± 0.44	5.72 ± 0.82
Week 3	6.32 ± 0.22	6.59 ± 0.62	6.59 ± 0.32	6.51 ± 0.20	7.77 ± 0.82	6.66 ± 0.52[c]
Week 13	4.78 ± 0.23	5.28 ± 0.37	4.72 ± 0.36	6.28 ± 0.30*[c]	6.63 ± 0.63*	5.20 ± 0.51[c]
Monocytes ($10^3/\mu L$)						
Week 13	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01[c]	0.02 ± 0.01	0.02 ± 0.02[c]
Eosinophils ($10^3/\mu L$)						
Day 5	0.11 ± 0.04	0.06 ± 0.02	0.09 ± 0.01	0.12 ± 0.04	0.08 ± 0.02	0.12 ± 0.04
Week 3	0.18 ± 0.06	0.15 ± 0.04	0.32 ± 0.08	0.12 ± 0.04	0.11 ± 0.05	0.19 ± 0.06[c]
Week 13	0.07 ± 0.02	0.07 ± 0.03	0.06 ± 0.02	0.10 ± 0.03[c]	0.08 ± 0.03	0.11 ± 0.05[c]
Thromboplastin time (seconds)						
Week 13	7.85 ± 0.23	7.95 ± 0.19	7.62 ± 0.28	7.60 ± 0.20	7.55 ± 0.18	7.56 ± 0.20[b]
Activated partial thromboplastin time (seconds)						
Week 13	29.34 ± 1.32[e]	27.15 ± 1.23[h]	26.57 ± 1.79[h]	28.00 ± 1.37[i]	28.90 ± 0.82[h]	28.53 ± 1.05[g]

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Study of *t*-Butylhydroquinone (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Female (continued)						
n	10	9	10	8	9	8
Clinical Chemistry						
Blood urea nitrogen (mg/dL)						
Day 5	20.2 ± 1.6[i]	21.5 ± 1.0[b]	20.5 ± 1.2[c]	17.8 ± 1.4[e]	15.5 ± 1.0*[e]	22.5[l]
Week 3	27.9 ± 1.3[e]	22.9 ± 1.3*[b]	23.3 ± 1.3*[b]	21.2 ± 1.8**[d]	16.4 ± 0.7**[e]	15.8 ± 1.6**[g]
Week 13	29.2 ± 1.9	25.1 ± 2.3[b]	28.5 ± 1.9[c]	19.0 ± 1.1**[e]	18.1 ± 0.8**	20.6 ± 2.6**[i]
Creatinine (mg/dL)						
Week 3	0.31 ± 0.03[g]	0.32 ± 0.03[f]	0.29 ± 0.02[h]	0.26 ± 0.02[g]	0.29 ± 0.01[j]	—
Week 13	0.32 ± 0.01[i]	0.34 ± 0.04[i]	0.34 ± 0.03[g]	0.26 ± 0.03[f]	0.24 ± 0.02[g]	0.33 ± 0.03[j]
Total protein (g/dL)						
Week 3	5.3 ± 0.1[f]	—	5.7 ± 0.1[j]	5.0[l]	5.5 ± 0.1[f]	—
Week 13	5.6 ± 0.1[g]	5.7[l]	5.4 ± 0.1[f]	—	5.3 ± 0.1[j]	—
Albumin (g/dL)						
Week 3	3.2 ± 0.0[f]	—	3.5 ± 0.1[j]	3.0[l]	3.4 ± 0.1[j]	—
Week 13	3.5 ± 0.0[e]	3.7 ± 0.2[f]	3.4 ± 0.1[f]	3.5 ± 0.1[j]	3.4 ± 0.2[j]	—
Alanine aminotransferase (IU/L)						
Day 5	28 ± 3[h]	30 ± 5[b]	28 ± 4[c]	33 ± 4[e]	25 ± 2[h]	31 ± 3[f]
Week 3	40 ± 13[e]	29 ± 4	24 ± 4[b]	39 ± 7[d]	34 ± 4[e]	35 ± 7[g]
Week 13	39 ± 6	30 ± 2[e]	40 ± 5[e]	40 ± 7[i]	36 ± 4	53 ± 19[f]
Alkaline phosphatase (IU/L)						
Day 5	229 ± 8[i]	199 ± 9[b]	204 ± 9[c]	210 ± 6[e]	172 ± 11**[e]	156 ± 18**[f]
Week 3	156 ± 7[i]	154 ± 4[i]	155 ± 3[e]	133 ± 7*[h]	111 ± 7**[h]	98 ± 14*[j]
Week 13	92 ± 4[b]	103 ± 5[h]	110 ± 7[f]	102 ± 9[g]	91 ± 5[g]	77[l]
Creatine kinase (IU/L)						
Day 5	160 ± 42	88 ± 16	99 ± 15	152 ± 43	73 ± 6	65 ± 10*
Week 3	32 ± 2[f]	34 ± 8[j]	39 ± 16[g]	38[l]	37 ± 8[g]	42[l]
Week 13	41 ± 6[e]	60 ± 26[g]	38 ± 3[g]	30[l]	35 ± 3[j]	—
Sorbitol dehydrogenase (IU/L)						
Week 3	27 ± 3[h]	23 ± 2[h]	27 ± 4[b]	23 ± 3	25 ± 5[h]	22 ± 3[g]
Week 13	27 ± 1[c]	28 ± 3[e]	26 ± 3[h]	23 ± 2[f]	30 ± 4[e]	32 ± 1[f]
Bile acids (μmol/L)						
Day 5	12.3 ± 0.8[g]	17.2 ± 1.9[i]	11.3 ± 0.3[g]	14.0 ± 1.5[f]	13.0 ± 1.5[g]	18.0[l]
Week 3	9.6 ± 1.1[c]	9.9 ± 1.7[d]	9.3 ± 1.2	12.1 ± 2.2[d]	8.8 ± 0.8	10.5 ± 1.4
Week 13	16.0 ± 1.3[c]	14.9 ± 1.8[b]	17.0 ± 1.6[c]	18.4 ± 1.9[e]	12.5 ± 1.4[d]	13.8 ± 2.9[i]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=9
[d] n=10
[e] n=7
[f] n=3
[g] n=4
[h] n=6
[i] n=5
[j] n=2
[k] Not measured at this exposure level
[l] n=1; no standard error calculated

TABLE G4
Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of t-Butylhydroquinone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
n	10	10	9	9
Hematocrit (%)	45.1 ± 0.4	46.2 ± 0.8	45.3 ± 0.4	46.0 ± 2.2
Hemoglobin (g/dL)	15.0 ± 0.1	15.3 ± 0.2	15.2 ± 0.1	15.1 ± 0.7
Erythrocytes ($10^6/\mu L$)	9.66 ± 0.08	10.08 ± 0.20	9.77 ± 0.12	9.92 ± 0.74
Reticulocytes ($10^6/\mu L$)	0.21 ± 0.01	0.20 ± 0.02	0.20 ± 0.02	0.47 ± 0.15*
Nucleated erythrocytes ($10^3/\mu L$)	0.04 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Mean cell volume (fL)	46.7 ± 0.2	45.9 ± 0.4	46.4 ± 0.2	47.2 ± 1.6
Mean cell hemoglobin (pg)	15.6 ± 0.1	15.2 ± 0.1*	15.6 ± 0.1	15.5 ± 0.4
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.1	33.1 ± 0.2	33.6 ± 0.2	32.9 ± 0.5
Platelets ($10^3/\mu L$)	1,283 ± 57	1,301 ± 75	1,240 ± 65	1,294 ± 94
Leukocytes ($10^3/\mu L$)	7.84 ± 0.38	8.63 ± 0.57	8.77 ± 0.40	8.21 ± 0.46
Segmented neutrophils ($10^3/\mu L$)	1.46 ± 0.16	1.73 ± 0.10	1.63 ± 0.16	1.54 ± 0.14[b]
Lymphocytes ($10^3/\mu L$)	6.13 ± 0.24	6.55 ± 0.59	6.80 ± 0.30	6.03 ± 0.38[b]
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.12 ± 0.03	0.19 ± 0.09	0.21 ± 0.05	0.19 ± 0.05
Eosinophils ($10^3/\mu L$)	0.13 ± 0.03	0.17 ± 0.03	0.13 ± 0.05	0.10 ± 0.04
Female				
n	9	8	9	6
Hematocrit (%)	44.5 ± 0.3	45.0 ± 0.4	44.4 ± 0.5	44.6 ± 0.2
Hemoglobin (g/dL)	14.7 ± 0.1	14.9 ± 0.1	14.7 ± 0.2	14.9 ± 0.1
Erythrocytes ($10^6/\mu L$)	9.78 ± 0.06	9.97 ± 0.10	9.79 ± 0.12	9.97 ± 0.08
Reticulocytes ($10^6/\mu L$)	0.19 ± 0.02	0.24 ± 0.02	0.25 ± 0.03	0.23 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Mean cell volume (fL)	45.5 ± 0.3	45.2 ± 0.4	45.3 ± 0.3	44.8 ± 0.3
Mean cell hemoglobin (pg)	15.1 ± 0.1	15.0 ± 0.1	15.0 ± 0.1	14.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.1 ± 0.1	33.1 ± 0.1	33.1 ± 0.2	33.3 ± 0.2
Platelets ($10^3/\mu L$)	1,165 ± 45	1,242 ± 48	1,249 ± 51	1,288 ± 58
Leukocytes ($10^3/\mu L$)	5.51 ± 0.39	5.78 ± 0.49	7.00 ± 0.45	6.28 ± 0.67
Segmented neutrophils ($10^3/\mu L$)	1.22 ± 0.15	1.03 ± 0.11	1.62 ± 0.15	1.80 ± 0.23
Lymphocytes ($10^3/\mu L$)	4.02 ± 0.27	4.46 ± 0.43	5.03 ± 0.36	4.23 ± 0.43
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.08 ± 0.04	0.11 ± 0.03	0.13 ± 0.05	0.09 ± 0.04
Eosinophils ($10^3/\mu L$)	0.19 ± 0.04	0.17 ± 0.03	0.21 ± 0.05	0.16 ± 0.06

* Significantly different ($P \le 0.05$) from the control group by Dunn's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS, ESTROUS CYCLE CHARACTERIZATION, AND TERATOLOGY

TABLE H1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Feed Study of t-Butylhydroquinone[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male				
n	10	10	10	10
Weights (g)				
Necropsy body wt	340 ± 7	339 ± 3	313 ± 7**	284 ± 6**
L. cauda	0.138 ± 0.004	0.149 ± 0.003*	0.142 ± 0.003	0.139 ± 0.003
L. testis	1.48 ± 0.03	1.58 ± 0.02**	1.49 ± 0.02	1.47 ± 0.01
L. epididymis	0.414 ± 0.008	0.434 ± 0.004*	0.412 ± 0.006	0.410 ± 0.004
Spermatid parameters				
Spermatid heads (10^7/g testis)	12.45 ± 0.68	11.28 ± 0.52	10.02 ± 0.42*	11.57 ± 0.50
Spermatid heads (10^7/testis)	18.35 ± 1.00	17.76 ± 0.72	14.89 ± 0.67*	16.96 ± 0.74
Spermatid count (mean/10^{-4} mL suspension)	917.3 ± 50.1	887.8 ± 36.2	744.3 ± 33.7*	848.0 ± 37.2
Epididymal spermatozoal parameters				
Motility (%)	92.77 ± 0.69	91.87 ± 0.48	92.79 ± 0.39	90.91 ± 0.72
Concentration (10^6/g cauda epididymal tissue)	680.7 ± 42.2	661.0 ± 39.8	632.7 ± 35.7	592.3 ± 28.5
Female				
n	10	10	10	10
Necropsy body wt (g)	201 ± 5	199 ± 3	184 ± 2**	173 ± 3**
Estrous cycle length (days)	5.00 ± 0.007	6.25 ± 0.35**[b]	6.10 ± 0.34*	5.44 ± 0.27[b]
Estrous stage (% of cycle)				
Diestrus	49.2	50.8	43.3	56.7
Proestrus	10.8	8.3	14.2	8.3
Estrus	32.5	32.5	32.5	27.5
Metestrus	7.5	8.3	10.0	7.5

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test (organ and body weights) or Dunn's test (spermatid and epididymal spermatozoal parameters)
** $P \leq 0.01$
[a] Data are presented as mean ± standard error.
[b] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

TABLE H2
Maternal Toxicity in F344/N Rats (F_0) Exposed to *t*-Butylhydroquinone in Feed During the Perinatal Exposure Phase of the 13-Week Study[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Number examined	16	16	16	16	16	16
Number pregnant	9 (56%)	10 (63%)	10 (63%)	11 (69%)	0**	0**
Maternal body weight (g)						
Day 1	141 ± 6	142 ± 6	141 ± 5	141 ± 6	140 ± 5	141 ± 5
Day 7	149 ± 6	152 ± 7	147 ± 5	143 ± 7**	131 ± 4**	114 ± 6**
Day 15	161 ± 8	163 ± 7	158 ± 5	153 ± 8**	141 ± 5**	112 ± 10**
Duration of gestation (days)	22.9 ± 0.3	23.0 ± 0.0	23.0 ± 0.0	23.3 ± 0.5	—	—

** Significantly different (P≤0.01) from the control group
[a] Data are presented as mean ± standard deviation.

TABLE H3
Developmental Toxicity in F344/N Rats (F_1) Following Maternal Exposure to *t*-Butylhydroquinone in Feed During the Perinatal Exposure Phase of the 13-Week Study[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Number of dams/litters examined	9	10	10	11
Pups delivered (total)	68	106	78	92
Pups delivered per litter	7.6 ± 3.6	10.6 ± 1.8	7.8 ± 3.4	8.4 ± 3.1
Pups surviving 4 days (precull) per number of pups delivered	66/68 (97%)	105/106 (99%)	77/78 (99%)	83/92 (90%)**
Pup weight per litter (g) Day 4 (precull)	6.8 ± 0.6	7.0 ± 0.7	6.6 ± 0.7	6.8 ± 0.7[b]
Pups surviving 28 days per number of pups selected on day 4 (postcull)	58/58 (100%)	78/79 (99%)	58/66 (88%)	43/69 (62%)**
Pup weight per litter (g) Day 28	49.2 ± 5.6	50.8 ± 6.3	45.1 ± 4.3[b]	42.0 ± 3.6[c]

** Significantly different (P≤0.01) from the control group
[a] Data are presented as mean ± standard deviation.
[b] n=9
[c] n=6

TABLE H4
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Feed Study of *t*-Butylhydroquinone[a]

	0 ppm	2,500 ppm	10,000 ppm	40,000 ppm
Male				
n	10	9	10	8
Weights (g)				
Necropsy body wt	34.1 ± 0.7	31.9 ± 0.7*	30.1 ± 0.4**	23.7 ± 0.4**
L. cauda	0.013 ± 0.001	0.012 ± 0.001	0.007 ± 0.001**[b]	0.009 ± 0.001**
L. testis	0.114 ± 0.003	0.109 ± 0.003	0.106 ± 0.002	0.101 ± 0.004**
L. epididymis	0.042 ± 0.002	0.038 ± 0.002	0.036 ± 0.001*	0.031 ± 0.001**
Spermatid parameters				
Spermatid heads (10^7/g testis)	22.84 ± 0.58	24.46 ± 0.95[c]	24.88 ± 1.36	25.65 ± 1.28[c]
Spermatid heads (10^7/testis)	2.60 ± 0.10	2.67 ± 0.11[c]	2.63 ± 0.13	2.61 ± 0.17[c]
Spermatid count (mean/10^{-4} mL suspension)	811.8 ± 31.4	833.6 ± 35.0[c]	823.8 ± 41.9	815.0 ± 51.9[c]
Epididymal spermatozoal parameters				
Motility (%)	92.54 ± 0.83	88.71 ± 1.17*	91.25 ± 0.64	89.21 ± 2.83
Concentration (10^6/g cauda epididymal tissue)	1,732 ± 123	2,054 ± 184	2,922 ± 426	1,822 ± 228
Female				
n	10	10	9	9
Necropsy body wt (g)	30.7 ± 0.7[b]	28.5 ± 1.0*[b]	24.1 ± 0.4**[d]	20.3 ± 0.5**
Estrous cycle length (days)	4.25 ± 0.13	4.25 ± 0.13	4.94 ± 0.40	5.80 ± 0.86*[e]
Estrous stage (% of cycle)				
Diestrus	31.7	33.3	27.8	44.4
Proestrus	17.5	15.0	13.9	14.8
Estrus	36.7	41.7	43.5	31.5
Metestrus	14.2	9.2	14.8	9.3
Unclear diagnosis	0.0	0.8	0.0	0.0

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test (organ and body weights) or Dunn's test (spermatid and epididymal spermatozoal parameters)
** $P \leq 0.01$
[a] Data are presented as mean ± standard error.
[b] n=9
[c] n=7
[d] n=8
[e] Estrous cycle was longer than 12 days or unclear in 4 of 9 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

PROCUREMENT AND CHARACTERIZATION OF *t*-BUTYLHYDROQUINONE

t-Butylhydroquinone was obtained in two lots (187-1 and 1089-1) from U.O.P., Inc., (Des Plaines, IL). Lot 187-1 was used in the 13-week, long-term, and 2-year studies. Lot 1089-1 was used in the long-term and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the *t*-butylhydroquinone studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

Each lot of the chemical, a fine beige powder, was identified as *t*-butylhydroquinone by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of *t*-butylhydroquinone (Figures I1 and I2).

The purity of each lot was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). Functional group titration was performed by dissolving samples in methanol, water, and 1 N sulfuric acid. Diphenylamine indicator solution was added to the samples and the samples were titrated with 0.1 N ceric sulfate to a colorimetric endpoint. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) acetone:toluene:chloroform (40:35:25), and 2) toluene:acetone (95:5) with phenol as a reference standard. Plates were examined under visible and ultraviolet light at 254 nm and sprayed with first a 0.4% methanolic solution of 2,6-dichloroquinonechloroimide and then 10% aqueous sodium carbonate. HPLC was performed for lot 187-1 using a Waters Resolve C_{18} column with a solvent system containing water:acetonitrile (90:10) with 1% glacial acetic acid at a flow rate of 1.0 mL/minute, and detection at 280 nm. HPLC was performed for lot 1089-1 using a Waters Resolve C_{18} column with a solvent system containing water:acetonitrile (75:25) with 1% glacial acetic acid for 20 minutes followed by 100% acetonitrile with 1% glacial acetic acid at a flow rate of 1.0 mL/minute, and detection at 280 nm.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for *t*-butylhydroquinone. Karl Fischer water analysis indicated less than 0.4% water for lot 187-1 and 0.16% water for lot 1089-1. Functional group titration indicated a purity of 99.6% $\pm$ 0.5% for lot 187-1 and 99.1% $\pm$ 0.4% for lot 1089-1. TLC of lot 187-1 indicated a major spot and two trace impurities using the first system and a major spot, one minor impurity, and one trace impurity using the second system. For lot 1089-1, both TLC systems indicated a major spot, one minor impurity, and one trace impurity. HPLC of lot 187-1 indicated a major peak and one impurity peak with an approximate area of 0.13% relative to the major peak. HPLC of lot 1089-1 indicated a major peak and no impurities with peak areas greater than 0.1% relative to the major peak. Additional HPLC analyses were performed using a linear gradation in the solvent system, changing it from 90:10 to 0:100 (lot 187-1) or from 75:25 to 0:100 (lot 1089-1) over a 20-minute period. These analyses resolved additional impurities for lots 187-1 and 1089-1 with peak areas of 0.3% to 0.4% relative to the major peak. Lots 1089-1 and 187-1 were concomitantly analyzed by the same HPLC method used for the initial purity analyses. The overall purity for each lot was 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory. Stability studies were performed using the HPLC methods described previously for the purity analysis, but with a solvent system ratio of 80:20. These studies indicated that *t*-butylhydroquinone was stable as a bulk chemical when stored for 2 weeks, protected from light, at temperatures up to 60° C. To ensure stability, the chemical was stored at room temperature in sealed containers, protected from light. Stability was monitored 9 weeks after the beginning of the 13-week studies and within 30 days after the end of the studies

using HPLC. For the long-term and 2-year studies, stability was monitored at approximately 4-month intervals and within 30 days after the end of the studies using HPLC. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations for the 13-week, long-term, and 2-year studies were prepared weekly. Formulations were prepared by first forming a premix of a small amount of feed and the required weight of chemical. This premix and additional feed were then mixed in a twin-shell blender for 15 minutes, with an intensifier bar used for the initial 5 minutes. Each dose formulation was poured into a labeled, double-thickness plastic bag that was placed in labeled containers and protected from light. Formulations were stored for no longer than 21 days (13-week studies) or 18 days (long-term and 2-year studies) at 5° C (Table I1).

Homogeneity analyses of the dose formulations were conducted by the analytical chemistry laboratory. Prior to the start of the 13-week studies, a preliminary mixing of the 2,500 ppm and 40,000 ppm dose formulations was performed. Triplicate samples were analyzed for homogeneity, and analytical results indicated that the samples were not homogeneous. The study laboratory changed the analytical method slightly (samples were diluted with mobile phase instead of the MRI-recommended acetonitrile) and 2 weeks after the start of the 13-week studies, results from the analysis of the 2,500 ppm dose formulations were within 10% of the theoretical value. Prior to the start of the long-term and 2-year studies, the study laboratory performed homogeneity analyses on the 125 ppm dose formulation (homogeneity determinations had been previously performed on greater concentrations). Three samples from this dose formulation, taken from three different areas of the blender, were analyzed in duplicate; results of the analyses were unacceptable, and a remix and second analysis were performed. Results of the second analyses were within 10% of theoretical values.

Stability studies of the 5,000 ppm dose formulation were conducted by the analytical chemistry laboratory. Samples (10 g) of the dose formulation were extracted with 100 mL of acetonitrile and shaken for 5 minutes. The extracts were centrifuged, and 25 mL aliquots of the extracts were mixed with 2 mL of internal standard solution (propiophenone, 10 mg/mL acetonitrile) and diluted to 100 mL with acetonitrile. Portions of the final diluted solutions were filtered (0.45 μm pore size) and analyzed using HPLC. HPLC was performed using a Waters μBondapack C_{18} column with a solvent system of water:acetonitrile:acetic acid (50:50:1) at a flow rate of 1.0 mL/minute. For the stability analysis, the 5,000 ppm formulation was prepared and stored for up to 21 days in the dark at room temperature, 5° C, or -20° C, or was stored for up to 7 days under animal room conditions. Stability of the 5,000 ppm formulation was confirmed for at least 3 weeks when stored in sealed containers in the dark at 5° C. A 5.3% loss of chemical was observed after 2 days of storage under animal room conditions. Based on these findings, the dose formulations were stored in sealed containers in the dark at 5° C for no longer than 3 weeks.

Periodic analyses of the dose formulations of *t*-butylhydroquinone were conducted at the study laboratory using HPLC. For the 13-week studies, dose formulations were analyzed at the beginning, in the middle, and at the end of the studies (Table I2). During the long-term and 2-year studies, dose formulations were analyzed approximately every 8 weeks (Table I3). In the 13-week studies, 98% (43/44) of the dose formulations used were within 10% of the target concentration with no value greater than 16% from the target concentration. In the long-term studies, 219 of the 220 dose formulations used for rats and 185 of the 186 dose formulations used for mice were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

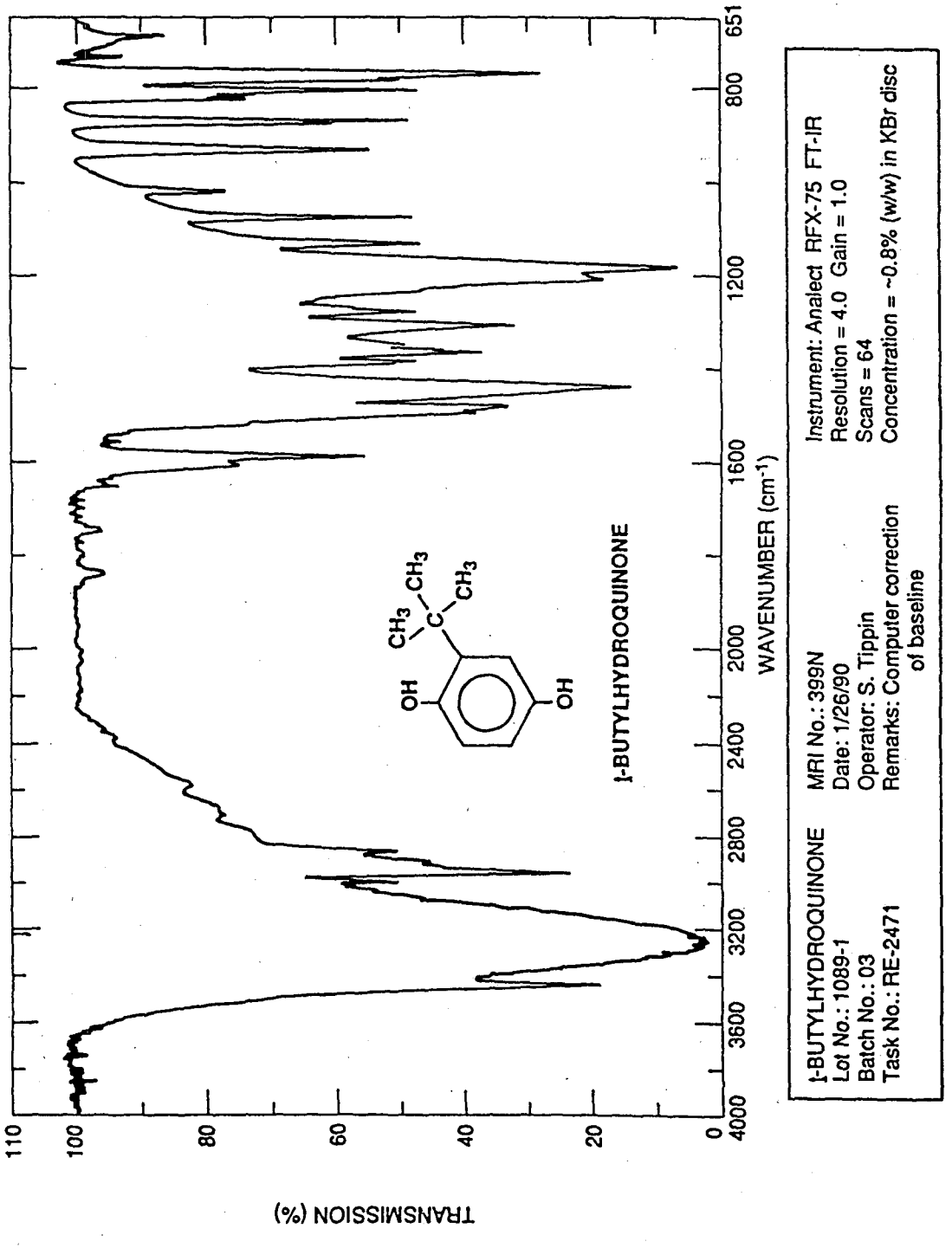


FIGURE I1
Infrared Absorption Spectrum of *t*-Butylhydroquinone

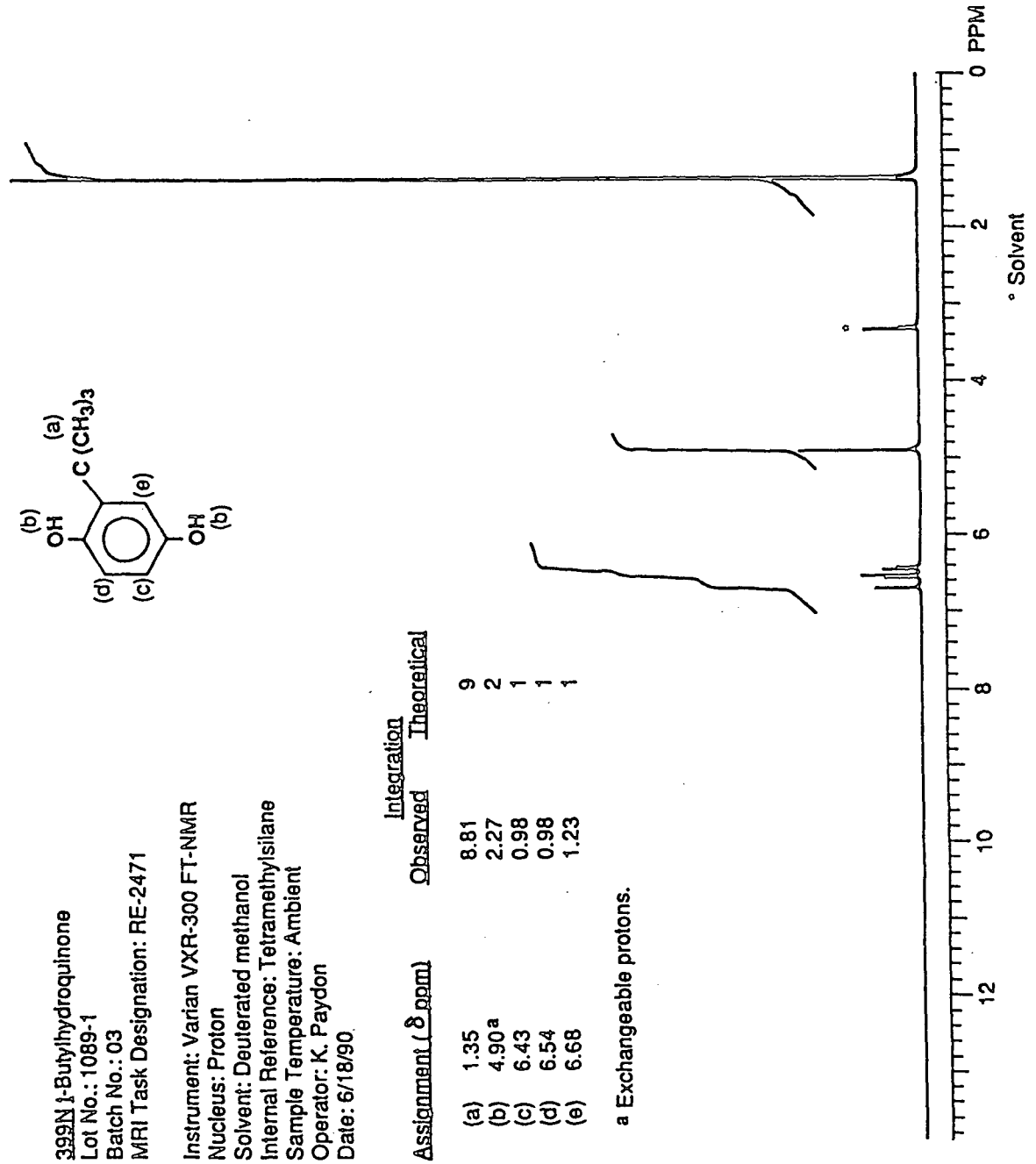


FIGURE I2
Nuclear Magnetic Resonance Spectrum of *t*-Butylhydroquinone

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of *t*-Butylhydroquinone

13-Week Studies	Long-Term Study	2-Year Study
Preparation		
A premix of feed and *t*-butylhydroquinone was prepared by mixing the chemical and feed in a beaker and stirring until a homogeneous mixture was obtained. The premix was then blended with feed in a Patterson-Kelly twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Doses were prepared weekly.	Same as 13-week studies	Same as 13-week study
Chemical Lot Number		
187-1	187-1 and 1089-1	187-1 and 1089-1
Maximum Storage Time		
21 days	18 days	18 days
Storage Conditions		
Formulations were stored in sealed containers in the dark at 5° C.	Same as 13-week studies	Same as 13-week studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Referee Laboratory		
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of t-Butylhydroquinone[a]

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)[b]	% Difference from Target
15 August 1988	22-23 August 1988	2.5	2.17[c,d]	-13
		2.5	2.34[c,d]	-6
		2.5	2.44[c,d]	-2
		40	36.0[c,d]	-10
		40	38.1[c,d]	-5
		40	38.2[c,d]	-4
Rats and Mice				
1 December 1988	2-3 December 1988	2.5	2.60[d,e]	+4
		2.5	2.64[d,f]	+6
		2.5	2.33[d,g,h]	-7
		2.5	2.50	0
		2.5	2.71	+8
		2.5	2.39[h]	-4
		5	4.98	0
		5	4.73[h]	-5
		5	5.05	+1
		5	5.00	0
		10	9.58	-4
		10	9.04[h]	-10
		10	9.68	-3
		20	20.2	+1
		40	38.5	-4
	4 December 1988	10	9.74	-3
12 January 1989	13 January 1989	2.5	2.30	-8
		2.5	2.29	-8
		2.5	2.18[c]	-13
		2.5	2.28	-9
		5	4.50	-10
		5	4.50	-10
		5	4.74	-5
		5	4.74	-5
		10	9.56	-4
		10	10.2	+2
		10	9.10	-9
		10	9.07	-9
		20	19.2	-4
		40	39.4	-2
17 January 1989	18 January 1989	2.5	2.52[i]	+1

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of *t*-Butylhydroquinone (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats and Mice (continued)				
9 February 1989	10 February 1989	2.5	2.62	+5
		2.5	2.26	-10
		2.5	2.39[h]	-4
		2.5	2.51[h]	0
		5	4.19	-16
		5	4.84	-3
		5	5.12	+2
		5	5.02	0
		10	9.50	-5
		10	9.82	-2
		10	9.08	-9
		10	9.42	-6
		20	19.0	-5
		40	38.0	-5
13 February 1989	14 February 1989	5	4.80[i]	-4

[a] 2.5 mg/g=2,500 ppm; 5 mg/g=5,000 ppm; 10 mg/g=10,000 ppm; 20 mg/g=20,000 ppm; 40 mg/g=40,000 ppm
[b] Results of duplicate analyses
[c] Not used for dosing
[d] Homogeneity analysis
[e] Sample selection from top of twin-shell blender
[f] Sample selection from middle of twin-shell blender
[g] Sample selection from bottom of twin-shell blender
[h] Results of triplicate analysis
[i] Results of remix

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the Long-Term and 2-Year Feed Studies of *t*-Butylhydroquinone[a]

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)[b]	% Difference from Target
Rats				
6 November 1989	7 November 1989	1.25	1.14	-9
		1.25	1.14	-9
		1.25	1.10[c]	-12
		2.5	2.44	-2
		2.5	2.44	-2
		2.5	2.46	-2
		5	4.87	-3
		5	4.86	-3
		5	4.85	-3
9 November 1989	9 November 1989	1.25	1.22[d]	-2
Rats and Mice				
20 November 1989	20-21 November 1989	1.25	1.32	+6
		1.25	1.35	+8
		1.25	1.26	+1
		1.25	1.26	+1
		2.5	2.54	+2
		2.5	2.55	+2
		2.5	2.62	+5
		2.5	2.66	+6
		5	5.23	+5
		5	5.14	+3
		5	5.20	+4
		5	5.18	+4
		5	5.24	+5
		5	5.12	+2
17 January 1990	18 January 1990	1.25	1.23	-2
		1.25	1.22	-2
		1.25	1.21	-3
		1.25	1.22	-2
		2.5	2.53	+1
		2.5	2.44	-2
		2.5	2.38	-5
		2.5	2.46	-2
		5	4.66	-7
		5	4.60	-8
		5	4.88	-2
		5	4.76	-5
		5	4.68	-6
		5	4.88	-2

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the Long-Term and 2-Year Feed Studies of *t*-Butylhydroquinone (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats and Mice (continued)				
21 March 1990	22-23 March 1990	1.25	1.16	-7
		1.25	1.20	-4
		1.25	1.18	-6
		1.25	1.17	-6
		1.25	1.23	-2
		2.5	2.35	-6
		2.5	2.33	-7
		2.5	2.25	-10
		2.5	2.30	-8
		2.5	2.30	-8
		5	4.72	-6
		5	4.64	-7
		5	4.69	-6
		5	4.78	-4
		5	4.54	-9
16 May 1990	17 May 1990	1.25	1.26	+1
		1.25	1.27	+2
		1.25	1.23	-2
		1.25	1.18	-6
		2.5	2.44	-2
		2.5	2.45	-2
		2.5	2.41	-4
		2.5	2.43	-3
		5	4.77	-5
		5	4.86	-3
		5	5.01	0
		5	4.92	-2
		5	4.61	-8
11 July 1990	12 July 1990	1.25	1.20	-4
		1.25	1.23	-2
		1.25	1.18	-6
		1.25	1.18	-6
		2.5	2.44	-2
		2.5	2.41	-4
		2.5	2.44	-2
		2.5	2.31	-8
		5	4.75	-5
		5	4.92	-2
		5	4.91	-2
		5	4.96	-1
		5	4.96	-1

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the Long-Term and 2-Year Feed Studies of *t*-Butylhydroquinone (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats and Mice (continued)				
5 September 1990	7 September 1990	1.25	1.24	-1
		1.25	1.22	-2
		1.25	1.24	-1
		1.25	1.18	-6
		2.5	2.42	-3
		2.5	2.48	-1
		2.5	2.44	-2
		2.5	2.54	+2
		5	4.86	-3
		5	4.78	-4
		5	4.89	-2
		5	5.06	+1
		5	4.96	-1
7 November 1990	8 November 1990	1.25	1.20	-4
		1.25	1.17	-6
		1.25	1.23	-2
		1.25	1.23	-2
		2.5	2.49	0
		2.5	2.44	-3
		2.5	2.50	0
		2.5	2.41	-4
		5	5.00	0
		5	4.91	-2
		5	5.05	+1
		5	4.91	-2
		5	4.86	-3
9 January 1991	10-11 January 1991	1.25	1.205	-4
		1.25	1.086[c]	-13
		1.25	1.201	-4
		1.25	1.163	-7
		2.5	2.459	-2
		2.5	2.424	-3
		2.5	2.459	-2
		2.5	2.362	-6
		5	4.889	-2
		5	4.545	-9
		5	4.689	-6
		5	4.462	-11
		5	4.902	-2
14 January 1991	14 January 1991	1.25	1.22[d]	-3

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the Long-Term and 2-Year Feed Studies of *t*-Butylhydroquinone (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats and Mice (continued)				
26-27 February 1991	28 February 1991	1.25	1.31	+5
		1.25	1.24	-1
		1.25	1.25	0
		1.25	1.20	-4
		2.5	2.31	-8
		2.5	2.45	-2
		2.5	2.47	-1
		2.5	2.42	-3
		5	4.91	-2
		5	5.07	+1
		5	4.80	-4
		5	4.77	-5
		5	4.97	-1
1 May 1991	2 May 1991	1.25	1.28	+2
		1.25	1.22	-2
		1.25	1.32	+6
		1.25	1.29	+3
		2.5	2.59	+4
		2.5	2.50	0
		2.5	2.55	+2
		2.5	2.39	-4
		5	5.05	+1
		5	4.88	-2
		5	5.10	+2
		5	4.94	-1
		5	5.08	+2
19 June 1991	20 June 1991	1.25	1.31	+5
		1.25	1.25	0
		1.25	1.25	0
		1.25	1.33	+6
		2.5	2.42	-3
		2.5	2.53	+1
		2.5	2.48	-1
		2.5	2.45	-2
		5	4.84	-3
		5	4.84	-3
		5	4.82	-4
		5	4.97	-1
		5	4.93	-1

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the Long-Term and 2-Year Feed Studies of *t*-Butylhydroquinone (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats and Mice (continued)				
14 August 1991	15-16 August 1991	1.25	1.27	+2
		1.25	1.17	-6
		1.25	1.20	-4
		1.25	1.21	-3
		2.5	2.38	-5
		2.5	2.37	-5
		2.5	2.48	-1
		2.5	2.25	-10
		5	4.76	-5
		5	4.91	-2
		5	4.76	-5
		5	4.83	-3
		5	4.79	-4
9 October 1991	10-11 October 1991	1.25	1.25	0
		1.25	1.21	-3
		1.25	1.22	-2
		1.25	1.26	+1
		2.5	2.46	-2
		2.5	2.45	-2
		2.5	2.50	0
		2.5	2.46	-2
		5	4.91	-2
		5	4.85	-3
		5	4.85	-3
		5	4.78	-4
		5	4.85	-3
20 November 1991	21-25 November 1991	1.25	1.19	-5
		1.25	1.19	-5
		1.25	1.20	-4
		1.25	1.19	-5
		2.5	2.42	-3
		2.5	2.48	-1
		2.5	2.26	-10
		2.5	2.44	-2
		5	4.95	-1
		5	4.80	-4
		5	4.80	-4
		5	4.67	-7
		5	4.78	-4

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the Long-Term and 2-Year Feed Studies of *t*-Butylhydroquinone (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Rats (continued)				
22 January 1992	23 January 1992	1.25	1.21	-3
		1.25	1.20	-4
		1.25	1.24	-1
		2.5	2.49	0
		2.5	2.42	-3
		2.5	2.60	+4
		5	5.01	0
		5	4.98	0
		5	4.90	-2
		5	5.03	+1
18 March 1992	19 March 1992	1.25	1.25	0
		1.25	1.26	+1
		2.5	2.52	+1
		2.5	2.48	-1
		5	5.03	+1
		5	5.00	0
		5	5.01	0
27 May 1992	28 May 1992	1.25	1.25	0
		1.25	1.26	+1
		2.5	2.47	-1
		2.5	2.49	0
		5	4.90	-2
		5	4.86	-3
		5	5.12	+2
22 July 1992	23 July 1992	5	4.92	-2

[a] 1.25 mg/g=1,250 ppm; 2.5 mg/g=2,500 ppm; 5 mg/g=5,000 ppm
[b] Duplicate analyses
[c] Not used for dosing
[d] Results of remix

TABLE I4
Results of Referee Analyses of Dose Formulations Administered to Rats and Mice in the 13-Week, Long-Term, and 2-Year Feed Studies of *t*-Butylhydroquinone

Date Prepared	Target Concentration (mg/g)	Determined Concentration (mg/g)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
1 December 1988	2.5	2.44	2.13
12 January 1989	5	4.74	4.68
Long-Term Study			
Rats			
6 November 1989	1.25	1.14	1.20
20 November 1989	5	5.14	4.53
17 January 1990	2.5	2.53	2.20
2-Year Study			
Mice			
20 November 1989	5	5.14	4.53
17 January 1990	2.5	2.53	2.20

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

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE LONG-TERM AND 2-YEAR FEED STUDIES OF *t*-BUTYLHYDROQUINONE

TABLE J1
Feed and Compound Consumption by Male Rats in the Long-Term Feed Study of *t*-Butylhydroquinone[a]

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)[b]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[c] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	13.9	99									
2	15.2	141	16.4	148	138	15.7	141	280	15.7	127	619
3	16.5	175									
4	18.2	209									
5	17.4	233									
6	20.8	267	19.0	266	89	19.0	260	183	18.3	244	375
7	17.2	283									
8	17.0	299									
9	16.9	313									
10	13.1	316	13.2	319	52	17.3	320	135	17.5	299	293
11	19.2	324									
12	17.4	344									
13	16.8	356	17.2	348	62	18.7	343	136	17.6	320	275
17	16.5	379	17.6	370	60	16.5	366	113	17.2	346	248
21	16.4	400	18.6	391	59	18.5	379	122	17.2	358	241
25	15.6	413	16.5	408	51	16.0	399	100	15.9	376	211
29	16.5	419	17.0	416	51	16.5	408	101	16.4	386	213
33	16.4	428	17.1	425	50	17.4	417	104	16.7	392	213
37	17.4	437	17.4	435	50	16.8	430	98	16.4	402	204
41	14.7	450	14.8	445	42	14.5	437	83	15.2	416	182
45	16.5	452	16.0	450	44	17.7	439	101	16.9	415	203
49	16.9	444	17.0	448	47	17.2	440	98	16.0	415	193
53	19.9	468	19.7	466	53	20.5	457	112	20.8	431	242
57	14.8	468	16.2	468	43	16.6	462	90	16.8	435	193
61	16.1	467	17.0	468	45	18.2	463	98	17.7	440	202
65	16.3	470	17.3	471	46	17.2	463	93	17.6	440	200
69	15.8	468	16.5	472	44	16.6	463	90	16.7	437	191
73	15.3	472	15.7	471	42	16.3	459	89	16.0	433	185
77	17.0	463	17.6	463	47	16.3	458	89	16.3	438	186
81	16.6	464	17.0	466	46	17.5	458	95	17.3	436	199
85	15.4	462	15.7	470	42	15.1	457	83	15.1	429	176
89	15.1	455	15.0	457	41	15.3	455	84	14.0	425	164
93	14.3	458	14.9	451	41	15.5	456	85	15.1	419	180
97	15.4	455	15.5	452	43	16.5	453	91	16.0	421	190
101	15.2	447	15.6	444	44	14.9	443	84	15.7	421	186
105	14.5	440	15.1	435	44	15.9	430	93	16.4	409	201
109	15.7	420	14.3	421	42	14.4	414	87	14.2	412	173
113	14.8	429	16.5	427	48	16.5	420	98	15.7	395	198
117	14.0	428	15.5	422	46	16.7	400	104	15.0	397	189
121	14.4	417	11.5	402	36	16.1	359	112	15.5	386	200
Mean for weeks											
1-13	16.9	258	16.5	271	85	17.7	266	183	17.3	247	390
14-52	16.3	425	16.9	421	51	16.8	413	102	16.4	390	212
53-121	15.6	453	15.9	452	44	16.4	443	93	16.2	422	192

[a] Feed consumption for controls measured weekly for the first 13 weeks and monthly thereafter.
[b] Grams of feed consumed per animal per day
[c] Milligrams of *t*-butylhydroquinone consumed per kilogram body weight per day

TABLE J2
Feed and Compound Consumption by Female Rats in the Long-Term Feed Study of *t*-Butylhydroquinone[a]

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)[b]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[c] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	10.8	92									
2	11.3	121	12.0	124	122	12.0	120	249	11.9	110	541
3	11.3	135									
4	11.6	147									
5	11.1	159									
6	13.7	171	12.4	168	93	12.2	162	188	11.3	154	367
7	11.6	177									
8	10.8	181									
9	10.7	186									
10	9.4	176	8.8	181	61	11.2	183	154	11.1	176	316
11	11.9	193									
12	10.5	196									
13	10.2	198	10.5	194	68	10.8	191	141	11.2	184	304
17	10.7	203	10.5	203	65	10.4	197	133	9.8	188	262
21	10.7	224	11.1	212	65	10.4	205	127	10.8	200	270
25	9.4	222	11.0	216	64	10.0	212	118	9.5	203	235
29	9.2	229	10.4	222	59	9.8	217	114	10.1	210	240
33	10.1	231	11.0	227	60	10.4	219	118	10.0	210	239
37	10.9	232	11.1	230	60	11.0	223	123	10.4	213	244
41	10.1	240	10.4	238	55	10.4	231	112	9.1	219	207
45	10.8	248	11.1	246	56	11.6	239	122	11.0	227	242
49	11.6	257	11.8	256	57	11.4	244	117	10.7	232	232
53	15.3	264	15.7	263	74	14.7	247	149	14.1	236	299
57	9.6	279	10.2	277	46	10.7	264	102	10.8	246	219
61	11.3	285	11.4	285	50	12.0	269	111	11.2	257	217
65	12.2	292	12.3	291	53	12.8	274	117	11.5	263	219
69	11.6	301	11.5	299	48	11.3	282	100	10.7	265	202
73	12.2	309	11.9	301	49	11.5	286	101	11.0	270	204
77	12.4	315	12.4	311	50	11.6	297	98	11.5	274	209
81	12.3	323	12.4	319	49	12.7	300	106	11.8	278	213
85	11.5	327	11.9	325	46	11.0	308	90	11.3	282	200
89	11.7	333	12.5	327	48	11.9	309	96	10.9	287	190
93	12.3	342	11.6	339	43	11.6	316	91	11.1	290	191
97	12.6	348	12.9	343	47	12.9	325	99	12.5	299	209
101	12.0	347	12.8	346	46	12.0	329	91	11.9	301	197
105	13.0	345	13.6	347	49	12.8	333	97	12.3	303	203
109	12.5	341	13.3	354	47	12.2	329	92	12.0	300	200
113	11.1	337	12.3	350	44	12.8	337	95	12.4	301	205
117	11.7	348	12.1	355	43	12.0	337	89	11.4	309	184
121	12.3	341	12.3	353	44	11.1	335	83	12.0	315	190
125	11.9	336	13.0	340	48	12.3	326	95	12.0	307	196
Mean for weeks											
1-13	11.2	164	11.0	167	86	11.5	164	183	11.4	156	382
14-52	10.4	232	10.9	228	60	10.6	221	120	10.2	211	241
53-125	12.1	322	12.4	322	49	12.1	305	100	11.7	283	208

[a] Feed consumption for controls measured weekly for the first 13 weeks and monthly thereafter.
[b] Grams of feed consumed per animal per day
[c] Milligrams of *t*-butylhydroquinone consumed per kilogram body weight per day

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

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	3.9	23.7	3.6	23.5	191	3.3	23.4	351	4.3	23.0	932
2	4.4	25.4	4.2	25.3	206	4.4	25.3	433	4.6	24.7	940
6	3.7	30.0	3.7	29.6	156	4.1	29.7	345	4.6	29.2	790
9	3.8	32.3	4.0	32.1	157	3.7	31.7	294	4.2	30.5	682
10	4.7	33.1	4.2	32.9	158	4.4	32.8	336	4.2	30.8	675
13	4.8	36.6	4.6	35.6	160	4.5	35.2	320	4.8	33.4	715
17	4.7	38.8	4.0	38.3	130	4.4	38.0	289	4.4	35.4	619
21	4.9	39.4	3.8	39.6	120	4.4	39.2	280	5.4	36.7	737
25	4.5	41.9	4.8	41.3	146	4.8	40.9	294	4.7	38.3	607
29	4.6	44.4	4.1	43.3	119	3.9	43.1	226	4.2	40.2	528
33	5.1	44.9	5.1	44.4	144	5.1	44.2	287	5.2	40.9	637
37	4.5	45.0	4.9	43.9	140	5.5	43.6	314	5.4	40.6	669
41	4.6	46.1	4.6	44.9	129	4.4	45.0	246	4.4	41.2	528
45	3.7	48.1	4.1	46.5	110	4.6	46.5	248	4.8	43.4	550
49	3.9	49.7	3.8	48.8	98	4.0	48.6	208	4.0	45.8	441
53	3.9	50.8	4.1	49.3	103	4.0	49.2	203	4.2	46.3	449
57	4.5	51.1	4.4	50.0	111	4.6	49.8	229	4.8	47.5	503
61	4.6	51.5	4.7	50.1	118	5.4	49.6	271	6.0	47.3	637
65	5.1	51.5	5.0	49.8	126	5.3	49.2	272	5.5	46.9	586
69	4.9	51.9	4.7	49.9	118	5.2	49.7	260	4.9	47.4	517
73	5.6	51.8	5.8	49.8	146	5.3	49.8	267	5.0	47.6	526
77	4.3	52.7	4.5	51.0	111	4.6	50.3	229	4.4	48.4	452
81	4.6	52.6	4.2	51.0	102	4.0	50.2	200	4.5	48.1	464
85	3.9	52.4	3.9	50.8	97	4.3	50.5	214	5.2	47.4	544
89	4.3	52.6	5.0	50.5	123	5.0	50.3	249	5.4	47.8	565
93	3.9	51.4	4.4	50.0	109	4.1	49.1	207	5.2	48.0	545
97	4.3	51.4	4.8	49.6	122	4.5	49.4	229	4.9	47.3	514
101	4.2	49.9	4.3	48.2	112	4.1	49.4	208	4.4	47.8	458
Mean for weeks											
1-13	4.2	30.2	4.0	29.8	171	4.1	29.7	347	4.4	28.6	789
14-52	4.5	44.3	4.4	43.4	126	4.6	43.2	266	4.7	40.3	591
53-101	4.5	51.7	4.6	50.0	115	4.6	49.7	234	4.9	47.5	520

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

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

Week	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.4	20.1	4.3	20.4	261	3.6	20.2	445	6.1	20.1	1,520
3	3.6	21.5	4.0	21.6	229	4.1	21.3	477	3.9	20.9	933
6	3.0	24.9	3.2	25.2	158	3.5	25.0	353	3.0	24.5	610
7	3.7	26.0	3.7	26.3	176	3.8	26.2	367	4.2	25.2	827
10	3.3	28.3	3.3	28.5	146	3.7	28.0	331	4.4	26.7	821
11	4.3	28.9	4.5	29.3	192	4.3	28.8	369	4.4	27.5	793
17	4.0	33.9	4.2	34.9	150	4.1	34.1	303	4.1	31.8	646
21	4.9	36.0	4.6	36.2	158	4.8	35.6	337	4.8	33.6	713
25	3.9	37.1	4.8	37.1	161	5.1	35.6	359	5.1	32.8	772
29	5.3	38.5	5.3	39.2	168	5.6	38.0	367	5.8	35.1	828
33	4.5	39.9	5.1	40.8	157	5.3	39.8	336	4.9	36.7	669
37	4.8	39.9	4.6	40.8	140	4.8	39.9	303	5.0	36.5	678
41	4.7	41.5	4.8	42.1	142	5.0	41.2	305	5.2	37.7	691
45	4.3	43.2	4.5	44.3	127	5.1	43.4	293	4.7	39.0	603
49	4.8	46.4	4.8	47.6	127	4.8	46.5	260	4.7	41.9	562
53	4.9	48.5	4.9	49.5	124	5.1	48.7	264	5.1	43.5	587
57	5.2	50.2	6.0	51.4	145	5.9	50.5	291	5.6	44.9	622
61	5.1	51.3	5.6	52.9	132	5.7	51.6	277	5.5	45.6	603
65	5.4	52.3	5.4	53.2	127	5.4	51.9	260	5.0	46.6	532
69	5.5	52.6	5.0	53.7	117	5.4	52.7	256	5.4	46.8	581
73	4.3	53.9	4.8	55.4	109	4.8	54.3	220	4.8	47.9	502
77	5.3	55.4	5.3	56.0	118	5.3	54.9	241	5.2	48.3	542
81	4.8	55.5	4.8	56.8	107	4.9	55.1	223	5.1	49.0	524
85	5.0	56.2	4.9	56.9	107	5.2	55.7	232	5.1	49.6	511
89	4.9	56.0	5.1	57.8	110	5.1	55.5	230	4.9	49.7	492
93	5.0	56.1	5.0	57.9	109	5.3	55.7	236	5.2	49.6	527
97	4.9	55.1	4.8	57.0	106	5.4	54.7	246	5.3	49.0	538
101	4.8	54.5	4.9	55.8	111	5.1	54.2	235	4.7	48.6	485
105	4.6	52.9	4.6	55.6	104	5.1	53.2	239	4.6	47.3	482
Mean for weeks											
1-13	3.7	25.0	3.8	25.2	194	3.8	24.9	391	4.3	24.2	917
14-52	4.6	39.6	4.7	40.3	148	5.0	39.3	318	4.9	36.1	685
53-105	5.0	53.6	5.1	55.0	116	5.3	53.5	247	5.1	47.6	538

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

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

TABLE K1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.6 ± 0.52	22.50 - 25.20	34
Crude Fat (% by weight)	5.30 ± 0.23	4.80 - 5.80	34
Crude Fiber (% by weight)	3.50 ± 0.42	2.60 - 4.80	34
Ash (% by weight)	6.50 ± 0.22	6.12 - 7.03	34
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 - 1.390	10
Cystine	0.306 ± 0.075	0.181 - 0.400	10
Glycine	1.160 ± 0.050	1.060 - 1.220	10
Histidine	0.580 ± 0.024	0.531 - 0.608	10
Isoleucine	0.917 ± 0.034	0.867 - 0.965	10
Leucine	1.972 ± 0.052	1.850 - 2.040	10
Lysine	1.273 ± 0.051	1.200 - 1.370	10
Methionine	0.437 ± 0.115	0.306 - 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 - 1.110	10
Threonine	0.896 ± 0.055	0.824 - 0.985	10
Tryptophan	0.223 ± 0.160	0.107 - 0.671	10
Tyrosine	0.677 ± 0.105	0.564 - 0.794	10
Valine	1.089 ± 0.057	0.962 - 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 - 2.570	9
Linolenic	0.277 ± 0.036	0.210 - 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,725 ± 1,375	4,290 - 12,540	34
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 - 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 - 48.9	9
Thiamine (ppm)	18.40 ± 2.50	12.0 - 25.0	34
Riboflavin (ppm)	7.92 ± 0.93	6.10 - 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 - 150.0	9
Pantothenic Acid (ppm)	30.30 ± 3.60	23.0 - 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 - 14.0	10
Folic Acid (ppm)	2.51 ± 0.64	1.80 - 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 - 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 - 65.0	10
Choline (ppm)	3,068 ± 314	2,400 - 3,430	9
Minerals			
Calcium (%)	1.20 ± 0.09	1.00 - 1.37	34
Phosphorus (%)	0.94 ± 0.05	0.80 - 1.03	34
Potassium (%)	0.887 ± 0.067	0.772 - 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 - 0.635	8
Sodium (%)	0.315 ± 0.034	0.258 - 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 - 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 - 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 - 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 - 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 - 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 - 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 - 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 - 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 - 1.150	6

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.44 ± 0.21	0.10 - 0.80	34
Cadmium (ppm)	0.13 ± 0.08	0.05 - 0.40	34
Lead (ppm)	0.35 ± 0.37	0.10 - 2.10	34
Mercury (ppm)	0.02 ± 0.01	0.02 - 0.05	34
Selenium (ppm)[c]	0.32 ± 0.11	0.02 - 0.44	33
Aflatoxins (ppb)[d]	<5.0		24
Nitrate nitrogen (ppm)[e]	9.94 ± 5.02	1.80 - 20.0	34
Nitrite nitrogen (ppm)[e]	0.24 ± 0.20	0.10 - 1.00	34
BHA (ppm)[f]	1.33 ± 0.82	1.00 - 4.00	33
BHT (ppm)[f]	1.28 ± 0.61	1.00 - 7.00	33
Aerobic plate count (CFU/g)	139,873 ± 169,234	4,700 - 630,000	34
Coliform (MPN/g)	19.4 ± 22.20	3.00 - 93.00	34
Escherichia coli (MPN/g)	3.24 ± 1.04	3.00 - 9.0	34
Total Nitrosoamines (ppb)[g]	7.08 ± 2.40	2.90 - 13.70	34
N-Nitrosodimethylamine (ppb)[g]	5.23 ± 1.35	2.90 - 9.40	34
N-Nitrosopyrrolidine (ppb)[g]	1.61 ± 1.17	0.00 - 4.70	34
Pesticides (ppm)			
α-BHC[j]	<0.01		31
β-BHC	<0.02		31
γ-BHC	<0.01		31
δ-BHC	<0.01		31
Heptachlor	<0.01		31
Aldrin	<0.01		31
Heptachlor epoxide	<0.01		31
DDE	<0.01		31
DDD	<0.01		31
DDT	<0.01		31
HCB	<0.01		31
Mirex	<0.01		31
Methoxychlor	<0.05		31
Dieldrin	<0.01		31
Endrin	<0.01		31
Telodrin	<0.01		31
Chlordane	<0.05		31
Toxaphene	<0.1		31
Estimated PCBs	<0.2		31
Ronnel	<0.01		31
Ethion	<0.02		31
Trithion	<0.05		31
Diazinon	<0.1		31
Methyl parathion	<0.02		31
Ethyl parathion	<0.02		31
Malathion	0.28 ± 0.26	<0.05 - 1.00	34
Endosulfan I	<0.01		31
Endosulfan II	<0.01		31
Endosulfan sulfate	<0.03		31

[a] CFU = colony forming units, MPN = most probable number, BHC is hexachlorocyclohexane or benzene hexachloride.
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] No selenium measurement was recorded for the lot milled on 4 May 1990.
[d] No aflatoxin measurement was recorded for the lot milled on 2 October 1989.
[e] Sources of contamination: alfalfa, grains, and fish meal
[f] Sources of contamination: soy oil and fish meal; no BHA or BHT measurements were recorded for the lot milled on 1 November 1989.
[g] All values were corrected for percent recovery.

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Most serum samples were collected from sentinel, untreated, or vehicle control rats and mice. At the end of the 13-week studies, blood was collected from five male and five female control rats and five male and five female sentinel mice. During the long-term rat study, samples were collected from 10 first-generation (F_0) females at necropsy; five male and five female sentinels at 6, 7, 12, and 13 months; one male sentinel at 14 months (insufficient serum was collected for analysis); one male sentinel at 16 months; five male and five female sentinels at 18 months; three male and four female sentinels at 19 months; one male and four female sentinels at 24 months; four male and one female sentinels at 25 months; five vehicle control or untreated females at 30 months; and four vehicle control or untreated females at 31 months. During the 2-year mouse study, samples were collected from four to five male and four to five female sentinels or controls at 6, 12, 18, and 24 months. Additional samples for ELISA determination of mouse hepatitis virus and Sendai, were taken from ten naive male sentinels at 17, 18, 19, 20, and 23 months. 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	
13-Week Study	
ELISA	
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
Long-Term Study	
ELISA	
Mycoplasma arthritidis	30, 31 months
Mycoplasma pulmonis	30, 31 months
PVM	F_0 necropsy, 6, 7, 12, 13, 16, 18, 19, 24, 25, 30, 31 months
RCV/SDA	F_0 necropsy, 6, 7, 12, 13, 18, 19, 25, 30 months
Sendai	F_0 necropsy, 6, 7, 12, 13, 16, 18, 19, 24, 25, 30, 31 months

Method and Test	Time of Analysis
RATS (continued)	
Long-Term Study (continued)	
Immunofluorescence Assay	
PVM	31 months
RCV/SDA	16, 18, 19, 24, 25 months
Hemagglutination Inhibition	
H-1	F_0 necropsy, 6, 7, 12, 13, 16, 18, 19, 24, 25, 30, 31 months
KRV	F_0 necropsy, 6, 7, 12, 13, 16, 18, 19, 24, 25, 30, 31 months
MICE	
13-Week Study	
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
Polyoma virus	Study termination
2-Year Study	
ELISA	
Ectromelia virus	6, 12, 18, and 24 months
EDIM	12, and 24 months
GDVII	6, 12, 18, and 24 months
LCM	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
MHV	6, 12, 17, 18, 19, 20, 23, and 24 months
M. arthritidis	24 months (females only)
M. pulmonis	24 months (females only)
PVM	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Sendai	6, 12, 17, 18, 19, 20, 23, and 24 months

Method and Test	Time of Analysis
MICE (continued)	
2-Year Study (continued)	
Immunofluorescence Assay	
EDIM	6, 18, and 24 (one female only) months
GDVII	18, and 24 (one male only) months
MVM	6 months
Mouse adenoma virus	24 (one female only) months
Reovirus 3	6 and 24 (one male and one female only) months
Hemagglutination Inhibition	
K	6, 12, 18, and 24 months
MVM	12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
Reovirus 3	6 months

Results of serology tests are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week, Long-Term, and 2-Year Studies of *t*-Butylhydroquinone

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
Rats		
Study termination	0/10	None
Mice		
Study termination	0/10	None
Long-Term Study		
Rats		
F_0 necropsy	0/10	None
6 months	0/10	None
7 months	0/10	None
12 months	0/10	None
13 months	0/10	None
16 months	0/1	None
18 months	0/11	None
19 months	0/7	None
24 months	0/5	None
25 months	0/5	None
30 months	1/5	*M. arthritidis*[a]
31 months	2/4	*M. arthritidis*[a]
2-Year Study		
Mice		
6 months	3/10[b]	Reovirus 3
12 months	0/10	None
17 months	0/10	None
18 months	0/18	None
19 months	0/10	None
20 months	0/10	None
23 months	0/10	None
24 months	1/10	Mouse hepatitis virus

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may be due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in rats with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.

[b] Western blot analysis of the three sera testing positive for Reovirus 3 were negative for specific antibodies. Therefore, the low level ELISA and immunofluorescence assay results were considered to be nonspecific due to the lack of increasing titer and the incidence in the colonies in which the positive results occurred.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD E1-02
Research Triangle Park, NC 27709

Official Business
Penalty for Private Use - $300

NIH Publication No. 97-3375
May 1997