NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

TETRAHYDROFURAN

(CAS NO. 109-99-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

June 1998

NTP TR 475

NIH Publication No. 98-3965

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. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). 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.

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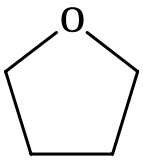
ABSTRACT



TETRAHYDROFURAN

CAS No. 109-99-9

Chemical Formula: C_4H_8O Molecular Weight: 72.10

Synonyms: Butylene oxide; cyclotetramethylene oxide; diethylene oxide; 1,4-epoxybutane; furanidine; hydrofuran; oxacyclopentane; oxolane; tetramethylene oxide

Tetrahydrofuran is used as a reaction medium for Grignard and metal hydride reactions; in the synthesis of butyrolactone, succinic acid, and 1,4-butanediol diacetate; in the fabrication of articles for packaging, transporting, and storing of foods; as a solvent for dyes and lacquers; and as a chemical intermediate in polymerization solvent for fat oils, unvulcanized rubber, resins, and plastics. Tetrahydrofuran is also an indirect food additive when it is in the contact surface of articles intended for use in food processing. Tetrahydrofuran was nominated for study because of the potential for occupational exposure in humans. Male and female F344/N rats and B6C3F$_1$ mice were exposed to tetrahydrofuran (approximately 99% pure) by inhalation for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, mouse bone marrow cells, and mouse peripheral blood erythrocytes.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to 0 (chamber control), 66, 200, 600, 1,800, or 5,000 ppm tetrahydrofuran by inhalation, 6 hours per day, 5 days per week, for 14 weeks. All rats survived until the end of the study. Final mean body weights and body weight gains of exposed groups of male and female rats were similar to those of the chamber controls. Immediately after exposure, male and female rats in the 5,000 ppm groups exhibited ataxia.

Hematologic and serum chemistry changes were minimal, with most values falling within physiologic ranges. Absolute and relative thymus and spleen weights of male and female rats exposed to 5,000 ppm were significantly less than those of the chamber controls. Absolute and relative liver weights of female rats exposed to 5,000 ppm were significantly greater than those of the chamber controls. Increased incidences of minimal to mild hyperplasia of the forestomach were observed in male and female rats exposed to 5,000 ppm. Minimal suppurative inflammation was associated with forestomach hyperplasia in two male and four female rats exposed to 5,000 ppm.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 66, 200, 600, 1,800, or 5,000 ppm

tetrahydrofuran by inhalation, 6 hours per day, 5 days per week, for 14 weeks. Two male mice exposed to 5,000 ppm died during weeks 2 and 8 of the study; one male mouse from the 5,000 ppm group was killed in a moribund state during week 4. All female mice survived until the end of the study. The final mean body weights and body weight gains of all exposed groups of male mice were similar to those of the chamber controls. The final mean body weight and body weight gain of the 5,000 ppm female mice were significantly greater than those of the chamber controls. Male and female mice exposed to 1,800 or 5,000 ppm were observed to be in a state of narcosis (described by stupor) during exposure periods. Mice exposed to 1,800 ppm were fully awake and alert immediately after exposure; however, mice exposed to 5,000 ppm required up to 2 hours for recovery.

Absolute and relative liver weights of male mice exposed to 600 ppm or greater and of female mice exposed to 1,800 or 5,000 ppm were significantly greater than those of the chamber controls. Absolute and relative thymus weights of male mice exposed to 600, 1,800, or 5,000 ppm were significantly less than those of the chamber controls. The incidences of minimal to mild centrilobular cytomegaly of the liver in male and female mice exposed to 5,000 ppm were significantly greater than those in the chamber controls. The adrenal glands of all female mice exposed to 5,000 ppm had mild degeneration of the X-zone of the innermost cortex. Uterine atrophy was observed in all female mice exposed to 5,000 ppm.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were exposed to 0, 200, 600, or 1,800 ppm tetrahydrofuran by inhalation, 6 hours per day, 5 days per week, for 105 weeks.

Survival and Body Weights

Survival rates and mean body weights of male and female rats exposed to tetrahydrofuran were similar to those of the chamber controls.

Pathology Findings

The incidences of renal tubule epithelial adenoma or carcinoma (combined) in exposed males occurred with a positive trend, and the incidences in 600 and 1,800 ppm males exceeded the historical range for chamber controls in 2-year NTP inhalation studies.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were exposed to 0, 200, 600, or 1,800 ppm tetrahydrofuran by inhalation, 6 hours per day, 5 days per week, for 105 weeks.

Survival, Body Weights, and Clinical Findings

After week 36, the survival of male mice exposed to 1,800 ppm was significantly less than that of the chamber controls. Mean body weights of male and female mice exposed to tetrahydrofuran were similar to those of the chamber controls throughout the study. Male mice exposed to 1,800 ppm were observed to be in a state of narcosis during and up to 1 hour after the exposure periods.

Pathology Findings

The incidences and multiplicity of hepatocellular neoplasms were significantly greater in female mice exposed to 1,800 ppm than in the chamber controls. The incidence of nephropathy in 200 ppm male mice was significantly greater than that in the chamber control group. Male mice exposed to 1,800 ppm had significantly greater incidences of nonneoplastic lesions of the urogenital tract than did the chamber controls. The incidences of inflammation of the penis and urethra and necrosis of the urethra in 1,800 ppm males were slightly greater than those in the chamber controls; these may have been secondary effects of ascending urinary tract infection.

GENETIC TOXICOLOGY

Tetrahydrofuran showed little evidence of mutagenic activity in a variety of *in vitro* and *in vivo* assays. It was not mutagenic in *S. typhimurium*, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These *in vitro* tests were conducted with and without exogenous metabolic activation from induced liver S9 enzymes. No increase in sex-linked recessive lethal mutations was detected in germ cells of male

D. melanogaster exposed to tetrahydrofuran by feeding or injection. Results of *in vivo* assays for induction of chromosomal aberrations and sister chromatid exchanges in mouse bone marrow cells were negative. A micronucleus test in male and female mice exposed to tetrahydrofuran for 14 weeks showed no significant increases in the frequency of micronucleated erythrocytes in peripheral blood of female mice, but in male mice, analysis of micronucleated normochromatic erythrocyte levels revealed a small increase above baseline that was concluded to be equivocal.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of tetrahydrofuran in male F344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of tetrahydrofuran in female F344/N rats exposed to 200, 600, or 1,800 ppm or male $B6C3F_1$ mice exposed to 200, 600, or 1,800 ppm. There was *clear evidence of carcinogenic activity* of tetrahydrofuran in female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms.

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

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations	Chamber control, 200, 600, or 1,800 ppm	Chamber control, 200, 600, or 1,800 ppm	Chamber control, 200, 600, or 1,800 ppm	Chamber control, 200, 600, or 1,800 ppm
Body weights	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group
2-Year survival rates	12/50, 6/50, 5/50, 6/50	25/50, 25/50, 26/50, 26/50	32/50, 31/50, 28/50, 12/50	29/50, 33/50, 26/50, 32/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	Kidney: renal tubule adenoma or carcinoma (1/50, 1/50, 4/50, 5/50)	None	None	Liver: hepatocellular adenoma (12/50, 17/50, 18/50, 31/48); hepatocellular carcinoma (6/50, 10/50, 10/50, 16/48); hepatocellular adenoma or carcinoma (17/50, 24/50, 26/50, 41/48)
Level of evidence of carcinogenic activity	Some evidence	No evidence	No evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Mouse bone marrow *in vivo*:	Negative			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Mouse bone marrow *in vivo*:	Negative			
Sex-linked recessive lethal mutations				
Drosophila melanogaster:	Negative			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	Equivocal in male mice; negative in female mice			

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 tetrahydrofuran on 11 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of tetrahydrofuran 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. R.S. Chhabra, NIEHS, introduced the toxicity and carcinogenesis studies of tetrahydrofuran by discussing uses of the chemical and rational for study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplastic lesions in male rats and female mice. The proposed conclusions were *some evidence of carcinogenic activity* of tetrahydrofuran in male F344/N rats, *no evidence of carcinogenic activity* in female F344/N rats and male B6C3F$_1$ mice, and *clear evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Dr. Brown, a principal reviewer, agreed with the proposed conclusions. In view of the central nervous system symptoms present in both species, he suggested that a comment be added to the discussion section regarding histologic studies of the central nervous system in both rats and mice in the 2-year studies. Dr. Chhabra agreed, noting that as with many solvents these are nonspecific types of effects. He said that the United States Environmental Protection Agency has asked industry to submit data on acute neurobehavioral toxicity studies.

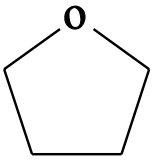
Dr. Ryan, the second principal reviewer, agreed with the proposed conclusions. She had initial reservations about the strength of renal neoplasm data in male rats but after reviewing historical control incidences of these neoplasms in inhalation studies she was persuaded that the level of evidence was appropriate.

Dr. LeBoeuf, the third principal reviewer, did not agree with the proposed conclusions in male rats and female mice. He stated that there was a marginal treatment-related effect in male rats and, further, a treatment-related effect on renal tubule hyperplasia was not observed, which he considered *equivocal evidence of carcinogenic activity*. He said that a detailed step-sectioning of the kidneys would be appropriate. Dr. Chhabra said that step sections were not called for as the staff was confident of the proposed conclusion of *some evidence of carcinogenic activity* based on the number of neoplasms in exposed animals contrasted with the historical rate. Dr. J.R. Hailey, NIEHS, noted that in almost all previous studies in which step sections were performed, ethylbenzene being the exception, if the level of evidence was *some evidence*, the additional sectioning did not support a change to *clear evidence*. Dr. LeBoeuf said that he would defer further comments on the conclusions in female mice until clarification of possible confounding effects of *Helicobacter hepaticus* present in the livers of mice.

Dr. LeBoeuf asked for further discussion around the relevance or interpretation of neoplasm induction when survival is so poor, and perhaps not attributable to neoplasm induction. Dr. J.K. Haseman, NIEHS, pointed out that in this study, male rat survival was low in all groups, exposed and controls alike. In response to a comment from Dr. W.T. Allaben, NCTR, Dr. Haseman agreed that high body weight could be a factor contributing to the overall poor survival in male rats. Dr. L.G. Hart, NIEHS, read comments into the record from Dr. F. Mirer, NTP Board member. Dr. Mirer said that a structural analogy of tetrahydrofuran to furan is misplaced; rather it should be diethyl ether. He commented that, because there were no differences between exposed and chamber control animals in weight gains or mortality, a higher exposure might have been tolerated increasing the sensitivity for detecting carcinogenic effects. Dr. Chhabra said that narcosis was induced at 1,800 ppm, precluding giving higher exposure concentrations.

Dr. Brown moved that the Technical Report on tetrahydrofuran be accepted with revisions discussed and the conclusions as written for male rats, *some evidence of carcinogenic activity*, for female rats and male mice, *no evidence of carcinogenic activity*, and for female mice, *clear evidence of carcinogenic activity*. Dr. Ryan seconded the motion, which was accepted unanimously with seven votes.

INTRODUCTION



TETRAHYDROFURAN

CAS No. 109-99-9

Chemical Formula: C_4H_8O Molecular Weight: 72.10

Synonyms: Butylene oxide; cyclotetramethylene oxide; diethylene oxide; 1,4-epoxybutane; furanidine; hydrofuran; oxacyclopentane; oxolane; tetramethylene oxide

CHEMICAL AND PHYSICAL PROPERTIES

Tetrahydrofuran is a colorless, volatile liquid with an ethereal odor and a pungent taste. Tetrahydrofuran is soluble in ethyl alcohol, ethyl ether, and water (30% at 25° C). It has a flash point of –17.2° C, a melting point of –108.5° C, a boiling point of 66° C, a vapor pressure of 114 mm Hg at 15° C and 204 mm Hg at 30° C, a specific gravity of 0.89, and a vapor density of 2.5 (Juntunen *et al.*, 1984; *Merck Index* online, 1993).

PRODUCTION, USE, AND HUMAN EXPOSURE

Tetrahydrofuran is an organic oxide which differs from a simple ether in that an oxygen atom within the molecule is part of a cyclic arrangement. The principal method of manufacture is by the catalytic hydrogenation of maleic anhydride or furan (*Merck Index* online, 1993). In 1988, tetrahydrofuran production in the United States was 9.38×10^7 pounds. In 1986, 8.12×10^4 pounds were imported (HSDB, 1996). Tetrahydrofuran is used as a reaction medium for Grignard and metal hydride reactions; in the synthesis of butyrolactone, succinic acid, and 1,4-butanediol diacetate; in the fabrication of articles for packaging, transporting, and storing foods; as a solvent for dyes and lacquers; and as a chemical intermediate in polymerization solvent for fat oils, unvulcanized rubber, resins, and plastics. Tetrahydrofuran is also an indirect food additive when it is in the contact surface of articles intended for use in food processing.

Human exposure is primarily from occupational exposure relating to its use as a solvent for resins, adhesives, printers' ink, and coatings. Approximately 90,000 workers in 3,000 plants are exposed from industries related to chemical and allied products and electric, gas, and sanitary services. Electricians, agricultural and biological technicians, electric power linemen, and cable linemen are potentially exposed to tetrahydrofuran. A maximum vapor concentration of 20 ppm was measured during open process coating of cellophane film (HSDB, 1996). The threshold limit value-time-weighted average for tetrahydrofuran is 200 ppm (590 mg/m^3). The short-term exposure limit is 250 ppm (737 mg/m^3) (ACGIH, 1996).

When used as a solvent, significant amounts of tetrahydrofuran may potentially be released into the environment and cause worker exposure because of its

high vapor pressure and water solubility. Once released into the environment, the behavior of tetrahydrofuran is not well understood and very little monitoring data are available. In the atmosphere, tetrahydrofuran should degrade rapidly. Tetrahydrofuran in water may be biodegradable. Spills on soil are expected to rapidly evaporate or leach into the groundwater. Tetrahydrofuran is not expected to bioaccumulate in fish or other aquatic organisms (HSDB, 1996).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

No information on tetrahydrofuran metabolism was found in the literature. Burka and Boyd (1985) have reviewed the metabolism of furan, the parent compound of tetrahydrofuran. Furan is metabolized to an electrophilic species. The subsequent reaction of electrophilic species with tissue nucleophiles takes place primarily at the site of necrosis. It is suggested that furan rings are important in the toxicity of compounds, while tetrahydrofuranyl or other analogues are not generally as toxic as the parent compound. Whether tetrahydrofuran is metabolized to more toxic chemicals is not known. If a carbon atom adjacent to the oxygen atom in the ring is hydroxylated, the product would be γ-butyrolactone, which possesses convulsive properties (Elovaara *et al.*, 1984). γ-Butyrolactone was evaluated for carcinogenicity by gavage administration at doses of 112 and 225 mg/kg in male F344/N rats, 225 and 450 mg/kg in female F344/N rats, and 262 and 525 mg/kg in male and female B6C3F_1 mice (NTP, 1992). There was equivocal evidence of carcinogenic activity of γ-butyrolactone in male mice based on marginally increased incidences of adrenal medulla pheochromocytoma and hyperplasia in the 262 mg/kg group.

In vitro studies show that tetrahydrofuran inhibits the metabolism of a number of drug substrates catalyzed by mixed-function oxidases (Kawalek and Andrews, 1980). Complaints of dizziness and central nervous system effects in workers in the plastic industry prompted Elovaara *et al*. (1984) to conduct an inhalation study in rats to determine body burden of tetrahydrofuran and its effect on activities of drug-metabolizing enzymes. Adult male rats were exposed to tetrahydrofuran vapor at 200, 1,000, or 2,000 ppm, 6 hours per day, 5 days per week, for 2 to 18 weeks. This study showed brain and perirenal fat tetrahydrofuran burdens to be linearly correlated to exposure concentration. After 2 weeks of exposure, the burden of tetrahydrofuran seemed to decrease; this effect may have been due to stimulation of oxidative metabolism, which was supported by increased 7-ethoxycoumarin-*o*-deethylase activity in liver and kidney microsomal preparations from week 2.

Tetrahydrofuran inhibited *O*-dealkylation of 7-ethoxycoumarin by liver microsomal cytochrome P_{450} from Sprague-Dawley rats pretreated with ethanol (Ullrich *et al.*, 1975); at a concentration of 10^{-2} M, tetrahydrofuran blocked 80% of this enzyme activity. Tetrahydrofuran produced a pronounced ligand-type optical difference spectrum in microsomes from ethanol-pretreated female rats, and these microsomes also showed evidence of a new low-spin cytochrome P_{450} species in the presence of tetrahydrofuran. Microsomes from female controls were significantly more sensitive to inhibition of *O*-dealkylation than those from males, providing evidence that well-known gender differences of drug metabolism in rats may be due to differences in the pattern of microsomal cytochrome P_{450} species in males and females (Ullrich *et al.*, 1975).

Humans

No studies on the absorption, distribution, metabolism, or excretion of tetrahydrofuran in humans were found in the literature.

TOXICITY

Experimental Animals

Katahira *et al.* (1982a,b) studied the acute toxicity of 20% tetrahydrofuran in olive oil by intraperitoneal injection in rats and mice. The LD_{50} was 1,900 mg/kg in rats and 2,500 mg/kg in mice. The LC_{50} was estimated to be 21,000 ppm in rats exposed to tetrahydrofuran for 3 hours by inhalation. Rats exposed to 100 to 200 ppm tetrahydrofuran showed no significant effects, except for slight local irritation symptoms such as redness of the nose and eyelids. Rats exposed to 5,000 ppm had marked edema or opacity of the cornea, salivation, and discharge or bleeding from the nasal mucosae. Cataleptoid posture, coma, and clonic muscle spasm indicating

irritation of the central nervous system were also observed.

Irritation of the upper respiratory tract and some injury to the liver and kidney were seen in a number of rats exposed to tetrahydrofuran at a concentration greater than 3,000 ppm, 8 hours a day, for 20 days. A concentration of 25,000 ppm produced anesthesia in dogs and mice (ACGIH, 1986).

Male Sprague-Dawley rats were exposed to 0, 100, 200, 1,000 or 5,000 ppm tetrahydrofuran by inhalation 4 hours a day, 5 days a week, for 12 weeks. Symptoms of intoxication (effects on the central nervous system) were seen in animals exposed to 1,000 or 5,000 ppm; the symptoms were greatest in intensity initially at 5,000 ppm. Later in the study, animals seemed to develop a tolerance to tetrahydrofuran based on the reduced magnitude of irritation effects. Glutamic-oxaloacetic transaminase, cholinesterase, and blood sugar values were increased in rats exposed to 1,000 or 5,000 ppm (Katahira, 1982a,b).

Ikeoka *et al.* (1983, 1984) studied the effects of tetrahydrofuran exposure on the morphology and ciliary activity of tracheal epithelium in rabbits at inhalation exposure concentrations ranging from 100 to 1,200 ppm for 4 hours. The epithelium was investigated by scanning and transmission electron microscopy. The authors concluded that tetrahydrofuran has transient or permanent inhibitory effects on tracheal ciliary activity of the fine structure of epithelial cells. These effects were related to exposure concentration.

Humans

Tetrahydrofuran vapors may cause irritation of the mucous membranes, respiratory system, and skin. Tetrahydrofuran is a strong narcotic. Acute toxicity could lead to narcosis, muscular hypotonia, and disappearance of corneal reflexes, followed by coma and death (HSDB, 1996). Juntunen *et al.* (1984) reported a case history of a 45-year-old man who had been exposed occupationally to tetrahydrofuran and had an appendectomy under enflurane anesthesia. Upon awakening, the patient had several generalized convulsions. Occupational history revealed that for the previous 2 years the patient had run his own business, using insulating materials containing a polyvinyl chloride polymer. The insulation procedure involved the use of the solvent tetrahydrofuran. This case history suggested that interactions of tetrahydrofuran and enflurane may provoke epileptic seizures.

Gosselin *et al.* (1976) assigned a toxicity rating of "very toxic" for tetrahydrofuran, with a probable oral lethal dose of 50 to 500 mg/kg in humans. Severe occipital headaches were reported among technicians testing the pharmacologic properties of tetrahydrofuran in animal experiments.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive toxicology studies on tetrahydrofuran have been performed in support of NTP studies (Mast *et al.*, 1992). These studies addressed the potential for tetrahydrofuran to cause developmental toxicity in rodents. In these studies, pregnant groups of Sprague-Dawley rats and Swiss (CD-1®) mice were exposed to 0, 600, 1,800, or 5,000 ppm tetrahydrofuran by inhalation, 6 hours per day, 7 days per week. Each group consisted of approximately 30 positively mated female rats or mice. Pregnant mice were exposed for 12 consecutive days on days 6 to 17 of gestation, and pregnant rats were exposed for 14 consecutive days on days 6 to 19 of gestation.

Pregnant rats did not exhibit overt symptoms of toxicity other than a reduction in mean body weight in the 5,000 ppm group. The number of implantations, the mean percentage of live pups per litter, the mean percentage of resorptions per litter, and the fetal sex ratio were not affected. Mean fetal body weights in the 5,000 ppm group of rats were significantly less then those in the control group. A total of 1,772 live fetuses in 120 litters were examined for abnormalities. The mean percentage of the litter affected was not significantly different between exposed and control groups for any malformation or variation (Mast *et al.*, 1992).

Mice exhibited overt symptoms of toxicity at the 1,800 and 5,000 ppm tetrahydrofuran concentrations (Mast *et al.*, 1992). Approximately 30% of the animals in the 1,800 ppm group and all the animals in the 5,000 ppm group experienced narcosis during and up to 1 hour after exposure. Seven pregnant female mice in the 5,000 ppm group died during the first

6 days of exposure; this group was removed from exposure to prevent further mortality, and these mice were subsequently provided fresh, filtered air until the end of the study. There were no maternal deaths in the 600 and 1,800 ppm groups. Mean body weights and uterine weights of pregnant mice in the 1,800 and 5,000 ppm groups were significantly less than those of the controls at the end of the study. There were reductions in the percentage of live fetuses per litter for mice in the 1,800 and 5,000 ppm groups. An increase in the incidences of reduced sternebral ossification was correlated to tetrahydrofuran exposure concentration, although differences between groups were not statistically significant. There were no increases in the incidences of other malformations or variations. These results suggest that tetrahydrofuran may be embryotoxic in mice, but if the conceptus survives, development as assessed by this experimental design continues in a normal fashion. The no-observable-adverse-effect level (NOAEL) for maternal toxicity was 1,800 ppm in both rats and mice. The NOAEL for developmental toxicity was 1,800 ppm in rats and 600 ppm in mice.

The developmental toxicity of tetrahydrofuran was studied in CD rats exposed to the chemical by inhalation at concentrations of 0, 200, 500, 2,500, and 5,000 ppm on gestational days 6 through 15 (USEPA/OTS, 1992). The mean number of implantations per dam and the incidence of malformed fetuses were not exposure related. At 5,000 ppm, the fetal variations of reduced body weight and less ossified sternae were significantly different from those of the controls. Embryotoxicity expressed as developmental delay occurred at 5,000 ppm.

CARCINOGENICITY

No experimental animal or human carcinogenicity or epidemiology studies related to tetrahydrofuran were found in the literature. NTP has performed carcinogenicity studies on furan, the parent compound of tetrahydrofuran. When furan was administered by gavage (2, 4, or 8 mg/kg body weight, 5 days a week, for 2 years), it was found to be carcinogenic in F344/N rats based on increased incidences of cholangiocarcinoma and hepatocellular neoplasms of the liver and increased incidences of mononuclear cell leukemia. In male and female $B6C3F_1$ mice, furan induced hepatocellular neoplasms and benign pheochromocytomas of the adrenal gland (NTP, 1993). 1,4-Dioxane, another cyclic ether solvent, is carcinogenic in rats and guinea pigs by the oral route of exposure. 1,4-Dioxane produced malignant tumors in the liver and nasal cavity in rats and tumors of the liver and gallbladder in guinea pigs. 1,4-Dioxane was a promotor in two-stage skin carcinogenic studies in mice. No carcinogenic effect was seen in one inhalation study in rats (IARC, 1976).

GENETIC TOXICITY

Tetrahydrofuran has shown no evidence of mutagenicity in the limited number of tests that have been reported. No induction of mutations was observed in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 treated with tetrahydrofuran, with or without liver S9 metabolic activation enzymes (Mortelmans *et al.*, 1986). No increases in sister chromatid exchanges or chromosomal aberrations were induced by tetrahydrofuran in cultured Chinese hamster ovary cells, with or without S9 (Galloway *et al.*, 1987). Tetrahydrofuran, administered by feeding or injection, did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Valencia *et al.*, 1985). Finally, *in vivo* treatment of male rats with tetrahydrofuran did not induce unscheduled DNA synthesis in hepatocytes (Mirsalis *et al.*, 1983).

STUDY RATIONALE

Tetrahydrofuran was nominated by the National Institute for Occupational Safety and Health to the NTP for carcinogenicity studies because of the high potential for occupational exposure and because of a lack of information on chronic toxicity and carcinogenicity. The Chemical Selection Working Group of the National Cancer Institute nominated tetrahydrofuran from the ethers class study as a representative of the tetrahydrofurans subclass. The nomination was based largely on potential human exposure because the suspicion of carcinogenicity of tetrahydrofuran could not be established on the basis of structure. Inhalation was chosen as the route of exposure because human exposure occurs primarily via this route. Fourteen-week and 2-year whole body inhalation studies were performed in male and female F344/N rats and $B6C3F_1$ mice.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TETRAHYDROFURAN

Tetrahydrofuran was obtained from ChemCentral (Kansas City, MO) in four lots. Lot WK8-6-86 was used during the 14-week studies and lots L-107, 012390, and B081690RS were used in the 2-year studies. Identity, purity, and stability analyses were conducted by the study laboratory and by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix H). Reports on analyses performed in support of the tetrahydrofuran studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

Lots WK8-6-86 and L-107, both clear, colorless liquids, were identified as tetrahydrofuran by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Lots 012390 and B081690RS, also clear, colorless liquids, were identified by infrared spectroscopy. The purities of lots WK8-6-86 and L-107 were determined by elemental analyses, Karl Fischer water analyses, and gas chromatography. The purity of lots 012390 and B081690RS were determined by gas chromatography. Elemental analyses for hydrogen and carbon were generally in agreement with the theoretical values for tetrahydrofuran. Karl Fischer water analysis indicated not more than 0.06% water for lot WK8-6-86 and less than 0.1% water for lot L-107. Gas chromatography of lots WK8-6-86 and L-107 indicated one major peak and no impurities with areas greater than 0.1% relative to the major peak. Peroxide concentrations were no greater than 3 ppm. The overall purity was determined to be approximately 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that tetrahydrofuran was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 25° C. To ensure stability, the bulk chemical was stored at room temperature in the original metal containers under a nitrogen blanket.

Stability was monitored during the 14-week and 2-year studies using gas chromatography; no degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

Tetrahydrofuran vapor was generated with a rotary evaporation system (Büchi Rotavapor, Model EL-131S, Büchi Laboratoriums Technik AG, Flavil, Switzerland). From the condensing column of the rotary evaporator, the vapor entered a short distribution manifold from which individual delivery lines carried metered amounts of vapor to each exposure chamber. When equilibrium was reached, each valve was opened to allow the flow of vapor into the chamber. At each chamber location, the vapor was injected into the chamber inlet duct where it was further diluted with charcoal- and HEPA-filtered chamber air to achieve the desired exposure concentration. Stainless-steel chambers designed at Battelle Northwest Laboratories were used for all studies (Hazleton 2000, Aberdeen, MD). The chamber was designed so that uniform vapor concentrations could be maintained throughout the chamber when catch pans were in position. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that tetrahydrofuran vapor and not aerosol was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

The chamber concentrations of tetrahydrofuran were monitored using an on-line gas chromatograph with a

flame ionization detector. Samples were drawn and analyzed from each exposure chamber, the control chamber, the exposure suite, the on-line standard, and a filtered air blank. Summaries of the chamber concentrations during the studies are presented in Appendix H.

CHAMBER ATMOSPHERE CHARACTERIZATION

The times for the exposure concentrations to build up to 90% of the final exposure concentration (T_{90}) and to decay to 10% of the exposure concentration (T_{10}) were measured in all studies with and without animals present. At a chamber airflow rate of 15 air changes per hour, the theoretical value for both T_{90} and T_{10} is approximately 12.5 minutes; the T_{90} value chosen for all studies was 12 minutes. Actual T_{90} values ranged from 5 to 15 minutes in the 14-week studies, with and without animals in the chambers, and from 7 to 15 minutes without animals and 8 to 18 minutes with animals in the 2-year studies. T_{10} values ranged from 7 to 10 minutes without animals and 9 to 14 minutes with animals in the 14-week studies; in the 2-year studies, T_{10} ranged from 9 to 13 minutes without animals and from 9 to 15 minutes with animals in the chambers. Uniformity of exposure concentrations in all chambers was acceptable.

The persistence of tetrahydrofuran in the 1,800 ppm exposure chamber after shutting off the system, with and without animals present, was monitored during the 2-year studies. The concentration of tetrahydrofuran in the exposure chamber fell to less than 1% of the beginning concentration within 30 minutes with no animals present; with animals present, the time to decay to less than 1% of the initial concentration ranged from 27 to 60 minutes. Tetrahydrofuran concentrations in the building exhaust and room air were also monitored during all studies.

Information supplied by the manufacturer indicated that all lots of tetrahydrofuran contained 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a stabilizer. BHT is less volatile than tetrahydrofuran and was expected to be depleted in the generated test atmosphere. BHT and peroxide concentrations were determined from samples taken from the generator reservoir for tetrahydrofuran stability analyses. BHT was analyzed with gas chromatography. Peroxide concentration in the generator flask was analyzed by iodometric titration with sodium thiosulfate to a colorimetric endpoint. No BHT or organic peroxides were observed in the exposure chambers in the 14-week studies. During the 2-year studies, no significant accumulation of peroxides was found. During all studies, tetrahydrofuran was monitored for stability in the generator reservoir and exposure chambers by gas chromatography. Results indicated that tetrahydrofuran was stable in the generator reservoir. No contaminants or degradation products were found during the 14-week studies. No other contaminants or degradation products at concentrations greater than 0.3% were found in distribution lines or in 200 or 1,800 ppm exposure chamber samples during the 2-year study. No enrichment of BHT was detected.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to tetrahydrofuran and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 13 to 15 days and were approximately 7 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female chamber control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix J).

Groups of 10 male and 10 female rats and mice were exposed to tetrahydrofuran at concentrations of 0, 66, 200, 600, 1,800, and 5,000 ppm by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 14 weeks. The chamber control animals were exposed to HEPA filtered air. Water was available *ad libitum*; feed was available *ad libitum* except during exposure periods. Rats and mice were housed individually. Clinical findings were recorded weekly. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 14-week studies, blood was collected from the retroorbital plexus of all rats for hematology and clinical chemistry analyses. Blood for hematology determinations was placed in collection tubes containing potassium EDTA as an anticoagulant. Blood for clinical chemistry evaluations was placed in tubes without anticoagulant and allowed to clot; these samples were then centrifuged and serum was removed. Erythrocyte and leukocyte counts, hematocrit, hemoglobin concentration, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and platelet counts were measured on an Ortho ELT-8/ds hematology counter (Ortho Instruments, Westwood, MA). Differential leukocyte counts, blood cell morphology, and nucleated erythrocyte counts were determined by light microscopic examination of blood films stained with Wright-Giemsa. Reticulocytes were counted as a reticulocyte/erythrocyte ratio using a Miller disc. Clinical chemistry determinations were performed on an Abbott VP chemistry analyzer (Abbott Laboratories, Abbott Park, IL) with commercially available reagents. The hematology and clinical chemistry parameters measured are listed in Table 1.

A necropsy was performed on all animals. The heart, liver, lung, right kidney, spleen, 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 chamber control and 5,000 ppm groups of rats and mice. Target organs were examined to a no-effect level in groups of animals exposed to lower concentrations of tetrahydrofuran. Additionally, all gross lesions and tissue masses and selected tissues of rats and mice in the lower exposure groups were examined. Table 1 lists the tissues and organs examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice were exposed to tetrahydrofuran at concentrations of 0, 200, 600, and 1,800 ppm by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA), for use in the 2-year studies. Rats and mice were quarantined for 14 or 15 days before the beginning of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 7 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Animal Maintenance

Rats and mice were housed individually. Water was available *ad libitum*; feed was available *ad libitum* except during exposure periods. Cages and racks were rotated within the inhalation chambers weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix I.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded monthly for 12 weeks (rats) or 13 weeks (mice), at week 15 (rats) or week 16 (mice), monthly thereafter through week 91 (rats) or week 92 and (mice) until the end of the studies. Body weights were recorded weekly for 12 weeks (rats) or 13 weeks (mice), and monthly thereafter through week 91 (rats) or week 92 (mice) until the end of the studies.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 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 were examined. Complete histopathologic examinations were performed on all animals. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management

System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the following organs: adrenal gland (male rats), bone marrow (male mice), brain (female mice), clitoral gland (female rats), epididymis (male mice), forestomach (male mice), kidney (male rats and mice), liver (male rats and male and female mice), lung (male and female rats and male mice), lymph nodes (male and female mice and male rats), mammary gland (female rats), penis (male mice), pituitary gland (male rats), prostate gland (male mice), skin (male and female mice and female rats), small intestine (female mice), spleen (male rats and mice), thyroid gland (male and female rats and male mice), urinary bladder (male mice), and uterus (female mice).

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

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, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the 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 chamber 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.

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). Clinical chemistry and hematology data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to 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).

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, neoplasm incidences from the NTP historical control database, which is updated yearly are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits 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 tetrahydrofuran was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, sister chromatid exchanges and chromosomal aberrations in mouse bone marrow cells, and increases in the frequency of micronucleated erythrocytes in peripheral blood of mice. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of tetrahydrofuran 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 molecular structure and the effects 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 chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical mutagenesis and the somatic mutation theory of cancer (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 correlate less 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 the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are 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 appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associationsbetween induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall under-standing of the risks associated with exposure to a particular chemical.

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Tetrahydrofuran

14-Week Studies	2-Year Studies
Study Laboratory Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Strain and Species Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source Simonsen Laboratories, Inc. (Gilroy, CA)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies Rats: 13 days Mice: 15 days	Rats: 14 days Mice: 15 days
Average Age When Studies Began 7 weeks	7 weeks
Date of First Exposure Rats: 10 February 1987 Mice: 12 February 1987	Rats: 14 December 1989 Mice: 7 December 1989
Duration of Exposure 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 14 weeks	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks
Date of Last Exposure Rats: 12 May (males) or 13 May (females) 1987 Mice: 14 May (males) or 15 May (females) 1987	Rats: 13 December 1991 Mice: 6 December 1991
Necropsy Dates Rats: 13 May (males) or 14 May (females) 1987 Mice: 15 May (males) or 16 May (females) 1987	Rats: 16-18 December 1991 Mice: 9-13 December 1991
Average Age at Necropsy 20 weeks	112 weeks
Size of Study Groups 10 males and 10 females	50 males and 50 females
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 14-week studies
Animals per Cage 1	1
Method of Animal Identification Toe clip	Tail tattoo

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Tetrahydrofuran (continued)

14-Week Studies	2-Year Studies
Diet NIH-07 open formula pelleted feed (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* except during exposure periods, changed weekly	Same as 14-week studies
Water Distribution Tap water (Richland municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Same as 14-week studies
Cages Stainless-steel wire-bottom (Hazleton Systems, Inc., Aberdeen, MD), rotated weekly	Same as 14-week studies
Bedding/Cage Board Techsorb® (Shepherd Specialty Papers, Inc., Kalamazoo, MI), changed during non-exposure periods, 7 days per week	Techsorb® (Shepherd Specialty Papers, Inc., Kalamazoo, MI), changed during non-exposure periods, 7 days per week, and untreated cageboard (Bunzl Cincinnati Paper Co., Cincinnati, OH)
Chambers Stainless steel (Lab Products, Inc., Aberdeen, MD), changed weekly	Same as 14-week studies
Chamber Air Supply Filters Single HEPA (Flanders Filters, Inc., San Rafael, CA) and charcoal (RSE, Inc., New Baltimore, MI); checked semiannually	Same as 14-week studies
Chamber Environment Temperature: 19.6° to 26.6° C Relative humidity: 29% to 75% Fluorescent light: 12 hours/day Chamber air changes: 15 ± 3 per hour	Temperature: 19.6° to 26.8° C Relative humidity: 22% to 82% Fluorescent light: 12 hours/day Chamber air changes: 11 to 22 per hour
Exposure Concentrations Chamber control, 66, 200, 600, 1,800, or 5,000 ppm	Chamber control, 200, 600, or 1,800 ppm
Type and Frequency of Observation Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded weekly.	Observed twice daily; animals were weighed weekly through week 12 (rats) or week 13 (mice), monthly thereafter through week 91 (rats) or week 92 (mice) and clinical findings were recorded initially, weekly through week 12 (rats) or week 13 (mice), at week 15 (rats) or week 16 (mice), monthly thereafter through week 91 (rats) or week 92 (mice), and every 2 weeks until the end of the studies.
Method of Sacrifice CO_2 asphyxiation	CO_2 asphyxiation
Necropsy Necropsy was performed on all animals. Organs weighed were heart, liver, lung, right kidney, spleen, and thymus.	Necropsy was performed on all animals.

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Tetrahydrofuran (continued)

14-Week Studies	2-Year Studies
Clinical Pathology Blood was collected from the retroorbital sinus of all rats at the end of the study. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and nucleated erythrocyte counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; platelet count; and total leukocyte count and differentials ***Clinical Chemistry***: urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids	None
Histopathology Complete histopathology was performed on all chamber control and 5,000 ppm rats and mice and all gross lesions, and target organs in lower exposure groups to a no-effect level. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland (rats), esophagus, gallbladder (mice), heart and aorta, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, larynx, liver, lung and mainstem bronchi, lymph nodes (mandibular, bronchial, mesenteric, and mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, spleen, sternebrae (with marrow), stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, femur with marrow, gallbladder (mice), heart and aorta, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, larynx, liver, lung and mainstem bronchi, lymph nodes (mandibular, bronchial, mesenteric, and mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

14-WEEK STUDY

All rats survived until the end of the study (Table 2). Final mean body weights and body weight gains of exposed groups of male and female rats were similar to those of the chamber controls. Immediately after exposure, male and female rats in the 5,000 ppm groups exhibited ataxia, which was described as irregular movement with lack of coordination.

TABLE 2
Survival and Body Weights of Rats in the 14-Week Inhalation Study of Tetrahydrofuran

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	109 ± 3	358 ± 6	249 ± 6	
66	10/10	108 ± 3	351 ± 7	243 ± 5	98
200	10/10	110 ± 3	365 ± 10	255 ± 8	102
600	10/10	106 ± 3	361 ± 5	255 ± 5	101
1,800	10/10	107 ± 3	366 ± 9	259 ± 6	102
5,000	10/10	111 ± 3	342 ± 7	231 ± 6	96
Female					
0	10/10	91 ± 2	205 ± 5	114 ± 4	
66	10/10	95 ± 2	205 ± 5	111 ± 4	100
200	10/10	92 ± 2	203 ± 4	112 ± 3	99
600	10/10	94 ± 2	212 ± 4	118 ± 3	103
1,800	10/10	93 ± 2	208 ± 4	115 ± 4	101
5,000	10/10	93 ± 2	212 ± 3	120 ± 3	103

[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group were not significant by Dunnett's test.

The 14-week hematology and clinical chemistry data for rats in the subchronic inhalation study of tetrahydrofuran are presented in Table G1. The hematologic and biochemical differences were minimal, with most values falling within physiologic ranges. These differences did not demonstrate a strong exposure relationship and only occurred in the 5,000 ppm groups; although they may represent a biologic effect, they were not considered toxicologically relevant. A minimal mature neutrophilia, evidenced by increased segmented neutrophil numbers, occurred in 5,000 ppm male rats. Neutrophilia

is often a result of an increased tissue demand for granulocytes due to inflammation; there was microscopic evidence of a mild suppurative submucosal gastric inflammation that could account for the neutrophilia. Minimal increases of serum bile acid concentration occurred in 5,000 ppm male and female rats and could be consistent with either a cholestatic event or hepatocellular injury. There was no evidence of cholestasis or hepatocellular necrosis/leakage. Serum bile acid concentration can be affected, however, by other mechanisms such as altered enterohepatic circulation and impaired hepatic function, and noncholestatic liver injury can increase circulating bile acid concentrations.

Absolute and relative thymus and spleen weights of male and female rats exposed to 5,000 ppm were significantly less than those of the chamber controls (Table F1). Absolute and relative liver weights of female rats exposed to 5,000 ppm were significantly greater than those of the chamber controls. The decreases in thymus and spleen weights were not accompanied by readily appreciable histopathologic changes and may have been due to stress associated with tetrahydrofuran administration in these groups.

No exposure-related gross lesions were observed in male or female rats at necropsy. Microscopically, the incidences of minimal to mild hyperplasia of the forestomach in male and female rats exposed to 5,000 ppm tetrahydrofuran were significantly greater than those in the chamber controls (Table 3). Minimal suppurative inflammation characterized by submucosal neutrophilic infiltrates and edema was associated with areas of forestomach hyperplasia in two male and four female rats exposed to 5,000 ppm. The gastric lesions may have been due to the irritant effect of tetrahydrofuran ingested during exposure.

TABLE 3
Incidences of Selected Nonneoplastic Lesions of the Forestomach in Rats in the 14-Week Inhalation Study of Tetrahydrofuran

	Chamber Control	66 ppm	200 ppm	600 ppm	1,800 ppm	5,000 ppm
Male						
Number Examined Microscopically	10	—[a]	—	—	10	10
Inflammation, Suppurative[b]	0				0	2 (2.0)[c]
Hyperplasia	0				0	5*
Female						
Number Examined Microscopically	10	—	—	—	10	10
Inflammation, Suppurative	0				0	4* (2.0)
Hyperplasia	0				0	8**

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

Exposure Concentration Selection Rationale: Based on clinically observed ataxia and organ weight and histopathologic effects observed in rats exposed to 5,000 ppm, the exposure concentrations selected for the 2-year inhalation study in rats were 0, 200, 600, and 1,800 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 1). Survival of male and female rats exposed to tetrahydrofuran was similar to that of the chamber controls. Survival of male rats was approximately 50% at week 91; however, increased mortality occurred in all groups of males during the last 55 days of the study.

Body Weights and Clinical Findings

Mean body weights of exposed groups of male and female rats were similar to those of the chamber controls throughout the study (Figure 2; Tables 5 and 6). No clinical findings related to tetrahydrofuran exposure were observed in male or female rats.

TABLE 4
Survival of Rats in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	1	1	0	0
Moribund	31	39	40	34
Natural deaths	6	4	5	10
Animals surviving to study termination	12	6	5	6
Percent probability of survival at end of study[b]	25	12	10	12
Mean survival (days)[c]	616	626	627	627
Survival analysis[d]	P=0.538	P=0.290	P=0.204	P=0.330
Female				
Animals initially in study	50	50	50	50
Moribund	18	22	19	19
Natural deaths	7	3	5	5
Animals surviving to study termination	25	25	26	26
Percent probability of survival at end of study	50	50	52	52
Mean survival (days)	657	665	685	671
Survival analysis	P=1.000N	P=1.000N	P=0.939N	P=1.000N

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

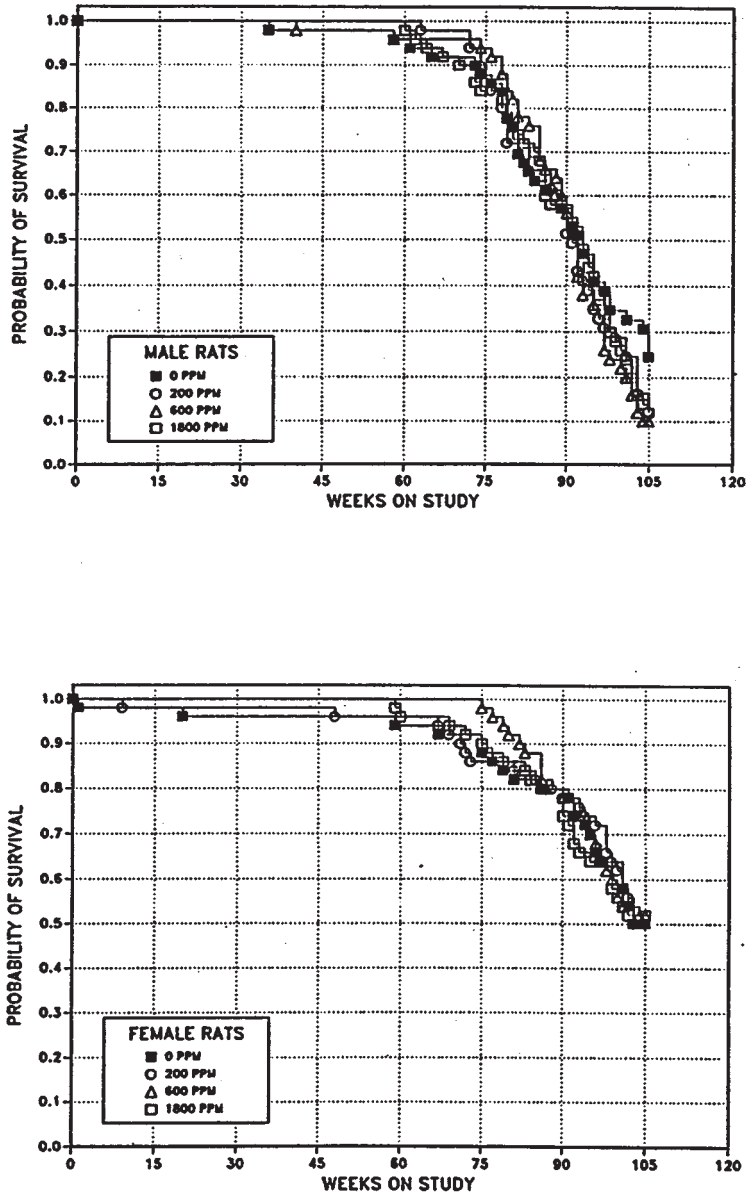


FIGURE 1
Kaplan-Meier Survival Curves for Rats Exposed to Tetrahydrofuran by Inhalation for 2 Years

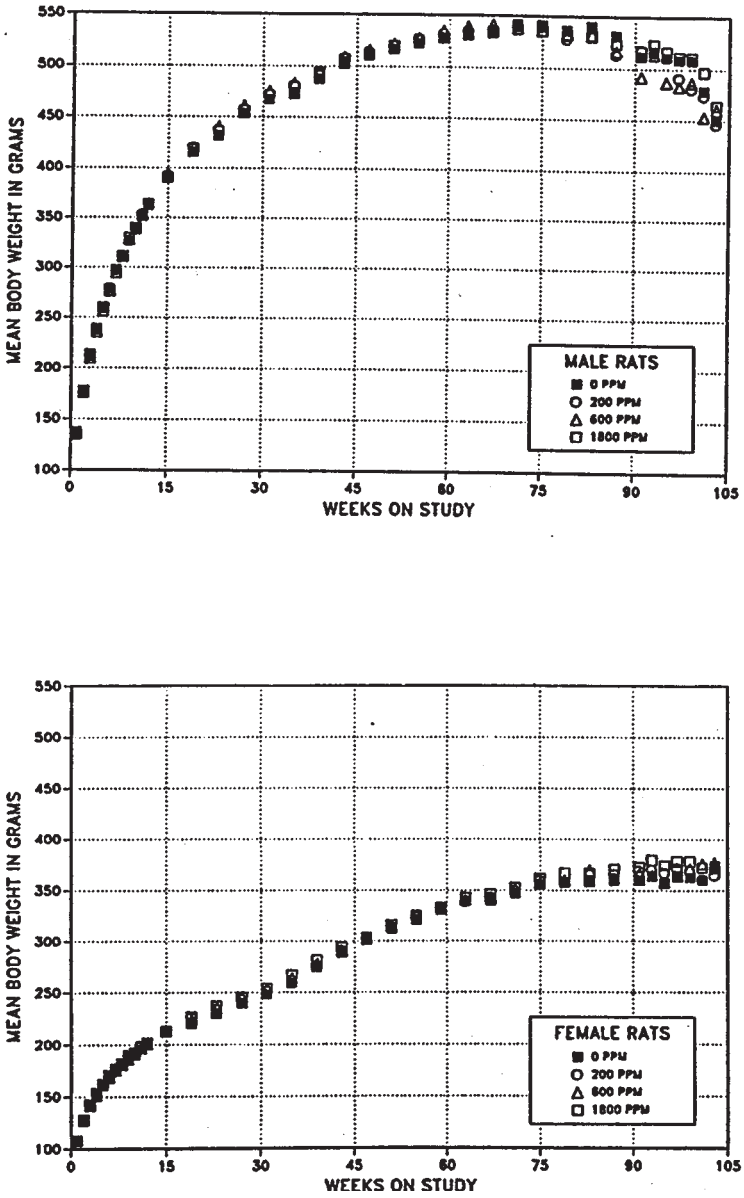


FIGURE 2
Growth Curves for Rats Exposed to Tetrahydrofuran by Inhalation for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran

Weeks on Study	Chamber Control		200 ppm			600 ppm			1,800 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	137	50	135	98	50	136	99	50	134	98	50
2	178	50	177	99	50	176	99	50	177	100	50
3	213	50	212	99	50	210	98	50	212	99	50
4	238	50	238	100	50	235	99	50	237	100	50
5	259	50	259	100	50	257	99	50	260	100	50
6	278	50	280	100	50	276	99	50	277	100	50
7	298	50	297	100	50	295	99	50	294	99	50
8	312	50	311	100	50	311	100	50	312	100	50
9	327	50	326	100	50	328	100	50	330	101	50
10	338	50	339	101	50	338	100	50	340	101	50
11	351	49	353	101	50	352	100	50	351	100	50
12	362	49	364	101	50	364	101	50	364	101	50
15	391	49	393	100	50	394	101	50	390	100	50
19	415	49	420	101	50	420	101	50	419	101	50
23	431	49	438	102	50	440	102	50	436	101	50
27	453	49	458	101	50	461	102	50	456	101	50
31	467	49	473	101	50	476	102	50	472	101	50
35	472	49	482	102	50	483	102	50	479	102	50
39	487	48	491	101	50	495	102	50	493	101	50
43	502	48	504	100	50	509	101	49	507	101	50
47	510	48	514	101	50	516	101	49	512	100	50
51	517	48	520	101	50	522	101	49	520	101	50
55	522	48	528	101	50	528	101	49	526	101	50
59	529	47	532	101	50	535	101	48	528	100	50
63	533	46	535	101	49	540	101	48	531	100	48
67	535	45	536	100	49	541	101	48	534	100	46
71	542	45	540	100	49	538	99	48	537	99	45
75	542	43	540	100	43	537	99	47	535	99	42
79	537	39	528	98	40	533	99	43	532	99	40
83	540	32	531	98	33	533	99	38	531	98	36
87	531	30	513	97	32	517	97	33	524	99	30
91	512	28	518	101	25	492	96	27	517	101	29
93	516	25	516	100	20	513	99	19	523	101	25
95	511	21	511	100	17	487	95	19	517	101	21
97	508	19	491	97	16	483	95	15	512	101	19
99	508	17	481	95	15	487	96	12	511	101	14
101	479	17	474	99	13	453	95	11	497	104	12
103	450	16	447	99	11	461	102	7	465	103	10
Means for weeks											
1-13	274		274	100		273	99		274	100	
14-52	465		469	101		472	102		468	101	
53-103	518		514	99		511	98		520	100	

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran

Weeks on Study	Chamber Control		200 ppm			600 ppm			1,800 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	108	50	108	101	50	108	100	50	107	99	50
2	127	49	127	100	50	127	100	50	128	101	50
3	143	49	143	100	50	141	99	50	142	100	50
4	152	49	153	101	50	151	100	50	154	102	50
5	161	49	163	101	50	161	100	50	163	101	50
6	170	49	170	100	50	168	99	50	171	101	50
7	177	49	178	100	50	175	99	50	177	100	50
8	181	49	182	101	50	181	100	50	183	101	50
9	188	49	189	101	49	186	99	50	190	101	50
10	191	49	193	102	49	191	100	50	192	101	50
11	196	49	199	102	49	197	101	50	198	101	50
12	200	49	202	101	49	201	100	50	202	101	50
15	212	49	214	101	49	213	101	50	213	100	50
19	220	49	226	103	49	224	102	50	227	103	50
23	229	48	234	102	49	234	102	50	237	103	50
27	239	48	243	101	49	245	103	50	246	103	50
31	248	48	251	101	49	254	102	50	254	103	50
35	259	48	262	101	49	264	102	50	267	103	50
39	275	48	276	101	49	278	101	50	282	103	50
43	289	48	291	101	49	291	101	50	294	102	50
47	301	48	303	101	49	302	100	50	303	101	50
51	312	48	314	101	48	315	101	50	316	101	50
55	321	48	324	101	48	325	102	50	326	102	50
59	330	47	333	101	48	333	101	50	333	101	50
63	339	47	338	100	48	340	100	50	343	101	48
67	340	46	343	101	47	343	101	50	346	102	48
71	347	46	350	101	45	351	101	50	353	102	47
75	356	44	360	101	43	357	101	49	362	102	46
79	357	42	359	100	43	360	101	47	367	103	43
83	358	41	365	102	42	370	103	44	367	102	42
87	359	40	366	102	41	362	101	41	371	103	40
91	360	39	369	103	39	368	102	39	373	104	36
93	364	37	370	102	39	365	100	39	380	104	33
95	357	36	367	103	37	358	100	36	374	105	32
97	364	33	372	102	36	364	100	33	378	104	32
99	362	32	369	102	32	371	103	30	378	104	32
101	360	31	361	100	31	376	104	28	372	103	28
103	374	25	365	98	28	377	101	27	372	99	26
Means for weeks											
1-13	166		167	101		166	100		167	101	
14-52	258		261	101		262	101		264	102	
53-103	353		357	101		358	101		362	103	

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

Kidney: The incidences of renal tubule epithelial adenoma were marginally increased in 600 and 1,800 ppm males. Two male rats receiving 1,800 ppm had renal tubule epithelial carcinomas. Renal tubule epithelial adenoma or carcinoma (combined) occurred with a positive trend in male rats (Tables 7 and A3). Histologically, the majority of the adenomas were well-circumscribed nodular masses (usually larger than 5 or more tubular diameters), some of which were detected grossly. Adenomas were composed of multiple solid nests of polygonal basophilic cells separated by a delicate vascular stroma. The neoplastic cells showed mild cellular and nuclear pleomorphism and atypia, and occasional mitotic cells were evident. Although not statistically significant, the incidences of adenoma or carcinoma (combined) in the 600 and 1,800 ppm males exceeded the historical range for chamber controls in 2-year NTP inhalation studies (Tables 7 and A4). Renal tubule neoplasms were not observed in exposed female rats (Table B1).

Mammary gland: The incidences of fibroadenoma in female rats exposed to 600 or 1,800 ppm tetrahydrofuran were slightly greater than those in the chamber controls (chamber controls, 23/50; 200 ppm, 22/50; 600 ppm, 29/50; 1,800 ppm, 31/50; Table B3). The trend was marginally significant (P=0.031), but the pairwise comparisons were not. The neoplasm incidences in all groups (including chamber controls) exceeded the historical control range for this neoplasm in NTP inhalation studies (Table B4). These high neoplasm incidences were likely due to that fact that the animals in this study were unusually heavy, and the incidence of mammary gland fibroadenoma is strongly correlated with body weight (Seilkop, 1995). There was also no evidence of an increase in the incidences of malignant mammary gland neoplasms in female rats (5/50, 5/50, 5/50, 3/50; Table B3). Male rats exposed to 1,800 ppm also had a slightly greater incidence of mammary gland fibroadenoma than that in the chamber controls (0/50, 2/50, 3/50, 4/50; Table A3), but this difference was not statistically significant. Neither of these marginal increases in mammary gland neoplasm incidences were considered to be chemical related.

Testes: The incidences of testicular adenoma in exposed male rats were greater than that in the chamber controls (23/50, 31/50, 31/50, 34/50; Table A3). Although the neoplasm incidence in the 1,800 ppm group was significantly elevated relative to the chamber controls, it was similar to the historical control incidence in NTP inhalation studies (68.7%; range, 54%-83%). Thus, the apparent increase may be an aberration due to an unusually low incidence of adenoma in the chamber controls.

TABLE 7
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Number Examined Microscopically	50	50	50	50
Nephropathy, Chronic[a]	48 (3.0)[b]	50 (2.9)	50 (3.1)	50 (3.0)
Renal Tubule, Adenoma				
Overall rate[c]	1/50 (2%)	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rate[d]	8.3%	16.7%	18.8%	18.6%
Terminal rate[e]	1/12 (8%)	1/6 (17%)	0/5 (0%)	0/6 (0%)
First incidence (days)	733 (T)	733 (T)	631	668
Logistic regression test[f]	P=0.213	P=0.602	P=0.159	P=0.262
Renal Tubule, Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Renal Tubule, Adenoma or Carcinoma[g]				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	8.3%	16.7%	18.8%	38.3%
Terminal rate	1/12 (8%)	1/6 (17%)	0/5 (0%)	1/6 (17%)
First incidence (days)	733 (T)	733 (T)	631	668
Logistic regression test	P=0.037	P=0.602	P=0.159	P=0.065

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals with kidney 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 chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[g] Historical incidence for 2-year NTP inhalation studies with chamber controls (mean ± standard deviation): 6/652 (0.9% ± 1.3%); range, 0%-4%

MICE

14-WEEK STUDY

Two male mice exposed to 5,000 ppm died during weeks 2 and 8 of the study; one male mouse from the 5,000 ppm group was killed in a moribund state during week 4. The two spontaneous deaths were attributed to suppurative pyelonephritis; the third mouse had no significant gross lesions that would explain the cause of moribundity. All female mice survived until the end of the study. The final mean body weights and body weight gains of all exposed groups of male mice were similar to those of the chamber controls (Table 8). The final mean body weight and body weight gain of the 5,000 ppm female mice were significantly greater than those of the chamber controls. Male and female mice exposed to 1,800 or 5,000 ppm were observed to be in a state of narcosis (described as stupor) during exposure periods. Mice exposed to 1,800 ppm were fully awake and alert immediately after exposure; however, mice exposed to 5,000 ppm required up to 2 hours for recovery.

TABLE 8
Survival and Body Weights of Mice in the 14-Week Inhalation Study of Tetrahydrofuran

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	24.4 ± 0.3	36.8 ± 0.8	12.5 ± 0.7	
66	10/10	24.7 ± 0.4	36.8 ± 0.5	12.1 ± 0.4	100
200	10/10	24.7 ± 0.3	35.3 ± 0.7	10.6 ± 0.5	96
600	10/10	24.4 ± 0.3	36.2 ± 0.8	11.8 ± 0.7	98
1,800	10/10	24.3 ± 0.4	36.4 ± 0.8	12.0 ± 0.6	99
5,000	7/10[c]	24.5 ± 0.4	34.8 ± 1.0	10.1 ± 0.8	95
Female					
0	10/10	20.0 ± 0.4	31.7 ± 1.1	11.8 ± 0.8	
66	10/10	19.6 ± 0.2	31.6 ± 0.6	12.0 ± 0.5	100
200	10/10	19.8 ± 0.3	33.1 ± 1.1	13.3 ± 1.0	104
600	10/10	19.7 ± 0.3	33.0 ± 0.9	13.3 ± 0.6	104
1,800	10/10	20.1 ± 0.3	32.4 ± 1.1	12.3 ± 1.0	102
5,000	10/10	20.0 ± 0.3	36.2 ± 0.9**	16.2 ± 0.7**	114

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Week of death: 2, 4, 8

Absolute and relative liver weights of male mice exposed to 600 ppm or greater and of female mice exposed to 1,800 or 5,000 ppm were significantly greater than those of the chamber controls (Table F2). Absolute and relative lung and heart weights of female mice exposed to 5,000 ppm were significantly less than those of the chamber controls. Absolute and relative thymus weights of male mice exposed to 600, 1,800, or 5,000 ppm were significantly less than those of the chamber controls. Absolute and relative spleen weights of male and female mice exposed to 5,000 ppm were significantly less than those of the

chamber controls. Although there were decreases in thymus and spleen weights, corresponding histopathologic changes were not readily appreciable. However, the spleens of male and female mice exposed to 5,000 ppm had smaller cross sections. The significance of these organ weight differences is not clear, but the differences may be due to stress associated with tetrahydrofuran administration.

No exposure-related gross lesions were observed in male or female mice at necropsy. Microscopically, the incidences of minimal to mild centrilobular cytomegaly of the liver in male and female mice exposed to 5,000 ppm were significantly greater than those in the chamber controls (Table 9). Cytomegalic hepatocytes had slight karyomegaly and increased cytoplasmic volume; the cytoplasm also appeared granular and less vacuolated than that of midzonal and periportal hepatocytes. The increase in liver weights and the mild histopathologic changes in the liver are suggestive of a treatment effect in the organ.

The adrenal glands of all female mice exposed to 5,000 ppm had mild degeneration of the X-zone of the innermost cortex (Table 9). In contrast to chamber control mice, the X-zones of exposed groups of female mice were thinner and lacked adipocytes (fat cells) that are normally present in this region of the adrenal cortex during early life. The X-zone of female mice typically undergoes regression with loss of fat cells by early adulthood. Uterine atrophy, characterized grossly by small uteri and microscopically by fewer numbers of uterine glands, was observed in all female mice exposed to 5,000 ppm (Table 9). Whether the adrenal gland X-zone degeneration or the uterine atrophy observed in this study represented an acceleration of normal aging changes due to a hormonal effect or an organ-specific, exposure-related, target-organ effect is not known.

TABLE 9
Incidences of Selected Nonneoplastic Lesions in Mice in the 14-Week Inhalation Study of Tetrahydrofuran

	Chamber Control	66 ppm	200 ppm	600 ppm	1,800 ppm	5,000 ppm
Male						
Liver[a]	10	—[b]	—	—	10	10
Cytomegaly, Centrilobular[c]	0				1 (1.0)[d]	7** (2.0)
Female						
Adrenal Cortex	10	—	—	—	10	10
Degeneration, Cortex, X-zone	0				0	10** (2.0)
Liver	10	—	—	—	10	10
Cytomegaly, Centrilobular	0				0	10** (1.0)
Uterus	10	—	—	—	10	10
Atrophy	0				0	10** (2.0)

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

Exposure Concentration Selection Rationale: Based on narcosis observed in male and female mice exposed to tetrahydrofuran, the exposure concentrations selected for the 2-year inhalation study in mice were 0, 200, 600, and 1,800 ppm. A transient state of narcosis was observed in 1,800 and 5,000 ppm mice immediately after exposure in the 14-week studies. The animals developed some tolerance to this effect by the end of the studies. It was predicted that male mice in the 1,800 ppm group in the 2-year studies might develop a complete tolerance to sedative effect and, therefore, sedation might not have any adverse effect on the survival related to tetrahydrofuran exposure.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 10 and in the Kaplan-Meier survival curves in Figure 3. After week 36, the survival of 1,800 ppm male mice was significantly less than that of the chamber controls; the average lifespan (456 days) of male mice in the 1,800 ppm exposure group was significantly less than that of the chamber controls (689 days). Survival of males exposed to 200 or 600 ppm and of all exposed female groups was similar to that of the chamber controls.

Body Weights and Clinical Findings

Mean body weights of male and female mice exposed to tetrahydrofuran were similar to those of the chamber controls throughout the study (Figure 4; Tables 11 and 12). Clinical findings related to exposure were not observed in female mice. Male mice exposed to 1,800 ppm were observed to be in a state of narcosis during and up to 1 hour after the exposure periods. The mice were limp, with their feet hanging through the mesh of the cage floor, and the preputial fur was wet with urine.

TABLE 10
Survival of Mice in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	11	12	18	24
Natural deaths	7	7	4	14
Animals surviving to study termination	32	31	28	12
Percent probability of survival at end of study[a]	64	62	56	24
Mean survival (days)[b]	689	671	666	456
Survival analysis[c]	P<0.001	P=0.839	P=0.384	P<0.001
Female				
Animals initially in study	50	50	50	50
Accidental deaths[d]	5	1	1	0
Moribund	13	10	20	13
Natural deaths	3	6	3	5
Animals surviving to study termination	29	33	26	32
Percent probability of survival at end of study	64	67	53	64
Mean survival (days)	615	672	665	678
Survival analysis	P=0.917	P=0.907N	P=0.439	P=1.000

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

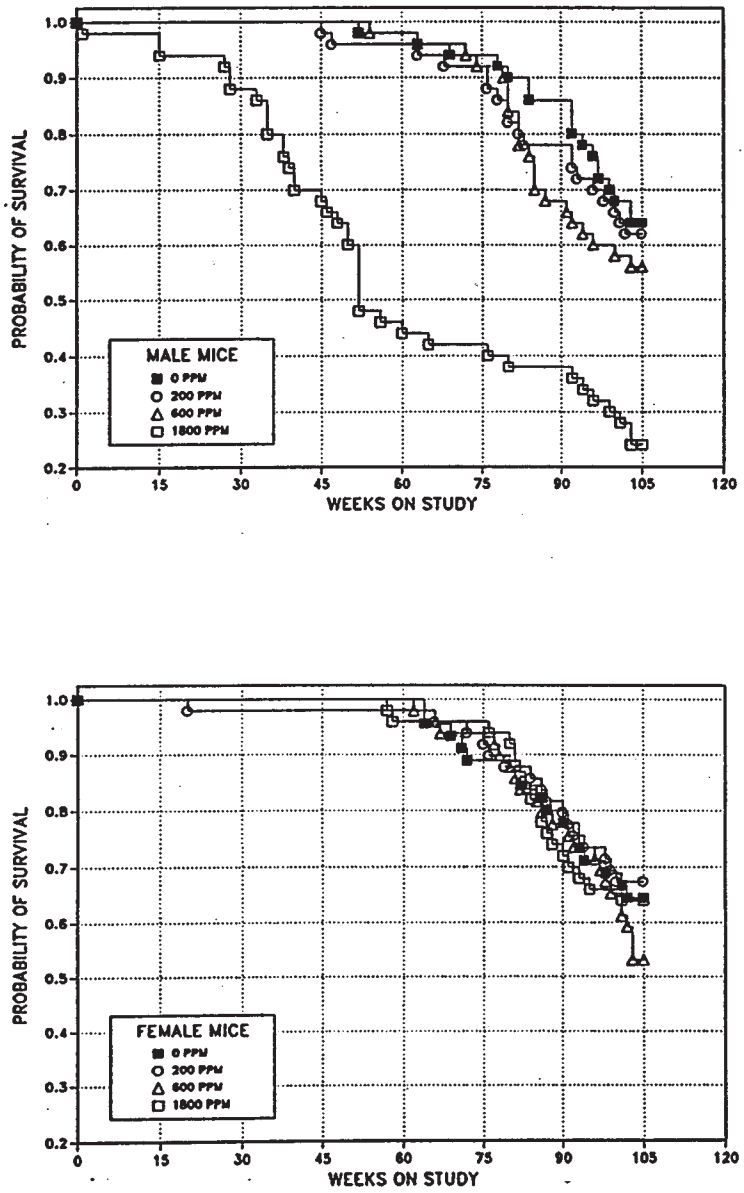


FIGURE 3
Kaplan-Meier Survival Curves for Mice Exposed to Tetrahydrofuran by Inhalation for 2 Years

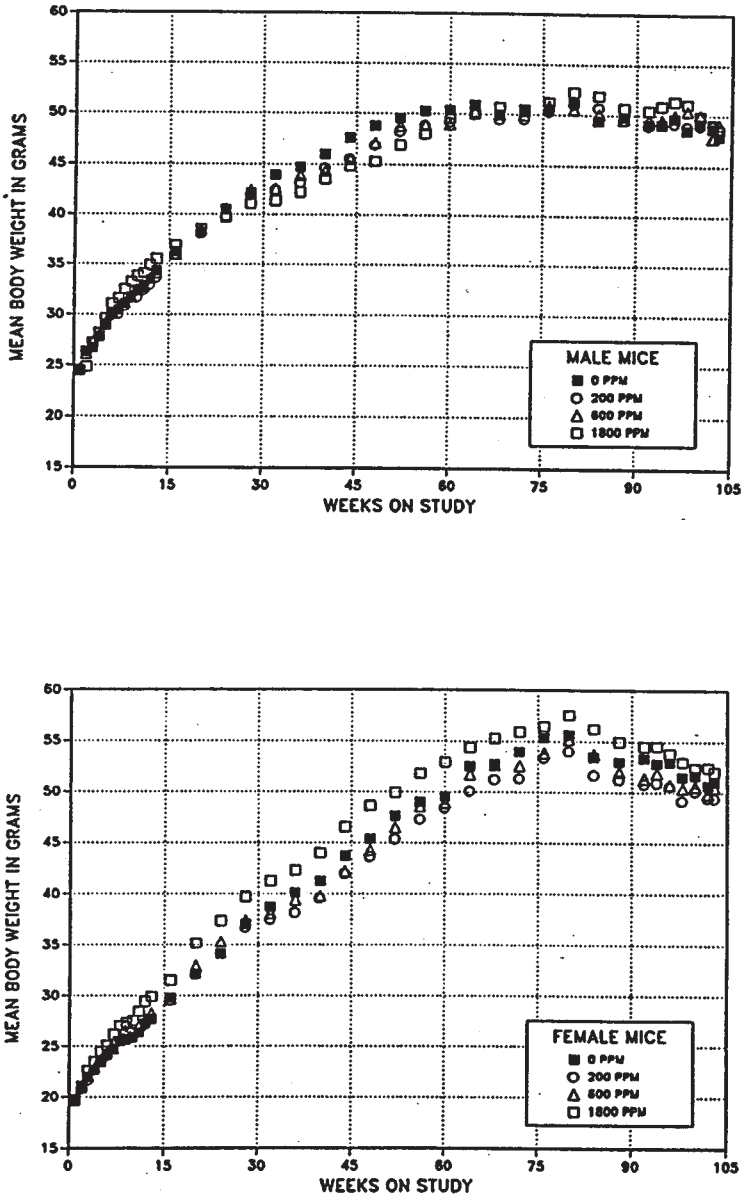


FIGURE 4
Growth Curves for Mice Exposed to Tetrahydrofuran by Inhalation for 2 Years

TABLE 11
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran

Weeks on Study	Chamber Control		200 ppm			600 ppm			1,800 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	24.5	50	24.5	100	50	24.7	101	50	24.4	100	50
2	26.3	50	26.3	100	50	26.1	99	50	24.9	95	49
3	26.7	50	27.2	102	50	27.3	102	50	27.2	102	49
4	27.8	50	27.8	100	50	28.1	101	50	28.2	101	49
5	28.8	50	29.0	101	50	29.4	102	50	29.6	103	49
6	30.0	50	29.9	100	50	30.2	101	50	31.1	104	49
7	30.4	50	30.0	99	50	30.8	101	50	31.6	104	49
8	31.1	50	30.8	99	50	31.1	100	50	32.5	105	49
9	31.7	50	31.8	100	50	31.7	100	50	33.3	105	49
10	32.4	50	31.7	98	50	32.4	100	50	33.8	104	49
11	32.9	50	32.4	99	50	32.7	99	50	34.1	104	49
12	33.5	50	32.9	98	50	33.6	100	50	35.0	105	49
13	34.4	50	33.6	98	50	34.2	99	50	35.6	104	49
16	36.2	50	36.0	99	50	36.0	99	50	36.9	102	47
20	38.2	50	38.1	100	50	38.5	101	50	38.5	101	47
24	40.5	50	39.8	98	50	40.5	100	50	39.7	98	47
28	42.1	50	41.9	100	50	42.4	101	50	41.1	98	46
32	43.9	50	42.5	97	50	42.5	97	50	41.4	94	44
36	44.7	50	43.2	97	50	43.9	98	50	42.2	94	40
40	45.9	50	44.6	97	50	44.3	97	50	43.5	95	37
44	47.6	50	45.5	96	50	45.5	96	50	44.8	94	35
48	48.7	50	46.8	96	48	47.1	97	50	45.3	93	33
52	49.5	50	48.2	97	48	48.8	99	50	46.9	95	30
56	50.2	49	48.9	97	48	48.9	97	49	48.0	96	24
60	50.3	49	49.2	98	48	48.9	97	49	49.5	98	22
64	50.9	48	50.0	98	47	50.2	99	48	50.0	98	22
68	49.9	48	49.5	99	47	50.0	100	48	50.7	102	21
72	50.3	47	49.5	98	46	50.0	99	48	50.5	100	21
76	50.5	47	50.3	100	45	50.9	101	46	51.2	101	21
80	51.2	46	51.0	100	43	50.5	99	45	52.3	102	20
84	49.4	45	50.7	103	39	50.1	101	39	51.9	105	19
88	49.8	43	49.5	99	39	49.6	100	34	50.7	102	19
92	49.0	43	48.9	100	38	49.6	101	33	50.4	103	19
94	49.0	40	49.1	100	36	49.5	101	32	50.9	104	18
96	49.6	39	49.2	99	36	50.0	101	31	51.4	104	17
98	48.5	36	48.9	101	35	50.4	104	30	51.1	105	16
100	49.2	35	49.0	100	34	50.0	102	30	49.9	101	15
102	48.7	34	49.0	101	32	47.8	98	29	49.1	101	14
103	47.9	33	48.7	102	31	49.1	103	29	48.5	101	13
Mean for weeks											
1-13	30.0		29.8	99		30.2	101		30.9	103	
14-52	43.7		42.7	98		43.0	98		42.0	96	
53-103	49.7		49.5	100		49.7	100		50.4	101	

TABLE 12
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran

Weeks on Study	Chamber Control		200 ppm			600 ppm			1,800 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	19.7	50	19.7	100	50	19.8	101	50	19.6	100	50
2	20.8	50	20.8	100	50	20.9	101	49	21.0	101	50
3	21.9	50	21.6	99	50	22.0	101	49	22.6	103	50
4	22.6	45	22.7	100	50	22.9	101	49	23.5	104	50
5	23.4	45	23.6	101	50	23.8	102	49	24.5	105	50
6	24.1	45	24.1	100	50	24.5	102	49	25.1	104	50
7	24.7	45	24.7	100	50	25.5	103	49	26.2	106	50
8	25.5	45	25.6	100	50	25.9	102	49	27.1	106	50
9	25.6	45	27.1	106	50	26.2	102	49	27.4	107	50
10	25.9	45	25.9	100	50	26.4	102	49	27.6	107	50
11	26.4	45	26.4	100	50	27.0	102	49	28.5	108	50
12	27.2	45	27.1	100	50	27.6	102	49	29.4	108	50
13	27.7	45	27.7	100	50	28.2	102	49	29.9	108	50
16	29.8	45	29.5	99	50	29.6	99	49	31.5	106	50
20	32.1	45	32.1	100	50	32.9	103	49	35.2	110	50
24	34.1	45	34.1	100	49	35.3	104	49	37.4	110	50
28	37.0	45	36.7	99	49	37.4	101	49	39.7	107	50
32	38.7	45	37.5	97	49	38.1	98	49	41.3	107	50
36	40.1	45	38.2	95	49	39.4	98	49	42.3	106	50
40	41.2	45	39.6	96	48	39.8	97	49	44.0	107	50
44	43.7	45	42.0	96	48	42.2	97	49	46.5	106	50
48	45.4	45	43.6	96	48	44.3	98	49	48.6	107	50
52	47.6	45	45.3	95	48	46.5	98	49	49.9	105	50
56	49.0	45	47.3	97	48	48.6	99	49	51.8	106	50
60	49.5	45	48.4	98	48	48.9	99	49	52.9	107	48
64	52.5	43	50.1	95	48	51.7	99	48	54.4	104	48
68	52.7	43	51.2	97	47	52.6	100	46	55.3	105	48
72	53.9	41	51.3	95	47	52.6	98	46	55.9	104	48
76	55.3	40	53.4	97	44	53.8	97	46	56.5	102	48
80	55.6	40	54.0	97	43	55.2	99	44	57.6	104	47
84	53.4	38	51.7	97	43	53.7	101	41	56.2	105	42
88	52.9	36	51.2	97	40	52.0	98	39	54.9	104	38
92	53.3	35	50.8	95	38	51.4	96	37	54.5	102	35
94	52.8	33	50.9	96	37	51.9	98	36	54.5	103	34
96	52.9	32	50.7	96	36	50.7	96	36	53.8	102	33
98	51.5	32	49.2	96	36	50.4	98	33	53.0	103	33
100	51.6	31	50.1	97	34	50.6	98	32	52.4	102	33
102	50.6	30	49.5	98	33	49.9	99	30	52.5	104	32
103	51.0	29	49.4	97	33	50.5	99	27	52.0	102	32
Mean for weeks											
1-13	24.3		24.4	100		24.7	102		25.6	105	
14-52	39.0		37.9	97		38.6	99		41.6	107	
53-103	52.4		50.6	97		51.5	98		54.3	104	

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, lung, and urogenital tract (kidney, penis, prostate gland, urethra, urinary bladder). 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 incidences of hepatocellular neoplasms (adenoma and carcinoma) in female mice exposed to 1,800 ppm were significantly greater than those in the chamber controls, and the incidences increased with a positive trend (Tables 13 and D3). In addition, the incidences of multiple hepatocellular neoplasms were increased in female mice exposed to 1,800 ppm (Tables 13 and D1). The incidences of combined hepatocellular neoplasms in female mice exposed to 1,800 ppm exceeded the historical range for chamber controls in 2-year NTP inhalation studies (Tables 13 and D4a). The incidences of hepatocellular neoplasms in exposed male mice were not significantly different from those in the chamber controls (Tables 13 and C3). The lower incidences of hepatocellular neoplasms in the 1,800 ppm male group were attributed to the low survival rate observed in this group. The incidences of combined hepatocellular neoplasms in male mice exposed to 200 ppm and in the chamber controls exceeded the historical control range for inhalation studies (Tables 13 and C4a). The incidence of combined hepatocellular neoplasms in male mice exposed to 600 ppm was at the upper limit of the historical range for chamber controls in 2-year inhalation studies. The incidence of liver necrosis was slightly elevated in 1,800 ppm female mice (Tables 13 and D5).

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Male				
Number Examined Microscopically	50	50	50	50
Basophilic Focus[a]	1	0	1	0
Clear Cell Focus	0	0	2	2
Eosinophilic Focus	11	8	10	5
Hematopoietic Cell Proliferation	0	1 (2.0)[b]	1 (2.0)	0
Mixed Cell Focus	1	1	0	0
Necrosis	8 (2.5)	5 (2.8)	6 (2.8)	4 (1.3)
Hepatocellular Adenoma (includes multiple)[c]				
Overall rate[d]	24/50 (48%)	19/50 (38%)	16/50 (32%)	14/50 (28%)
Adjusted rate[e]	60.5%	53.4%	48.7%	59.0%
Terminal rate[f]	17/32 (53%)	15/31 (48%)	12/28 (43%)	4/12 (33%)
First incidence (days)	362	324	440	245
Logistic regression test[g]	P=0.506N	P=0.211N	P=0.142N	P=0.414N
Hepatocellular Carcinoma (includes multiple)				
Overall rate	14/50 (28%)	13/50 (26%)	14/50 (28%)	9/50 (18%)
Adjusted rate	33.3%	28.9%	31.4%	50.0%
Terminal rate	6/32 (19%)	3/31 (10%)	2/28 (7%)	4/12 (33%)
First incidence (days)	481	441	376	359
Logistic regression test	P=0.459	P=0.412N	P=0.270N	P=0.363

(continued)

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Male (continued)				
Hepatocellular Adenoma or Carcinoma[h]				
Overall rate	35/50 (70%)	31/50 (62%)	30/50 (60%)	18/50 (36%)
Adjusted rate	77.2%	67.9%	66.9%	73.4%
Terminal rate	22/32 (69%)	17/31 (55%)	14/28 (50%)	6/12 (50%)
First incidence (days)	362	324	376	245
Logistic regression test	P=0.105N	P=0.210N	P=0.121N	P=0.175N
Female				
Number Examined Microscopically	50	50	50	48
Eosinophilic Focus	7	9	7	11
Hematopoietic Cell Proliferation	0	1 (2.0)	2 (2.5)	3 (1.7)
Necrosis	3 (2.0)	0	0	7 (1.9)
Hepatocellular Adenoma (includes multiple)				
Overall rate	12/50 (24%)	17/50 (34%)	18/50 (36%)	31/48 (65%)
Adjusted rate	35.9%	47.1%	52.5%	76.8%
Terminal rate	8/29 (28%)	14/33 (42%)	11/26 (42%)	23/32 (72%)
First incidence (days)	648	640	469	399
Logistic regression test	P<0.001	P=0.249	P=0.188	P<0.001
Hepatocellular Adenoma, Multiple				
Overall rate	2/50 (4%)	3/50 (6%)	5/50 (10%)	12/48 (25%)
Hepatocellular Carcinoma (includes multiple)				
Overall rate	6/50 (12%)	10/50 (20%)	10/50 (20%)	16/48 (33%)
Adjusted rate	16.5%	26.3%	30.0%	40.8%
Terminal rate	2/29 (7%)	6/33 (18%)	5/26 (19%)	10/32 (31%)
First incidence (days)	478	552	544	562
Logistic regression test	P=0.012	P=0.234	P=0.229	P=0.014
Hepatocullular Carcinoma, Multiple				
Overall rate	2/50 (4%)	4/50 (8%)	1/50 (2%)	6/48 (13%)
Hepatocellular Adenoma or Carcinoma[i]				
Overall rate	17/50 (34%)	24/50 (48%)	26/50 (52%)	41/48 (85%)
Adjusted rate	46.3%	61.3%	69.1%	93.0%
Terminal rate	10/29 (34%)	18/33 (55%)	15/26 (58%)	29/32 (91%)
First incidence (days)	478	552	469	399
Logistic regression test	P<0.001	P=0.188	P=0.086	P<0.001

[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year NTP inhalation studies with chamber controls (mean ± standard deviation): 200/947 (21.1% ± 11.6%); range, 4%-46%
[d] Number of animals with neoplasm per number of animals with liver examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to kill as nonfatal. A negative trend or lower incidence in an exposure group is indicated by **N**.
[h] Historical incidence: 358/947 (37.8% ± 12.5%); range, 11%-60%
[i] Historical incidence: 200/937 (21.3% ± 11.9%); range, 3%-54%

Lung: The incidences of alveolar/bronchiolar adenoma in male mice exposed to 200 or 600 ppm were significantly less than that in the chamber control group (chamber control, 18/50; 200 ppm, 7/50; 600 ppm, 8/50; 1,800 ppm, 4/50); however, there was no significant difference in the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) (21/50, 16/50, 15/50, 7/50; Table C3). The incidence of alveolar/bronchiolar adenoma in the chamber control group was at the upper limit of the NTP historical control range for inhalation studies in male mice (Table C4b). The lower incidences of lung neoplasms in male mice exposed to 1,800 ppm were most likely related to the lower survival rate in this group.

Urogenital tract: Male mice exposed to 1,800 ppm had significantly greater incidences of nonneoplastic lesions of the urogenital tract than those in the chamber controls. These lesions (which occurred primarily among the 26 animals dying during the first 52 weeks of the study) included suppurative inflammation of the kidney (3/49, 5/50, 5/49, 18/50), urinary bladder (3/48, 6/49, 6/46, 16/48), prostate gland (3/48, 4/43, 4/44, 14/47), and preputial skin (7/47, 7/50, 7/48, 18/50); hydronephrosis of the kidney (3/49, 3/50, 5/49, 18/50); and transitional epithelial hyperplasia of the urinary bladder (0/48, 1/49, 1/46, 5/48; Table C5). The incidence of nephropathy in 200 ppm male mice was significantly greater than that in the chamber control group (31/49, 40/50, 33/49, 14/50). The decreased incidence of nephropathy in 1,800 ppm male mice was related to decreased survival in this group. The inflammatory urogenital tract lesions were considered to be the most likely cause of the lower survival rate observed in this exposure group. The character of the inflammatory lesions suggested an ascending bacterial infection. Prolonged wetting of the preputial fur during exposure-related narcosis may have predisposed these animals to a preputial, and subsequently, an ascending urogenital tract bacterial infection resulting in moribundity and ultimately death. The incidences of inflammation of the penis (0/1, 1/2, 1/2, 9/27) and urethra (0/0, 3/3, 1/1, 12/14) and necrosis of the urethra (0/0, 0/3, 1/1, 5/14) in 1,800 ppm males were slightly greater than those in the chamber controls.

Increased incidences of hyperplasia of the bone marrow (5/49, 6/50, 7/49, 14/50) and iliac lymph nodes (0/1, 3/4, 3/4, 5/5), hematopoietic cell proliferation of the spleen (9/48, 13/49, 14/47, 18/49), and thymic atrophy (2/35, 2/37, 4/34, 9/36) were observed in 1,800 ppm males (Table C5). These changes were of marginal significance and were considered to be secondary reactive responses to acute inflammation of the urinary and urogenital tracts.

GENETIC TOXICOLOGY

Tetrahydrofuran has been tested in a variety of mutagenicity assays and the results were, with one exception, negative. Tetrahydrofuran was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested in two different laboratories in a preincubation protocol with doses up to 10,000 μg/plate; all tests were conducted with and without Aroclor-induced rat or hamster liver S9 (Mortelmans *et al.*, 1986; Table E1). Tetrahydrofuran did not induce sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3) in cultured Chinese hamster ovary cells when tested at doses up to 5,000 μg/mL, with or without S9 (Galloway *et al.*, 1987). Unusually high frequencies of aberrant cells were observed in the chromosome aberration test in both control and tetrahydrofuran-treated cultures; however, the trend test was insignificant for all trials and no single dose group showed aberration frequencies that differed significantly from the control value, with one exception. In the second trial conducted with S9, the middle-level dose of 3,000 μg/mL produced a positive response; because the trend test for this trial was not significant, and because the responses for the complete data set were not correlated with increasing dose, this trial was concluded to be equivocal, and the overall call for the assay was negative. No induction of sex-linked recessive lethal mutations was noted in male *Drosophila melanogaster* exposed by feeding or by injection to a dose of 10,000, 40,000, or 125,000 ppm tetrahydrofuran (Valencia *et al.*, 1985; Table E4).

Little evidence for genetic toxicity of tetrahydrofuran was noted in *in vivo* assays. Results of the mouse bone marrow sister chromatid exchange assay were negative (Table E5). Tetrahydrofuran (500, 1,000, or 2,000 mg/kg) did not induce chromosomal aberrations in mouse bone marrow cells at either 17 or 36 hours (Table E6). Although results from the initial 24-hour sister chromatid exchange test were positive, a repeat

test gave negative results, and the results of the single trial performed with a 42-hour sample time were also negative. The frequencies of micronucleated erythrocytes were determined in peripheral blood samples obtained from male and female mice at the completion of the 14-week toxicity study (Table E7). In female mice, neither polychromatic nor normochromatic erythrocytes had elevated frequencies of micronuclei, but in male mice, there was a small increase in the frequency of micronucleated normochromatic erythrocytes that was concluded to represent an equivocal response (trend test P=0.074). No significant increase in the frequency of micronucleated polychromatic erythrocytes was noted in male mice.

DISCUSSION AND CONCLUSIONS

Tetrahydrofuran was evaluated for toxicity and carcinogenicity in 14-week and 2-year studies in male and female F344/N rats and B6C3F$_1$ mice, using whole body inhalation as the route of exposure.

Many organic solvents, including chlorinated hydrocarbons, alcohols, ethers, esters, and ketones, have the potential, upon acute high-level vapor exposure, to cause narcosis and death (Snyder and Andrews, 1996). In the 14-week toxicity study of tetrahydrofuran, male and female rats in the 5,000 ppm groups exhibited ataxia after exposure. Male and female mice exposed to 1,800 or 5,000 ppm were observed to be in a state of narcosis during exposures. The intensity of central nervous system depression decreased with the duration of exposure, suggesting that the animals developed some tolerance to this effect. Katahira *et al*., (1982b) has reported similar neurotoxic effects in male Sprague-Dawley rats exposed to tetrahydrofuran concentrations ranging from 100 to 5,000 ppm by inhalation for 12 weeks.

The complaints of dizziness and central nervous system effects in workers in the plastic industry prompted Elovaara *et al*. (1984) to perform an inhalation study in rats to determine body burden of tetrahydrofuran and its effect on activities of drug metabolism enzymes. The exposure-dependent brain and perirenal fat tetrahydrofuran burdens were determined to be linearly correlated. After 2 weeks of exposure, the burden of tetrahydrofuran seemed to decrease. It is possible that the tolerance to central nervous system effects seen in the laboratory animals was due to tetrahydrofuran's stimulation of its own metabolism. It has been suggested that central nervous system toxicity produced by solvents of diverse structure is a general effect and results from a physical interaction of solvent with the cell membranes of nervous system tissues (Snyder and Andrews, 1996). From the current 14-week studies, it cannot be established whether the clinical findings of central nervous system toxicity observed were primary or secondary to tetrahydrofuran exposure. No morphologic changes were observed in the central nervous system, and no specific neurotoxicity studies were performed to determine the mechanism(s) of toxicity. Simonsen *et al*. (1994) evaluated existing neurotoxicity data on 10 chemicals, including tetrahydrofuran, and reported that the tetrahydrofuran neurotoxicity data in animals were limited. They classified tetrahydrofuran as possibly neurotoxic in humans. Further study is needed to more fully describe and characterize tetrahydrofuran neurotoxicity in experimental animals and humans.

The liver has been identified as a target organ of tetrahydrofuran toxicity in rats (HSDB, 1996). In the 14-week rat study, the only effect on the liver of rats was the increased absolute and relative liver weight of the 5,000 ppm females. However, minimal increases of the serum bile acid concentration in female rats were observed in the absence of cholestasis or hepatocellular necrosis, which is a change consistent with decreased or altered hepatocellular function. The histopathologic changes in male and female mice exposed to 5,000 ppm tetrahydrofuran for 14 weeks suggested that the liver was the target organ of toxicity, as shown by the increased incidences of centrilobular hepatocytomegaly. At the 1,800 ppm exposure concentrations, liver weight increases and mild histopathologic changes in the liver were consistent with the treatment effect of tetrahydrofuran. Also at the lower exposure concentrations, liver weights were increased, but no histopathologic changes were observed.

Fatty vacuolization of the inner portion (X-zone) of the adrenal cortex is a normal occurrence in young female mice and is a change associated with the normal regression of the X-zone. In the female mouse, the X-zone begins to regress with sexual maturity and disappears completely with pregnancy (Dunn, 1970; Ribelin, 1984). In the current study, the fatty vacuolar changes were not present, and mild degeneration of the X-zone occurred in all 5,000 ppm female mice. This degeneration of the X-zone and uterine atrophy in the 5,000 ppm females may have been a direct effect of tetrahydrofuran on these tissues

or possibly the result of a hormonal effect by perturbation of the pituitary-hypothalamic-end organ axis.

Mild irritant effects of tetrahydrofuran vapor have been reported in the literature (HSDB, 1996). The minimum inflammatory changes in the forestomach of rats exposed to 5,000 ppm tetrahydrofuran may have been due to the irritant effect of tetrahydrofuran ingested during the exposure period.

Based on the results from the 14-week toxicity studies, exposure concentrations of 200, 600, and 1,800 ppm tetrahydrofuran were selected for the 2-year carcinogenicity studies in rats and mice. In the 14-week studies, a transient state of narcosis (described as stupor) was observed in some 1,800 and 5,000 ppm mice immediately after exposure. The animals developed some tolerance to this effect by the end of the studies. At the time of the exposure concentration selection for the 2-year studies, it was predicted that male mice in the 1,800 ppm group in the 2-year study might develop a complete tolerance to the sedative effect, and therefore sedation might not have any adverse effect on the survival related to tetrahydrofuran exposure. The prediction was clearly incorrect, and 26 males in the 1,800 ppm group died during the first year of the study. A number of male mice exposed to 1,800 ppm were observed to be in a state of narcosis during and up to 1 hour after exposures. Prolonged wetting of the preputial fur during exposure-induced narcosis may have predisposed these animals to a preputial, and subsequently an ascending urogenital tract, bacterial infection that resulted in moribundity and ultimately death. Therefore, the highest exposure concentration (1,800 ppm) selected for male mice in this study exceeded the maximum tolerated dose. The survival of exposed groups of male and female rats and of female mice was similar to that of the chamber control groups. The mean body weights of exposed groups of rats and mice were similar to those of the chamber control groups throughout the studies.

An increase in the incidences of renal tubular neoplasms in male rats exposed to tetrahydrofuran was considered to be related to the administration of tetrahydrofuran. Several factors predicated the assertion of a carcinogenic effect in the male rat kidney. First, there were increased incidences of relatively uncommon spontaneous renal neoplasms (less than 1% in NTP 2-year studies) in male rats exposed to 600 ppm (8%) or 1,800 ppm (10%). Second, the neoplasms in the 1,800 ppm group included two carcinomas, rare neoplasms that had not been seen in 652 chamber control animals. Last, there were no chemical-related increases in the incidences or severities of age-related degenerative renal disease (chronic progressive nephropathy) in exposed male rats. Marginal to slight increases in renal tubule neoplasms often accompany chemical-related exacerbation of nephropathy in rats. Therefore, it is often difficult to determine if neoplasms of the renal tubule develop as a direct effect of chemical administration or as an indirect effect secondary to the exacerbated nephropathy. The apparent lack of such a concentration-related increase in the incidences or severities of nephropathy in exposed male rats in this study suggests that the increased incidences of renal neoplasms were not related to nephropathy, but were treatment-related effects.

In female mice exposed to 1,800 ppm tetrahydrofuran, the incidences of hepatocellular neoplasms were significantly greater than those of the chamber controls and the incidences increased with a positive trend. Using a logistic regression model (Seilkop, 1995), it was determined that the body weight differences did not account for the sizable increase in the liver neoplasm rate observed in the exposed groups of females (85% vs. 34% in chamber controls). Also, there were multiple hepatocellular neoplasms in some of the exposed female mice.

There was no indication of an increase in the incidences of hepatocellular neoplasms in male mice. There are several possible reasons for this. The male mice study may not have been sensitive enough to a tetrahydrofuran-induced carcinogenic effect, due to a very high incidence of hepatocellular neoplasms in the chamber controls (70%) and to the lower survival rate of 1,800 ppm mice. Alternatively, there may be an inherent gender difference in tetrahydrofuran-induced hepatocellular neoplasms in mice. The liver was also one of the major sites of carcinogenicity identified for furan and 1,4-dioxane, chemicals structurally related to tetrahydrofuran (IARC, 1976; NTP, 1993). Furan, when administered by gavage, was carcinogenic in rats based on increased incidences of cholangiocarcinoma, hepatocellular neoplasms, and

mononuclear cell leukemia. In male and female mice, furan induced hepatocellular neoplasms and benign pheochromocytomas of the adrenal gland (NTP, 1993). 1,4-Dioxane, a cyclic ether solvent structurally related to tetrahydrofuran, was carcinogenic in rats and guinea pigs when administered by gavage. 1,4-Dioxane produced malignant neoplasms in the liver and nasal cavity in rats and neoplasms of the liver and the gallbladder in guinea pigs (IARC, 1976). It was also a promotor in a two-stage skin carcinogenesis study in mice.

The differences in tetrahydrofuran-induced neoplasms between rats and mice and males and females could be due to differences in the metabolism and disposition of tetrahydrofuran. There is very little information in the literature on the toxicokinetics and cellular toxicity on this widely used solvent. Based on the limited information available from genotoxicity studies, the carcinogenic activity of tetrahydrofuran observed in the current studies is most likely through nongenotoxic modes of action. Tetrahydrofuran was not mutagenic in a variety of *in vitro* and *in vivo* assays. The presence of kidney lesions only in exposed male rats may have been a result of degenerative hyaline droplet nephropathy progression to neoplasm formation, a species- and gender-specific lesion possibly mediated through nongenotoxic modes of action (Swenberg, 1993). There were no tetrahydrofuran-related nonneoplastic lesions of the kidney observed in animals in the 14-week or 2-year studies. However, Kawata and Ito (1984) reported the kidney as one of the target organs of tetrahydrofuran toxicity. In that study, marginal increases in protein casts in the intercavity of the kidney tubules and hyaline droplet degeneration were observed after tetrahydrofuran exposure by inhalation for 12 weeks at 3,000 ppm. In contrast to the kidney, increased incidences of cytomegaly were observed in the livers of 5,000 ppm male and female mice in the 14-week study, and the incidence of liver necrosis were slightly elevated in the 1,800 ppm female mice in the 2-year study, indicating that the liver is a clear target organ in mice.

Based on the current 14-week inhalation toxicity study in mice and on previously reported developmental toxicity studies (Mast *et al.*, 1992), the no-observable-adverse-affect level (NOAEL) for nonneoplastic lesions from tetrahydrofuran is 600 ppm in mice. In the current 2-year mouse study, the incidences of hepatocellular neoplasms in female mice exposed to 200 ppm (the lowest exposure concentration used) were elevated (48%) relative to controls (34%). These results may have some implications for the current occupational exposure limit of 200 ppm.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of tetrahydrofuran in male F344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of tetrahydrofuran in female F344/N rats exposed to 200, 600, or 1,800 ppm or male $B6C3F_1$ mice exposed to 200, 600, or 1,800 ppm. There was *clear evidence of carcinogenic activity* of tetrahydrofuran in female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms.

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

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF TETRAHYDROFURAN

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran[a]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1		
Moribund	31	39	40	34
Natural deaths	6	4	5	10
Survivors				
Terminal sacrifice	12	6	5	6
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, colon	(49)	(48)	(48)	(45)
Histiocytic sarcoma	1 (2%)			
Intestine large, cecum	(49)	(48)	(48)	(46)
Histiocytic sarcoma	1 (2%)			
Intestine small, duodenum	(49)	(48)	(49)	(48)
Intestine small, jejunum	(47)	(46)	(48)	(44)
Leiomyosarcoma			1 (2%)	
Intestine small, ileum	(47)	(47)	(47)	(44)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)			
Hepatocellular adenoma		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)			
Osteosarcoma, metastatic, bone			2 (4%)	
Mesentery	(15)	(17)	(18)	(10)
Histiocytic sarcoma	1 (7%)			
Osteosarcoma, metastatic, bone			1 (6%)	
Oral mucosa	(3)			(1)
Squamous cell papilloma				1 (100%)
Pancreas	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(49)	(50)
Squamous cell papilloma	1 (2%)			
Stomach, glandular	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Tongue	(1)		(2)	(1)
Squamous cell papilloma	1 (100%)		2 (100%)	1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Carcinoma	1 (2%)			

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Endocrine System (continued)				
Adrenal medulla	(48)	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)	3 (6%)	1 (2%)
Pheochromocytoma complex				1 (2%)
Pheochromocytoma benign	14 (29%)	4 (8%)	10 (20%)	11 (22%)
Pheochromocytoma benign, multiple	4 (8%)	7 (14%)	3 (6%)	3 (6%)
Pancreatic islets	(50)	(50)	(50)	(49)
Adenoma	4 (8%)	2 (4%)	1 (2%)	2 (4%)
Carcinoma	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Pituitary gland	(49)	(49)	(48)	(50)
Craniopharyngioma		1 (2%)		
Pars distalis, adenoma	33 (67%)	34 (69%)	40 (83%)	27 (54%)
Pars distalis, adenoma, multiple				2 (4%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	4 (8%)	4 (8%)		4 (8%)
C-cell, carcinoma	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Follicular cell, adenoma	2 (4%)		1 (2%)	
Follicular cell, carcinoma	1 (2%)		1 (2%)	1 (2%)
General Body System				
Peritoneum	(2)	(2)		(1)
Histiocytic sarcoma	1 (50%)			
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(49)	(50)	(50)	(50)
Adenoma	2 (4%)	2 (4%)		2 (4%)
Carcinoma	3 (6%)	1 (2%)		4 (8%)
Prostate	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	12 (24%)	14 (28%)	16 (32%)	23 (46%)
Interstitial cell, adenoma	11 (22%)	17 (34%)	15 (30%)	11 (22%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Lymph node	(16)	(19)	(18)	(16)
Iliac, histiocytic sarcoma	1 (6%)			
Renal, histiocytic sarcoma	1 (6%)			
Lymph node, bronchial	(45)	(45)	(44)	(43)
Histiocytic sarcoma	1 (2%)			
Histiocytic sarcoma, metastatic, thymus				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Lymph node, mandibular	(46)	(50)	(49)	(48)
Histiocytic sarcoma	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(49)	(49)
Histiocytic sarcoma	1 (2%)			

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Hematopoietic System (continued)				
Lymph node, mediastinal	(48)	(50)	(46)	(49)
Histiocytic sarcoma	1 (2%)			
Histiocytic sarcoma, metastatic, thymus				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Osteosarcoma, metastatic, bone			1 (2%)	
Thymus	(50)	(49)	(48)	(50)
Histiocytic sarcoma	1 (2%)			1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Thymoma benign	1 (2%)			
Thymoma malignant				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Fibroadenoma		1 (2%)	3 (6%)	4 (8%)
Fibroadenoma, multiple		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Fibroma, multiple			1 (2%)	
Keratoacanthoma	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Keratoacanthoma, multiple		1 (2%)		
Schwannoma malignant	1 (2%)			
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma		1 (2%)		
Trichoepithelioma	1 (2%)			1 (2%)
Pinna, squamous cell papilloma		1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	5 (10%)	3 (6%)	2 (4%)
Subcutaneous tissue, fibrosarcoma				1 (2%)
Subcutaneous tissue, histiocytic sarcoma				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, skeletal muscle			1 (2%)	
Humerus, osteosarcoma			1 (2%)	
Rib, osteosarcoma			1 (2%)	
Skeletal muscle	(1)	(1)	(1)	
Histiocytic sarcoma			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Glioma benign				1 (2%)

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		3 (6%)	1 (2%)	
Alveolar/bronchiolar carcinoma			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Histiocytic sarcoma, metastatic, thymus				1 (2%)
Osteosarcoma, metastatic, bone			2 (4%)	
Osteosarcoma, metastatic, uncertain primary site		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Squamous cell carcinoma		1 (2%)		
Pleura	(2)	(1)	(2)	
Histiocytic sarcoma, metastatic, skeletal muscle			1 (50%)	
Special Senses System				
Zymbal's gland	(1)	(1)		(2)
Carcinoma	1 (100%)	1 (100%)		1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Pelvis, transitional epithelium, carcinoma				1 (2%)
Renal tubule, adenoma	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Renal tubule, adenoma, multiple				1 (2%)
Renal tubule, carcinoma				2 (4%)
Urinary bladder	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)			
Transitional epithelium, carcinoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	2 (4%)
Leukemia mononuclear	30 (60%)	29 (58%)	27 (54%)	32 (64%)
Mesothelioma benign		1 (2%)		
Mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)	1 (2%)

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	48	49	49	50
Total primary neoplasms	140	142	147	153
Total animals with benign neoplasms	47	47	48	47
Total benign neoplasms	96	104	103	100
Total animals with malignant neoplasms	37	33	32	42
Total malignant neoplasms	44	38	44	53
Total animals with metastatic neoplasms	1	1	4	1
Total metastatic neoplasms	2	1	13	3
Total animals with malignant neoplasms of uncertain primary site		1		

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control

Number of Days on Study	0737	0244	0406	0422	0453	0508	0514	0526	0546	0547	0549	0551	0554	0562	0663	0663	0733	0755	0787	0802	0621	0621	0635	0635	0639
Carcass ID Number	0333	0019	0020	0013	0118	0444	0211	0111	0445	0406	0334	0330	0550	0355	0244	0288	0207	0404	0393	0266	0233	0466	0161	0275	0332
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Histiocytic sarcoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Histiocytic sarcoma																									
Mesentery			+													+	+	+			+	+		+	
Histiocytic sarcoma																									
Oral mucosa		+									+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel								+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, pleura																					X				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X		
Adrenal medulla	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign															X						X	X		X	
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma			X	X			X	X		X	X	X		X	X	X			X	X				X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X							X													
C-cell, carcinoma																									
Follicular cell, adenoma							X												X						
Follicular cell, carcinoma																									

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	6 4 9	6 4 9	6 6 0	6 6 1	6 6 3	6 7 3	6 8 3	6 8 3	7 0 5	7 2 3	7 2 9	7 2 9	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 1 2	0 2 2	0 1 0	0 0 5	0 4 7	0 3 6	0 4 2	0 4 9	0 1 4	0 4 0	0 1 5	0 2 5	0 3 1	0 0 1	0 0 3	0 0 8	0 2 9	0 4 3	0 0 2	0 3 7	0 3 8	0 0 9	0 1 7	0 4 1	0 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma						X																				1
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma						X																				1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																			X							1
Histiocytic sarcoma						X																				1
Mesentery					+	+										+	+	+	+	+	+					15
Histiocytic sarcoma						X																				1
Oral mucosa														+												3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Tongue									+																	1
Squamous cell papilloma									X																	1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, pleura																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Pheochromocytoma benign	X	X			X				X		X		X	X		X			X				X			14
Pheochromocytoma benign, multiple				X						X		X									X					4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X												X											X		4
Carcinoma																			X							1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X				X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		33
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X													X											4
C-cell, carcinoma						X											X									2
Follicular cell, adenoma																										2
Follicular cell, carcinoma			X																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	0 7 3	2 4 4	4 0 6	4 2 2	4 5 3	5 0 8	5 1 4	5 2 6	5 4 6	5 4 7	5 4 9	5 5 1	5 5 4	5 6 2	5 6 3	5 6 3	5 7 3	5 7 5	5 8 7	6 0 2	6 2 1	6 2 1	6 3 5	6 3 5	6 3 9
Carcass ID Number	0 3 3	0 1 9	0 2 0	0 1 3	0 1 8	0 4 4	0 2 1	0 1 1	0 4 5	0 0 6	0 3 4	0 3 0	0 5 0	0 3 5	0 2 4	0 2 8	0 0 7	0 0 4	0 3 9	0 2 6	0 2 3	0 4 6	0 1 6	0 2 7	0 3 2
General Body System																									
Peritoneum																									
Histiocytic sarcoma																									
Tissue NOS								+																	
Genital System																									
Coagulating gland												+													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Carcinoma					X				X				X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X		X		X		X		X								
Interstitial cell, adenoma																		X	X			X	X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node						+			+	+			+		+	+						+	+		+
Iliac, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mesothelioma malignant, metastatic, pleura																					X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																		X							
Schwannoma malignant								X																	
Trichoepithelioma																									
Subcutaneous tissue, fibroma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	6 4 9	6 4 9	6 6 0	6 6 1	6 6 3	6 7 3	6 8 3	6 8 3	7 0 5	7 2 3	7 2 9	7 2 9	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 1 2	0 2 2	0 1 0	0 0 5	0 4 7	0 3 6	0 4 2	0 4 9	0 1 4	0 4 0	0 1 5	0 2 5	0 3 1	0 0 1	0 0 3	0 0 8	0 2 9	0 4 3	0 0 2	0 3 7	0 3 8	0 0 9	0 1 7	0 4 1	0 4 8	Total Tissues/ Tumors
General Body System																										
Peritoneum						+				+																2
Histiocytic sarcoma						X																				1
Tissue NOS																										1
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis					+																					1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Adenoma																									X	2
Carcinoma																										3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X			X		X				X		X	X	X										12
Interstitial cell, adenoma	X										X		X					X	X				X		X	11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Lymph node	+			+		+										+			+	+				+		16
Iliac, histiocytic sarcoma						X																				1
Renal, histiocytic sarcoma						X																				1
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Histiocytic sarcoma						X																				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	46
Histiocytic sarcoma						X																				1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Histiocytic sarcoma						X																				1
Mesothelioma malignant, metastatic, pleura																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Thymoma benign		X																								1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X											X										3
Schwannoma malignant																										1
Trichoepithelioma																					X					1
Subcutaneous tissue, fibroma									X						X											2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	0737	2444	4046	4422	4523	5088	5144	5216	5446	5447	5449	5511	5514	5622	5663	5673	7735	7787	8702	6021	6221	6341	6355	6339
Carcass ID Number	0333	0019	0200	0113	0118	0444	0221	0111	0445	0306	0334	0330	0550	0355	0224	0228	0307	0404	0339	0226	0223	0416	0116	0232
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																					
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord			+																					
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura									+												+			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Zymbal's gland																								
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Renal tubule, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Leukemia mononuclear				X		X							X		X		X	X	X	X	X	X		X
Mesothelioma malignant																					X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	6 4 9	6 4 9	6 6 0	6 6 1	6 6 3	6 7 3	6 8 3	6 8 3	7 0 5	7 2 3	7 2 9	7 2 9	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 1 2	0 2 2	0 1 0	0 0 5	0 4 7	0 3 6	0 4 2	0 4 9	0 1 4	0 4 0	0 1 5	0 2 5	0 3 1	0 0 1	0 0 3	0 0 8	0 2 9	0 4 3	0 0 2	0 3 7	0 3 8	0 0 9	0 1 7	0 4 1	0 4 8	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland		+																								1
Carcinoma		X																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Renal tubule, adenoma																					X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Leukemia mononuclear	X	X		X	X		X	X				X	X	X	X	X	X		X	X	X	X	X	X	X	30
Mesothelioma malignant										X																2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	6 3 5	6 3 9	6 3 9	6 4 3	6 4 6	6 5 3	6 6 0	6 6 0	6 7 2	6 7 7	6 9 1	7 0 1	7 0 7	7 1 5	7 1 9	7 1 9	7 1 9	7 2 9	7 2 9	7 3 3	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 4 8	2 0 1	2 0 9	2 4 5	2 1 7	2 2 7	2 0 6	2 1 2	2 3 3	2 4 2	2 2 9	2 1 0	2 4 7	2 3 9	2 2 2	2 3 7	2 4 1	2 0 3	2 4 0	2 3 6	2 0 4	2 0 2	2 1 5	2 3 4	2 3 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X																								1
Mesentery	+						+		+		+												+	+		17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth						+																				2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant								X																		1
Pheochromocytoma benign							X									X	X				X					4
Pheochromocytoma benign, multiple											X		X		X				X							7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Carcinoma																						X				2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Craniopharyngioma																						X				1
Pars distalis, adenoma	X		X			X			X	X	X	X	X	X	X	X	X	X	X		X			X	X	34
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X							X	X			4
C-cell, carcinoma													X								X					2
General Body System																										
Peritoneum			+																							2
Tissue NOS	+																									1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													2
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma								X			X	X	X	X			X	X		X	X		X		X	14
Interstitial cell, adenoma		X	X	X	X	X			X	X					X	X						X		X		17

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	439	502	503	514	514	519	523	528	540	540	551	551	551	552	559	575	575	579	607	607	614	624	626	629	630
Carcass ID Number	219	249	244	216	250	231	243	244	218	226	207	214	246	211	205	220	238	208	213	233	230	221	232	225	228
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+			+			+	+	+				+	+	+		+			+		
Lymph node, bronchial	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Fibroadenoma, multiple												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X					
Keratoacanthoma, multiple																									
Squamous cell papilloma																								X	
Pinna, squamous cell papilloma																									
Subcutaneous tissue, fibroma																X								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							+		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Osteosarcoma, metastatic, uncertain																									
Primary site																									
Squamous cell carcinoma																									X
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																									
Trachea	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland									+																
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X						X	X	X		X		X				X	X	X	X		X	X	X	X
Mesothelioma benign				X																					
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	6 3 5	6 3 9	6 3 9	6 4 3	6 4 6	6 5 3	6 6 0	6 6 0	6 7 2	6 7 7	6 9 1	7 0 1	7 0 7	7 1 5	7 1 9	7 1 9	7 1 9	7 2 9	7 2 9	7 3 3	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 4 8	2 0 1	2 0 9	2 4 5	2 1 7	2 2 7	2 0 6	2 1 2	2 3 3	2 4 2	2 2 9	2 1 0	2 4 7	2 3 9	2 2 2	2 3 7	2 4 1	2 0 3	2 4 0	2 3 6	2 0 4	2 0 2	2 1 5	2 3 4	2 3 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+						+			+			+		+	+	+		+	19
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																			X							1
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma			X	X																						3
Keratoacanthoma, multiple																X										1
Squamous cell papilloma																										1
Pinna, squamous cell papilloma												X														1
Subcutaneous tissue, fibroma		X																				X			X	5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X						X												3
Osteosarcoma, metastatic, uncertain																										
Primary site																X										1
Squamous cell carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura						+																				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X		X	X	X		X	X	X	X				X	X	X	X		X		X	29
Mesothelioma benign																										1
Mesothelioma malignant			X																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	6 3 9	6 3 9	6 3 9	6 4 2	6 4 5	6 4 6	6 6 3	6 7 3	6 7 3	6 7 3	6 7 7	6 7 7	6 8 0	6 9 9	7 0 7	7 1 1	7 1 4	7 1 5	7 1 9	7 2 3	7 3 3	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 3 4	4 3 5	4 4 0	4 4 7	4 2 8	4 1 7	4 3 2	4 0 9	4 1 4	4 4 1	4 1 8	4 4 6	4 4 5	4 3 8	4 2 7	4 0 1	4 0 3	4 5 0	4 0 2	4 1 5	4 3 1	4 1 2	4 0 4	4 1 0	4 3 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma						X																				1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									1
Osteosarcoma, metastatic, bone																	X									2
Mesentery				+	+	+	+	+	+			+										+		+		18
Osteosarcoma, metastatic, bone																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+									+														2
Squamous cell papilloma			X									X														2
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																	X									1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																				X		X				3
Pheochromocytoma benign			X				X			X					X	X							X			10
Pheochromocytoma benign, multiple								X											X							3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Carcinoma															X						X					2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X	X	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma															X		X								X	3
Follicular cell, adenoma																										1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	2 7 5	4 0 1	5 1 7	5 3 1	5 4 4	5 4 5	5 4 7	5 5 1	5 5 8	5 6 1	5 6 1	5 7 5	5 9 0	5 9 1	5 9 1	5 9 2	5 9 7	6 1 4	6 2 1	6 2 2	6 2 6	6 2 9	6 3 1	6 3 5	6 3 9
Carcass ID Number	4 2 0	4 4 8	4 1 6	4 0 8	4 1 1	4 3 0	4 3 9	4 0 7	4 4 9	4 2 5	4 2 6	4 4 3	4 3 6	4 1 3	4 2 3	4 4 2	4 2 9	4 2 4	4 2 2	4 0 6	4 3 3	4 0 5	4 4 4	4 1 9	4 2 1
Genital System (continued)																								
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X			X				X	X	X			X		
Interstitial cell, adenoma											X				X	X					X		X	
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+					+	+		+		+	+	+		+	+	+	
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Osteosarcoma, metastatic, bone																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																					X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																								
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma								X																
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma, multiple																								
Keratoacanthoma																								
Subcutaneous tissue, fibroma																						X		
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, skeletal muscle																								
Humerus, osteosarcoma																					X			
Rib, osteosarcoma																								
Skeletal muscle																								
Histiocytic sarcoma																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant														X										
Spinal cord										+														
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X					
Alveolar/bronchiolar carcinoma																				X				
Osteosarcoma, metastatic, bone																					X			
Pheochromocytoma malignant, metastatic, adrenal medulla																								
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura											+													
Histiocytic sarcoma, metastatic, skeletal muscle																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	6 3 9	6 3 9	6 3 9	6 4 2	6 4 5	6 4 6	6 6 3	6 7 3	6 7 3	6 7 3	6 7 7	6 7 7	6 8 0	6 9 9	7 0 7	7 1 1	7 1 4	7 1 5	7 1 9	7 2 3	7 3 3	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 3 4	4 3 5	4 4 0	4 4 7	4 2 8	4 1 7	4 3 2	4 0 9	4 1 4	4 4 1	4 1 8	4 4 6	4 4 5	4 3 8	4 2 7	4 0 1	4 0 3	4 5 0	4 0 2	4 1 5	4 3 1	4 1 2	4 0 4	4 1 0	4 3 7	Total Tissues/ Tumors
Genital System (continued)																										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma					X	X	X							X		X	X					X	X	X	X	16
Interstitial cell, adenoma			X	X				X	X	X	X							X	X	X	X					15
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+							+	+			+		+		+			+			+	18
Lymph node, bronchial	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	44
Osteosarcoma, metastatic, bone																	X									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Osteosarcoma, metastatic, bone																	X									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Osteosarcoma, metastatic, bone																	X									1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma			X									X														3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma, multiple																						X				1
Keratoacanthoma																									X	1
Subcutaneous tissue, fibroma						X											X									3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, skeletal muscle						X																				1
Humerus, osteosarcoma																										1
Rib, osteosarcoma																	X									1
Skeletal muscle						+																				1
Histiocytic sarcoma						X																				1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Osteosarcoma, metastatic, bone																	X									2
Pheochromocytoma malignant, metastatic, adrenal medulla																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura						+																				2
Histiocytic sarcoma, metastatic, skeletal muscle						X																				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	2 7 5	4 0 1	5 1 7	5 3 1	5 4 4	5 4 5	5 4 7	5 5 1	5 5 8	5 6 1	5 6 1	5 7 5	5 9 0	5 9 1	5 9 1	5 9 2	5 9 7	6 1 4	6 2 1	6 2 2	6 2 6	6 2 9	6 3 1	6 3 5	6 3 9
Carcass ID Number	4 2 0	4 4 8	4 1 6	4 0 8	4 1 1	4 3 0	4 3 9	4 0 7	4 4 9	4 2 5	4 2 6	4 4 3	4 3 6	4 1 3	4 2 3	4 4 2	4 2 9	4 2 4	4 2 2	4 0 6	4 3 3	4 0 5	4 4 4	4 1 9	4 2 1
Special Senses System																								
Eye			+																				+	
Lacrimal gland																+								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																						X		
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Leukemia mononuclear			X		X							X	X		X		X	X	X		X		X	
Mesothelioma malignant											X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	6 3 9	6 3 9	6 3 9	6 4 2	6 4 5	6 4 6	6 6 3	6 7 3	6 7 3	6 7 3	6 7 7	6 7 7	6 8 0	6 9 9	7 0 7	7 1 1	7 1 4	7 1 5	7 1 9	7 2 3	7 3 3	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 3 4	4 3 5	4 4 0	4 4 7	4 2 8	4 1 7	4 3 2	4 0 9	4 1 4	4 4 1	4 1 8	4 4 6	4 4 5	4 3 8	4 2 7	4 0 1	4 0 3	4 5 0	4 0 2	4 1 5	4 3 1	4 1 2	4 0 4	4 1 0	4 3 7	Total Tissues/ Tumors
Special Senses System																										
Eye																					+					3
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma							X	X	X																	4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, carcinoma																					X					1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Leukemia mononuclear	X		X	X	X			X	X		X	X	X		X	X	X		X	X		X		X	X	27
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm

Number of Days on Study	41	43	44	46	48	50	51	51	51	54	54	55	56	56	57	58	59	59	59	59	59	60	60	63	63	64	64
	17	11	17	33	88	55	11	16	66	68	51	62	66	22	33	44	96	77	77	77	77	07	55	35	44	45
Carcass ID Number	61	61	61	63	64	63	62	60	61	60	63	60	63	62	61	62	60	62	62	64	61	63	63	37	39	36
	17	19	18	38	41	32	23	02	15	06	34	04	30	25	14	27	09	21	22	44	13	33	33	77	99	36
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+												+							+		+		+	+
Oral mucosa						+																					
Squamous cell papilloma						X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																											
Squamous cell papilloma																											
Tooth			+																			+					
Cardiovascular System																											
Blood vessel						+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																											
Pheochromocytoma complex																								X			
Pheochromocytoma benign			X									X									X					X	
Pheochromocytoma benign, multiple																											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																											
Carcinoma																								X			
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X	X	X	X	X			X	X			X	X							X	X				
Pars distalis, adenoma, multiple																											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X					
C-cell, carcinoma																											
Follicular cell, carcinoma																X											
General Body System																											
Peritoneum																									+		
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X											
Carcinoma																						X					X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	651	656	657	660	667	668	677	678	680	686	689	699	704	710	714	719	719	727	730	733	734	734	734	735	735	
Carcass ID Number	626	608	650	648	607	624	635	642	640	612	645	647	643	629	620	628	631	616	601	603	610	611	646	605	649	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+														+							+		+		10
Oral mucosa																										1
Squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+																			1
Squamous cell papilloma							X																			1
Tooth																										2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																		X								1
Pheochromocytoma complex																										1
Pheochromocytoma benign							X				X		X	X					X	X					X	11
Pheochromocytoma benign, multiple		X									X					X										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X										X					2
Carcinoma		X										X														3
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X			X	X	X			X	X		X		X	X		X	X	X		X			27
Pars distalis, adenoma, multiple				X					X																	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X								X										X					4
C-cell, carcinoma				X																						1
Follicular cell, carcinoma																										1
General Body System																										
Peritoneum																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																								+		1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														2
Carcinoma																	X				X					4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	4 1 7	4 3 1	4 4 7	4 6 3	4 8 8	5 0 5	5 1 1	5 1 6	5 4 6	5 4 8	5 5 1	5 6 2	5 6 6	5 7 2	5 8 3	5 9 4	5 9 6	5 9 7	5 9 7	5 9 7	6 0 7	6 3 5	6 3 5	6 4 4	6 4 5
Carcass ID Number	6 1 7	6 1 9	6 1 8	6 3 8	6 4 1	6 3 2	6 2 3	6 0 2	6 1 5	6 0 6	6 3 4	6 0 4	6 3 0	6 2 5	6 1 4	6 2 7	6 0 9	6 2 1	6 2 2	6 4 4	6 1 3	6 3 3	6 3 7	6 3 9	6 3 6
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma													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, bronchial	+	+	+	+	+	+	+	M	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, thymus							X																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, thymus							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Thymoma malignant																				X					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma															X						X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																X							X		
Squamous cell carcinoma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, histiocytic sarcoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma benign																									
Spinal cord												+													
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, thymus							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																									+
Carcinoma																									X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	651	656	657	660	667	668	677	678	680	686	689	699	704	710	714	719	719	727	730	733	734	734	734	734	735	
Carcass ID Number	62606	60868	65300	64808	60207	62404	63535	64202	64040	61202	64545	64477	64303	62909	62040	62808	63101	61616	61001	60303	61010	61101	61146	60505	60449	Total Tissues/ Tumors
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X		X	X		X	X	X	X		X	X			X		X	X	X	X	X		X	X	23
Interstitial cell, adenoma														X	X		X									11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+			+											+			+			16
Lymph node, bronchial	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	43
Histiocytic sarcoma, metastatic, thymus																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Histiocytic sarcoma, metastatic, thymus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																X	X									4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										2
Squamous cell carcinoma																									X	1
Trichoepithelioma													X													1
Subcutaneous tissue, fibroma													X									X				2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, histiocytic Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma benign																					X					1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, thymus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																		+		+						2
Zymbal's gland																					+					2
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	4 1 7	4 3 1	4 4 7	4 6 3	4 8 8	5 0 5	5 1 1	5 1 6	5 4 6	5 4 8	5 5 1	5 6 2	5 6 6	5 7 2	5 8 3	5 9 4	5 9 6	5 9 7	5 9 7	5 9 7	6 0 7	6 3 5	6 3 5	6 4 4	6 4 5
Carcass ID Number	6 1 7	6 1 9	6 1 8	6 3 8	6 4 1	6 3 2	6 2 3	6 0 2	6 1 5	6 0 6	6 3 4	6 0 4	6 3 0	6 2 5	6 1 4	6 2 7	6 0 9	6 2 1	6 2 2	6 4 4	6 1 3	6 3 3	6 3 7	6 3 9	6 3 6
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, carcinoma																									
Renal tubule, adenoma																									
Renal tubule, adenoma, multiple																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X								X										
Leukemia mononuclear		X	X	X		X			X	X	X	X	X			X	X	X	X	X	X	X	X		X
Mesothelioma malignant																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	651	655	657	660	667	668	677	678	680	686	689	699	704	710	714	719	721	727	730	733	734	744	745	755	735	
Carcass ID Number	62606	60808	65050	64048	60707	62404	63535	64242	64040	61202	64545	64447	64043	62929	62200	62808	63131	61616	61001	60303	61010	61101	61146	64046	60505	64049	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, transitional epithelium, carcinoma																								X			1
Renal tubule, adenoma						X							X														2
Renal tubule, adenoma, multiple												X															1
Renal tubule, carcinoma															X											X	2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											2
Leukemia mononuclear	X	X	X		X	X	X	X		X	X			X		X				X	X			X			32
Mesothelioma malignant																											1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	18/48 (38%)	11/50 (22%)	13/50 (26%)	14/49 (29%)
Adjusted rate[b]	71.9%	60.9%	61.4%	70.0%
Terminal rate[c]	5/11 (45%)	1/6 (17%)	1/5 (20%)	2/6 (33%)
First incidence (days)	563	575	517	447
Life table test[d]	P=0.453	P=0.404N	P=0.535	P=0.536
Logistic regression test[d]	P=0.421N	P=0.087N	P=0.170N	P=0.227N
Cochran-Armitage test[d]	P=0.442N			
Fisher exact test[d]		P=0.072N	P=0.157N	P=0.236N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	0/48 (0%)	1/50 (2%)	3/50 (6%)	1/49 (2%)
Adjusted rate	0.0%	5.3%	35.1%	12.5%
Terminal rate	0/11 (0%)	0/6 (0%)	1/5 (20%)	0/6 (0%)
First incidence (days)	—[e]	660	590	727
Life table test	P=0.429	P=0.462	P=0.047	P=0.375
Logistic regression test	P=0.511	P=0.503	P=0.107	P=0.432
Cochran-Armitage test	P=0.514			
Fisher exact test		P=0.510	P=0.129	P=0.505
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	18/48 (38%)	12/50 (24%)	16/50 (32%)	16/49 (33%)
Adjusted rate	71.9%	63.1%	76.5%	74.7%
Terminal rate	5/11 (45%)	1/6 (17%)	2/5 (40%)	2/6 (33%)
First incidence (days)	563	575	517	447
Life table test	P=0.313	P=0.490N	P=0.270	P=0.370
Logistic regression test	P=0.536	P=0.134N	P=0.397N	P=0.387N
Cochran-Armitage test	P=0.513			
Fisher exact test		P=0.109N	P=0.360N	P=0.387N
Kidney (Renal Tubule): Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rate	8.3%	16.7%	18.8%	18.6%
Terminal rate	1/12 (8%)	1/6 (17%)	0/5 (0%)	0/6 (0%)
First incidence (days)	733 (T)	733 (T)	631	668
Life table test	P=0.195	P=0.602	P=0.120	P=0.213
Logistic regression test	P=0.213	P=0.602	P=0.159	P=0.262
Cochran-Armitage test	P=0.224			
Fisher exact test		P=0.753N	P=0.181	P=0.309
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	8.3%	16.7%	18.8%	38.3%
Terminal rate	1/12 (8%)	1/6 (17%)	0/5 (0%)	1/6 (17%)
First incidence (days)	733 (T)	733 (T)	631	668
Life table test	P=0.031	P=0.602	P=0.120	P=0.042
Logistic regression test	P=0.037	P=0.602	P=0.159	P=0.065
Cochran-Armitage test	P=0.044			
Fisher exact test		P=0.753N	P=0.181	P=0.102

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	15.2%	3.1%	0.0%
Terminal rate	0/12 (0%)	0/6 (0%)	0/5 (0%)	0/6 (0%)
First incidence (days)	—	540	621	—
Life table test	P=0.308N	P=0.097	P=0.513	—
Logistic regression test	P=0.280N	P=0.121	P=0.500	—
Cochran-Armitage test	P=0.281N			
Fisher exact test		P=0.121	P=0.500	—
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	0.0%	15.2%	6.3%	0.0%
Terminal rate	0/12 (0%)	0/6 (0%)	0/5 (0%)	0/6 (0%)
First incidence (days)	—	540	621	—
Life table test	P=0.314N	P=0.097	P=0.258	—
Logistic regression test	P=0.289N	P=0.121	P=0.237	—
Cochran-Armitage test	P=0.291N			
Fisher exact test		P=0.121	P=0.247	—
Mammary Gland: Fibroadenoma				
Overall rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	0.0%	14.7%	12.3%	24.8%
Terminal rate	0/12 (0%)	0/6 (0%)	0/5 (0%)	0/6 (0%)
First incidence (days)	—	551	551	583
Life table test	P=0.061	P=0.175	P=0.116	P=0.041
Logistic regression test	P=0.076	P=0.238	P=0.120	P=0.062
Cochran-Armitage test	P=0.075			
Fisher exact test		P=0.247	P=0.121	P=0.059
Pancreatic Islets: Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	1/50 (2%)	2/49 (4%)
Adjusted rate	19.9%	5.9%	5.6%	22.2%
Terminal rate	1/12 (8%)	0/6 (0%)	0/5 (0%)	1/6 (17%)
First incidence (days)	547	575	673	689
Life table test	P=0.451N	P=0.450N	P=0.331N	P=0.516N
Logistic regression test	P=0.386N	P=0.335N	P=0.185N	P=0.365N
Cochran-Armitage test	P=0.385N			
Fisher exact test		P=0.339N	P=0.181N	P=0.349N
Pancreatic Islets: Carcinoma				
Overall rate	1/50 (2%)	2/50 (4%)	2/50 (4%)	3/49 (6%)
Adjusted rate	8.3%	19.0%	27.3%	14.1%
Terminal rate	1/12 (8%)	1/6 (17%)	1/5 (20%)	0/6 (0%)
First incidence (days)	733 (T)	575	707	635
Life table test	P=0.205	P=0.348	P=0.263	P=0.240
Logistic regression test	P=0.246	P=0.474	P=0.302	P=0.279
Cochran-Armitage test	P=0.259			
Fisher exact test		P=0.500	P=0.500	P=0.301

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)	5/49 (10%)
Adjusted rate	27.2%	23.9%	31.3%	33.2%
Terminal rate	2/12 (17%)	1/6 (17%)	1/5 (20%)	1/6 (17%)
First incidence (days)	547	575	673	635
Life table test	P=0.394	P=0.591	P=0.638	P=0.437
Logistic regression test	P=0.484	P=0.505N	P=0.420N	P=0.593
Cochran-Armitage test	P=0.493			
Fisher exact test		P=0.500N	P=0.357N	P=0.617
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	33/49 (67%)	34/49 (69%)	40/48 (83%)	29/50 (58%)
Adjusted rate	96.5%	90.5%	100.0%	86.5%
Terminal rate	11/12 (92%)	3/6 (50%)	5/5 (100%)	3/6 (50%)
First incidence (days)	406	503	401	417
Life table test	P=0.473N	P=0.138	P=0.014	P=0.402
Logistic regression test	P=0.091N	P=0.555	P=0.075	P=0.198N
Cochran-Armitage test	P=0.107N			
Fisher exact test		P=0.500	P=0.055	P=0.226N
Preputial Gland: Carcinoma				
Overall rate	3/49 (6%)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted rate	7.0%	2.1%	0.0%	30.3%
Terminal rate	0/11 (0%)	0/6 (0%)	0/5 (0%)	1/6 (17%)
First incidence (days)	453	503	—	607
Life table test	P=0.184	P=0.306N	P=0.113N	P=0.427
Logistic regression test	P=0.195	P=0.398N	P=0.148N	P=0.503
Cochran-Armitage test	P=0.208			
Fisher exact test		P=0.301N	P=0.117N	P=0.511
Preputial Gland: Adenoma or Carcinoma				
Overall rate	5/49 (10%)	3/50 (6%)	0/50 (0%)	6/50 (12%)
Adjusted rate	17.2%	11.4%	0.0%	37.1%
Terminal rate	1/11 (9%)	0/6 (0%)	0/5 (0%)	1/6 (17%)
First incidence (days)	406	439	—	583
Life table test	P=0.217	P=0.405N	P=0.046N	P=0.404
Logistic regression test	P=0.236	P=0.444N	P=0.041N	P=0.502
Cochran-Armitage test	P=0.256			
Fisher exact test		P=0.346N	P=0.027N	P=0.514
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	15.3%	19.4%	20.0%	6.2%
Terminal rate	1/12 (8%)	0/6 (0%)	1/5 (20%)	0/6 (0%)
First incidence (days)	575	607	733 (T)	594
Life table test	P=0.379N	P=0.399	P=0.456N	P=0.538N
Logistic regression test	P=0.336N	P=0.495	P=0.325N	P=0.496N
Cochran-Armitage test	P=0.338N			
Fisher exact test		P=0.500	P=0.309N	P=0.500N

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	3/50 (6%)	6/50 (12%)	1/50 (2%)	2/50 (4%)
Adjusted rate	15.3%	28.0%	20.0%	6.2%
Terminal rate	1/12 (8%)	0/6 (0%)	1/5 (20%)	0/6 (0%)
First incidence (days)	575	607	733 (T)	594
Life table test	P=0.262N	P=0.175	P=0.456N	P=0.538N
Logistic regression test	P=0.219N	P=0.235	P=0.325N	P=0.496N
Cochran-Armitage test	P=0.221N			
Fisher exact test		P=0.243	P=0.309N	P=0.500N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	6/50 (12%)	1/50 (2%)	3/50 (6%)
Adjusted rate	15.3%	28.0%	20.0%	21.8%
Terminal rate	1/12 (8%)	0/6 (0%)	1/5 (20%)	1/6 (17%)
First incidence (days)	575	607	733 (T)	594
Life table test	P=0.458N	P=0.175	P=0.456N	P=0.576
Logistic regression test	P=0.394N	P=0.235	P=0.325N	P=0.663N
Cochran-Armitage test	P=0.395N			
Fisher exact test		P=0.243	P=0.309N	P=0.661N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Squamous Cell Carcinoma				
Overall rate	4/50 (8%)	6/50 (12%)	1/50 (2%)	4/50 (8%)
Adjusted	23.0%	28.0%	20.0%	27.9%
Terminal	2/12 (17%)	0/6 (0%)	1/5 (20%)	1/6 (17%)
First incidence (days)	575	607	733 (T)	594
Life table test	P=0.562N	P=0.248	P=0.348N	P=0.498
Logistic regression test	P=0.480N	P=0.351	P=0.210N	P=0.635
Cochran-Armitage test	P=0.477N			
Fisher exact test		P=0.370	P=0.181N	P=0.643N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	13.7%	40.2%	34.8%	23.1%
Terminal rate	1/12 (8%)	2/6 (33%)	1/5 (20%)	1/6 (17%)
First incidence (days)	705	575	629	704
Life table test	P=0.487N	P=0.104	P=0.150	P=0.506
Logistic regression test	P=0.375N	P=0.187	P=0.260	P=0.610
Cochran-Armitage test	P=0.363N			
Fisher exact test		P=0.218	P=0.339	P=0.691N
Skin (Subutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	2/50 (4%)	5/50 (10%)	4/50 (8%)	3/50 (6%)
Adjusted rate	13.7%	40.2%	34.8%	24.9%
Terminal rate	1/12 (8%)	2/6 (33%)	1/5 (20%)	1/6 (17%)
First incidence (days)	705	575	629	516
Life table test	P=0.520	P=0.104	P=0.150	P=0.326
Logistic regression test	P=0.553N	P=0.187	P=0.260	P=0.485
Cochran-Armitage test	P=0.547N			
Fisher exact test		P=0.218	P=0.339	P=0.500

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Testes: Adenoma				
Overall rate	23/50 (46%)	31/50 (62%)	31/50 (62%)	34/50 (68%)
Adjusted rate	78.9%	100.0%	100.0%	96.8%
Terminal rate	7/12 (58%)	6/6 (100%)	5/5 (100%)	5/6 (83%)
First incidence (days)	546	439	561	505
Life table test	P=0.040	P=0.013	P=0.009	P=0.009
Logistic regression test	P=0.036	P=0.062	P=0.077	P=0.018
Cochran-Armitage test	P=0.048			
Fisher exact test		P=0.080	P=0.080	P=0.021
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/50 (8%)	4/50 (8%)	0/50 (0%)	4/50 (8%)
Adjusted rate	16.1%	41.3%	0.0%	28.1%
Terminal rate	1/12 (8%)	2/6 (33%)	0/5 (0%)	1/6 (17%)
First incidence (days)	453	607	—	607
Life table test	P=0.465	P=0.468	P=0.098N	P=0.542
Logistic regression test	P=0.570	P=0.644	P=0.066N	P=0.640N
Cochran-Armitage test	P=0.568			
Fisher exact test		P=0.643N	P=0.059N	P=0.643N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	12.9%	23.1%	35.4%	4.5%
Terminal rate	1/12 (8%)	1/6 (17%)	1/5 (20%)	0/6 (0%)
First incidence (days)	673	707	707	660
Life table test	P=0.493N	P=0.525	P=0.262	P=0.589N
Logistic regression test	P=0.415N	P=0.620	P=0.342	P=0.522N
Cochran-Armitage test	P=0.378N			
Fisher exact test		P=0.691N	P=0.500	P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	6/50 (12%)	3/50 (6%)	5/50 (10%)
Adjusted rate	27.6%	59.4%	35.4%	31.4%
Terminal rate	2/12 (17%)	3/6 (50%)	1/5 (20%)	1/6 (17%)
First incidence (days)	453	607	707	607
Life table test	P=0.556	P=0.366	P=0.475N	P=0.612
Logistic regression test	P=0.453N	P=0.597	P=0.247N	P=0.496N
Cochran-Armitage test	P=0.446N			
Fisher exact test		P=0.620N	P=0.243N	P=0.500N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rate	9.4%	0.0%	5.7%	2.9%
Terminal rate	0/12 (0%)	0/6 (0%)	0/5 (0%)	0/6 (0%)
First incidence (days)	514	—	591	594
Life table test	P=0.414N	P=0.131N	P=0.472N	P=0.296N
Logistic regression test	P=0.443N	P=0.127N	P=0.518N	P=0.320N
Cochran-Armitage test	P=0.429N			
Fisher exact test		P=0.121N	P=0.500N	P=0.309N

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	30/50 (60%)	29/50 (58%)	27/50 (54%)	32/50 (64%)
Adjusted rate	96.1%	90.7%	90.7%	84.6%
Terminal rate	11/12 (92%)	4/6 (67%)	3/5 (60%)	3/6 (50%)
First incidence (days)	422	439	517	431
Life table test	P=0.215	P=0.203	P=0.231	P=0.182
Logistic regression test	P=0.338	P=0.465N	P=0.283N	P=0.454
Cochran-Armitage test	P=0.318			
Fisher exact test		P=0.500N	P=0.343N	P=0.418
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	47/50 (94%)	48/50 (96%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	12/12 (100%)	6/6 (100%)	5/5 (100%)	6/6 (100%)
First incidence (days)	406	439	401	417
Life table test	P=0.306	P=0.136	P=0.094	P=0.183
Logistic regression test	P=0.438N	P=0.290N	P=0.639N	P=0.386N
Cochran-Armitage test	P=0.597N			
Fisher exact test		P=0.661N	P=0.500	P=0.661N
All Organs: Malignant Neoplasms				
Overall rate	37/50 (74%)	34/50 (68%)	32/50 (64%)	42/50 (84%)
Adjusted rate	97.0%	96.2%	95.9%	94.2%
Terminal rate	11/12 (92%)	5/6 (83%)	4/5 (80%)	4/6 (67%)
First incidence (days)	422	439	517	431
Life table test	P=0.084	P=0.265	P=0.306	P=0.089
Logistic regression test	P=0.070	P=0.259N	P=0.121N	P=0.204
Cochran-Armitage test	P=0.063			
Fisher exact test		P=0.330N	P=0.194N	P=0.163
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	49/50 (98%)	49/50 (98%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	12/12 (100%)	6/6 (100%)	5/5 (100%)	6/6 (100%)
First incidence (days)	406	439	401	417
Life table test	P=0.243	P=0.118	P=0.099	P=0.137
Logistic regression test	P=0.493	P=0.435N	—[f]	—
Cochran-Armitage test	P=0.193			
Fisher exact test		P=0.500	P=0.500	P=0.247

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, lung, 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 chamber 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 chamber 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
[f] Value of statistic cannot be computed.

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
CS2 (*o*-Chlorobenzalmalononitrile)	1/50	0/50	1/50
Acetonitrile	1/48	0/48	1/48
2-Chloroacetophenone	1/49	0/49	1/49
l-Epinephrine Hydrochloride	0/50	0/50	0/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	0/50	0/50
Ozone	2/50	0/50	2/50
Total	5/347 (1.4%)	0/347 (0%)	5/347 (1.4%)
Standard deviation	1.5%		1.5%
Range	0%-4%		0%-4%
Overall Historical Incidence			
Total	6/652 (0.9%)	0/652 (0%)	6/652 (0.9%)
Standard deviation	1.3%		1.3%
Range	0%-4%		0%-4%

[a] Data as of 12 May 1995

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Tetrahydrofuran[a]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1		
Moribund	31	39	40	34
Natural deaths	6	4	5	10
Survivors				
Terminal sacrifice	12	6	5	6
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(49)	(48)	(48)	(45)
Parasite metazoan	3 (6%)	6 (13%)	4 (8%)	5 (11%)
Muscularis, mineralization			1 (2%)	
Intestine large, rectum	(49)	(49)	(48)	(48)
Parasite metazoan	1 (2%)	3 (6%)	2 (4%)	4 (8%)
Intestine large, cecum	(49)	(48)	(48)	(46)
Necrosis			1 (2%)	
Parasite metazoan	4 (8%)	3 (6%)	4 (8%)	6 (13%)
Ulcer	1 (2%)			
Artery, inflammation, granulomatous			1 (2%)	
Intestine small, ileum	(47)	(47)	(47)	(44)
Peyer's patch, hyperplasia			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	6 (12%)	3 (6%)	4 (8%)
Basophilic focus		1 (2%)	1 (2%)	2 (4%)
Clear cell focus		2 (4%)	2 (4%)	1 (2%)
Degeneration, cystic	9 (18%)	6 (12%)	9 (18%)	13 (26%)
Eosinophilic focus			1 (2%)	
Hepatodiaphragmatic nodule	3 (6%)	2 (4%)		5 (10%)
Hyperplasia, reticulum cell				1 (2%)
Inflammation, granulomatous	1 (2%)			
Vacuolization cytoplasmic	4 (8%)	3 (6%)	7 (14%)	3 (6%)
Bile duct, hyperplasia	7 (14%)	7 (14%)	6 (12%)	6 (12%)
Hepatocyte, necrosis	3 (6%)	2 (4%)	2 (4%)	5 (10%)
Hepatocyte, regeneration			1 (2%)	
Periportal, fibrosis			1 (2%)	1 (2%)
Serosa, fibrosis		1 (2%)		
Serosa, inflammation, chronic		1 (2%)		
Mesentery	(15)	(17)	(18)	(10)
Artery, inflammation, chronic	1 (7%)			
Fat, hemorrhage	3 (20%)			1 (10%)
Fat, inflammation, granulomatous	5 (33%)	1 (6%)	2 (11%)	
Fat, mineralization		1 (6%)	2 (11%)	
Fat, necrosis	8 (53%)	15 (88%)	12 (67%)	9 (90%)
Oral mucosa	(3)			(1)
Hyperplasia	1 (33%)			
Inflammation, suppurative	1 (33%)			
Ulcer	1 (33%)			
Gingival, cyst	1 (33%)			
Gingival, foreign body	1 (33%)			

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

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Atrophy	18 (36%)	11 (22%)	7 (14%)	17 (34%)
Artery, inflammation, chronic			1 (2%)	1 (2%)
Artery, inflammation, granulomatous		1 (2%)		
Stomach, forestomach	(50)	(49)	(49)	(50)
Diverticulum	1 (2%)			1 (2%)
Hyperkeratosis	5 (10%)	2 (4%)	3 (6%)	5 (10%)
Hyperplasia	10 (20%)	14 (29%)	8 (16%)	11 (22%)
Inflammation, suppurative	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Mineralization	2 (4%)		2 (4%)	2 (4%)
Necrosis			1 (2%)	1 (2%)
Ulcer	6 (12%)	10 (20%)	3 (6%)	6 (12%)
Stomach, glandular	(50)	(50)	(50)	(50)
Edema			1 (2%)	
Inflammation, suppurative	2 (4%)			
Metaplasia, squamous			1 (2%)	
Mineralization	7 (14%)	1 (2%)	7 (14%)	5 (10%)
Ulcer	1 (2%)	2 (4%)		1 (2%)
Tooth		(2)	(1)	(2)
Developmental malformation		1 (50%)	1 (100%)	
Inflammation, suppurative		1 (50%)		2 (100%)
Cardiovascular System				
Blood vessel	(43)	(50)	(49)	(44)
Mineralization	3 (7%)		4 (8%)	2 (5%)
Thrombosis		1 (2%)		
Aorta, mineralization	1 (2%)			2 (5%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	8 (16%)	6 (12%)	6 (12%)	6 (12%)
Mineralization	3 (6%)		3 (6%)	3 (6%)
Atrium, thrombosis	1 (2%)	4 (8%)	3 (6%)	5 (10%)
Endocardium, hyperplasia			1 (2%)	
Myocardium, inflammation, suppurative				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Vacuolization cytoplasmic	14 (28%)	8 (16%)	6 (12%)	3 (6%)
Adrenal medulla	(48)	(50)	(50)	(49)
Hyperplasia	21 (44%)	19 (38%)	24 (48%)	27 (55%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia			1 (2%)	2 (4%)
Parathyroid gland	(46)	(48)	(49)	(46)
Hyperplasia	7 (15%)	5 (10%)	10 (20%)	11 (24%)
Pituitary gland	(49)	(49)	(48)	(50)
Cyst	5 (10%)	6 (12%)	4 (8%)	8 (16%)
Hemorrhage	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Craniopharyngeal duct, cyst		1 (2%)		
Pars distalis, angiectasis		1 (2%)		
Pars distalis, hyperplasia	1 (2%)	3 (6%)	3 (6%)	5 (10%)
Pars intermedia, hyperplasia	1 (2%)			1 (2%)

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
Inflammation, suppurative				1 (2%)
Ultimobranchial cyst		1 (2%)		
C-cell, hyperplasia	5 (10%)	3 (6%)	3 (6%)	6 (12%)
Follicular cell, hyperplasia			1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Hyperplasia, tubular		1 (2%)		
Inflammation, granulomatous		1 (2%)		
Spermatocele		1 (2%)		
Artery, inflammation, suppurative		1 (2%)		
Penis	(1)			(1)
Inflammation, suppurative	1 (100%)			
Preputial gland	(49)	(50)	(50)	(50)
Cyst		2 (4%)	1 (2%)	1 (2%)
Hyperplasia	2 (4%)	1 (2%)	3 (6%)	3 (6%)
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, suppurative	3 (6%)	1 (2%)	9 (18%)	6 (12%)
Prostate	(50)	(50)	(50)	(50)
Inflammation, suppurative	6 (12%)	5 (10%)	5 (10%)	3 (6%)
Epithelium, hyperplasia	2 (4%)	1 (2%)		5 (10%)
Seminal vesicle	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Cyst				1 (2%)
Inflammation, suppurative			2 (4%)	
Testes	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)	
Inflammation, granulomatous			1 (2%)	1 (2%)
Artery, inflammation	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Germinal epithelium, atrophy	11 (22%)	7 (14%)	5 (10%)	7 (14%)
Interstitial cell, hyperplasia	3 (6%)	2 (4%)	3 (6%)	3 (6%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia, reticulum cell	1 (2%)	1 (2%)		1 (2%)
Myelofibrosis			1 (2%)	

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Hematopoietic System (continued)				
Lymph node	(16)	(19)	(18)	(16)
Iliac, inflammation, suppurative			1 (6%)	
Iliac, pigmentation	1 (6%)			
Lumbar, pigmentation	1 (6%)			
Pancreatic, hyperplasia, histiocytic		1 (5%)		
Renal, ectasia	1 (6%)	3 (16%)		3 (19%)
Renal, fibrosis		1 (5%)		
Renal, hemorrhage	1 (6%)	2 (11%)		
Renal, hyperplasia, histiocytic		1 (5%)	1 (6%)	
Renal, pigmentation	1 (6%)			
Renal, deep cervical, angiectasis			1 (6%)	
Lymph node, bronchial	(45)	(45)	(44)	(43)
Fibrosis		3 (7%)		
Hemorrhage			1 (2%)	1 (2%)
Lymph node, mandibular	(46)	(50)	(49)	(48)
Hemorrhage	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		1 (2%)
Lymph node, mesenteric	(50)	(50)	(49)	(49)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)	2 (4%)	
Lymph node, mediastinal	(48)	(50)	(46)	(49)
Angiectasis		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)	3 (7%)	1 (2%)
Spleen	(50)	(50)	(50)	(50)
Accessory spleen	3 (6%)		2 (4%)	
Fibrosis	14 (28%)	13 (26%)	16 (32%)	17 (34%)
Hematopoietic cell proliferation				1 (2%)
Hemorrhage				1 (2%)
Necrosis	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Thymus	(50)	(49)	(48)	(50)
Hemorrhage	1 (2%)		2 (4%)	
Hyperplasia, lymphoid			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	5 (10%)	3 (6%)	3 (6%)	
Epithelium, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis	5 (10%)			
Hyperplasia	3 (6%)			
Inflammation, granulomatous	1 (2%)			1 (2%)
Inflammation, suppurative	5 (10%)	1 (2%)	2 (4%)	1 (2%)
Necrosis			1 (2%)	
Ulcer	4 (8%)	1 (2%)	4 (8%)	2 (4%)
Epidermis, cyst	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Prepuce, ulcer				1 (2%)
Subcutaneous tissue, hemorrhage		1 (2%)	1 (2%)	
Subcutaneous tissue, mineralization			1 (2%)	

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Degeneration				1 (2%)
Fibrosis			5 (10%)	1 (2%)
Fracture		1 (2%)		1 (2%)
Hemorrhage				1 (2%)
Hyperostosis				1 (2%)
Femur, hyperplasia			1 (2%)	
Turbinate, maxilla, fracture	1 (2%)			
Turbinate, maxilla, hemorrhage	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Demyelination		1 (2%)		
Developmental malformation	1 (2%)			
Gliosis			1 (2%)	
Hemorrhage	8 (16%)	5 (10%)	7 (14%)	11 (22%)
Hydrocephalus	1 (2%)	1 (2%)		
Mineralization	1 (2%)			
Necrosis	1 (2%)			
Meninges, hyperplasia	1 (2%)			
Ventricle, hydrocephalus	7 (14%)	7 (14%)	9 (18%)	4 (8%)
Spinal cord	(1)		(1)	(1)
Hemorrhage				1 (100%)
Respiratory System				
Larynx	(50)	(49)	(50)	(49)
Foreign body	3 (6%)	5 (10%)	3 (6%)	8 (16%)
Inflammation, suppurative	3 (6%)	1 (2%)	2 (4%)	3 (6%)
Epiglottis, metaplasia, squamous				1 (2%)
Epithelium, hyperplasia	1 (2%)	2 (4%)	1 (2%)	4 (8%)
Epithelium, metaplasia, squamous	2 (4%)		3 (6%)	5 (10%)
Glands, inflammation, suppurative	3 (6%)	1 (2%)	3 (6%)	2 (4%)
Respiratory epithelium, epiglottis, hyperplasia				1 (2%)
Lung	(50)	(50)	(50)	(50)
Hemorrhage	16 (32%)	12 (24%)	17 (34%)	18 (36%)
Alveolar epithelium, fibrosis	1 (2%)	2 (4%)	1 (2%)	4 (8%)
Alveolar epithelium, hyperplasia	3 (6%)	4 (8%)	4 (8%)	6 (12%)
Alveolar epithelium, infiltration cellular, histiocyte	7 (14%)	7 (14%)	8 (16%)	10 (20%)
Alveolar epithelium, inflammation, suppurative				1 (2%)
Alveolar epithelium, mineralization			3 (6%)	
Artery, infiltration cellular, histiocyte	1 (2%)			
Artery, mineralization	2 (4%)		1 (2%)	3 (6%)
Bronchiole, hyperplasia				1 (2%)
Bronchiole, metaplasia, squamous		1 (2%)		
Mediastinum, fibrosis	1 (2%)			

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Respiratory System (continued)				
Nose	(50)	(49)	(49)	(50)
Foreign body	6 (12%)	3 (6%)	5 (10%)	6 (12%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)			
Inflammation, suppurative	8 (16%)	2 (4%)	8 (16%)	6 (12%)
Glands, dilatation, focal		1 (2%)		
Goblet cell, respiratory epithelium, hypertrophy	3 (6%)		1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)		1 (2%)	
Respiratory epithelium, hyperplasia	3 (6%)	1 (2%)	3 (6%)	3 (6%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)		2 (4%)
Pleura	(2)	(1)	(2)	
Inflammation, chronic	1 (50%)	1 (100%)		
Trachea	(50)	(49)	(50)	(49)
Inflammation, suppurative		1 (2%)		
Epithelium, hyperplasia				1 (2%)
Special Senses System				
Eye			(3)	(2)
Cataract			1 (33%)	
Anterior chamber, inflammation, suppurative				1 (50%)
Cornea, inflammation, chronic			1 (33%)	
Cornea, mineralization			2 (67%)	1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	3 (6%)	3 (6%)	2 (4%)	5 (10%)
Fibrosis	1 (2%)			
Inflammation, suppurative				1 (2%)
Metaplasia, osseous				1 (2%)
Nephropathy, chronic	48 (96%)	50 (100%)	50 (100%)	50 (100%)
Thrombosis	1 (2%)		1 (2%)	3 (6%)
Cortex, necrosis			1 (2%)	3 (6%)
Pelvis, dilatation	2 (4%)	1 (2%)		
Pelvis, transitional epithelium, hyperplasia	16 (32%)	13 (26%)	16 (32%)	18 (36%)
Pelvis, transitional epithelium, inflammation, suppurative		1 (2%)		1 (2%)
Renal tubule, degeneration	1 (2%)			
Renal tubule, hyperplasia	7 (14%)	5 (10%)	6 (12%)	7 (14%)
Renal tubule, inflammation, suppurative	1 (2%)			
Renal tubule, mineralization	8 (16%)	7 (14%)	2 (4%)	5 (10%)
Renal tubule, pigmentation, hemosiderin				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Hemorrhage	2 (4%)	1 (2%)		2 (4%)
Inflammation, suppurative	2 (4%)	1 (2%)		
Transitional epithelium, hyperplasia	2 (4%)	1 (2%)		3 (6%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF TETRAHYDROFURAN

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	22	19	19
Natural deaths	7	3	5	5
Survivors				
Terminal sacrifice	25	25	26	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(47)	(49)	(49)	(46)
Polyp adenomatous	1 (2%)			
Sarcoma stromal, metastatic, uterus				1 (2%)
Intestine large, rectum	(48)	(50)	(50)	(47)
Intestine large, cecum	(47)	(49)	(46)	(45)
Carcinoma		1 (2%)		
Intestine small, duodenum	(46)	(49)	(49)	(47)
Intestine small, ileum	(45)	(49)	(46)	(45)
Liver	(50)	(49)	(50)	(50)
Osteosarcoma, metastatic, spleen			1 (2%)	
Mesentery	(6)	(9)	(9)	(3)
Osteosarcoma, metastatic, spleen			1 (11%)	
Pancreas	(48)	(50)	(50)	(49)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(49)	(49)	(50)	(49)
Squamous cell papilloma		1 (2%)		
Stomach, glandular	(49)	(49)	(50)	(49)
Tongue		(1)		(1)
Squamous cell papilloma		1 (100%)		1 (100%)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma malignant	2 (4%)			1 (2%)
Pheochromocytoma benign		1 (2%)	3 (6%)	3 (6%)
Islets, pancreatic	(48)	(50)	(50)	(49)
Adenoma	1 (2%)	1 (2%)		1 (2%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(49)	(49)	(50)	(50)
Pars distalis, adenoma	32 (65%)	38 (78%)	38 (76%)	34 (68%)
Pars distalis, adenoma, multiple	1 (2%)			
Thyroid gland	(48)	(50)	(50)	(49)
C-cell, adenoma	2 (4%)	3 (6%)	6 (12%)	4 (8%)
C-cell, carcinoma	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma				1 (2%)

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
General Body System				
None				
Genital System				
Clitoral gland	(48)	(48)	(46)	(49)
Adenoma	1 (2%)			
Carcinoma	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Ovary	(50)	(50)	(50)	(50)
Granulosa-theca tumor malignant		1 (2%)		
Granulosa-theca tumor benign				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Leiomyoma		1 (2%)		
Polyp stromal	5 (10%)	8 (16%)	8 (16%)	6 (12%)
Sarcoma stromal	1 (2%)	1 (2%)		1 (2%)
Vagina	(1)		(1)	
Polyp			1 (100%)	
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node	(7)	(7)	(6)	(5)
Lymph node, bronchial	(46)	(45)	(41)	(45)
Osteosarcoma, metastatic, spleen			1 (2%)	
Lymph node, mandibular	(45)	(47)	(48)	(44)
Lymph node, mesenteric	(48)	(50)	(50)	(50)
Lymph node, mediastinal	(48)	(48)	(48)	(46)
Carcinoma, metastatic, islets, pancreatic				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Osteosarcoma			1 (2%)	
Thymus	(50)	(50)	(49)	(48)
Thymoma malignant				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma	5 (10%)	5 (10%)	5 (10%)	2 (4%)
Carcinoma, multiple				1 (2%)
Fibroadenoma	14 (28%)	14 (28%)	23 (46%)	26 (52%)
Fibroadenoma, multiple	9 (18%)	8 (16%)	6 (12%)	5 (10%)
Skin	(50)	(50)	(50)	(50)
Amelanotic melanoma, benign			1 (2%)	
Keratoacanthoma	1 (2%)		1 (2%)	
Squamous cell papilloma	1 (2%)	1 (2%)		
Pinna, melanoma benign			1 (2%)	
Subcutaneous tissue, fibroma			2 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, lipoma			1 (2%)	
Subcutaneous tissue, liposarcoma	1 (2%)			
Subcutaneous tissue, sarcoma				1 (2%)

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Rib, osteosarcoma	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Carcinoma, metastatic, islets, pancreatic				1 (2%)
Carcinoma, metastatic, mammary gland				1 (2%)
Granulosa-theca tumor malignant, metastatic, ovary		1 (2%)		
Special Senses System				
Zymbal's gland			(1)	
Carcinoma			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Granulosa-theca tumor malignant, metastatic, ovary		1 (2%)		
Lipoma	1 (2%)			
Renal tubule, carcinoma	1 (2%)			
Urinary bladder	(49)	(50)	(50)	(49)
Transitional epithelium, papilloma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	17 (34%)	17 (34%)	18 (36%)	22 (44%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	46	47	49	48
Total primary neoplasms	103	108	122	119
Total animals with benign neoplasms	42	45	48	43
Total benign neoplasms	71	79	92	82
Total animals with malignant neoplasms	27	25	23	30
Total malignant neoplasms	32	29	30	37
Total animals with metastatic neoplasms		1	1	3
Total metastatic neoplasms		2	3	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 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 0 5	1 0 6	1 1 2	1 1 9	1 2 1	1 2 7	1 2 8	1 2 9	1 4 1	1 4 2	1 4 3	1 0 3	1 0 8	1 2 5	1 3 2	1 3 3	1 3 5	1 3 6	1 4 6	1 0 1	1 0 2	1 0 4	1 2 4	1 2 6	1 3 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous												X														1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+					+														+				6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma								X																		1
Parathyroid gland	+	+	M	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X		X		X	X		X		X		X	X	X		X	X	X			X	X	32
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma							X																X			2
C-cell, carcinoma			X														X									2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma															X											1
Carcinoma											X															1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oviduct							+																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X					X				X										X						5
Sarcoma stromal																										1
Vagina	+																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 0 5	1 0 6	1 1 2	1 1 9	1 2 1	1 2 7	1 2 8	1 2 9	1 4 1	1 4 2	1 4 3	1 0 3	1 0 8	1 2 5	1 3 2	1 3 3	1 3 5	1 3 6	1 4 6	1 0 1	1 0 2	1 0 4	1 2 4	1 2 6	1 3 4	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																									7
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mandibular	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X					1
Carcinoma																				X				X	5
Fibroadenoma			X		X				X		X				X		X		X		X			X	14
Fibroadenoma, multiple				X		X				X			X	X								X			9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																				X					1
Squamous cell papilloma												X													1
Subcutaneous tissue, liposarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, osteosarcoma																				X					1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Eye							+																+		3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																X									1
Renal tubule, carcinoma																						X			1
Urethra																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X												X		X		X				17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 0 1	3 0 7	3 1 1	3 1 7	3 2 0	3 2 7	3 3 1	3 3 6	3 4 1	3 4 6	3 4 2	3 1 8	3 2 3	3 2 4	3 2 8	3 4 0	3 4 3	3 4 5	3 5 0	3 0 3	3 0 8	3 1 4	3 1 5	3 1 6	3 3 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery			+										+			+	+						+	+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue	+																									1
Squamous cell papilloma	X																									1
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma			X																							1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X		X	X	X		X	X	X		X	X	X	X		X	X	X	X	X	X	X	38
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X		X		3
C-cell, carcinoma																										1
General Body System																										
Tissue NOS														+												1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Polyp stromal		X									X										X	X				8
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	0 5 8	3 3 6	4 6 7	4 7 8	4 9 1	5 0 0	5 0 5	5 6 5	5 9 2	6 1 4	6 2 4	6 5 1	6 5 8	6 7 0	6 8 1	6 8 1	6 8 1	6 8 7	6 9 5	7 0 5	7 0 5	7 1 4	7 1 9	7 1 9	7 1 9
Carcass ID Number	3 3 2	3 1 0	3 4 8	3 4 2	3 0 2	3 2 2	3 3 9	3 2 5	3 4 9	3 0 9	3 3 3	3 2 9	3 2 1	3 0 4	3 0 6	3 1 9	3 3 5	3 2 6	3 4 7	3 3 4	3 3 7	3 1 3	3 0 5	3 3 0	3 4 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+			+			+								+		+	+			
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X												X	
Fibroadenoma				X	X							X			X		X			X				X	X
Fibroadenoma, multiple																X			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary													X												
Nose	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, 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 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 0 1	3 0 7	3 1 1	3 1 7	3 2 0	3 2 7	3 3 1	3 3 6	3 4 1	3 4 6	3 1 2	3 1 8	3 2 3	3 2 4	3 2 8	3 4 0	3 4 3	3 4 5	3 5 0	3 0 3	3 0 8	3 1 4	3 1 5	3 1 6	3 3 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										7
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mandibular	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma														X			X				X					5
Fibroadenoma													X							X		X	X	X	X	14
Fibroadenoma, multiple								X		X	X	X			X	X										8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																							X			1
Subcutaneous tissue, fibrosarcoma																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye								+												+						3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																		X								1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X		X											X		X	X				X	17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	5 0 4	5 0 9	5 1 0	5 1 2	5 1 7	5 1 8	5 2 5	5 4 5	5 4 9	5 0 6	5 0 7	5 1 1	5 1 3	5 3 2	5 3 3	5 3 7	5 3 8	5 0 2	5 0 8	5 1 9	5 2 0	5 3 0	5 3 1	5 4 7	5 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Mesentery						+			+								+									9
Osteosarcoma, metastatic, spleen																										1
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign												X						X								3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																				X						1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X		X	X			X	X	X	X	X		X	X			X	X	X	38
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X									X				X						6
C-cell, carcinoma																	X									2
Follicular cell, adenoma										X																1
General Body System																										
Tissue NOS												+														2
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X					X						X	X								X			8
Vagina					+																					1
Polyp					X																					1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	5 1 9	5 3 8	5 4 7	5 5 9	5 6 9	5 7 5	5 9 7	5 9 7	5 9 7	6 0 7	6 2 6	6 4 9	6 4 9	6 6 0	6 6 3	6 6 7	6 7 4	6 7 7	6 8 3	6 8 7	6 9 9	6 9 9	7 0 5	7 2 7	7 3 3
Carcass ID Number	5 1 4	5 2 3	5 2 7	5 2 6	5 0 1	5 2 8	5 3 6	5 4 0	5 4 1	5 0 5	5 2 1	5 1 6	5 2 9	5 3 4	5 2 2	5 4 3	5 2 4	5 3 9	5 1 5	5 3 5	5 4 4	5 4 8	5 4 6	5 4 2	5 0 3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																+				+		+		+	
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+
Osteosarcoma, metastatic, spleen														X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma														X											
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X															X				X	X		
Fibroadenoma	X	X				X	X	X			X					X				X	X		X	X	X
Fibroadenoma, multiple									X						X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Amelanotic melanoma, benign																									
Keratoacanthoma																									
Pinna, melanoma benign																		X							
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X					X	X				X		X		X		X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	5 0 4	5 0 9	5 1 0	5 1 2	5 1 7	5 1 8	5 2 5	5 4 5	5 4 9	5 0 6	5 0 7	5 1 1	5 1 3	5 3 2	5 3 3	5 3 7	5 3 8	5 0 2	5 0 8	5 1 9	5 2 0	5 3 0	5 3 1	5 4 7	5 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+	+																			6
Lymph node, bronchial	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	41
Osteosarcoma, metastatic, spleen																										1
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma						X																				5
Fibroadenoma		X		X				X	X		X		X	X	X						X	X	X			23
Fibroadenoma, multiple					X		X												X	X						6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Amelanotic melanoma, benign																						X				1
Keratoacanthoma														X												1
Pinna, melanoma benign																										1
Subcutaneous tissue, fibroma							X																	X		2
Subcutaneous tissue, lipoma												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant		X																								1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye													+													1
Zymbal's gland										+																1
Carcinoma										X																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X	X	X			X				X						X	X	X	X			18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 1 1	7 2 0	7 2 7	7 3 8	7 3 9	7 4 2	7 4 5	7 4 7	7 0 3	7 0 8	7 1 4	7 1 7	7 2 2	7 2 3	7 2 4	7 3 3	7 3 5	7 3 6	7 4 4	7 4 9	7 5 0	7 1 3	7 2 1	7 2 9	7 3 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma stromal, metastatic, uterus																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+						+							+			3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue				+																						1
Squamous cell papilloma				X																						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant			X																							1
Pheochromocytoma benign												X								X						3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma																					X					1
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X		X	34
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma								X		X											X					4
C-cell, carcinoma											X									X						2
Follicular cell, carcinoma																		X								1
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma														X				X								3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X						X						X			X						6
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	4 1 2	4 2 0	4 7 8	4 9 8	5 2 3	5 3 2	5 4 9	5 7 5	5 8 8	5 9 7	6 2 4	6 2 9	6 3 0	6 3 4	6 4 1	6 4 3	6 4 6	6 6 1	6 9 1	6 9 1	6 9 9	7 0 5	7 1 4	7 3 3
Carcass ID Number	7 4 8	7 3 0	7 3 7	7 1 8	7 1 0	7 0 9	7 1 5	7 4 3	7 2 8	7 1 6	7 4 6	7 3 2	7 4 1	7 0 6	7 0 1	7 0 4	7 1 9	7 2 6	7 0 5	7 3 1	7 4 0	7 0 7	7 2 5	7 1 2	7 0 2
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymph node					+			+	+													+		
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mandibular	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+
Thymoma malignant												X												
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X											
Carcinoma, multiple																								
Fibroadenoma			X									X			X	X	X	X	X		X	X	X		X
Fibroadenoma, multiple										X										X				X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, sarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																								
Carcinoma, metastatic, mammary gland													X											
Nose	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								+
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Leukemia mononuclear					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 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 1 1	7 2 0	7 2 7	7 3 8	7 3 9	7 4 2	7 4 5	7 4 7	7 0 3	7 0 8	7 1 4	7 1 7	7 2 2	7 2 3	7 2 4	7 3 3	7 3 5	7 3 6	7 4 4	7 4 9	7 5 0	7 1 3	7 2 1	7 2 9	7 3 4	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																								X		1
Lymph node																+										5
Lymph node, bronchial	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Carcinoma, metastatic, islets, pancreatic																					X					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																X										2
Carcinoma, multiple										X																1
Fibroadenoma		X	X	X			X	X		X			X		X	X		X	X			X	X	X	X	26
Fibroadenoma, multiple					X				X																	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																								X		1
Subcutaneous tissue, sarcoma																	X									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																					X					1
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye			+																	+						3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																								X		1
Leukemia mononuclear									X	X					X	X	X		X	X			X			22

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	0/50 (0%)	1/50 (2%)	3/49 (6%)	3/50 (6%)
Adjusted rate[b]	0.0%	2.4%	9.6%	10.3%
Terminal rate[c]	0/25 (0%)	0/25 (0%)	2/26 (8%)	2/26 (8%)
First incidence (days)	—[e]	614	538	641
Life table test[d]	P=0.111	P=0.505	P=0.135	P=0.122
Logistic regression test[d]	P=0.109	P=0.495	P=0.113	P=0.120
Cochran-Armitage test[d]	P=0.108			
Fisher exact test[d]		P=0.500	P=0.117	P=0.121
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/49 (6%)	4/50 (8%)
Adjusted rate	5.7%	2.4%	9.6%	14.0%
Terminal rate	0/25 (0%)	0/25 (0%)	2/26 (8%)	3/26 (12%)
First incidence (days)	642	614	538	641
Life table test	P=0.164	P=0.497N	P=0.510	P=0.327
Logistic regression test	P=0.167	P=0.501N	P=0.489	P=0.337
Cochran-Armitage test	P=0.165			
Fisher exact test		P=0.500N	P=0.490	P=0.339
Clitoral Gland: Carcinoma				
Overall rate	1/48 (2%)	1/48 (2%)	1/46 (2%)	3/49 (6%)
Adjusted rate	4.2%	4.2%	3.8%	10.0%
Terminal rate	1/24 (4%)	1/24 (4%)	1/26 (4%)	2/25 (8%)
First incidence (days)	733 (T)	733 (T)	733 (T)	498
Life table test	P=0.164	P=0.763	P=0.745N	P=0.319
Logistic regression test	P=0.162	P=0.763	P=0.745N	P=0.314
Cochran-Armitage test	P=0.164			
Fisher exact test		P=0.753N	P=0.742	P=0.316
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	2/48 (4%)	1/48 (2%)	1/46 (2%)	3/49 (6%)
Adjusted rate	8.3%	4.2%	3.8%	10.0%
Terminal rate	2/24 (8%)	1/24 (4%)	1/26 (4%)	2/25 (8%)
First incidence (days)	733 (T)	733 (T)	733 (T)	498
Life table test	P=0.294	P=0.500N	P=0.472N	P=0.517
Logistic regression test	P=0.286	P=0.500N	P=0.472N	P=0.511
Cochran-Armitage test	P=0.292			
Fisher exact test		P=0.500N	P=0.516N	P=0.510
Mammary Gland: Fibroadenoma				
Overall rate	23/50 (46%)	22/50 (44%)	29/50 (58%)	31/50 (62%)
Adjusted rate	68.8%	61.3%	73.1%	79.3%
Terminal rate	15/25 (60%)	12/25 (48%)	16/26 (62%)	18/26 (69%)
First incidence (days)	634	478	519	478
Life table test	P=0.066	P=0.468N	P=0.227	P=0.113
Logistic regression test	P=0.031	P=0.478N	P=0.211	P=0.056
Cochran-Armitage test	P=0.038			
Fisher exact test		P=0.500N	P=0.158	P=0.080

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	24/50 (48%)	22/50 (44%)	29/50 (58%)	31/50 (62%)
Adjusted rate	71.9%	61.3%	73.1%	79.3%
Terminal rate	16/25 (64%)	12/25 (48%)	16/26 (62%)	18/26 (69%)
First incidence (days)	634	478	519	478
Life table test	P=0.081	P=0.397N	P=0.284	P=0.150
Logistic regression test	P=0.042	P=0.393N	P=0.277	P=0.083
Cochran-Armitage test	P=0.050			
Fisher exact test		P=0.421N	P=0.212	P=0.114
Mammary Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	5/50 (10%)	3/50 (6%)
Adjusted rate	15.7%	17.3%	14.9%	10.1%
Terminal rate	2/25 (8%)	3/25 (12%)	1/26 (4%)	2/26 (8%)
First incidence (days)	642	651	547	630
Life table test	P=0.293N	P=0.615N	P=0.623	P=0.375N
Logistic regression test	P=0.272N	P=0.623N	P=0.616N	P=0.354N
Cochran-Armitage test	P=0.274N			
Fisher exact test		P=0.630N	P=0.630N	P=0.357N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	27/50 (54%)	25/50 (50%)	33/50 (66%)	32/50 (64%)
Adjusted rate	74.3%	70.2%	77.8%	79.9%
Terminal rate	16/25 (64%)	15/25 (60%)	17/26 (65%)	18/26 (69%)
First incidence (days)	634	478	519	478
Life table test	P=0.167	P=0.399N	P=0.245	P=0.249
Logistic regression test	P=0.109	P=0.390N	P=0.219	P=0.180
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.421N	P=0.154	P=0.208
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	33/49 (67%)	38/49 (78%)	38/50 (76%)	34/50 (68%)
Adjusted rate	79.7%	92.4%	85.8%	89.2%
Terminal rate	17/25 (68%)	21/24 (88%)	20/26 (77%)	22/26 (85%)
First incidence (days)	467	336	519	412
Life table test	P=0.422N	P=0.255	P=0.328	P=0.506
Logistic regression test	P=0.349N	P=0.156	P=0.270	P=0.545
Cochran-Armitage test	P=0.363N			
Fisher exact test		P=0.183	P=0.232	P=0.558
Thyroid Gland (C-cell): Adenoma				
Overall rate	2/48 (4%)	3/50 (6%)	6/50 (12%)	4/49 (8%)
Adjusted rate	8.0%	10.4%	19.3%	14.3%
Terminal rate	2/25 (8%)	2/25 (8%)	3/26 (12%)	3/26 (12%)
First incidence (days)	733 (T)	651	649	691
Life table test	P=0.340	P=0.505	P=0.144	P=0.352
Logistic regression test	P=0.326	P=0.509	P=0.143	P=0.321
Cochran-Armitage test	P=0.344			
Fisher exact test		P=0.520	P=0.148	P=0.349

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	4/48 (8%)	3/50 (6%)	8/50 (16%)	6/49 (12%)
Adjusted rate	16.0%	10.4%	24.9%	21.8%
Terminal rate	4/25 (16%)	2/25 (8%)	4/26 (15%)	5/26 (19%)
First incidence (days)	733 (T)	651	649	691
Life table test	P=0.260	P=0.496N	P=0.193	P=0.389
Logistic regression test	P=0.237	P=0.489N	P=0.189	P=0.349
Cochran-Armitage test	P=0.260			
Fisher exact test		P=0.477N	P=0.199	P=0.383
Uterus: Stromal Polyp				
Overall rate	5/50 (10%)	8/50 (16%)	8/50 (16%)	6/50 (12%)
Adjusted rate	18.1%	25.7%	26.5%	19.5%
Terminal rate	4/25 (16%)	4/25 (16%)	5/26 (19%)	4/26 (15%)
First incidence (days)	634	651	674	532
Life table test	P=0.524N	P=0.293	P=0.294	P=0.511
Logistic regression test	P=0.542N	P=0.283	P=0.289	P=0.503
Cochran-Armitage test	P=0.530N			
Fisher exact test		P=0.277	P=0.277	P=0.500
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	6/50 (12%)	9/50 (18%)	8/50 (16%)	7/50 (14%)
Adjusted rate	20.7%	27.2%	26.5%	21.9%
Terminal rate	4/25 (16%)	4/25 (16%)	5/26 (19%)	4/26 (15%)
First incidence (days)	634	478	674	532
Life table test	P=0.534N	P=0.307	P=0.399	P=0.498
Logistic regression test	P=0.535N	P=0.294	P=0.405	P=0.505
Cochran-Armitage test	P=0.534N			
Fisher exact test		P=0.288	P=0.387	P=0.500
All Organs: Mononuclear Cell Leukemia				
Overall rate	17/50 (34%)	17/50 (34%)	18/50 (36%)	22/50 (44%)
Adjusted rate	41.5%	45.3%	51.5%	52.9%
Terminal rate	4/25 (16%)	7/25 (28%)	10/26 (38%)	8/26 (31%)
First incidence (days)	411	467	575	523
Life table test	P=0.174	P=0.559N	P=0.528	P=0.243
Logistic regression test	P=0.199	P=0.581	P=0.507	P=0.294
Cochran-Armitage test	P=0.142			
Fisher exact test		P=0.583N	P=0.500	P=0.206
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	45/50 (90%)	48/50 (96%)	43/50 (86%)
Adjusted rate	97.6%	95.7%	100.0%	97.7%
Terminal rate	24/25 (96%)	23/25 (92%)	26/26 (100%)	25/26 (96%)
First incidence (days)	467	336	519	412
Life table test	P=0.495N	P=0.417	P=0.286	P=0.509
Logistic regression test	P=0.377N	P=0.298	P=0.146	P=0.607
Cochran-Armitage test	P=0.513N			
Fisher exact test		P=0.277	P=0.046	P=0.500

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	25/50 (50%)	23/50 (46%)	30/50 (60%)
Adjusted rate	62.6%	64.1%	61.0%	70.2%
Terminal rate	10/25 (40%)	12/25 (48%)	12/26 (46%)	14/26 (54%)
First incidence (days)	411	467	547	498
Life table test	P=0.258	P=0.422N	P=0.288N	P=0.375
Logistic regression test	P=0.220	P=0.413N	P=0.249N	P=0.462
Cochran-Armitage test	P=0.212			
Fisher exact test		P=0.421N	P=0.274N	P=0.343
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	47/50 (94%)	49/50 (98%)	48/50 (96%)
Adjusted rate	97.8%	97.9%	100.0%	98.0%
Terminal rate	24/25 (96%)	24/25 (96%)	26/26 (100%)	25/26 (96%)
First incidence (days)	411	336	519	412
Life table test	P=0.445	P=0.538	P=0.468	P=0.455
Logistic regression test	P=0.511	P=0.588	P=0.436	P=0.547
Cochran-Armitage test	P=0.305			
Fisher exact test		P=0.500	P=0.181	P=0.339

(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, 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 chamber 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 chamber 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 B4
Historical Incidence of Mammary Gland Neoplasms in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls			
	Fibroadenoma	Adenoma	Carcinoma	Fibroadenoma, Adenoma, or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories				
CS2 (*o*-Chlorobenzalmalononitrile)	16/50	0/50	1/50	17/50
Acetonitrile	16/48	0/48	2/48	17/48
2-Chloroacetophenone	12/50	0/50	2/50	13/50
l-Epinephrine Hydrochloride	10/50	0/50	2/50	11/50
Chloroethane	11/50	2/50	0/50	13/50
Hexachlorocyclopentadiene	12/50	0/50	3/50	14/50
Ozone	20/50	1/50	4/50	23/50
Total	97/348 (27.9%)	3/348 (0.9%)	14/348 (4.0%)	108/348 (31.0%)
Standard deviation	7.3%	1.6%	2.6%	8.1%
Range	20%-40%	0%-4%	0%-8%	22%-46%
Overall Historical Incidence				
Total	180/653 (27.6%)	8/653 (1.2%)	25/653 (3.8%)	202/653 (30.9%)
Standard deviation	7.7%	1.5%	2.7%	9.1%
Range	16%-42%	0%-4%	0%-8%	16%-46%

[a] Data as of 12 May 1995

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Tetrahydrofuran[a]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	22	19	19
Natural deaths	7	3	5	5
Survivors				
Terminal sacrifice	25	25	26	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(47)	(49)	(49)	(46)
Parasite metazoan	1 (2%)	1 (2%)	5 (10%)	7 (15%)
Intestine large, rectum	(48)	(50)	(50)	(47)
Parasite metazoan	6 (13%)	2 (4%)	6 (12%)	5 (11%)
Intestine large, cecum	(47)	(49)	(46)	(45)
Parasite metazoan	2 (4%)	3 (6%)	4 (9%)	7 (16%)
Ulcer		1 (2%)		
Intestine small, ileum	(45)	(49)	(46)	(45)
Parasite metazoan				1 (2%)
Liver	(50)	(49)	(50)	(50)
Angiectasis	3 (6%)	4 (8%)	1 (2%)	
Basophilic focus	6 (12%)	2 (4%)		6 (12%)
Clear cell focus	6 (12%)	7 (14%)		6 (12%)
Degeneration, cystic	2 (4%)			2 (4%)
Hemorrhage		1 (2%)		
Hepatodiaphragmatic nodule	6 (12%)	5 (10%)	3 (6%)	10 (20%)
Hyperplasia, reticulum cell	2 (4%)			
Inflammation, granulomatous		2 (4%)		
Vacuolization cytoplasmic	7 (14%)	16 (33%)	12 (24%)	3 (6%)
Bile duct, hyperplasia				1 (2%)
Hepatocyte, necrosis	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hepatocyte, regeneration		1 (2%)		
Serosa, fibrosis	1 (2%)			
Mesentery	(6)	(9)	(9)	(3)
Fat, inflammation, granulomatous	2 (33%)			1 (33%)
Fat, mineralization		1 (11%)		
Fat, necrosis	4 (67%)	8 (89%)	7 (78%)	2 (67%)
Oral mucosa			(1)	
Hyperplasia			1 (100%)	
Pancreas	(48)	(50)	(50)	(49)
Atrophy	3 (6%)	6 (12%)	4 (8%)	7 (14%)
Stomach, forestomach	(49)	(49)	(50)	(49)
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	6 (12%)	7 (14%)	3 (6%)	3 (6%)
Inflammation, suppurative	1 (2%)	3 (6%)		2 (4%)
Necrosis		1 (2%)		
Ulcer	2 (4%)	5 (10%)	1 (2%)	2 (4%)

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

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(49)	(50)	(49)
Mineralization	1 (2%)			1 (2%)
Necrosis	1 (2%)			
Ulcer	2 (4%)		2 (4%)	
Tooth		(1)		
Developmental malformation		1 (100%)		
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, thrombosis	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy			1 (2%)	1 (2%)
Atrium, thrombosis	2 (4%)	1 (2%)	1 (2%)	
Endocardium, hemorrhage			1 (2%)	
Endocardium, atrium, fibrosis				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)		
Necrosis		1 (2%)		
Vacuolization cytoplasmic	6 (12%)	10 (20%)	7 (14%)	11 (22%)
Zona reticularis, pigmentation	1 (2%)			
Adrenal medulla	(50)	(50)	(49)	(50)
Hemorrhage		1 (2%)		
Hyperplasia	4 (8%)	2 (4%)	9 (18%)	6 (12%)
Necrosis			1 (2%)	
Pancreatic islets	(48)	(50)	(50)	(49)
Hyperplasia	1 (2%)			
Parathyroid gland	(43)	(43)	(46)	(42)
Hyperplasia		1 (2%)		2 (5%)
Pituitary gland	(49)	(49)	(50)	(50)
Cyst	9 (18%)	6 (12%)	4 (8%)	6 (12%)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	
Pars distalis, hyperplasia	5 (10%)	3 (6%)	6 (12%)	2 (4%)
Pars intermedia, hyperplasia				1 (2%)
Pars nervosa, cyst	1 (2%)			
Thyroid gland	(48)	(50)	(50)	(49)
Ultimobranchial cyst		1 (2%)		1 (2%)
C-cell, hyperplasia	5 (10%)	6 (12%)	7 (14%)	10 (20%)
General Body System				
None				

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Genital System				
Clitoral gland	(48)	(48)	(46)	(49)
Cyst			1 (2%)	1 (2%)
Hyperplasia	1 (2%)	4 (8%)	3 (7%)	1 (2%)
Inflammation, chronic	2 (4%)			3 (6%)
Inflammation, granulomatous	1 (2%)			
Inflammation, suppurative	2 (4%)	3 (6%)	3 (7%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Cyst	9 (18%)	3 (6%)	5 (10%)	4 (8%)
Bilateral, cyst		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Atrophy		2 (4%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hyperplasia, reticulum cell	3 (6%)	1 (2%)		1 (2%)
Myelofibrosis	1 (2%)			2 (4%)
Lymph node	(7)	(7)	(6)	(5)
Iliac, hyperplasia, histiocytic	1 (14%)			
Iliac, hyperplasia, lymphoid	2 (29%)			
Iliac, pigmentation	1 (14%)			
Lumbar, pigmentation	1 (14%)			
Pancreatic, pigmentation		1 (14%)		
Renal, hyperplasia, lymphoid	2 (29%)			
Lymph node, bronchial	(46)	(45)	(41)	(45)
Hemorrhage		1 (2%)		1 (2%)
Lymph node, mandibular	(45)	(47)	(48)	(44)
Hyperplasia, lymphoid			1 (2%)	
Infiltration cellular, histiocyte	1 (2%)			
Lymph node, mesenteric	(48)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Inflammation, suppurative		1 (2%)		
Necrosis	1 (2%)			
Lymph node, mediastinal	(48)	(48)	(48)	(46)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Inflammation, suppurative	1 (2%)			
Pigmentation	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Accessory spleen				1 (2%)
Angiectasis		1 (2%)		
Fibrosis		1 (2%)	1 (2%)	3 (6%)
Hematopoietic cell proliferation	3 (6%)	1 (2%)		1 (2%)
Hemorrhage	2 (4%)	3 (6%)		1 (2%)
Necrosis		2 (4%)	1 (2%)	2 (4%)
Pigmentation		1 (2%)		
Thymus	(50)	(50)	(49)	(48)
Cyst		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)	

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	3 (6%)	1 (2%)		
Hyperplasia				1 (2%)
Inflammation, suppurative				1 (2%)
Duct, dilatation			1 (2%)	
Duct, metaplasia, squamous	1 (2%)			
Epithelium, hyperplasia		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis	3 (6%)			
Hyperplasia	1 (2%)			
Inflammation, suppurative	1 (2%)			
Ulcer		2 (4%)	3 (6%)	1 (2%)
Epidermis, cyst	2 (4%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Cartilage, sternum, degeneration, mucoid	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Gliosis	1 (2%)			
Hemorrhage	6 (12%)	3 (6%)	5 (10%)	5 (10%)
Necrosis			1 (2%)	
Meninges, hyperplasia				1 (2%)
Ventricle, hydrocephalus	5 (10%)	8 (16%)	8 (16%)	1 (2%)
Respiratory System				
Larynx	(50)	(50)	(48)	(48)
Foreign body	6 (12%)	2 (4%)	6 (13%)	7 (15%)
Inflammation, suppurative	3 (6%)	1 (2%)		1 (2%)
Epiglottis, metaplasia, squamous	1 (2%)	1 (2%)		
Epithelium, hyperplasia	3 (6%)	3 (6%)	3 (6%)	8 (17%)
Epithelium, metaplasia, squamous	2 (4%)	1 (2%)	2 (4%)	5 (10%)
Glands, inflammation, suppurative	3 (6%)		1 (2%)	1 (2%)
Lung	(50)	(50)	(49)	(50)
Hemorrhage	8 (16%)	15 (30%)	11 (22%)	10 (20%)
Inflammation, granulomatous			1 (2%)	
Alveolar epithelium, fibrosis	1 (2%)			
Alveolar epithelium, hyperplasia		2 (4%)	3 (6%)	1 (2%)
Alveolar epithelium, infiltration cellular, histiocyte	5 (10%)	3 (6%)	4 (8%)	2 (4%)
Alveolar epithelium, pigmentation	1 (2%)			

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Respiratory System (continued)				
Nose	(49)	(49)	(50)	(49)
Foreign body	1 (2%)	3 (6%)	3 (6%)	2 (4%)
Inflammation, suppurative	2 (4%)	4 (8%)	4 (8%)	3 (6%)
Goblet cell, respiratory epithelium, hypertrophy	1 (2%)			1 (2%)
Nasolacrimal duct, inflammation, suppurative		4 (8%)	2 (4%)	1 (2%)
Nasopharyngeal duct, hyperplasia		1 (2%)		
Olfactory epithelium, metaplasia		1 (2%)		
Olfactory epithelium, metaplasia, squamous				1 (2%)
Respiratory epithelium, hyperplasia			1 (2%)	1 (2%)
Respiratory epithelium, metaplasia, squamous			1 (2%)	1 (2%)
Special Senses System				
Eye	(3)	(3)	(1)	(3)
Atrophy	1 (33%)			
Cataract	1 (33%)	2 (67%)	1 (100%)	2 (67%)
Bilateral, cataract				1 (33%)
Cornea, hyperplasia	1 (33%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		2 (4%)		1 (2%)
Nephropathy, chronic	48 (96%)	44 (88%)	43 (86%)	42 (84%)
Cortex, necrosis		1 (2%)		
Papilla, necrosis	1 (2%)			
Pelvis, dilatation	1 (2%)			
Renal tubule, degeneration			1 (2%)	
Renal tubule, mineralization	47 (94%)	46 (92%)	50 (100%)	46 (92%)
Renal tubule, pigmentation			1 (2%)	
Urinary bladder	(49)	(50)	(50)	(49)
Hemorrhage	1 (2%)			1 (2%)
Inflammation, suppurative	1 (2%)			
Ulcer	1 (2%)			
Transitional epithelium, hyperplasia		2 (4%)		1 (2%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF TETRAHYDROFURAN

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	12	18	24
Natural deaths	7	7	4	14
Survivors				
Terminal sacrifice	32	31	28	12
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(46)	(44)	(38)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, jejunum	(45)	(45)	(46)	(37)
Carcinoma	1 (2%)		1 (2%)	1 (3%)
Intestine small, ileum	(46)	(46)	(46)	(40)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma		1 (2%)		
Hemangiosarcoma	1 (2%)	1 (2%)	2 (4%)	
Hepatocellular carcinoma	10 (20%)	9 (18%)	8 (16%)	5 (10%)
Hepatocellular carcinoma, multiple	4 (8%)	4 (8%)	6 (12%)	4 (8%)
Hepatocellular adenoma	19 (38%)	14 (28%)	14 (28%)	9 (18%)
Hepatocellular adenoma, multiple	5 (10%)	5 (10%)	2 (4%)	5 (10%)
Hepatocholangiocarcinoma	3 (6%)		1 (2%)	
Histiocytic sarcoma			1 (2%)	
Mesentery	(3)	(3)	(2)	
Cholangiocarcinoma, metastatic, liver		1 (33%)		
Hemangioma			1 (50%)	
Hemangiosarcoma		1 (33%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (33%)			
Pancreas	(48)	(48)	(46)	(48)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Tooth		(1)	(2)	
Odontoma			1 (50%)	
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Hemangiosarcoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(48)	(50)	(49)	(50)
Adenoma	3 (6%)	1 (2%)		
Adrenal medulla	(48)	(50)	(49)	(50)
Pheochromocytoma benign	1 (2%)		1 (2%)	
Islets, pancreatic	(48)	(48)	(46)	(48)
Adenoma				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Endocrine System (continued)				
Pituitary gland	(45)	(47)	(45)	(47)
Pars distalis, adenoma	1 (2%)		1 (2%)	
Thyroid gland	(49)	(50)	(49)	(49)
Follicular cell, adenoma	4 (8%)		1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Sarcoma		1 (2%)		
Preputial gland	(50)	(49)	(50)	(48)
Prostate	(48)	(43)	(44)	(47)
Seminal vesicle	(48)	(48)	(46)	(46)
Sarcoma	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Interstitial cell, adenoma		1 (2%)		
Hematopoietic System				
Lymph node, bronchial	(33)	(32)	(36)	(26)
Carcinoma, metastatic, lung			1 (3%)	
Cholangiocarcinoma, metastatic, liver		1 (3%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (3%)			
Lymph node, mesenteric	(47)	(48)	(46)	(41)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Lymph node, mediastinal	(36)	(40)	(39)	(32)
Cholangiocarcinoma, metastatic, liver		1 (3%)		
Hepatocholangiocarcinoma, metastatic, liver	2 (6%)			
Spleen	(48)	(49)	(47)	(49)
Hemangiosarcoma			1 (2%)	
Thymus	(35)	(37)	(34)	(36)
Cholangiocarcinoma, metastatic, liver		1 (3%)		
Integumentary System				
Skin	(47)	(50)	(48)	(50)
Prepuce, sarcoma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Subcutaneous tissue, sarcoma, metastatic, epididymis		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Skeletal muscle	(2)	(1)		
Cholangiocarcinoma, metastatic, liver		1 (100%)		
Hepatocholangiocarcinoma, metastatic, liver	2 (100%)			
Nervous System				
None				
Respiratory System				
Larynx	(48)	(49)	(48)	(48)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	16 (32%)	6 (12%)	7 (14%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)	1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma	6 (12%)	9 (18%)	6 (12%)	3 (6%)
Carcinoma			1 (2%)	
Carcinoma, metastatic, harderian gland	1 (2%)			
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Hemangiosarcoma, metastatic, skin				1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)	3 (6%)	
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)		1 (2%)	
Mediastinum, hemangiosarcoma		1 (2%)		
Mediastinum, hepatocholangiocarcinoma, metastatic, liver	2 (4%)			
Special Senses System				
Harderian gland	(4)	(4)	(4)	(3)
Adenoma	1 (25%)	3 (75%)	3 (75%)	1 (33%)
Carcinoma	3 (75%)			1 (33%)
Urinary System				
Kidney	(49)	(50)	(49)	(50)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Renal tubule, adenoma	1 (2%)			
Urinary bladder	(48)	(49)	(46)	(48)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Lymphoma malignant	2 (4%)	1 (2%)	2 (4%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	39	44	21
Total primary neoplasms	86	61	61	36
Total animals with benign neoplasms	36	27	26	17
Total benign neoplasms	54	31	32	21
Total animals with malignant neoplasms	24	25	26	12
Total malignant neoplasms	32	30	29	15
Total animals with metastatic neoplasms	4	3	5	1
Total metastatic neoplasms	17	12	6	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 Inhalation Study of Tetrahydrofuran: Chamber Control

Number of Days on Study	3 6 2	4 4 0	4 8 1	5 4 4	5 5 7	5 8 2	5 8 2	6 3 8	6 3 8	6 4 4	6 5 8	6 7 0	6 7 5	6 7 8	6 9 0	6 9 9	7 1 9	7 2 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 2 3	0 1 3	0 3 5	0 0 8	0 3 8	0 1 9	0 4 4	0 2 0	0 4 0	0 3 7	0 2 2	0 1 1	0 1 4	0 2 1	0 2 9	0 4 1	0 0 5	0 2 6	0 0 6	0 2 5	0 2 7	0 3 2	0 3 3	0 3 9	0 4 2
Alimentary System																								
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	+	A	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, cecum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	+	A	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Carcinoma																								
Intestine small, ileum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X
Hepatocellular carcinoma			X		X						X				X			X						X
Hepatocellular carcinoma, multiple				X			X						X											
Hepatocellular adenoma	X	X									X			X	X					X			X	
Hepatocellular adenoma, multiple								X				X												
Hepatocholangiocarcinoma													X											
Mesentery																					+			
Hepatocholangiocarcinoma, metastatic, liver																								
Pancreas	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X											
Endocrine System																								
Adrenal cortex	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					
Adrenal medulla	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	A	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, adenoma																								
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 3	0 4 9	0 5 0	0 0 2	0 0 4	0 0 9	0 1 2	0 1 6	0 0 3	0 3 4	0 3 6	0 4 8	0 0 3	0 1 0	0 1 5	0 1 7	0 1 8	0 3 1	0 4 5	0 4 6	0 4 7	0 0 7	0 1 1	0 2 4	0 2 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma																				X						1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma		X			X						X	X														10
Hepatocellular carcinoma, multiple														X												4
Hepatocellular adenoma			X		X		X			X			X		X	X	X		X	X		X			X	19
Hepatocellular adenoma, multiple				X																	X					5
Hepatocholangiocarcinoma								X												X						3
Mesentery								+															+			3
Hepatocholangiocarcinoma, metastatic, liver								X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma										X									X							3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																		X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	M	+	+	+	M	+	M	+	I	+	+	+	+	M	M	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Pars distalis, adenoma																X										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma									X		X						X							X		4
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	3 6 2	4 4 0	4 8 1	5 4 4	5 5 7	5 8 2	5 8 2	6 3 8	6 3 8	6 4 4	6 5 8	6 7 0	6 7 5	6 7 8	6 9 0	6 9 9	7 1 9	7 2 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 2 3	0 1 3	0 3 5	0 0 8	0 3 8	0 1 9	0 4 4	0 2 0	0 4 0	0 3 7	0 2 2	0 1 1	0 1 4	0 2 1	0 2 9	0 4 1	0 0 5	0 2 6	0 0 6	0 2 5	0 2 7	0 3 2	0 3 3	0 3 9	0 4 2
Genital System																									
Epididymis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Penis	+																								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma										X															
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																X									
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+																	
Lymph node, bronchial	A	+	M	M	+	+	M	M	M	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+	+	+	+	+
Lymph node, mesenteric	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mediastinal	M	M	+	M	M	+	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Hepatocholangiocarcinoma, metastatic, liver													X												
Spleen	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	+	+	+	+	+	+	M	M	M	M	M	M	+	+	+	M	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	I	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Skeletal muscle													+												
Hepatocholangiocarcinoma, metastatic, liver													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X								X		X				X	X		X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma					X																			X	
Carcinoma, metastatic, harderian gland						X																			
Hepatocellular carcinoma, metastatic, liver				X																					
Hepatocholangiocarcinoma, metastatic, liver													X												
Mediastinum, hepatocholangiocarcinoma, metastatic, liver													X												
Nose	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 3	0 4 9	0 5 0	0 0 2	0 0 4	0 0 9	0 1 2	0 1 6	0 3 0	0 3 4	0 3 6	0 4 8	0 0 3	0 1 0	0 1 5	0 1 7	0 1 8	0 3 1	0 4 5	0 4 6	0 4 7	0 0 7	0 1 1	0 2 4	0 2 8	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma														X												1
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										1
Lymph node, bronchial	+	+	+	M	+	M	+	M	M	M	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	33
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver								X																		1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	M	+	+	36
Hepatocholangiocarcinoma, metastatic, liver								X																		2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	M	M	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	35
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Skeletal muscle								+																		2
Hepatocholangiocarcinoma, metastatic, liver								X																		2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X	X			X		X	X										X	X	X			X	16
Alveolar/bronchiolar adenoma, multiple														X				X								2
Alveolar/bronchiolar carcinoma		X											X	X										X		6
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver								X																		2
Mediastinum, hepatocholangiocarcinoma, metastatic, liver								X																		2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 3	0 4 9	0 5 0	0 0 2	0 0 4	0 0 9	0 1 2	0 1 6	0 3 0	0 3 4	0 3 6	0 4 8	0 4 3	0 1 0	0 1 5	0 1 7	0 1 8	0 3 1	0 4 5	0 4 6	0 4 7	0 4 7	0 1 1	0 1 4	0 2 8	Total Tissues/ Tumors	
Special Senses System																											
Harderian gland																										4	
Adenoma																										1	
Carcinoma																										3	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Hepatocholangiocarcinoma, metastatic, liver																										1	
Renal tubule, adenoma													X													1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma														X												1	
Lymphoma malignant							X												X							2	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 0 8	2 1 7	2 2 1	2 2 8	2 3 0	2 3 4	2 3 8	2 0 6	2 0 7	2 0 9	2 1 0	2 1 3	2 1 9	2 2 0	2 3 6	2 4 7	2 0 2	2 1 5	2 1 8	2 2 4	2 2 7	2 4 1	2 4 2	2 4 8	2 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cholangiocarcinoma, metastatic, liver																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma			X		X																					9
Hepatocellular carcinoma, multiple																		X								4
Hepatocellular adenoma		X		X						X					X		X				X					14
Hepatocellular adenoma, multiple			X				X				X		X										X			5
Mesentery					+														+							3
Cholangiocarcinoma, metastatic, liver																										1
Hemangiosarcoma																			X							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	+	M	+	+	I	M	M	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	M	32
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma					X																					1
Penis					+																					2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	M	+	+	+	M	+	M	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	43
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma				X																						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	3 1 4	3 2 4	4 4 1	4 7 5	5 2 6	5 3 2	5 4 4	5 5 4	5 5 4	5 7 4	5 7 7	6 3 8	6 4 4	6 4 6	6 6 6	6 8 5	6 9 4	7 0 6	7 1 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4
Carcass ID Number	2 3 3	2 1 6	2 1 4	2 0 4	2 2 3	2 3 9	2 2 5	2 3 5	2 4 0	2 4 4	2 2 2	2 3 7	2 2 9	2 4 9	2 1 1	2 4 5	2 3 1	2 1 2	2 3 2	2 0 5	2 2 6	2 4 3	2 4 6	2 0 1	2 0 3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+		+											
Lymph node, bronchial	+	+	M	+	+	+	M	M	+	M	M	M	M	+	+	+	+	+	+	M	+	M	+	+	+
Cholangiocarcinoma, metastatic, liver				X																					
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver				X																					
Lymph node, mediastinal	M	M	M	+	+	+	M	+	+	M	+	+	+	M	+	I	+	M	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+	+	I	I	+	M	+	+	+	+
Cholangiocarcinoma, metastatic, liver				X																					
Integumentary System																									
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prepuce, sarcoma																									X
Subcutaneous tissue, sarcoma, metastatic, epididymis																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Cholangiocarcinoma, metastatic, liver				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X			X							X							
Alveolar/bronchiolar adenoma, multiple																	X								
Alveolar/bronchiolar carcinoma						X							X		X					X	X		X		
Cholangiocarcinoma, metastatic, liver				X																					
Hepatocellular carcinoma, metastatic, liver									X																
Mediastinum, hemangiosarcoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland													+												
Adenoma																									
Lacrimal gland																			+						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 0 8	2 1 7	2 2 1	2 2 8	2 3 0	2 3 4	2 3 8	2 0 6	2 0 7	2 0 9	2 1 0	2 1 3	2 1 9	2 2 0	2 3 6	2 4 7	2 0 2	2 1 5	2 1 8	2 2 4	2 2 7	2 4 1	2 4 2	2 4 8	2 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+													+							4
Lymph node, bronchial	+	+	+	M	+	M	+	M	M	+	+	+	M	M	+	+	M	+	+	M	+	+	+	M	+	32
Cholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	+	M	+	+	+	+	+	M	+	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cholangiocarcinoma, metastatic, liver																										1
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	40
Cholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	M	M	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Cholangiocarcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prepuce, sarcoma																										1
Subcutaneous tissue, sarcoma, metastatic, epididymis					X																					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Cholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																				X			X	6
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma										X										X				X		9
Cholangiocarcinoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										1
Mediastinum, hemangiosarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Harderian gland					+												+							+		4
Adenoma					X												X							X		3
Lacrimal gland																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	3 1 4	3 2 4	4 4 1	4 7 5	5 2 6	5 3 2	5 4 4	5 5 4	5 5 4	5 7 4	5 7 7	6 3 8	6 4 4	6 4 6	6 6 6	6 8 5	6 9 4	7 0 6	7 1 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4
Carcass ID Number	2 3 3	2 1 6	2 1 4	2 0 4	2 2 3	2 3 9	2 2 5	2 3 5	2 4 0	2 4 4	2 2 2	2 3 7	2 2 9	2 4 9	2 1 1	2 4 5	2 3 1	2 1 2	2 3 2	2 0 5	2 2 6	2 4 3	2 4 6	2 0 1	2 0 3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver				X																					
Ureter												+													
Urethra		+										+													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	734	734	734	734	734	734	734	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	20808	21707	22121	22828	23030	23434	23838	24006	24007	24009	24010	24013	24019	24020	24036	24047	24102	24115	24118	24124	24227	24241	24242	24248	24250	Total Tissues/ Tumors	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Cholangiocarcinoma, metastatic, liver																										1	
Ureter																										1	
Urethra						+																				3	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymphoma malignant		X																								1	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm

Number of Days on Study	3 7 6	4 4 0	5 0 4	5 1 2	5 5 1	5 5 4	5 5 8	5 6 0	5 6 9	5 7 4	5 7 4	5 8 2	5 9 4	5 9 4	5 9 5	6 0 4	6 3 1	6 4 4	6 5 8	6 6 6	6 9 4	7 2 1	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 3 4	4 4 1	4 3 2	4 1 7	4 2 2	4 4 3	4 1 0	4 3 6	4 2 5	4 3 9	4 4 4	4 4 7	4 1 8	4 4 2	4 3 8	4 1 1	4 0 7	4 2 9	4 2 4	4 1 4	4 0 2	4 3 0	4 0 3	4 0 9	4 2 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	A	+	+	+	+	+	I	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma	X		X	X	X							X					X								
Hepatocellular carcinoma, multiple							X		X	X					X			X	X						
Hepatocellular adenoma		X						X								X						X		X	X
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma											X														
Histiocytic sarcoma																									
Mesentery								+																	
Hemangioma																									
Pancreas	A	A	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Tooth																				+					
Odontoma																				X					
Cardiovascular System																									
Blood vessel																			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																						X			
Islets, pancreatic	A	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	+	M	+	M	M	M	+	M	+	M	+	M	+	+	+	+	+	M	+
Pituitary gland	A	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X																	
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Coagulating gland													+												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung						X																			
Penis	+									+															
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	A	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+
Seminal vesicle	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 2 8	4 3 7	4 4 8	4 4 9	4 5 0	4 0 4	4 0 6	4 1 2	4 1 6	4 1 9	4 2 0	4 2 3	4 3 1	4 3 3	4 4 6	4 0 1	4 0 8	4 1 3	4 1 5	4 2 7	4 3 5	4 4 0	4 0 5	4 2 1	4 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma	X																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																	X								2
Hepatocellular carcinoma						X																	X			8
Hepatocellular carcinoma, multiple																										6
Hepatocellular adenoma	X	X	X					X			X		X	X					X							14
Hepatocellular adenoma, multiple									X			X														2
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma																					X					1
Mesentery																	+									2
Hemangioma																	X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Tooth									+																	2
Odontoma																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	M	+	+	M	I	M	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma										X																1
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, lung																										1
Penis																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 2 8	4 3 7	4 4 8	4 4 9	4 5 0	4 0 4	4 0 6	4 1 2	4 1 6	4 1 9	4 2 0	4 2 3	4 3 1	4 3 3	4 4 6	4 0 1	4 0 8	4 1 3	4 1 5	4 2 7	4 3 5	4 4 0	4 0 5	4 2 1	4 4 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										4
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	36
Carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																					X					1
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	I	+	+	39
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																		X								1
Thymus	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	34
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X			X						X								X			X		7
Alveolar/bronchiolar adenoma, multiple								X																		1
Alveolar/bronchiolar carcinoma	X				X												X			X					6
Carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										3
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Harderian gland															+									+		4
Adenoma															X									X		3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																					X					1
Lymphoma malignant										X	X															2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	3 5 9	3 8 6	4 1 4	4 5 2	5 2 7	5 5 4	6 3 9	6 5 8	6 7 0	6 8 7	7 0 6	7 1 5	7 2 1	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	6 4 8	6 3 8	6 0 7	6 2 8	6 1 3	6 4 3	6 4 7	6 2 0	6 3 3	6 1 7	6 3 5	6 2 7	6 0 3	6 0 9	6 3 6	6 4 2	6 2 2	6 2 9	6 3 7	6 1 1	6 1 5	6 1 6	6 2 4	6 3 1	6 3 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	A	+	+	+	+	M	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	38
Intestine large, colon	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Carcinoma																							X			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X		X							X							X			5
Hepatocellular carcinoma, multiple										X			X				X								X	4
Hepatocellular adenoma				X		X	X				X				X								X			9
Hepatocellular adenoma, multiple					X			X				X				X						X				5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma											X															1
Parathyroid gland	+	+	+	M	+	M	+	+	+	M	M	I	+	M	+	+	+	+	+	+	+	+	+	+	M	30
Pituitary gland	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma												X														1
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis	+	+									+															27
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	0 0 1 1 1 1 2 2 2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 3 0 9 0 8 9 9 2 3 4 4 6 6 7 7 7 1 2 3 4 4 5 5 5 5 5 7 9 2 9 0 1 9 9 0 5 0 5 3 5 5 3 1 5 6 9 9 9 9 9 9
Carcass ID Number	6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 4 3 1 2 3 0 0 0 0 1 0 5 4 1 1 1 4 4 2 4 0 2 2 3 4 5 9 9 3 4 6 2 4 1 0 5 0 0 2 8 4 1 6 5 9 8 1 6 0 4
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + + +
Lymph node, bronchial	M M M + M M M M + + M M M M M M + M + + M + + + M
Lymph node, mandibular	+ + M + M + M + M + M + + M M M M + + + + + + + +
Lymph node, mesenteric	+ + M + + + M M + M M + + + + + + M A + + + + + +
Lymph node, mediastinal	M + M + + + + M M M + M + M + M + M + M + M M M M
Spleen	+ + + + + + A + + + + + + + + + + + + + + + + + +
Thymus	+ + + M M + M M + + + + M + + M + + + + + + + + +
Integumentary System	
Mammary gland	M M M M M M M M M M M M M M M M M M M M M M M M M
Skin	+ +
Subcutaneous tissue, hemangiosarcoma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Larynx	+ + + + + + A + + + + + + M + + + + + + + + + + +
Lung	+ +
Alveolar/bronchiolar adenoma	
Alveolar/bronchiolar carcinoma	
Hemangiosarcoma, metastatic, skin	
Nose	+ +
Trachea	+ + + + + + A + + + + + + M + + + + + + + + + + +
Special Senses System	
Eye	
Harderian gland	+
Adenoma	
Carcinoma	
Urinary System	
Kidney	+ +
Urethra	+ + + + + + + + + + + + + + + + + + +
Urinary bladder	+ + + A + + A + + + + + + + + + + + + + + + + + +
Systemic Lesions	
Multiple organs	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	3 5 9	3 8 6	4 1 4	4 5 2	5 2 7	5 5 4	6 3 9	6 5 8	6 7 0	6 8 7	7 0 6	7 1 5	7 2 1	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	6 4 8	6 3 8	6 0 7	6 2 8	6 1 3	6 4 3	6 4 7	6 2 0	6 3 3	6 1 7	6 3 5	6 2 7	6 0 3	6 0 9	6 3 6	6 4 2	6 2 2	6 2 9	6 3 7	6 1 1	6 1 5	6 1 6	6 2 4	6 3 1	6 3 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																					5
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	+	M	M	+	M	+	M	+	+	+	+	M	M	M	+	26
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	M	+	M	M	+	+	M	+	35
Lymph node, mesenteric	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	32
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	I	+	M	M	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	I	+	M	+	+	36
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																	X									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X	X				X					X			4
Alveolar/bronchiolar carcinoma								X				X												X		3
Hemangiosarcoma, metastatic, skin																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye															+											1
Harderian gland								+							+											3
Adenoma								X																		1
Carcinoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										14
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	3/48 (6%)	1/50 (2%)	0/49 (0%)	0/50 (0%)
Adjusted rate[b]	9.4%	3.2%	0.0%	0.0%
Terminal rate[c]	3/32 (9%)	1/31 (3%)	0/28 (0%)	0/12 (0%)
First incidence (days)	733 (T)	733 (T)	—[e]	—
Life table test[d]	P=0.194N	P=0.316N	P=0.145N	P=0.336N
Logistic regression test[d]	P=0.194N	P=0.316N	P=0.145N	P=0.336N
Cochran-Armitage test[d]	P=0.094N			
Fisher exact test[d]		P=0.293N	P=0.117N	P=0.114N
Harderian Gland: Adenoma				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.5%	9.7%	10.3%	5.6%
Terminal rate	0/32 (0%)	3/31 (10%)	2/28 (7%)	0/12 (0%)
First incidence (days)	658	733 (T)	721	658
Life table test	P=0.485	P=0.289	P=0.255	P=0.574
Logistic regression test	P=0.533	P=0.284	P=0.262	P=0.664
Cochran-Armitage test	P=0.418N			
Fisher exact test		P=0.309	P=0.309	P=0.753N
Harderian Gland: Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	8.3%	0.0%	0.0%	8.3%
Terminal rate	2/32 (6%)	0/31 (0%)	0/28 (0%)	1/12 (8%)
First incidence (days)	582	—	—	733 (T)
Life table test	P=0.694	P=0.135N	P=0.148N	P=0.669N
Logistic regression test	P=0.646N	P=0.121N	P=0.121N	P=0.579N
Cochran-Armitage test	P=0.442N			
Fisher exact test		P=0.121N	P=0.121N	P=0.309N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	10.6%	9.7%	10.3%	13.4%
Terminal rate	2/32 (6%)	3/31 (10%)	2/28 (7%)	1/12 (8%)
First incidence (days)	582	733 (T)	721	658
Life table test	P=0.479	P=0.531N	P=0.578N	P=0.585
Logistic regression test	P=0.559	P=0.521N	P=0.540N	P=0.653N
Cochran-Armitage test	P=0.304N			
Fisher exact test		P=0.500N	P=0.500N	P=0.339N
Liver: Hepatocellular Adenoma				
Overall rate	24/50 (48%)	19/50 (38%)	16/50 (32%)	14/50 (28%)
Adjusted rate	60.5%	53.4%	48.7%	59.0%
Terminal rate	17/32 (53%)	15/31 (48%)	12/28 (43%)	4/12 (33%)
First incidence (days)	362	324	440	245
Life table test	P=0.097	P=0.273N	P=0.199N	P=0.181
Logistic regression test	P=0.506N	P=0.211N	P=0.142N	P=0.414N
Cochran-Armitage test	P=0.041N			
Fisher exact test		P=0.210N	P=0.076N	P=0.032N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	14/50 (28%)	13/50 (26%)	14/50 (28%)	9/50 (18%)
Adjusted rate	33.3%	28.9%	31.4%	50.0%
Terminal rate	6/32 (19%)	3/31 (10%)	2/28 (7%)	4/12 (33%)
First incidence (days)	481	441	376	359
Life table test	P=0.161	P=0.557N	P=0.455	P=0.190
Logistic regression test	P=0.459	P=0.412N	P=0.270N	P=0.363
Cochran-Armitage test	P=0.136N			
Fisher exact test		P=0.500N	P=0.588N	P=0.171N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	35/50 (70%)	31/50 (62%)	30/50 (60%)	18/50 (36%)
Adjusted rate	77.2%	67.9%	66.9%	73.4%
Terminal rate	22/32 (69%)	17/31 (55%)	14/28 (50%)	6/12 (50%)
First incidence (days)	362	324	376	245
Life table test	P=0.181	P=0.407N	P=0.501N	P=0.237
Logistic regression test	P=0.105N	P=0.210N	P=0.121N	P=0.175N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.263N	P=0.201N	P<0.001N
Liver: Hepatocholangiocarcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	8.7%	0.0%	2.4%	0.0%
Terminal rate	2/32 (6%)	0/31 (0%)	0/28 (0%)	0/12 (0%)
First incidence (days)	675	—	574	—
Life table test	P=0.303N	P=0.132N	P=0.362N	P=0.329N
Logistic regression test	P=0.219N	P=0.130N	P=0.305N	P=0.291N
Cochran-Armitage test	P=0.156N			
Fisher exact test		P=0.121N	P=0.309N	P=0.121N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	18/50 (36%)	7/50 (14%)	8/50 (16%)	4/50 (8%)
Adjusted rate	51.0%	19.0%	26.6%	30.8%
Terminal rate	15/32 (47%)	3/31 (10%)	7/28 (25%)	3/12 (25%)
First incidence (days)	582	554	512	721
Life table test	P=0.230N	P=0.017N	P=0.043N	P=0.183N
Logistic regression test	P=0.137N	P=0.014N	P=0.043N	P=0.110N
Cochran-Armitage test	P=0.004N			
Fisher exact test		P=0.010N	P=0.020N	P<0.001N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	6/50 (12%)	9/50 (18%)	7/50 (14%)	3/50 (6%)
Adjusted rate	17.5%	25.4%	21.4%	19.6%
Terminal rate	5/32 (16%)	6/31 (19%)	4/28 (14%)	1/12 (8%)
First incidence (days)	557	532	554	658
Life table test	P=0.538	P=0.261	P=0.408	P=0.509
Logistic regression test	P=0.455N	P=0.263	P=0.455	P=0.619
Cochran-Armitage test	P=0.097N			
Fisher exact test		P=0.288	P=0.500	P=0.243N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	21/50 (42%)	16/50 (32%)	15/50 (30%)	7/50 (14%)
Adjusted rate	57.7%	41.1%	45.5%	46.0%
Terminal rate	17/32 (53%)	9/31 (29%)	11/28 (39%)	4/12 (33%)
First incidence (days)	557	532	512	658
Life table test	P=0.437N	P=0.270N	P=0.288N	P=0.444N
Logistic regression test	P=0.213N	P=0.248N	P=0.248N	P=0.280N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.204N	P=0.149N	P=0.002N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/49 (8%)	0/50 (0%)	1/49 (2%)	1/49 (2%)
Adjusted rate	12.5%	0.0%	3.6%	7.1%
Terminal rate	4/32 (13%)	0/31 (0%)	1/28 (4%)	0/12 (0%)
First incidence (days)	733 (T)	—	733 (T)	715
Life table test	P=0.613N	P=0.066N	P=0.220N	P=0.548N
Logistic regression test	P=0.590N	P=0.066N	P=0.220N	P=0.517N
Cochran-Armitage test	P=0.299N			
Fisher exact test		P=0.056N	P=0.181N	P=0.181N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	5.9%	6.2%	10.7%	8.3%
Terminal rate	1/32 (3%)	1/31 (3%)	3/28 (11%)	1/12 (8%)
First incidence (days)	699	706	733 (T)	733 (T)
Life table test	P=0.529	P=0.679	P=0.434	P=0.673
Logistic regression test	P=0.559	P=0.673	P=0.422	P=0.698
Cochran-Armitage test	P=0.378N			
Fisher exact test		P=0.691N	P=0.500	P=0.500N
All Organs: Benign Neoplasms				
Overall rate	36/50 (72%)	27/50 (54%)	26/50 (52%)	17/50 (34%)
Adjusted rate	85.4%	70.5%	75.7%	71.6%
Terminal rate	26/32 (81%)	20/31 (65%)	20/28 (71%)	6/12 (50%)
First incidence (days)	362	324	440	245
Life table test	P=0.187	P=0.109N	P=0.176N	P=0.336
Logistic regression test	P=0.327N	P=0.056N	P=0.103N	P=0.167N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.048N	P=0.032N	P<0.001N
All Organs: Malignant Neoplasms				
Overall rate	24/50 (48%)	25/50 (50%)	26/50 (52%)	12/50 (24%)
Adjusted rate	56.0%	55.7%	57.5%	65.2%
Terminal rate	14/32 (44%)	12/31 (39%)	10/28 (36%)	6/12 (50%)
First incidence (days)	481	441	376	359
Life table test	P=0.290	P=0.424	P=0.261	P=0.306
Logistic regression test	P=0.430N	P=0.504	P=0.547N	P=0.570
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.500	P=0.421	P=0.011N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	39/50 (78%)	44/50 (88%)	21/50 (42%)
Adjusted rate	95.9%	82.7%	93.4%	86.7%
Terminal rate	30/32 (94%)	23/31 (74%)	25/28 (89%)	9/12 (75%)
First incidence (days)	362	324	376	245
Life table test	P=0.224	P=0.216N	P=0.388	P=0.386
Logistic regression test	P=0.017N	P=0.020N	P=0.225N	P=0.011N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.020N	P=0.243N	P<0.001N

(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 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 chamber 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 chamber 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 C4a
Historical Incidence of Hepatocellular Neoplasms in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	13/50	11/50	21/50
Acetonitrile	13/50	7/50	19/50
Allyl Glycidyl Ether	15/49	10/49	23/49
2-Chloroacetophenone	5/50	11/50	16/50
l-Epinephrine Hydrochloride	10/50	12/50	20/50
Chloroethane	6/50	9/50	15/50
Hexachlorocyclopentadiene	19/50	7/50	24/50
CS2 (*o*-Chlorobenzalmalononitrile)	4/49	14/49	18/49
Ozone	23/50	12/50	30/50
Total	108/448 (24.1%)	93/448 (20.8%)	186/448 (41.5%)
Standard deviation	13.0%	4.9%	9.2%
Range	8%-46%	14%-29%	30%-60%
Overall Historical Incidence			
Total	200/947 (21.1%)	184/947 (19.4%)	358/947 (37.8%)
Standard deviation	11.6%	5.8%	12.5%
Range	4%-46%	9%-29%	11%-60%

[a] Data as of 12 May 1995

TABLE C4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	18/50	5/50	21/50
Acetonitrile	6/50	4/50	10/50
Allyl Glycidyl Ether	7/50	0/50	7/50
2-Chloroacetophenone	7/50	6/50	11/50
l-Epinephrine Hydrochloride	11/50	5/50	15/50
Chloroethane	3/50	2/50	5/50
Hexachlorocyclopentadiene	11/49	0/49	11/49
CS2 (*o*-Chlorobenzalmalononitrile)	7/49	7/49	14/49
Ozone	6/50	8/50	14/50
Total	76/448 (17.0%)	37/448 (8.3%)	108/448 (24.1%)
Standard deviation	8.7%	5.8%	9.5%
Range	6%-36%	0%-16%	10%-42%
Overall Historical Incidence			
Total	141/947 (14.9%)	75/947 (7.9%)	205/947 (21.7%)
Standard deviation	7.0%	5.7%	8.0%
Range	6%-36%	0%-16%	10%-42%

[a] Data as of 12 May 1995

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran[a]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	12	18	24
Natural deaths	7	7	4	14
Survivors				
Terminal sacrifice	32	31	28	12
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(46)	(44)	(38)
Degeneration, hyaline	1 (2%)	1 (2%)		
Inflammation	1 (2%)	1 (2%)		
Epithelium, hyperplasia	1 (2%)			1 (3%)
Intestine large, cecum	(47)	(47)	(46)	(40)
Muscularis, hyperplasia				1 (3%)
Intestine small, duodenum	(44)	(45)	(45)	(40)
Ulcer		1 (2%)		
Epithelium, hyperplasia	1 (2%)			
Intestine small, jejunum	(45)	(45)	(46)	(37)
Peyer's patch, hyperplasia		1 (2%)	1 (2%)	
Intestine small, ileum	(46)	(46)	(46)	(40)
Peyer's patch, hyperplasia			1 (2%)	
Peyer's patch, inflammation			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Basophilic focus	1 (2%)		1 (2%)	
Clear cell focus			2 (4%)	2 (4%)
Congestion	2 (4%)			
Degeneration, fatty, focal	1 (2%)			
Eosinophilic focus	11 (22%)	8 (16%)	10 (20%)	5 (10%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Infiltration cellular, histiocyte	1 (2%)			
Inflammation, chronic	1 (2%)		1 (2%)	
Mixed cell focus	1 (2%)	1 (2%)		
Necrosis	8 (16%)	5 (10%)	6 (12%)	4 (8%)
Centrilobular, necrosis		1 (2%)		
Mesentery	(3)	(3)	(2)	
Fat, necrosis	2 (67%)	1 (33%)	1 (50%)	
Pancreas	(48)	(48)	(46)	(48)
Amyloid deposition	1 (2%)			
Atrophy	1 (2%)	4 (8%)		1 (2%)
Basophilic focus			1 (2%)	
Cytoplasmic alteration	1 (2%)			
Hypertrophy		1 (2%)		1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Basophilic focus			1 (2%)	
Stomach, forestomach	(49)	(50)	(48)	(49)
Hyperplasia			1 (2%)	
Ulcer	1 (2%)			1 (2%)
Epithelium, hyperplasia	1 (2%)			1 (2%)

[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 Inhalation Study of Tetrahydrofuran
(continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Alimentary System (continued)				
Stomach, glandular	(48)	(48)	(46)	(48)
Degeneration, hyaline				1 (2%)
Erosion			1 (2%)	3 (6%)
Infiltration cellular, mast cell			1 (2%)	
Inflammation, suppurative				2 (4%)
Mineralization	1 (2%)			
Epithelium, hyperplasia		2 (4%)		
Tooth		(1)	(2)	
Developmental malformation		1 (100%)	1 (50%)	
Cardiovascular System				
Blood vessel			(1)	
Aorta, inflammation			1 (100%)	
Aorta, pigmentation, hemosiderin			1 (100%)	
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	28 (57%)	36 (72%)	35 (70%)	14 (28%)
Hyperplasia, atypical			1 (2%)	
Endocrine System				
Adrenal cortex	(48)	(50)	(49)	(50)
Hemorrhage			1 (2%)	
Hyperplasia	7 (15%)	5 (10%)	6 (12%)	2 (4%)
Hypertrophy	20 (42%)	24 (48%)	19 (39%)	10 (20%)
Capsule, hyperplasia			1 (2%)	1 (2%)
Adrenal medulla	(48)	(50)	(49)	(50)
Hyperplasia		2 (4%)		1 (2%)
Islets, pancreatic	(48)	(48)	(46)	(48)
Hyperplasia	6 (13%)	2 (4%)	3 (7%)	2 (4%)
Pituitary gland	(45)	(47)	(45)	(47)
Pars distalis, cyst	5 (11%)		1 (2%)	1 (2%)
Pars distalis, hyperplasia	2 (4%)	2 (4%)	1 (2%)	
Thyroid gland	(49)	(50)	(49)	(49)
Follicular cell, hyperplasia	16 (33%)	12 (24%)	9 (18%)	3 (6%)
General Body System				
None				
Genital System				
Coagulating gland			(1)	(1)
Inflammation, suppurative			1 (100%)	
Epididymis	(49)	(50)	(50)	(50)
Granuloma sperm		1 (2%)	1 (2%)	
Inflammation		1 (2%)		1 (2%)
Penis	(1)	(2)	(2)	(27)
Congestion				1 (4%)
Inflammation, suppurative		1 (50%)	1 (50%)	9 (33%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran
(continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Genital System (continued)				
Preputial gland	(50)	(49)	(50)	(48)
Cyst	5 (10%)	3 (6%)	1 (2%)	1 (2%)
Inflammation	8 (16%)	16 (33%)	9 (18%)	9 (19%)
Duct, hyperplasia		1 (2%)		
Prostate	(48)	(43)	(44)	(47)
Inflammation, suppurative	3 (6%)	4 (9%)	4 (9%)	14 (30%)
Seminal vesicle	(48)	(48)	(46)	(46)
Angiectasis			1 (2%)	
Inflammation, chronic		2 (4%)		
Inflammation, suppurative				1 (2%)
Testes	(50)	(50)	(50)	(50)
Atrophy	5 (10%)	3 (6%)	2 (4%)	2 (4%)
Mineralization			1 (2%)	
Interstitial cell, hyperplasia	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Angiectasis	1 (2%)			
Hyperplasia	5 (10%)	6 (12%)	7 (14%)	14 (28%)
Infiltration cellular, mast cell			2 (4%)	
Lymph node	(1)	(4)	(4)	(5)
Iliac, hyperplasia		3 (75%)	3 (75%)	5 (100%)
Renal, hyperplasia	1 (100%)	1 (25%)		
Lymph node, bronchial	(33)	(32)	(36)	(26)
Hyperplasia	2 (6%)	3 (9%)	1 (3%)	
Lymph node, mandibular	(42)	(40)	(43)	(35)
Hyperplasia	4 (10%)	1 (3%)		
Lymph node, mesenteric	(47)	(48)	(46)	(41)
Angiectasis	2 (4%)	1 (2%)	1 (2%)	
Congestion		1 (2%)		
Hematopoietic cell proliferation	2 (4%)	2 (4%)		
Hyperplasia	3 (6%)	1 (2%)	3 (7%)	1 (2%)
Lymph node, mediastinal	(36)	(40)	(39)	(32)
Hyperplasia		2 (5%)	1 (3%)	
Spleen	(48)	(49)	(47)	(49)
Atrophy				1 (2%)
Hematopoietic cell proliferation	9 (19%)	13 (27%)	14 (30%)	18 (37%)
Hyperplasia, lymphoid	5 (10%)	2 (4%)	3 (6%)	
Thymus	(35)	(37)	(34)	(36)
Atrophy	2 (6%)	2 (5%)	4 (12%)	9 (25%)
Hyperplasia, lymphoid			1 (3%)	
Integumentary System				
Skin	(47)	(50)	(48)	(50)
Inflammation, suppurative		1 (2%)	2 (4%)	
Prepuce, inflammation, suppurative	7 (15%)	7 (14%)	7 (15%)	18 (36%)
Subcutaneous tissue, infiltration cellular, mast cell		1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Tetrahydrofuran
(continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Synovial tissue, inflammation, chronic			1 (2%)	
Nervous System				
None				
Respiratory System				
Larynx	(48)	(49)	(48)	(48)
Epiglottis, metaplasia, squamous		2 (4%)	1 (2%)	
Lung	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Infiltration cellular, histiocyte	5 (10%)	7 (14%)	7 (14%)	1 (2%)
Inflammation, chronic, focal		2 (4%)	1 (2%)	
Pigmentation, hemosiderin		1 (2%)		
Thrombosis				1 (2%)
Alveolar epithelium, hyperplasia	6 (12%)	1 (2%)	1 (2%)	1 (2%)
Perivascular, infiltration cellular, mononuclear cell		1 (2%)		
Nose	(48)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Inflammation, suppurative		3 (6%)	2 (4%)	4 (8%)
Nasolacrimal duct, inflammation, suppurative	3 (6%)	1 (2%)		2 (4%)
Olfactory epithelium, atrophy, focal	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Special Senses System				
None				
Urinary System				
Kidney	(49)	(50)	(49)	(50)
Glomerulosclerosis	2 (4%)			
Hydronephrosis	3 (6%)	3 (6%)	5 (10%)	18 (36%)
Inflammation, suppurative	3 (6%)	5 (10%)	5 (10%)	18 (36%)
Metaplasia, osseous		1 (2%)	2 (4%)	3 (6%)
Mineralization			1 (2%)	
Nephropathy	31 (63%)	40 (80%)	33 (67%)	14 (28%)
Cortex, cyst	2 (4%)	1 (2%)		1 (2%)
Pelvis, necrosis				3 (6%)
Renal tubule, hyperplasia	2 (4%)	2 (4%)	1 (2%)	
Renal tubule, hypertrophy				1 (2%)
Renal tubule, necrosis				2 (4%)
Ureter		(1)		
Inflammation, suppurative		1 (100%)		
Urethra		(3)	(1)	(14)
Inflammation, suppurative		3 (100%)	1 (100%)	12 (86%)
Necrosis			1 (100%)	5 (36%)
Urinary bladder	(48)	(49)	(46)	(48)
Calculus, gross observation				3 (6%)
Calculus, microscopic observation only		1 (2%)		2 (4%)
Inflammation, suppurative	3 (6%)	6 (12%)	6 (13%)	16 (33%)
Transitional epithelium, hyperplasia		1 (2%)	1 (2%)	5 (10%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF TETRAHYDROFURAN

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	5	1	1	
Moribund	13	10	20	13
Natural deaths	3	6	3	5
Survivors				
Terminal sacrifice	29	33	26	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(45)	(44)	(46)	(46)
Intestine small, jejunum	(45)	(44)	(46)	(46)
Carcinoma				1 (2%)
Polyp adenomatous		1 (2%)		
Intestine small, ileum	(46)	(45)	(46)	(46)
Liver	(50)	(50)	(50)	(48)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma	4 (8%)	6 (12%)	9 (18%)	10 (21%)
Hepatocellular carcinoma, multiple	2 (4%)	4 (8%)	1 (2%)	6 (13%)
Hepatocellular adenoma	10 (20%)	14 (28%)	13 (26%)	19 (40%)
Hepatocellular adenoma, multiple	2 (4%)	3 (6%)	5 (10%)	12 (25%)
Hepatocholangiocarcinoma	1 (2%)	1 (2%)		
Hepatocholangiocarcinoma, multiple	1 (2%)			
Histiocytic sarcoma	3 (6%)			
Osteosarcoma, metastatic, bone				1 (2%)
Mesentery	(6)	(9)	(9)	(9)
Carcinoma, metastatic, islets, pancreatic		1 (11%)		
Carcinoma, metastatic, ovary			1 (11%)	
Fibrous histiocytoma				1 (11%)
Hemangiosarcoma		1 (11%)	1 (11%)	
Histiocytic sarcoma	1 (17%)		1 (11%)	
Sarcoma	1 (17%)			
Oral mucosa				(1)
Squamous cell carcinoma				1 (100%)
Pancreas	(48)	(49)	(48)	(46)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Carcinoma, metastatic, ovary			1 (2%)	
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Histiocytic sarcoma			1 (2%)	
Salivary glands	(50)	(50)	(50)	(48)
Stomach, forestomach	(50)	(49)	(49)	(47)
Squamous cell papilloma	1 (2%)	2 (4%)		
Stomach, glandular	(49)	(48)	(48)	(47)
Carcinoma, metastatic, ovary			1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(48)
Hemangiosarcoma	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(46)
Adrenal medulla	(49)	(49)	(50)	(45)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign		1 (2%)		2 (4%)
Islets, pancreatic	(48)	(49)	(47)	(46)
Carcinoma		1 (2%)		
Pituitary gland	(47)	(48)	(48)	(48)
Pars distalis, adenoma	10 (21%)	8 (17%)	14 (29%)	8 (17%)
Pars intermedia, adenoma		1 (2%)	1 (2%)	
Thyroid gland	(50)	(50)	(49)	(47)
C-cell, adenoma	1 (2%)			
C-cell, carcinoma				2 (4%)
Follicular cell, adenoma	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Ovary	(49)	(50)	(50)	(46)
Carcinoma			1 (2%)	
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Cystadenoma			2 (4%)	1 (2%)
Histiocytic sarcoma	2 (4%)			
Teratoma benign			1 (2%)	
Uterus	(49)	(50)	(49)	(49)
Adenoma			1 (2%)	
Carcinoma, metastatic, ovary			1 (2%)	
Deciduoma benign	1 (2%)			
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Polyp stromal	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(46)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	2 (4%)			
Sarcoma				1 (2%)
Lymph node	(5)	(4)	(4)	(2)
Renal, histiocytic sarcoma	1 (20%)			
Lymph node, bronchial	(36)	(41)	(39)	(41)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (3%)			
Lymph node, mandibular	(40)	(41)	(39)	(41)
Hemangioma	1 (3%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(45)	(46)	(47)	(45)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Carcinoma, metastatic, ovary			1 (2%)	
Histiocytic sarcoma	1 (2%)		2 (4%)	
Lymph node, mediastinal	(37)	(36)	(41)	(38)
Carcinoma, metastatic, islets, pancreatic		1 (3%)		
Carcinoma, metastatic, ovary			1 (2%)	
Fibrous histiocytoma, metastatic, mesentery				1 (3%)
Hepatocellular carcinoma, metastatic, liver		1 (3%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (3%)		
Spleen	(49)	(50)	(49)	(46)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Histiocytic sarcoma			1 (2%)	
Thymus	(40)	(44)	(38)	(44)
Integumentary System				
Mammary gland	(48)	(49)	(50)	(50)
Carcinoma			1 (2%)	1 (2%)
Skin	(49)	(50)	(50)	(50)
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			
Subcutaneous tissue, sarcoma			1 (2%)	3 (6%)
Subcutaneous tissue, sarcoma, metastatic, mesentery	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)			
Osteosarcoma	1 (2%)	1 (2%)		2 (4%)
Skeletal muscle	(2)	(1)		
Carcinoma, metastatic, islets, pancreatic		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(49)
Histiocytic sarcoma	2 (4%)			
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Carcinoma, metastatic, ovary			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	5 (10%)	3 (6%)	3 (6%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Histiocytic sarcoma	3 (6%)			
Osteosarcoma, metastatic, bone				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Mediastinum, fibrous histiocytoma, metastatic, mesentery				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Respiratory System (continued)				
Mediastinum, hemangiosarcoma			1 (2%)	
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Special Senses System				
Harderian gland	(4)	(2)	(2)	(1)
Adenoma	2 (50%)	1 (50%)	2 (100%)	1 (100%)
Carcinoma		1 (50%)		
Urinary System				
Kidney	(50)	(49)	(49)	(46)
Carcinoma, metastatic, ovary			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	3 (6%)			
Urinary bladder	(47)	(48)	(47)	(45)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)		2 (4%)	
Lymphoma malignant	7 (14%)	2 (4%)	4 (8%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	34	38	41	44
Total primary neoplasms	58	59	74	83
Total animals with benign neoplasms	21	29	31	37
Total benign neoplasms	32	38	49	48
Total animals with malignant neoplasms	21	18	21	28
Total malignant neoplasms	26	21	25	35
Total animals with metastatic neoplasms	3	6	5	5
Total metastatic neoplasms	4	20	12	9

[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 Inhalation Study of Tetrahydrofuran: Chamber Control

Number of Days on Study	0 1 9	0 1 9	0 1 9	0 1 9	0 1 9	4 4 2	4 4 2	4 7 8	4 9 5	5 0 2	5 7 2	5 7 4	5 9 9	6 0 4	6 3 0	6 4 8	6 5 1	6 5 2	6 8 0	7 0 6	7 0 8	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 0 0 6	1 0 0 7	1 0 0 8	1 0 0 9	1 1 0 0	1 4 0 0	1 4 4 0 7	1 3 3 8	1 1 3 7	1 3 4 4	1 4 1 1	1 3 1 7	1 2 4 4	1 3 1 1	1 1 4 4	1 4 4 4	1 3 5 5	1 4 5 8	1 2 0 8	1 1 2 2	1 2 6 6	1 1 5 5	1 2 5 5	1 2 9 9	1 3 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	M	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	A	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma													X	X											
Hepatocellular carcinoma, multiple								X										X							
Hepatocellular adenoma																X	X	X	X			X	X		
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma																X									
Hepatocholangiocarcinoma, multiple															X										
Histiocytic sarcoma						X					X								X						
Mesentery											+					+			+	+				+	
Histiocytic sarcoma											X														
Sarcoma																				X					
Pancreas	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver								X																	
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	I	+	+	+	+	+	M	M	M	M	+	M	+	+	+	+	+	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																	X			X	X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																						X			
Follicular cell, carcinoma																									
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 Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 3 3	1 3 6	1 3 9	1 4 3	1 4 9	1 0 4	1 1 6	1 4 5	1 4 6	1 5 0	1 0 1	1 0 2	1 0 5	1 1 8	1 2 0	1 2 1	1 3 2	1 4 2	1 0 3	1 1 1	1 1 3	1 1 9	1 2 2	1 2 3	1 2 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X		X																		4
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X		X								X								X						10
Hepatocellular adenoma, multiple																	X				X					2
Hepatocholangiocarcinoma																										1
Hepatocholangiocarcinoma, multiple																										1
Histiocytic sarcoma																										3
Mesentery									+																	6
Histiocytic sarcoma																										1
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	I	M	+	+	M	+	+	M	+	+	M	+	+	M	M	+	M	M	30
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	47
Pars distalis, adenoma			X									X					X				X		X		X	10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X																	1
Follicular cell, adenoma																	X									2
Follicular cell, carcinoma																									X	1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	0 1 9	0 1 9	0 1 9	0 1 9	0 1 9	4 4 2	4 4 2	4 7 8	4 9 5	5 0 2	5 7 2	5 7 4	5 9 9	6 0 4	6 3 0	6 4 8	6 5 1	6 5 2	6 8 0	7 0 6	7 0 8	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 0 0 6	1 0 0 7	1 0 0 8	1 0 0 9	1 1 0 0	1 4 0 0	1 4 4 7	1 3 4 8	1 1 3 7	1 3 3 4	1 4 1 1	1 3 3 7	1 2 4 4	1 3 1 1	1 1 4 4	1 4 4 4	1 3 5 5	1 4 5 8	1 2 8 8	1 1 2 2	1 2 6 6	1 1 5 5	1 2 5 5	1 2 9 9	1 3 3 0
Genital System																								
Clitoral gland	M	+	+	M	+	+	+	+	+	+	+	M	M	M	+	+	+	M	M	+	+	M	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X								X						
Uterus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma benign																				X					
Histiocytic sarcoma																			X						
Polyp stromal																	X								
Hematopoietic System																									
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Histiocytic sarcoma						X													X						
Lymph node											+	+	+	+											
Renal, histiocytic sarcoma											X														
Lymph node, bronchial	M	M	+	M	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	M	M	+
Histiocytic sarcoma																			X						
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Hemangioma									X																
Lymph node, mesenteric	M	+	+	A	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Lymph node, mediastinal	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Thymus	+	+	M	+	+	M	M	+	+	+	+	+	M	M	+	M	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma						X																			
Subcutaneous tissue, sarcoma, metastatic, mesentery																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Osteosarcoma																									
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X					X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 5 0	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 3 3	1 3 6	1 3 9	1 4 3	1 4 9	1 0 4	1 1 6	1 4 5	1 4 6	1 5 0	1 0 1	1 0 2	1 0 5	1 1 8	1 2 0	1 2 1	1 3 2	1 4 2	1 0 3	1 1 1	1 1 3	1 1 9	1 2 2	1 2 3	1 2 7	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	38
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Deciduoma benign																										1
Histiocytic sarcoma																										1
Polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										2
Lymph node															+											5
Renal, histiocytic sarcoma																										1
Lymph node, bronchial	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	36
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	M	M	M	+	M	+	+	40
Hemangioma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Histiocytic sarcoma																										1
Lymph node, mediastinal	M	+	M	+	+	M	+	M	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	37
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	40
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma, metastatic, mesentery																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Osteosarcoma																X										1
Skeletal muscle					+																		+			2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: Chamber Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 3 3	1 3 6	1 3 9	1 4 3	1 4 9	1 0 4	1 1 6	1 4 5	1 4 6	1 5 0	1 0 1	1 0 2	1 0 5	1 1 8	1 2 0	1 2 1	1 2 2	1 4 2	1 0 3	1 1 1	1 1 3	1 1 9	1 2 2	1 2 3	1 2 7	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																								X		1
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland		+																							+	4
Adenoma																									X	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Lymphoma malignant		X			X					X									X		X					7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 4 3	3 4 4	3 0 5	3 1 0	3 1 2	3 1 8	3 1 9	3 2 0	3 2 2	3 3 5	3 4 9	3 0 4	3 0 8	3 2 1	3 3 0	3 3 3	3 3 4	3 3 8	3 4 1	3 4 6	3 4 8	3 0 9	3 1 4	3 2 6	3 2 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Polyp adenomatous																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Hemangiosarcoma										X																1
Hepatocellular carcinoma				X																	X		X			6
Hepatocellular carcinoma, multiple					X																					4
Hepatocellular adenoma							X		X			X	X				X	X	X		X	X			X	14
Hepatocellular adenoma, multiple																										3
Hepatocholangiocarcinoma																										1
Mesentery																		+					+	+	+	9
Carcinoma, metastatic, islets, pancreatic																										1
Hemangiosarcoma																						X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, islets, pancreatic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma	X																									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																						X				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Parathyroid gland	+	M	M	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Pars distalis, adenoma															X		X	X								8
Pars intermedia, adenoma										X																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	1 3 4	2 7 3	4 6 0	5 0 4	5 2 5	5 2 6	5 5 2	5 8 2	6 0 1	6 0 9	6 3 0	6 3 5	6 4 0	6 5 2	6 8 0	6 9 0	6 9 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	3 0 3	3 2 7	3 4 5	3 2 3	3 3 6	3 1 7	3 4 7	3 4 0	3 4 2	3 3 1	3 0 2	3 2 4	3 0 7	3 5 0	3 0 6	3 1 6	3 1 5	3 0 1	3 1 1	3 1 3	3 2 5	3 2 8	3 3 2	3 3 7	3 3 9
Genital System																									
Clitoral gland	M	M	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X												
Polyp stromal						X								X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, bronchial	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic							X																		
Hepatocellular carcinoma, metastatic, liver										X															
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	I	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic							X																		
Lymph node, mediastinal	+	+	M	I	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic							X																		
Hepatocellular carcinoma, metastatic, liver										X															
Hepatocholangiocarcinoma, metastatic, liver									X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle							+																		
Carcinoma, metastatic, islets, pancreatic							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 4 3	3 4 4	3 0 5	3 1 0	3 1 2	3 1 8	3 1 9	3 2 0	3 2 2	3 3 5	3 4 9	3 0 4	3 0 8	3 2 1	3 3 0	3 3 3	3 3 4	3 3 8	3 4 1	3 4 6	3 4 8	3 0 9	3 1 4	3 2 6	3 2 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Polyp stromal	X																		X							4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+				+									+			+		4
Lymph node, bronchial	+	+	M	+	M	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	41
Carcinoma, metastatic, islets, pancreatic																										1
Hepatocellular carcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	M	M	41
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, metastatic, islets, pancreatic																										1
Lymph node, mediastinal	+	+	+	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	M	M	M	I	M	+	36
Carcinoma, metastatic, islets, pancreatic																										1
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				1
Thymus	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma								X																		1
Skeletal muscle																										1
Carcinoma, metastatic, islets, pancreatic																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 200 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 4 3	3 4 4	3 0 5	3 1 0	3 1 2	3 1 8	3 1 9	3 2 0	3 2 2	3 3 5	3 4 9	3 0 4	3 0 8	3 2 1	3 3 0	3 3 3	3 3 4	3 3 8	3 4 1	3 4 6	3 4 8	3 0 9	3 1 4	3 2 6	3 2 9	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			2
Alveolar/bronchiolar carcinoma			X																							1
Hepatocellular carcinoma, metastatic, liver																						X				5
Hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland								+			+															2
Adenoma								X																		1
Carcinoma											X															1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant												X														2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 2 3	5 2 9	5 3 6	5 4 5	5 0 3	5 1 1	5 2 0	5 3 1	5 3 8	5 4 7	5 5 0	5 3 4	5 3 9	5 4 1	5 0 1	5 0 6	5 0 9	5 1 0	5 1 5	5 1 6	5 1 8	5 2 5	5 3 5	5 4 2	5 4 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X						X						X				X	X								9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X		X				X	X						X				X	X					13
Hepatocellular adenoma, multiple								X					X	X												5
Mesentery					+							+	+				+							+		9
Carcinoma, metastatic, ovary																										1
Hemangiosarcoma					X																					1
Histiocytic sarcoma																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, ovary																										1
Histiocytic sarcoma																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, ovary																										1
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant															X											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	M	M	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X		X		X		X				X			X	X							X	X	X	X	14
Pars intermedia, adenoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma														X												3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Cystadenoma		X	X																							2
Teratoma benign																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	0 2 9	4 2 9	4 6 0	4 6 9	5 3 6	5 4 4	5 5 5	5 6 6	5 7 4	5 9 4	5 9 9	6 1 0	6 3 1	6 3 9	6 7 0	6 7 4	6 8 0	6 9 0	7 0 6	7 0 6	7 0 8	7 1 5	7 2 0	7 2 1	7 3 3
Carcass ID Number	5 2 1	5 1 2	5 4 8	5 3 7	5 4 0	5 3 3	5 0 2	5 2 2	5 2 6	5 4 3	5 2 7	5 0 7	5 3 2	5 1 7	5 1 9	5 1 3	5 4 6	5 2 8	5 0 5	5 2 4	5 3 0	5 0 4	5 4 9	5 0 8	5 1 4
Genital System (continued)																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma, metastatic, ovary																						X			
Polyp stromal																	X								
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+	+			+									
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	+	I	M	+	M	M	+	M	+	+	M	+	M	+	+	+
Lymph node, mandibular	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	A	+	+	+	+	+
Carcinoma, metastatic, ovary																						X			
Histiocytic sarcoma										X															
Lymph node, mediastinal	+	+	M	M	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, ovary																						X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	M	+	+	M	+	M	+	+	+	M	+	M	+	+	+	M	M	+	+	+	I	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord				+																					
Respiratory System																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma												X													
Carcinoma, metastatic, ovary																						X			
Hepatocellular carcinoma, metastatic, liver						X		X																	
Sarcoma, metastatic, skin									X																
Mediastinum, hemangiosarcoma																									
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 2 3	5 2 9	5 3 6	5 4 5	5 0 3	5 1 1	5 2 0	5 3 1	5 3 8	5 4 7	5 5 0	5 3 4	5 3 9	5 4 1	5 0 1	5 0 6	5 0 9	5 1 0	5 1 5	5 1 6	5 1 8	5 2 5	5 3 5	5 4 2	5 4 4	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X															1
Carcinoma, metastatic, ovary																										1
Polyp stromal										X																2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node												+														4
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	39
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	I	+	+	M	+	M	+	+	+	+	M	M	+	+	+	39
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, ovary																										1
Histiocytic sarcoma																								X		2
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	41
Carcinoma, metastatic, ovary																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma														X												1
Histiocytic sarcoma																								X		1
Thymus	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	38
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma			X																							1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X	X											3
Alveolar/bronchiolar adenoma, multiple			X																							1
Alveolar/bronchiolar carcinoma															X											2
Carcinoma, metastatic, ovary																										1
Hepatocellular carcinoma, metastatic, liver																	X									3
Sarcoma, metastatic, skin																										1
Mediastinum, hemangiosarcoma														X												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 600 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 2 3	5 2 9	5 3 6	5 4 5	5 0 3	5 1 1	5 2 0	5 3 1	5 3 8	5 4 7	5 5 0	5 3 4	5 3 9	5 4 1	5 0 1	5 0 6	5 0 9	5 1 0	5 1 5	5 1 6	5 1 8	5 2 5	5 3 5	5 4 2	5 4 4	Total Tissues/ Tumors
Special Senses System																										
Harderian gland												+												+		2
Adenoma												X												X		2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, ovary																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																								X		2
Lymphoma malignant																	X		X							4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm

Number of Days on Study	3 9 9	4 0 3	5 2 7	5 5 8	5 6 2	5 6 6	5 7 4	5 7 7	5 8 2	5 9 8	5 9 9	6 0 4	6 1 0	6 2 8	6 3 1	6 4 5	6 6 4	7 0 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	7 1 3	7 2 8	7 4 3	7 0 8	7 4 5	7 1 1	7 2 5	7 4 6	7 0 6	7 0 5	7 3 8	7 2 3	7 3 2	7 0 3	7 1 0	7 4 7	7 3 3	7 2 6	7 0 7	7 1 6	7 1 7	7 2 0	7 2 2	7 2 4	7 3 1
Alimentary System																									
Esophagus	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Intestine small, ileum	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X						X	X						X			X			X	
Hepatocellular carcinoma, multiple						X	X																		X
Hepatocellular adenoma	X		X	X			X		X			X	X		X				X						
Hepatocellular adenoma, multiple																						X	X		
Osteosarcoma, metastatic, bone																									
Mesentery		+					+	+				+													
Fibrous histiocytoma							X																		
Oral mucosa																									
Squamous cell carcinoma																									
Pancreas	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery							X																		
Salivary glands	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel									+																
Heart	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	M	+	+	+	+	+	A	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	A	M	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X														
Islets, pancreatic	A	A	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	A	+	+	+	+	M	+	M	A	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+
Pituitary gland	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X			X			X	X			
Thyroid gland	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
Peritoneum																+									
Genital System																									
Clitoral gland	+	+	+	+	+	+	I	A	+	+	+	+	M	I	+	+	M	+	+	+	+	+	+	+	I
Ovary	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																					X				
Uterus	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal								X																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 3 5	7 4 0	7 4 1	7 4 4	7 0 2	7 0 4	7 1 4	7 1 8	7 1 9	7 2 1	7 3 0	7 4 9	7 0 9	7 1 2	7 1 5	7 2 7	7 2 9	7 3 9	7 4 2	7 4 8	7 0 1	7 0 5	7 3 4	7 3 6	7 3 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma						X				X					X							X				10
Hepatocellular carcinoma, multiple							X							X						X						6
Hepatocellular adenoma				X	X	X				X	X		X		X				X					X	X	19
Hepatocellular adenoma, multiple	X		X					X	X							X	X	X		X	X		X			12
Osteosarcoma, metastatic, bone																									X	1
Mesentery			+									+			+		+	+								9
Fibrous histiocytoma																										1
Oral mucosa							+																			1
Squamous cell carcinoma							X																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrous histiocytoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pheochromocytoma benign															X											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	M	+	+	+	+	+	M	I	+	M	M	+	+	M	M	+	M	+	+	+	+	+	+	M	M	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma									X				X									X	X			8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, carcinoma															X	X										2
Follicular cell, adenoma																					X					1
General Body System																										
Peritoneum																										1
Genital System																										
Clitoral gland	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	46
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	3 9 9	4 0 3	5 2 7	5 5 8	5 6 2	5 6 6	5 7 4	5 7 7	5 8 2	5 9 8	5 9 9	6 0 4	6 1 0	6 2 8	6 3 1	6 4 5	6 6 4	7 0 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	7 1 3	7 2 8	7 4 3	7 0 8	7 4 5	7 1 1	7 2 5	7 4 6	7 0 6	7 0 5	7 3 8	7 2 3	7 3 2	7 0 3	7 1 0	7 4 7	7 3 3	7 2 6	7 0 7	7 1 6	7 1 7	7 2 0	7 2 2	7 2 4	7 3 1
Hematopoietic System																									
Bone marrow	+	A	+	+	I	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma														X											
Lymph node													+												
Lymph node, bronchial	+	A	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Fibrous histiocytoma, metastatic, mesentery							X																		
Lymph node, mandibular	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	M	+	M
Lymph node, mesenteric	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	+	+	M	M	+	M	+	M	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery							X																		
Spleen	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	A	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma															X								X		
Musculoskeletal System																									
Bone	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma										X															
Nervous System																									
Brain	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																X		
Alveolar/bronchiolar carcinoma												X													
Hepatocellular carcinoma, metastatic, liver						X						X													
Osteosarcoma, metastatic, bone																									
Mediastinum, fibrous histiocytoma, metastatic, mesentery							X																		
Nose	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant											X	X	X												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran: 1,800 ppm
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 3 5	7 4 0	7 4 1	7 4 4	7 0 2	7 0 4	7 1 4	7 1 8	7 1 9	7 2 1	7 3 0	7 4 9	7 0 9	7 1 2	7 1 5	7 2 7	7 2 9	7 3 9	7 4 2	7 4 8	7 0 1	7 0 5	7 3 4	7 3 6	7 3 7	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma																									1
Lymph node																+									2
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	M	+	+	+	+	+	+	41
Fibrous histiocytoma, metastatic, mesentery																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Lymph node, mediastinal	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	38
Fibrous histiocytoma, metastatic, mesentery																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma									X																3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma																								X	2
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																					X				3
Alveolar/bronchiolar carcinoma																				X					2
Hepatocellular carcinoma, metastatic, liver							X																		3
Osteosarcoma, metastatic, bone																								X	1
Mediastinum, fibrous histiocytoma, metastatic, mesentery																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Special Senses System																									
Harderian gland																					+				1
Adenoma																					X				1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant										X			X												5

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Liver: Hepatocellular Adenoma				
Overall rate[a]	12/50 (24%)	17/50 (34%)	18/50 (36%)	31/48 (65%)
Adjusted rate[b]	35.9%	47.1%	52.5%	76.8%
Terminal rate[c]	8/29 (28%)	14/33 (42%)	11/26 (42%)	23/32 (72%)
First incidence (days)	648	640	469	399
Life table test[d]	P<0.001	P=0.313	P=0.119	P=0.001
Logistic regression test[d]	P<0.001	P=0.249	P=0.188	P<0.001
Cochran-Armitage test[d]	P<0.001			
Fisher exact test[d]		P=0.189	P=0.138	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	6/50 (12%)	10/50 (20%)	10/50 (20%)	16/48 (33%)
Adjusted rate	16.5%	26.3%	30.0%	40.8%
Terminal rate	2/29 (7%)	6/33 (18%)	5/26 (19%)	10/32 (31%)
First incidence (days)	478	552	544	562
Life table test	P=0.027	P=0.297	P=0.210	P=0.035
Logistic regression test	P=0.012	P=0.234	P=0.229	P=0.014
Cochran-Armitage test	P=0.009			
Fisher exact test		P=0.207	P=0.207	P=0.011
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	17/50 (34%)	24/50 (48%)	26/50 (52%)	41/48 (85%)
Adjusted rate	46.3%	61.3%	69.1%	93.0%
Terminal rate	10/29 (34%)	18/33 (55%)	15/26 (58%)	29/32 (91%)
First incidence (days)	478	552	469	399
Life table test	P<0.001	P=0.253	P=0.056	P<0.001
Logistic regression test	P<0.001	P=0.188	P=0.086	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.111	P=0.053	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	3/49 (6%)
Adjusted rate	3.4%	6.1%	14.2%	8.4%
Terminal rate	1/29 (3%)	2/33 (6%)	3/26 (12%)	2/32 (6%)
First incidence (days)	733 (T)	733 (T)	690	574
Life table test	P=0.332	P=0.545	P=0.158	P=0.344
Logistic regression test	P=0.321	P=0.545	P=0.186	P=0.330
Cochran-Armitage test	P=0.294			
Fisher exact test		P=0.500	P=0.181	P=0.301
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	5/50 (10%)	5/49 (10%)
Adjusted rate	6.9%	9.1%	16.4%	13.7%
Terminal rate	2/29 (7%)	3/33 (9%)	3/26 (12%)	3/32 (9%)
First incidence (days)	733 (T)	733 (T)	610	574
Life table test	P=0.220	P=0.559	P=0.196	P=0.259
Logistic regression test	P=0.212	P=0.559	P=0.241	P=0.245
Cochran-Armitage test	P=0.183			
Fisher exact test		P=0.500	P=0.218	P=0.210

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	10/47 (21%)	8/48 (17%)	14/48 (29%)	8/48 (17%)
Adjusted rate	32.7%	23.4%	47.3%	23.4%
Terminal rate	7/27 (26%)	6/31 (19%)	11/26 (42%)	6/32 (19%)
First incidence (days)	651	582	599	631
Life table test	P=0.306N	P=0.292N	P=0.222	P=0.287N
Logistic regression test	P=0.298N	P=0.285N	P=0.330	P=0.267N
Cochran-Armitage test	P=0.386N			
Fisher exact test		P=0.378N	P=0.259	P=0.378N
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	2.4%	8.9%
Terminal rate	0/29 (0%)	0/33 (0%)	0/26 (0%)	2/32 (6%)
First incidence (days)	—[e]	—	574	631
Life table test	P=0.025	—	P=0.515	P=0.136
Logistic regression test	P=0.022	—	P=0.476	P=0.135
Cochran-Armitage test	P=0.021			
Fisher exact test		—	P=0.500	P=0.121
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/49 (6%)	1/47 (2%)
Adjusted rate	6.9%	3.0%	9.1%	3.1%
Terminal rate	2/29 (7%)	1/33 (3%)	1/26 (4%)	1/32 (3%)
First incidence (days)	733 (T)	733 (T)	599	733 (T)
Life table test	P=0.451N	P=0.455N	P=0.481	P=0.465N
Logistic regression test	P=0.460N	P=0.455N	P=0.530	P=0.465N
Cochran-Armitage test	P=0.494N			
Fisher exact test		P=0.500N	P=0.490	P=0.523N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	3/49 (6%)	1/47 (2%)
Adjusted rate	10.3%	3.0%	9.1%	3.1%
Terminal rate	3/29 (10%)	1/33 (3%)	1/26 (4%)	1/32 (3%)
First incidence (days)	733 (T)	733 (T)	599	733 (T)
Life table test	P=0.325N	P=0.259N	P=0.637	P=0.269N
Logistic regression test	P=0.331N	P=0.259N	P=0.633N	P=0.269N
Cochran-Armitage test	P=0.365N			
Fisher exact test		P=0.309N	P=0.651	P=0.332N
Uterus: Stromal Polyp				
Overall rate	1/50 (2%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	2.9%	10.6%	6.7%	2.3%
Terminal rate	0/29 (0%)	2/33 (6%)	1/26 (4%)	0/32 (0%)
First incidence (days)	651	526	680	577
Life table test	P=0.328N	P=0.221	P=0.501	P=0.747N
Logistic regression test	P=0.336N	P=0.186	P=0.522	P=0.753
Cochran-Armitage test	P=0.340N			
Fisher exact test		P=0.181	P=0.500	P=0.753N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	2.6%	8.5%	7.7%	0.0%
Terminal rate	0/29 (0%)	2/33 (6%)	2/26 (8%)	0/32 (0%)
First incidence (days)	599	640	733 (T)	—
Life table test	P=0.183N	P=0.347	P=0.481	P=0.490N
Logistic regression test	P=0.175N	P=0.324	P=0.522	P=0.525N
Cochran-Armitage test	P=0.187N			
Fisher exact test		P=0.309	P=0.500	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	4.9%	8.5%	11.5%	0.0%
Terminal rate	0/29 (0%)	2/33 (6%)	3/26 (12%)	0/32 (0%)
First incidence (days)	495	640	733 (T)	—
Life table test	P=0.124N	P=0.549	P=0.483	P=0.220N
Logistic regression test	P=0.121N	P=0.497	P=0.513	P=0.283N
Cochran-Armitage test	P=0.128N			
Fisher exact test		P=0.500	P=0.500	P=0.247N
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Adjusted rate	7.6%	0.0%	6.2%	0.0%
Terminal rate	0/29 (0%)	0/33 (0%)	1/26 (4%)	0/32 (0%)
First incidence (days)	442	—	594	—
Life table test	P=0.170N	P=0.109N	P=0.487N	P=0.113N
Logistic regression test	P=0.194N	P=0.140N	P=0.528N	P=0.145N
Cochran-Armitage test	P=0.173N			
Fisher exact test		P=0.121N	P=0.500N	P=0.121N
All Organs: Malignant Lymphoma				
Overall rate	7/50 (14%)	2/50 (4%)	4/50 (8%)	5/50 (10%)
Adjusted rate	21.4%	5.5%	12.7%	13.3%
Terminal rate	5/29 (17%)	1/33 (3%)	2/26 (8%)	2/32 (6%)
First incidence (days)	502	635	631	599
Life table test	P=0.573N	P=0.059N	P=0.288N	P=0.324N
Logistic regression test	P=0.576N	P=0.066N	P=0.227N	P=0.343N
Cochran-Armitage test	P=0.570			
Fisher exact test		P=0.080N	P=0.262N	P=0.380N
All Organs: Benign Neoplasms				
Overall rate	21/50 (42%)	29/50 (58%)	31/50 (62%)	37/50 (74%)
Adjusted rate	56.6%	72.4%	85.6%	85.7%
Terminal rate	13/29 (45%)	22/33 (67%)	21/26 (81%)	26/32 (81%)
First incidence (days)	495	526	469	399
Life table test	P=0.014	P=0.235	P=0.031	P=0.016
Logistic regression test	P=0.005	P=0.159	P=0.064	P=0.004
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.081	P=0.036	P=0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	18/50 (36%)	21/50 (42%)	28/50 (56%)
Adjusted rate	51.6%	44.4%	54.8%	64.6%
Terminal rate	10/29 (34%)	11/33 (33%)	10/26 (38%)	17/32 (53%)
First incidence (days)	442	552	544	562
Life table test	P=0.091	P=0.227N	P=0.537	P=0.258
Logistic regression test	P=0.098	P=0.211N	P=0.344N	P=0.280
Cochran-Armitage test	P=0.036			
Fisher exact test		P=0.341N	P=0.580N	P=0.115
All Organs: Benign or Malignant Neoplasms				
Overall rate	34/50 (68%)	38/50 (76%)	41/50 (82%)	44/50 (88%)
Adjusted rate	79.0%	86.3%	95.3%	93.5%
Terminal rate	20/29 (69%)	27/33 (82%)	24/26 (92%)	29/32 (91%)
First incidence (days)	442	526	469	399
Life table test	P=0.131	P=0.546N	P=0.115	P=0.188
Logistic regression test	P=0.049	P=0.490	P=0.204	P=0.059
Cochran-Armitage test	P=0.016			
Fisher exact test		P=0.252	P=0.083	P=0.014

(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, 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 chamber 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 chamber 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 Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	11/49	4/49	15/49
Acetonitrile	4/49	7/49	9/49
Allyl Glycidyl Ether	1/50	5/50	6/50
2-Chloroacetophenone	4/50	8/50	12/50
l-Epinephrine Hydrochloride	2/50	1/50	3/50
Chloroethane	0/49	3/49	3/49
Hexachlorocyclopentadiene	5/49	4/49	9/49
CS2 (*o*-Chlorobenzalmalononitrile)	4/50	7/50	11/50
Ozone	20/50	15/50	27/50
Total	51/446 (11.4%)	54/446 (12.1%)	95/446 (21.3%)
Standard deviation	12.5%	8.1%	14.8%
Range	0%-40%	2%-30%	6%-54%
Overall Historical Incidence			
Total	114/937 (12.2%)	103/937 (11.0%)	200/937 (21.3%)
Standard deviation	9.7%	6.7%	11.9%
Range	0%-40%	0%-30%	3%-54%

[a] Data as of 12 May 1995

TABLE D4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	4/50	0/50	4/50
Acetonitrile	7/49	1/49	8/49
Allyl Glycidyl Ether	0/50	0/50	0/50
2-Chloroacetophenone	4/50	3/50	6/50
l-Epinephrine Hydrochloride	3/50	2/50	5/50
Chloroethane	2/49	3/49	5/49
Hexachlorocyclopentadiene	4/48	3/48	7/48
CS2 (*o*-Chlorobenzalmalononitrile)	4/50	1/50	5/50
Ozone	4/50	2/50	6/50
Total	32/446 (7.2%)	15/446 (3.4%)	46/446 (10.3%)
Standard deviation	3.8%	2.5%	4.6%
Range	0%-14%	0%-6%	0%-16%
Overall Historical Incidence			
Total	61/939 (6.5%)	38/939 (4.1%)	97/939 (10.3%)
Standard deviation	3.2%	3.2%	3.7%
Range	0%-14%	0%-12%	0%-16%

[a] Data as of 12 May 1995

TABLE D4c
Historical Incidence of Stromal Polyp of the Uterus in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	2/50
Acetonitrile	2/49
Allyl Glycidyl Ether	0/50
2-Chloroacetophenone	3/50
l-Epinephrine Hydrochloride	0/50
Chloroethane	2/49
Hexachlorocyclopentadiene	0/49
CS2 (*o*-Chlorobenzalmalononitrile)	3/50
Ozone	1/50
Total	13/447 (2.9%)
Standard deviation	2.5%
Range	0%-6%
Overall Historical Incidence	
Total	26/941 (2.8%)
Standard deviation	2.3%
Range	0%-6%

[a] Data as of 12 May 1995

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

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	5	1	1	
Moribund	13	10	20	13
Natural deaths	3	6	3	5
Survivors				
Terminal sacrifice	29	33	26	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(44)	(45)	(44)
Degeneration, hyaline	1 (2%)			
Inflammation	1 (2%)			1 (2%)
Intestine small, ileum	(46)	(45)	(46)	(46)
Diverticulum				1 (2%)
Ulcer				1 (2%)
Liver	(50)	(50)	(50)	(48)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Basophilic focus	1 (2%)			1 (2%)
Clear cell focus		1 (2%)		1 (2%)
Eosinophilic focus	7 (14%)	9 (18%)	7 (14%)	11 (23%)
Hematopoietic cell proliferation		1 (2%)	2 (4%)	3 (6%)
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule	1 (2%)			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
Mixed cell focus		3 (6%)		1 (2%)
Necrosis	3 (6%)			7 (15%)
Pigmentation	1 (2%)			
Thrombosis				1 (2%)
Vacuolization cytoplasmic, focal		1 (2%)		
Bile duct, cyst	1 (2%)	1 (2%)		
Mesentery	(6)	(9)	(9)	(9)
Inflammation, chronic			1 (11%)	
Fat, hemorrhage				1 (11%)
Fat, necrosis	3 (50%)	6 (67%)	4 (44%)	7 (78%)
Pancreas	(48)	(49)	(48)	(46)
Atrophy	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Basophilic focus				1 (2%)
Cytoplasmic alteration	1 (2%)	1 (2%)		
Hyperplasia		1 (2%)	2 (4%)	2 (4%)
Hypertrophy	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Inflammation			1 (2%)	
Duct, cyst		1 (2%)	1 (2%)	

[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 Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(49)	(49)	(47)
Angiectasis				1 (2%)
Infiltration cellular, mast cell	1 (2%)			
Inflammation				1 (2%)
Ulcer	3 (6%)	1 (2%)		2 (4%)
Epithelium, hyperplasia	2 (4%)		1 (2%)	1 (2%)
Stomach, glandular	(49)	(48)	(48)	(47)
Erosion	2 (4%)		1 (2%)	2 (4%)
Infiltration cellular, mast cell	1 (2%)			
Inflammation, suppurative	1 (2%)	1 (2%)		
Mineralization	1 (2%)			
Ulcer		1 (2%)		
Epithelium, hyperplasia				1 (2%)
Tooth			(1)	
Developmental malformation			1 (100%)	
Cardiovascular System				
Blood vessel	(1)			(1)
Inflammation				1 (100%)
Mineralization	1 (100%)			
Heart	(50)	(50)	(50)	(48)
Cardiomyopathy	17 (34%)	28 (56%)	25 (50%)	22 (46%)
Hemorrhage	1 (2%)			
Mineralization	1 (2%)			1 (2%)
Artery, inflammation	1 (2%)		2 (4%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(46)
Hematopoietic cell proliferation			1 (2%)	1 (2%)
Hyperplasia	2 (4%)	1 (2%)		
Hypertrophy	3 (6%)	4 (8%)	5 (10%)	3 (7%)
Necrosis	1 (2%)			1 (2%)
Capsule, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Adrenal medulla	(49)	(49)	(50)	(45)
Hyperplasia	4 (8%)	8 (16%)	1 (2%)	1 (2%)
Necrosis	1 (2%)			1 (2%)
Islets, pancreatic	(48)	(49)	(47)	(46)
Hyperplasia				1 (2%)
Parathyroid gland	(30)	(33)	(33)	(34)
Cyst			1 (3%)	
Pituitary gland	(47)	(48)	(48)	(48)
Hyperplasia	1 (2%)			
Pars distalis, cyst				1 (2%)
Pars distalis, hyperplasia	14 (30%)	12 (25%)	16 (33%)	20 (42%)
Pars intermedia, hyperplasia	1 (2%)	3 (6%)		
Thyroid gland	(50)	(50)	(49)	(47)
Angiectasis	1 (2%)			
Inflammation	1 (2%)			
C-cell, hyperplasia				1 (2%)
Follicular cell, hyperplasia	14 (28%)	10 (20%)	15 (31%)	10 (21%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
General Body System				
Peritoneum				(1)
Inflammation, suppurative				1 (100%)
Genital System				
Clitoral gland	(38)	(40)	(43)	(41)
Inflammation	1 (3%)	1 (3%)		
Ovary	(49)	(50)	(50)	(46)
Amyloid deposition	1 (2%)			
Angiectasis	3 (6%)			1 (2%)
Atrophy	8 (16%)	5 (10%)	9 (18%)	9 (20%)
Cyst	19 (39%)	15 (30%)	14 (28%)	17 (37%)
Hyperplasia	1 (2%)			
Inflammation			1 (2%)	
Pigmentation, hemosiderin			1 (2%)	
Artery, inflammation			1 (2%)	
Corpus luteum, hyperplasia			1 (2%)	
Granulosa cell, hyperplasia	1 (2%)			
Interstitial cell, hyperplasia		1 (2%)		1 (2%)
Uterus	(49)	(50)	(49)	(49)
Adenomyosis				1 (2%)
Angiectasis	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Hydrometra	3 (6%)	5 (10%)		11 (22%)
Hyperplasia, cystic	41 (84%)	41 (82%)	44 (90%)	41 (84%)
Inflammation, suppurative	1 (2%)			2 (4%)
Thrombosis		1 (2%)		1 (2%)
Endometrium, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Serosa, cyst			1 (2%)	
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(46)
Angiectasis	1 (2%)			
Hyperplasia			4 (8%)	2 (4%)
Hyperplasia, histiocytic	2 (4%)			
Infiltration cellular, mast cell		1 (2%)		
Lymph node	(5)	(4)	(4)	(2)
Degeneration, cystic		1 (25%)		
Hemorrhage		1 (25%)		
Iliac, hyperplasia	2 (40%)		1 (25%)	
Lumbar, angiectasis				1 (50%)
Lumbar, hyperplasia	1 (20%)			
Renal, hyperplasia			1 (25%)	
Lymph node, bronchial	(36)	(41)	(39)	(41)
Hyperplasia	1 (3%)	3 (7%)	6 (15%)	2 (5%)
Lymph node, mandibular	(40)	(41)	(39)	(41)
Hyperplasia	5 (13%)	2 (5%)	4 (10%)	3 (7%)
Pigmentation, hemosiderin				1 (2%)
Lymph node, mesenteric	(45)	(46)	(47)	(45)
Angiectasis		1 (2%)	1 (2%)	
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia	2 (4%)	3 (7%)	5 (11%)	3 (7%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Hematopoietic System (continued)				
Lymph node, mediastinal	(37)	(36)	(41)	(38)
Hematopoietic cell proliferation				1 (3%)
Hyperplasia	3 (8%)		4 (10%)	1 (3%)
Spleen	(49)	(50)	(49)	(46)
Angiectasis	1 (2%)			
Hematopoietic cell proliferation	10 (20%)	8 (16%)	10 (20%)	8 (17%)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Infiltration cellular, mast cell		1 (2%)		
Thymus	(40)	(44)	(38)	(44)
Amyloid deposition	1 (3%)			
Angiectasis				1 (2%)
Atrophy	5 (13%)	3 (7%)	3 (8%)	2 (5%)
Hyperplasia, lymphoid	1 (3%)	1 (2%)	1 (3%)	2 (5%)
Integumentary System				
Mammary gland	(48)	(49)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		
Skin	(49)	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)		
Epidermis, hyperplasia			1 (2%)	
Subcutaneous tissue, angiectasis				1 (2%)
Subcutaneous tissue, edema	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(49)
Arthrosis				2 (4%)
Fibrous osteodystrophy	19 (38%)	23 (46%)	16 (32%)	15 (31%)
Cranium, fracture			1 (2%)	
Vertebra, fracture		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)	1 (2%)	
Hydrocephalus			1 (2%)	
Meninges, infiltration cellular, mononuclear cell	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Spinal cord		(1)	(1)	
Degeneration			1 (100%)	
Hemorrhage		1 (100%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)		
Infiltration cellular, histiocyte	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, chronic, focal	2 (4%)		2 (4%)	
Alveolar epithelium, hyperplasia	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Mediastinum, inflammation			1 (2%)	
Perivascular, infiltration cellular, mononuclear cell		1 (2%)	3 (6%)	
Nose	(50)	(50)	(48)	(49)
Inflammation, suppurative			2 (4%)	
Nasolacrimal duct, inflammation, suppurative	1 (2%)		1 (2%)	
Olfactory epithelium, atrophy, focal		3 (6%)	1 (2%)	
Special Senses System				
None				
Urinary System				
Kidney	(50)	(49)	(49)	(46)
Amyloid deposition	1 (2%)	2 (4%)		
Glomerulosclerosis	1 (2%)			
Hydronephrosis		1 (2%)	1 (2%)	
Hyperplasia, lymphoid	2 (4%)	1 (2%)		
Metaplasia, osseous	1 (2%)	3 (6%)	2 (4%)	
Nephropathy	17 (34%)	17 (35%)	19 (39%)	13 (28%)
Pigmentation	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

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

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of tetrahydrofuran. By experimental design, 10,000 μg/plate was selected as the high dose. All trials were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Tetrahydrofuran 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 tetrahydrofuran. The high dose was limited to 5,000 μg/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with tetrahydrofuran in McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing tetrahydrofuran 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 tetrahydrofuran, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no tetrahydrofuran and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity;

increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) 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 tetrahydrofuran for 12 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 tetrahydrofuran and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 12 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.

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

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

DROSOPHILA MELANOGASTER TEST PROTOCOL

The assays for induction of sex-linked recessive lethal (SLRL) mutations were performed with adult flies as described by Valencia *et al.* (1985). Tetrahydrofuran was supplied as a coded aliquot by Radian Corporation. It was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, tetrahydrofuran was retested by injection into adult males.

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

Toxicity tests were performed to set concentrations of tetrahydrofuran at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on an aqueous solution of tetrahydrofuran in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a solution of tetrahydrofuran dissolved in saline and allowed to recover for 24 hours. A concurrent saline control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier postmeiotic stages). For the larval feeding experiment, Canton-S males and females were mated and eggs

were exposed in vials with standard cornmeal feed containing tetrahydrofuran in solvent (5% ethanol) or solvent alone (Valencia *et al.*, 1989). Adult emergent males were mated at approximately 24 hours of age with two successive harems of three to five *Basc* females to establish two single-day broods. For both the adult and larval exposure experiments, F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

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

MOUSE BONE MARROW SISTER CHROMATID EXCHANGE TEST PROTOCOL

A dose range-finding study was performed in the absence of adequate toxicity information from the literature. The highest dose was limited by toxicity. Tetrahydrofuran was tested for the induction of SCEs in mouse bone marrow by two protocols. Male B6C3F_1 mice (five animals per dose group) were injected intraperitoneally with tetrahydrofuran dissolved in corn oil (injection volume = 0.4 mL). Solvent control mice received equivalent injections of corn oil only. The positive controls were mitomycin-C (23-hour harvest time) and acrylamide (42-hour harvest time).

The first protocol had a standard harvest time of 23 hours, and the second protocol had a delayed harvest of 42 hours. The mice were implanted subcutaneously with a BrdU tablet (McFee *et al.*, 1983) 24 hours before harvest (1 hour before chemical treatment in the case of the standard protocol). The use of BrdU allowed selection of the appropriate cell population (cells in the second metaphase following tetrahydrofuran treatment) for scoring. Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were killed 23 or 42 hours after treatment. One or both femurs were removed, and the marrow was flushed out with phosphate-buffered saline (pH 7.0). The cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained with fluorescence-plus-Giemsa and scored.

Twenty-five second-division metaphase cells were scored from each of four animals per treatment. Responses were evaluated as SCEs/cell, and the data were analyzed by a trend test (Margolin *et al.*, 1986).

MOUSE BONE MARROW CHROMOSOMAL ABERRATIONS TEST PROTOCOL

A dose range-finding study was performed in the absence of adequate toxicity information from the literature. The highest dose was limited by toxicity. Tetrahydrofuran was tested for induction of Abs in mouse bone marrow by two different protocols. The first protocol used a standard harvest time of 17 hours and the second protocol used a delayed harvest time of 36 hours.

Male B6C3F$_1$ mice (10 animals per dose group) were injected intraperitoneally with tetrahydrofuran dissolved in corn oil (injection volume=0.4 mL). Solvent control mice received equivalent injections of phosphate-buffered saline only. The positive control was mitomycin-C. The mice were subcutaneously implanted with a BrdU tablet (McFee *et al.*, 1983) 18 hours before the scheduled harvest. (For the standard protocol, this required BrdU implantation to precede injection with tetrahydrofuran by 1 hour.) The use of BrdU allowed selection of the appropriate cell population for scoring. (Abs induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were killed 17 or 36 hours after tetrahydrofuran injection (18 hours after BrdU dosing). One or both femurs were removed and the marrow was flushed out with phosphate-buffered saline (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained and scored.

Fifty first-division metaphase cells were scored from each of eight animals per treatment. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The data were analyzed by a trend test (Margolin *et al.*, 1986).

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). At the end of the 14-week toxicity study, peripheral blood samples were obtained from male and female mice, and smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. Slides were scanned at 630 or 1,000× magnification with a semiautomated image analysis system to determine the frequency of micronuclei in 2,000 polychromatic erythrocytes (PCEs) and 10,000 normochromatic erythrocytes (NCEs) in up to 10 animals per exposure group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs and PCEs were analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposed 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 less than or equal to 0.025 or if the P value for any single exposure group is less than or equal to 0.025 divided by the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitude of those effects.

RESULTS

Tetrahydrofuran has been tested in a variety of mutagenicity assays and the results were, with one exception, negative. Tetrahydrofuran was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537 when tested in two different laboratories in a preincubation protocol with doses up to 10,000 μg/plate; all tests were conducted with and without Aroclor-induced rat or hamster liver S9 (Mortelmans *et al.*, 1986; Table E1). Tetrahydrofuran did not induce SCEs (Table E2) or Abs (Table E3) in cultured CHO cells when tested at doses up to 5,000 μg/mL, with or without S9 (Galloway *et al.*, 1987). Unusually high frequencies of aberrant cells were observed in the Abs test in both control and tetrahydrofuran-treated cultures; however, the trend test was insignificant for all trials and no single dose group showed aberration frequencies that differed significantly from the control value, with one exception.

In the second trial conducted with S9, the middle dose of 3,000 μg/mL produced a positive response; because the trend test for this trial was not significant, and because the responses for the complete data set were not correlated with increasing dose, this trial was concluded to be equivocal, and the overall call for the assay was negative. No induction of SLRL mutations was noted in male *Drosophila melanogaster* exposed by feeding or by injection to a dose of 10,000, 40,000, or 125,000 ppm tetrahydrofuran (Valencia *et al.*, 1985; Table E4).

Little evidence for genetic toxicity of tetrahydrofuran was noted in *in vivo* assays. Results of the mouse bone marrow SCE assay were negative (Table E5). Tetrahydrofuran (500, 1,000, or 2,000 mg/kg) did not induce Abs in mouse bone marrow cells (Table E6) at either the 17- or 36-hour sample times employed in this assay. Although results from the initial 23-hour SCE test were positive, a repeat test gave negative results, and the results of the single trial performed with a 42-hour sample time were also negative. The frequencies of micronucleated erythrocytes were determined in peripheral blood samples obtained from male and female mice at the completion of the 14-week toxicity study (Table E7). In female mice, neither polychromatic nor normochromatic erythrocytes had elevated frequencies of micronuclei, but in male mice, there was a small increase in the frequency of micronucleated normochromatic erythrocytes that was concluded to represent an equivocal response (trend test P=0.074). No significant increase in the frequency of micronucleated polychromatic erythrocytes was noted in male mice.

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

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at Case Western Reserve University							
TA100	0	111 ± 5.0	118 ± 6.7	175 ± 6.6	152 ± 12.2	144 ± 9.6	138 ± 6.0
	100	93 ± 1.5	120 ± 10.7	138 ± 4.6	141 ± 10.7	143 ± 2.6	155 ± 10.1
	333	90 ± 4.5	113 ± 9.3	142 ± 5.7	140 ± 13.9	141 ± 17.9	133 ± 5.0
	1,000	99 ± 5.9	113 ± 8.5	140 ± 5.1	135 ± 7.5	122 ± 6.6	125 ± 6.9
	3,333	100 ± 1.5	114 ± 6.0	144 ± 5.1	124 ± 0.7	137 ± 17.0	139 ± 10.8
	10,000	88 ± 1.5	106 ± 6.5	128 ± 1.5	135 ± 15.1	128 ± 10.7	130 ± 4.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		649 ± 11.3	706 ± 18.9	2,111 ± 25.3	1,560± 78.4	971 ± 3.1	1,618 ± 46.2
TA1535	0	6 ± 0.7	8 ± 1.2	9 ± 2.6	8 ± 1.0	9 ± 0.9	5 ± 1.9
	100	5 ± 0.7	5 ± 0.7	9 ± 0.3	9 ± 1.8	7 ± 0.3	5 ± 1.5
	333	6 ± 1.2	6 ± 0.9	5 ± 0.3	6 ± 1.2	7 ± 0.6	6 ± 0.9
	1,000	6 ± 1.3	6 ± 1.2	4 ± 1.2	5 ± 0.7	9 ± 0.0	8 ± 1.8
	3,333	4 ± 0.3	6 ± 0.6	5 ± 0.9	4 ± 0.6	6 ± 0.3	5 ± 0.6
	10,000	7 ± 0.9	7 ± 1.5	5 ± 0.9	6 ± 2.3	5 ± 0.3	5 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		393 ± 29.4	562 ± 47.9	94 ± 4.7	61 ±11.5	56 ± 6.1	115 ± 7.1
TA1537	0	7 ± 2.0	7 ± 2.0	9 ± 1.2	7 ± 1.5	9 ± 1.7	10 ± 1.2
	100	1 ± 0.3	2 ± 0.6	7 ± 1.8	7 ± 1.9	13 ± 0.7	11 ± 2.0
	333	3 ± 0.3	7 ± 2.0	8 ± 0.7	8 ± 1.7	10 ± 1.2	8 ± 1.7
	1,000	4 ± 0.9	4 ± 0.6	5 ± 0.3	8 ± 2.2	11 ± 2.5	11 ± 2.6
	3,333	4 ± 0.9	4 ± 0.3	6 ± 0.9	8 ± 2.2	9 ± 0.7	17 ± 7.0
	10,000	3 ± 0.5	—[d]	6 ± 1.2	9 ± 2.7	8 ± 1.0	7 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		232 ± 28.0	718 ± 17.5	43 ± 5.7	98 ± 9.4	49 ± 8.2	192 ± 5.5
TA98	0	17 ± 1.0	13 ± 2.1	17 ± 1.3	16 ± 3.5	16 ± 0.9	16 ± 0.9
	100	12 ± 1.7	10 ± 2.9	16 ± 1.8	12 ± 1.3	18 ± 0.7	15 ± 1.8
	333	13 ± 3.5	11 ± 1.0	20 ± 0.7	18 ± 2.0	20 ± 0.3	15 ± 2.4
	1,000	13 ± 2.0	9 ± 1.0	17 ± 0.3	14 ± 1.5	23 ± 2.7	18 ± 2.8
	3,333	17 ± 1.7	12 ± 1.3	18 ± 1.2	15 ± 2.7	14 ± 0.3	14 ± 2.6
	10,000	12 ± 0.3	11 ± 1.2	16 ± 1.2	15 ± 0.9	16 ± 2.0	14 ± 3.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		340 ± 18.2	244 ± 26.6	1,431 ± 31.3	1,808 ± 63.0	450 ± 26.0	1,153 ± 127.0

TABLE E1
Mutagenicity of Tetrahydrofuran in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at EG&G Mason Research Institute							
TA100	0	125 ± 4.9	142 ± 4.0	116 ± 15.4	145 ± 3.1	126 ± 12.8	146 ± 4.4
	100	137 ± 10.7	118 ± 5.0	131 ± 6.6	128 ± 7.7	123 ± 11.6	141 ± 3.2
	333	122 ± 0.0	120 ± 7.3	108 ± 8.8	131 ± 14.7	118 ± 7.3	125 ± 1.5
	1,000	134 ± 4.3	126 ± 2.9	117 ± 9.7	130 ± 6.0	125 ± 1.5	126 ± 4.8
	3,333	132 ± 4.6	135 ± 4.1	123 ± 0.9	124 ± 4.3	129 ± 10.9	124 ± 10.6
	10,000	132 ± 0.3	130 ± 7.5	109 ± 6.2	135 ± 2.9	119 ± 8.1	139 ± 11.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		2,217 ± 54.4	1,169 ± 29.8	1,518 ± 60.1	1,223 ± 96.9	1,028 ± 13.0	1,000 ± 71.9
TA1535	0	31 ± 1.8	39 ± 6.1	9 ± 0.3	14 ± 1.0	11 ± 2.7	12 ± 2.6
	100	41 ± 2.6	33 ± 4.3	13 ± 2.2	10 ± 0.9	8 ± 1.9	13 ± 3.2
	333	27 ± 1.3	32 ± 3.7	9 ± 1.2	10 ± 1.8	14 ± 1.8	10 ± 0.7
	1,000	37 ± 3.4	28 ± 0.9	9 ± 2.0	11 ± 2.0	13 ± 0.9	14 ± 3.1
	3,333	37 ± 1.0	33 ± 4.8	12 ± 1.2	12 ± 1.5	11 ± 0.7	9 ± 2.9
	10,000	34 ± 4.8	28 ± 1.9	9 ± 2.6	15 ± 4.7	10 ± 0.7	16 ± 1.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,599 ± 71.9	753 ± 14.8	76 ± 2.0	63 ± 1.3	55 ± 1.8	46 ± 2.4
TA1537	0	6 ± 0.9	7 ± 2.7	9 ± 1.2	7 ± 0.0	8 ± 0.3	8 ± 2.2
	100	6 ± 1.2	7 ± 1.8	6 ± 0.3	9 ± 2.2	9 ± 1.0	10 ± 1.2
	333	7 ± 1.2	13 ± 0.7	8 ± 1.2	9 ± 0.6	8 ± 2.1	7 ± 2.0
	1,000	6 ± 1.2	10 ± 0.3	10 ± 2.1	10 ± 1.8	9 ± 0.9	8 ± 0.6
	3,333	8 ± 3.5	7 ± 1.8	8 ± 1.0	10 ± 2.0	10 ± 2.6	7 ± 0.6
	10,000	5 ± 0.7	8 ± 0.7	10 ± 0.3	11 ± 0.3	7 ± 1.3	11 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		351 ± 9.7	274 ± 2.2	118 ± 6.2	122 ± 11.8	49 ± 0.7	66 ± 2.7
TA98	0	19 ± 2.6	14 ± 1.2	38 ± 6.1	35 ± 3.8	24 ± 0.6	28 ± 2.2
	100	15 ± 1.9	17 ± 2.4	26 ± 2.1	29 ± 5.7	25 ± 3.0	32 ± 4.3
	333	16 ± 2.3	26 ± 1.8	25 ± 1.5	29 ± 0.9	23 ± 2.4	26 ± 2.8
	1,000	19 ± 1.5	19 ± 2.2	31 ± 0.9	29 ± 4.9	29 ± 1.9	32 ± 5.4
	3,333	18 ± 2.3	17 ± 0.9	29 ± 1.5	34 ± 9.8	29 ± 2.9	29 ± 2.4
	10,000	18 ± 1.8	18 ± 1.2	28 ± 2.3	40 ± 3.0	29 ± 0.3	31 ± 3.1
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,860 ± 77.9	1,351 ± 14.4	1,247 ± 14.6	1,049 ± 27.7	654 ± 33.5	788 ± 62.6

[a] The detailed protocol and data are presented in Mortelmans *et al*. (1986).
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.
[d] Toxic

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

Compound	Dose (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Summary: Negative								
Distilled water		50	1,051	489	0.46	9.8	26.0	
Mitomycin-C	0.005	50	1,050	1,174	1.11	23.5	26.0	140.31*
Tetrahydrofuran	500	50	1,047	393	0.37	7.9	26.0	–19.33
	1,600	50	1,048	434	0.41	8.7	26.0	–10.99
	5,000	50	1,047	421	0.40	8.4	26.0	–13.58
					P=0.955[c]			
+S9								
Summary: Negative								
Distilled water		100	2,093	1,023	0.48	10.2	26.0	
Cyclophosphamide	1.0	100	2,086	1,492	0.71	14.9	26.0	46.33*
Tetrahydrofuran	500	50	1,050	506	0.48	10.1	26.0	–1.41
	1,600	50	1,047	519	0.49	10.4	26.0	1.42
	5,000	50	1,049	543	0.51	10.9	26.0	5.90
					P=0.149			

* Positive response (≥20% increase over solvent control)
[a] Study was performed at Columbia University. A detailed description of the protocol and these data are 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 relative SCEs/chromosome tested by the linear regression trend test versus log of the dose

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

-S9					+S9				
Dose (μg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)
Trial 1 — Harvest time: 14.0 hours Summary: Negative					**Trial 1** — Harvest time: 14.0 hours Summary: Negative				
Distilled water					Distilled water				
	100	7	0.07	7.0		100	8	0.08	8.0
Mitomycin-C					Cyclophosphamide				
0.15	50	23	0.46	30.0	15	100	28	0.28	23.0
Tetrahydrofuran					Tetrahydrofuran				
500	100	8	0.08	8.0	500	100	11	0.11	7.0
1,600	100	17	0.17	16.0	1,600	100	11	0.11	10.0
5,000	100	8	0.08	8.0	5,000	100	13	0.13	13.0
				P=0.201[b]					P=0.085
Trial 2 — Harvest time: 14.0 hours Summary: Negative					**Trial 2** — Harvest time: 14.0 hours Summary: Equivocal				
Distilled water					Distilled water				
	100	4	0.04	4.0		100	3	0.03	3.0
Mitomycin-C					Cyclophosphamide				
0.15	50	26	0.52	40.0	15	100	21	0.21	18.0
Tetrahydrofuran					Tetrahydrofuran				
3,000	100	7	0.07	7.0	1,000	100	4	0.04	4.0
4,000	100	9	0.09	7.0	2,000	100	6	0.06	6.0
5,000	100	9	0.09	6.0	3,000	100	12	0.12	12.0*
					4,000	100	8	0.08	7.0
					5,000	100	12	0.12	8.0
				P=0.281					P=0.016

* Positive ($P \leq 0.05$)
[a] Study was performed at Columbia University. A detailed description of the protocol and these data are presented in Galloway *et al*. (1987).
Abs=aberrations
[b] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

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

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Feed	10,000	2	0	1/2,680	0/2,591	3/2,373	4/7,644 (0.05%)
	0			5/2,385	1/2,275	0/2,118	6/6,778 (0.09%)
Injection	40,000	0	0	2/2,159	0/2,113	1/2,118	3/6,390 (0.05%)
	0			1/1,956	4/1,955	1/1,780	6/5,691 (0.11%)
Feed	125,000	9	75	0/288	0/4	0/80	0/372
	0			0/1,158	0/964	2/774	2/2,896 (0.07%)

[a] Study was performed at Bowling Green State University. A detailed description of the protocol and these data are presented in Valencia *et al.* (1985). Results were not significant for total number of lethal mutations/total number of X chromosomes tested by a normal approximation to the binomial test (Margolin *et al*., 1983).
[b] Total number of lethal mutations/total number of X chromosomes tested for three mating trials

TABLE E5
Induction of Sister Chromatid Exchanges in Mouse Bone Marrow Cells by Tetrahydrofuran[a]

Compound	Dose (mg/kg)	Mean SCEs/Cell
23-Hour Exposure		
Trial 1		
Mitomycin-C[b]	0.5	7.04 ± 0.505
Tetrahydrofuran	0[c]	3.79 ± 0.278
	500	3.91 ± 0.317
	1,000	3.67 ± 0.254
	2,000	6.27 ± 0.298*
		P<0.001[d]
Trial 2		
Mitomycin-C	0.5	10.48 ± 1.516
Tetrahydrofuran	0	5.70 ± 0.203
	1,500	6.02 ± 0.618
	2,000	5.62 ± 0.407
	2,500	—[e]
		P=0.476
42-Hour Exposure		
Acrylamide[b]	160	9.37 ± 0.293
Tetrahydrofuran	0	5.05 ± 0.910
	500	5.86 ± 0.750
	1,000	4.05 ± 0.222
	2,000	4.29 ± 0.209
		P=0.079

* Significantly different (P<0.008) from the controls
[a] Study was performed at Brookhaven National Laboratories. A detailed description of the protocol is presented in McFee *et al.* (1992). SCE=sister chromatid exchange. Data for mean SCEs/cell are given as mean ± standard error.
[b] Positive control
[c] Solvent control
[d] Significance tested by the one-tailed trend test (Margolin *et al.*, 1986); significant at P<0.025
[e] Lethal

TABLE E6
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Tetrahydrofuran[a]

Compound	Dose (mg/kg)	Abs/Cell[b]	Cells with Abs (%)
Trial 1 – Sample time: 17 hours			
Phosphate buffered saline[c]		1.6 ± 0.02	2.75
Tetrahydrofuran	500	1.6 ± 0.03	2.75
	1,000	1.3 ± 0.01	0.75
	2,000	2.3 ± 0.02	1.75
Mitomycin-C[d]	1.0	4.6 ± 0.06	6.00
			P=0.908[e]
Trial 2 – Sample time: 36 hours			
Phosphate buffered saline		0.8 ± 0.01	0.75
Tetrahydrofuran	500	1.3 ± 0.01	0.75
	1,000	1.1 ± 0.02	1.75
	2,000	0.9 ± 0.01	0.75
Mitomycin-C	1.0	6.5 ± 0.10	8.00
			P=0.433

[a] Study was performed at Brookhaven National Laboratory. A detailed description of the protocol is presented in McFee *et al.* (1992). Tetrahydrofuran was dissolved in phosphate buffered saline and administered by intraperitoneal injection. Abs=aberrations
[b] Mean ± standard error
[c] Solvent control
[d] Positive control. Dissolved in phosphate buffered saline and administered by intraperitoneal injection (volume = 0.4 mL)
[e] Significance tested by the one-tailed trend test (Margolin *et al.*, 1986); significant at $P < 0.025$

TABLE E7
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with Tetrahydrofuran by Inhalation for 14 Weeks[a]

Compound	Dose (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated Cells/1,000 Cells[b]	
			PCEs	NCEs
Male				
Chamber control		10	1.50 ± 0.29	1.18 ± 0.09
Tetrahydrofuran	600	10	1.69 ± 0.25	1.27 ± 0.10
	1,800	10	1.79 ± 0.22	1.58 ± 0.08*
	5,000	7	1.47 ± 0.27	1.41 ± 0.13
			P=0.297[c]	P=0.074[c]
Female				
Chamber control		10	1.85 ± 0.38	1.43 ± 0.18
Tetrahydrofuran	600	10	1.01 ± 0.24	1.16 ± 0.07
	1,800	10	1.34 ± 0.31	1.15 ± 0.07
	5,000	10	1.29 ± 0.19	1.18 ± 0.08
			P=0.627	P=0.846

* Significantly different (P=0.004) from the chamber controls
[a] Study was performed at the U.S. Department of Agriculture. A detailed description of the protocol is presented in MacGregor *et al.* (1990). PCE=polychromatic erythrocyte; NCE=normochromatic erythrocyte
[b] Mean ± standard error
[c] Significance of micronucleated cells/1,000 cells tested by the one-tailed trend test (Margolin *et al.*, 1986); significant at $P < 0.025$

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 14-Week Inhalation Study of Tetrahydrofuran[a]

	Chamber Control	66 ppm	200 ppm	600 ppm	1,800 ppm	5,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	361 ± 6	353 ± 7	368 ± 11	364 ± 6	372 ± 9	343 ± 7
Heart						
Absolute	0.959 ± 0.019	0.930 ± 0.020	0.949 ± 0.032	0.950 ± 0.016	0.982 ± 0.028	0.970 ± 0.019
Relative	2.66 ± 0.05	2.64 ± 0.03	2.58 ± 0.03	2.61 ± 0.03	2.64 ± 0.04	2.83 ± 0.04**
R. Kidney						
Absolute	1.124 ± 0.028	1.072 ± 0.030	1.169 ± 0.029	1.119 ± 0.026	1.186 ± 0.038	1.158 ± 0.030
Relative	3.11 ± 0.04	3.04 ± 0.04	3.18 ± 0.04	3.07 ± 0.04	3.19 ± 0.05	3.37 ± 0.05**
Liver						
Absolute	12.651 ± 0.651	11.499 ± 0.487	12.455 ± 0.405	12.401 ± 0.417	12.908 ± 0.384	12.797 ± 0.308
Relative	34.92 ± 1.34	32.53 ± 0.85	33.84 ± 0.29	34.04 ± 0.79	34.72 ± 0.45	37.28 ± 0.57*
Lung						
Absolute	1.862 ± 0.041	1.855 ± 0.067	1.926 ± 0.097	1.938 ± 0.067	1.951 ± 0.061	2.022 ± 0.075
Relative	5.15 ± 0.07	5.28 ± 0.23	5.24 ± 0.21	5.33 ± 0.17	5.26 ± 0.15	5.90 ± 0.23*
Spleen						
Absolute	0.689 ± 0.018	0.663 ± 0.017	0.724 ± 0.030	0.702 ± 0.015	0.695 ± 0.024	0.582 ± 0.019**
Relative	1.91 ± 0.04	1.88 ± 0.02	1.97 ± 0.05	1.93 ± 0.02	1.87 ± 0.06	1.69 ± 0.03**
Thymus						
Absolute	0.362 ± 0.015	0.353 ± 0.010	0.334 ± 0.009	0.345 ± 0.014	0.327 ± 0.015	0.279 ± 0.015**
Relative	1.00 ± 0.03	1.00 ± 0.03	0.92 ± 0.04	0.95 ± 0.04	0.88 ± 0.03*	0.81 ± 0.04**
Female						
Necropsy body wt	205 ± 5	207 ± 5	205 ± 4	210 ± 3	209 ± 4	214 ± 3
Heart						
Absolute	0.645 ± 0.020	0.613 ± 0.015	0.618 ± 0.013	0.641 ± 0.030	0.630 ± 0.012	0.685 ± 0.012
Relative	3.15 ± 0.09	2.96 ± 0.03	3.01 ± 0.04	3.04 ± 0.13	3.01 ± 0.04	3.21 ± 0.05
R. Kidney						
Absolute	0.716 ± 0.014	0.722 ± 0.017	0.713 ± 0.012	0.737 ± 0.022	0.729 ± 0.015	0.778 ± 0.016*
Relative	3.50 ± 0.07	3.49 ± 0.04	3.47 ± 0.04	3.50 ± 0.08	3.49 ± 0.08	3.64 ± 0.04
Liver						
Absolute	6.622 ± 0.133	6.426 ± 0.165	6.323 ± 0.189	6.625 ± 0.222	6.708 ± 0.191	7.776 ± 0.172**
Relative	32.36 ± 0.81	31.05 ± 0.69	30.76 ± 0.59	31.52 ± 1.08	32.02 ± 0.54	36.41 ± 0.87**
Lung						
Absolute	1.276 ± 0.043	1.275 ± 0.055	1.251 ± 0.032	1.326 ± 0.026	1.239 ± 0.035	1.379 ± 0.035
Relative	6.21 ± 0.16	6.15 ± 0.22	6.09 ± 0.11	6.32 ± 0.16	5.91 ± 0.10	6.47 ± 0.22
Spleen						
Absolute	0.460 ± 0.022	0.428 ± 0.015	0.408 ± 0.008	0.429 ± 0.018	0.439 ± 0.011	0.379 ± 0.014**
Relative	2.26 ± 0.14	2.07 ± 0.08	1.99 ± 0.04	2.04 ± 0.08	2.10 ± 0.04	1.77 ± 0.06**
Thymus						
Absolute	0.266 ± 0.010	0.262 ± 0.015	0.258 ± 0.010	0.248 ± 0.016	0.262 ± 0.010	0.212 ± 0.007**
Relative	1.29 ± 0.04	1.26 ± 0.06	1.26 ± 0.04	1.17 ± 0.06	1.25 ± 0.04	0.99 ± 0.03**

* Significantly different ($P \leq 0.05$) from the chamber 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 Mice in the 14-Week Inhalation Study of Tetrahydrofuran[a]

	Chamber Control	66 ppm	200 ppm	600 ppm	1,800 ppm	5,000 ppm
Male						
n	10	10	10	10	10	7
Necropsy body wt	36.7 ± 0.8	36.9 ± 0.4	35.8 ± 0.7	36.3 ± 0.7	36.6 ± 0.8	32.7 ± 1.0**
Heart						
Absolute	0.155 ± 0.006	0.162 ± 0.005	0.154 ± 0.004	0.160 ± 0.003	0.151 ± 0.004	0.141 ± 0.005
Relative	4.23 ± 0.14	4.40 ± 0.12	4.30 ± 0.06	4.43 ± 0.12	4.13 ± 0.12	4.33 ± 0.10
R. Kidney						
Absolute	0.313 ± 0.010	0.323 ± 0.010	0.310 ± 0.008	0.315 ± 0.006	0.306 ± 0.007	0.291 ± 0.014
Relative	8.55 ± 0.27	8.76 ± 0.24	8.65 ± 0.13	8.71 ± 0.19	8.39 ± 0.25	8.90 ± 0.30
Liver						
Absolute	1.613 ± 0.037	1.667 ± 0.022	1.695 ± 0.037	1.722 ± 0.031*	1.789 ± 0.035**	1.964 ± 0.060**
Relative	44.00 ± 0.57	45.24 ± 0.27	47.28 ± 0.37**	47.52 ± 0.60**	48.94 ± 0.81**	60.03 ± 0.33**
Lung						
Absolute	0.227 ± 0.005	0.235 ± 0.006	0.241 ± 0.006	0.238 ± 0.005	0.229 ± 0.006	0.213 ± 0.010
Relative	6.20 ± 0.10	6.38 ± 0.17	6.73 ± 0.14	6.57 ± 0.08	6.27 ± 0.18	6.51 ± 0.23
Spleen						
Absolute	0.069 ± 0.002	0.075 ± 0.002	0.071 ± 0.002	0.073 ± 0.002	0.070 ± 0.003	0.043 ± 0.003**
Relative	1.89 ± 0.06	2.04 ± 0.04	1.99 ± 0.07	2.02 ± 0.07	1.91 ± 0.04	1.31 ± 0.07**
Thymus						
Absolute	0.047 ± 0.003	0.045 ± 0.003	0.042 ± 0.002	0.039 ± 0.001*	0.036 ± 0.003**	0.027 ± 0.002**
Relative	1.27 ± 0.06	1.23 ± 0.08	1.17 ± 0.05	1.08 ± 0.05*	0.99 ± 0.07**	0.81 ± 0.05**
Female						
n	10	10	10	10	10	10
Necropsy body wt	32.4 ± 1.0	32.2 ± 0.6	33.3 ± 1.1	32.5 ± 0.7	33.1 ± 1.1	33.3 ± 1.1
Heart						
Absolute	0.140 ± 0.004	0.134 ± 0.003	0.134 ± 0.002	0.131 ± 0.004	0.139 ± 0.003	0.124 ± 0.003**
Relative	4.35 ± 0.14	4.18 ± 0.13	4.07 ± 0.16	4.04 ± 0.11	4.21 ± 0.08	3.75 ± 0.12**
R. Kidney						
Absolute	0.218 ± 0.007[b]	0.221 ± 0.005	0.216 ± 0.002	0.216 ± 0.006	0.220 ± 0.004	0.222 ± 0.006
Relative	6.74 ± 0.21[b]	6.88 ± 0.18	6.56 ± 0.24	6.66 ± 0.16	6.67 ± 0.15	6.69 ± 0.15
Liver						
Absolute	1.592 ± 0.036	1.574 ± 0.035	1.609 ± 0.034	1.551 ± 0.034	1.733 ± 0.045*	1.814 ± 0.074**
Relative	49.38 ± 0.94	48.95 ± 0.92	48.66 ± 1.30	47.79 ± 0.60	52.51 ± 1.22*	54.42 ± 0.96**
Lung						
Absolute	0.236 ± 0.007	0.228 ± 0.004	0.231 ± 0.007	0.228 ± 0.006	0.227 ± 0.005	0.211 ± 0.007*
Relative	7.31 ± 0.15	7.09 ± 0.14	6.96 ± 0.14	7.03 ± 0.14	6.89 ± 0.21	6.38 ± 0.26**
Spleen						
Absolute	0.109 ± 0.004	0.108 ± 0.004	0.103 ± 0.004	0.100 ± 0.003	0.103 ± 0.003	0.053 ± 0.004**
Relative	3.40 ± 0.15	3.36 ± 0.12	3.12 ± 0.14	3.09 ± 0.12	3.13 ± 0.12	1.58 ± 0.09**
Thymus						
Absolute	0.051 ± 0.003	0.055 ± 0.003	0.056 ± 0.002	0.053 ± 0.002	0.052 ± 0.003	0.046 ± 0.003
Relative	1.57 ± 0.09	1.71 ± 0.08	1.71 ± 0.10	1.64 ± 0.06	1.59 ± 0.11	1.36 ± 0.08

* Significantly different ($P \leq 0.05$) from the chamber 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

APPENDIX G
HEMATOLOGY AND
CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Tetrahydrofuran[a]

	Chamber Control	66 ppm	200 ppm	600 ppm	1,800 ppm	5,000 ppm
Male						
n	9	10	10	10	10	10
Hematology						
Hematocrit (%)	46.1 ± 0.3	45.9 ± 0.4	46.2 ± 0.3	46.0 ± 0.4	46.5 ± 0.3	49.2 ± 0.5**
Hemoglobin (g/dL)	15.3 ± 0.1	15.3 ± 0.1	15.4 ± 0.1	15.2 ± 0.1	15.5 ± 0.1	16.2 ± 0.2**
Erythrocytes ($10^6/\mu L$)	9.64 ± 0.07	9.64 ± 0.09	9.74 ± 0.08	9.60 ± 0.08	9.72 ± 0.08	9.93 ± 0.08
Reticulocytes ($10^6/\mu L$)	0.14 ± 0.02	0.17 ± 0.02	0.15 ± 0.01	0.13 ± 0.03	0.16 ± 0.02	0.13 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00*	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.9 ± 0.3	47.6 ± 0.2	47.3 ± 0.2	47.8 ± 0.1	48.0 ± 0.3	49.6 ± 0.2**
Mean cell hemoglobin (pg)	15.9 ± 0.1	15.9 ± 0.1	15.8 ± 0.1	15.8 ± 0.1	15.9 ± 0.1	16.3 ± 0.0**
Mean cell hemoglobin concentration (g/dL)	33.3 ± 0.1	33.3 ± 0.1	33.4 ± 0.1	33.0 ± 0.1	33.3 ± 0.1	32.9 ± 0.1
Platelets ($10^3/\mu L$)	487.9 ± 14.8	486.5 ± 15.5	490.6 ± 14.9	478.2 ± 17.8	469.1 ± 13.3	481.8 ± 12.1
Leukocytes ($10^3/\mu L$)	6.09 ± 0.40	5.74 ± 0.32	5.92 ± 0.34	6.33 ± 0.38	6.85 ± 0.43	5.77 ± 0.21
Segmented neutrophils ($10^3/\mu L$)	0.74 ± 0.04	0.85 ± 0.10	0.72 ± 0.06	0.82 ± 0.08	1.03 ± 0.14	1.31 ± 0.10**
Lymphocytes ($10^3/\mu L$)	5.04 ± 0.38	4.69 ± 0.27	4.82 ± 0.31	5.26 ± 0.31	5.60 ± 0.32	4.26 ± 0.20
Monocytes ($10^3/\mu L$)	0.27 ± 0.04	0.15 ± 0.02	0.30 ± 0.05	0.20 ± 0.03	0.19 ± 0.04	0.18 ± 0.04
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.05 ± 0.02	0.09 ± 0.03	0.04 ± 0.01	0.04 ± 0.02	0.03 ± 0.01
Clinical Chemistry						
Urea nitrogen (mg/dL)	20.7 ± 0.6	19.7 ± 0.4	21.7 ± 0.5	20.8 ± 0.6	20.7 ± 1.0	19.8 ± 0.5
Creatinine (mg/dL)	0.93 ± 0.05	0.86 ± 0.05	0.96 ± 0.04	0.88 ± 0.03	0.91 ± 0.04	0.84 ± 0.05
Total protein (g/dL)	7.6 ± 0.1	7.4 ± 0.1	7.6 ± 0.1	7.4 ± 0.1	7.6 ± 0.1	7.5 ± 0.1
Albumin (g/dL)	5.2 ± 0.1	5.1 ± 0.1	5.3 ± 0.1	5.1 ± 0.1	5.3 ± 0.0	5.2 ± 0.1
Alanine aminotransferase (IU/L)	54 ± 4	71 ± 7	65 ± 4	72 ± 7	54 ± 4	48 ± 3
Alkaline phosphatase (IU/L)	400 ± 20	383 ± 22	406 ± 13	395 ± 13	400 ± 18[b]	335 ± 10*
Creatine kinase (IU/L)	173 ± 23	129 ± 12	138 ± 19	212 ± 48	151 ± 35	118 ± 14[b]
Sorbitol dehydrogenase (IU/L)	16 ± 1	19 ± 3	16 ± 1	19 ± 1	15 ± 1	13 ± 1
Bile acids ($\mu mol/L$)	15.2 ± 2.2	13.0 ± 1.9	18.6 ± 3.7	14.6 ± 2.3	12.6 ± 2.2	25.7 ± 7.5[b]

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Tetrahydrofuran (continued)

	Chamber Control	66 ppm	200 ppm	600 ppm	1,800 ppm	5,000 ppm
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	46.8 ± 0.6	46.6 ± 0.3	46.0 ± 0.2	47.0 ± 0.6	46.5 ± 0.5	51.0 ± 0.3**
Hemoglobin (g/dL)	15.7 ± 0.2	15.6 ± 0.1	15.4 ± 0.1	15.7 ± 0.2	15.5 ± 0.2	16.8 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.29 ± 0.08	9.15 ± 0.05	9.06 ± 0.06	9.26 ± 0.12	9.17 ± 0.11	9.97 ± 0.08**
Reticulocytes ($10^6/\mu L$)	0.11 ± 0.01	0.11 ± 0.02	0.10 ± 0.01	0.10 ± 0.02	0.10 ± 0.01	0.13 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	50.3 ± 0.4	50.9 ± 0.2	50.7 ± 0.2	50.7 ± 0.2	50.5 ± 0.3	51.3 ± 0.2*
Mean cell hemoglobin (pg)	16.9 ± 0.1	17.0 ± 0.1	17.0 ± 0.0	16.9 ± 0.1	16.9 ± 0.1	16.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.2	33.4 ± 0.2	33.4 ± 0.1	33.3 ± 0.2	33.3 ± 0.2	33.0 ± 0.1
Platelets ($10^3/\mu L$)	512.2 ± 9.5	474.0 ± 17.2	524.5 ± 11.8	529.0 ± 52.0	531.4 ± 15.3	547.0 ± 8.8
Leukocytes ($10^3/\mu L$)	5.16 ± 0.41	5.39 ± 0.28	4.97 ± 0.33	5.76 ± 0.20	5.64 ± 0.42	5.07 ± 0.34
Segmented neutrophils ($10^3\mu L$)	0.84 ± 0.14	0.75 ± 0.11	0.64 ± 0.08	0.90 ± 0.13	1.27 ± 0.29	1.00 ± 0.08
Lymphocytes ($10^3/\mu L$)	4.07 ± 0.32	4.39 ± 0.27	4.07 ± 0.28	4.65 ± 0.23	4.16 ± 0.33	3.81 ± 0.29
Monocytes ($10^3/\mu L$)	0.20 ± 0.05	0.23 ± 0.02	0.21 ± 0.03	0.19 ± 0.03	0.17 ± 0.03	0.26 ± 0.04
Eosinophils ($10^3/\mu L$)	0.04 ± 0.01	0.02 ± 0.01	0.05 ± 0.02	0.02 ± 0.01	0.03 ± 0.01	0.01 ± 0.01
Clinical Chemistry						
Urea nitrogen (mg/dL)	23.5 ± 1.3	21.9 ± 0.9	23.2 ± 0.9	20.8 ± 1.0	22.0 ± 1.1	18.7 ± 0.9**
Creatinine (mg/dL)	0.98 ± 0.04	0.99 ± 0.04	0.93 ± 0.04	0.99 ± 0.04	0.96 ± 0.04	0.81 ± 0.04*
Total protein (g/dL)	7.6 ± 0.1	7.6 ± 0.2	7.7 ± 0.1	7.6 ± 0.1	7.5 ± 0.1	7.5 ± 0.1
Albumin (g/dL)	5.5 ± 0.1	5.5 ± 0.1	5.4 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	5.3 ± 0.1
Alanine aminotransferase (IU/L)	55 ± 6	57 ± 6	55 ± 3	46 ± 8	51 ± 6	41 ± 4
Alkaline phosphatase (IU/L)	332 ± 21	355 ± 17	344 ± 11	347 ± 30	301 ± 9	343 ± 13
Creatine kinase (IU/L)	132 ± 16	133 ± 19	115 ± 15	138 ± 24	145 ± 19	122 ± 13
Sorbitol dehydrogenase (IU/L)	17 ± 1	18 ± 2	16 ± 1	16 ± 2	16 ± 1	13 ± 1
Bile acids (μmol/L)	20.2 ± 3.6	19.7 ± 4.0	20.7 ± 2.3[b]	22.3 ± 5.6	18.9 ± 2.2	36.1 ± 4.4*

* Significantly different ($P \leq 0.05$) from the chamber 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=9

APPENDIX H
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF TETRAHYDROFURAN

Tetrahydrofuran was obtained from ChemCentral (Kansas City, MO) in four lots. Lot WK8-6-86 was used during the 14-week studies, and lots L-107, 012390, and B081690RS were used in the 2-year studies. Identity, purity, and stability analyses were conducted by the study laboratory and by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the tetrahydrofuran studies are on file at the National Institute of Environmental Health Sciences.

Lots WK8-6-86 and L-107, both clear, colorless liquids, were identified as tetrahydrofuran by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Lots 012390 and B081690RS, also clear, colorless liquids, were identified as tetrahydrofuran by infrared spectroscopy. All spectra were consistent with the literature spectra (Przybytez, 1980; *Aldrich*, 1974, 1981, 1985) of tetrahydrofuran. The infrared and nuclear magnetic resonance spectra of tetrahydrofuran are presented in Figures H1 and H2. The boiling point and density of lot L-107 were also consistent with literature references (*Merck Index*, 1989; Lide, 1992).

Initially, samples from two subbatches of lot WK8-6-86 were analyzed by gas chromatography to ensure that the subbatches were of equivalent purity. Gas chromatography was performed using a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used:

A) 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport glass column, with an oven temperature program of 40° C for 5 minutes, then 40° to 170° C at 10° C per minute, and

B) 80/100 Carbopack C/0.1% SP-1000 glass column, with an oven temperature program of 40° C for 5 minutes, then 40° to 220° C at 10° C per minute.

Results indicated that the purities of the two subbatches were identical within the limits of experimental error. The purities of lots WK8-6-86 and L-107 were determined by elemental analyses, Karl Fisher water analyses, and gas chromatography by systems A and B, as described above. The purity of lot 012390 was determined by gas chromatography using system A described above but with an isothermal oven temperature of 70° C. Peroxide concentrations were analyzed for each lot with commercially available test strips.

For lot WK8-6-86, elemental analysis for hydrogen was in agreement with the theoretical value for tetrahydrofuran, while the result for carbon was slightly low. Karl Fischer water analysis indicated less than or equal to 0.06% water. Both gas chromatography systems indicated one major peak and no impurities with areas greater than or equal to 0.1% relative to the major peak. Major peak comparisons of lot WK8-6-86 with lot C052981 (not used in the current studies) using system A indicated a purity of 100.3 $\pm$ 0.5% for lot WK8-6-86 relative to lot C052981. Lot WK8-6-86 contained less than 1.5 ppm peroxide and the overall purity was determined to be approximately 99%.

For lot L-107, elemental analysis for carbon was in agreement with the theoretical value for tetrahydrofuran, while the result for hydrogen was slightly low. Karl Fischer water analysis indicated less than 0.1% water. Both gas chromatography systems indicated one major peak and no impurities with areas greater than or equal to 0.1% relative to the major peak. Major peak comparisons of lot L-107 with lot C052981 using system A indicated a purity of 100.3 $\pm$ 0.3% for lot L-107 relative to lot C052981.

Lot L-107 contained less than 3 ppm peroxide and the overall purity was determined to be greater than 99%.

For lot 012390, only a major peak comparison with a previously analyzed lot of tetrahydrofuran (lot C052981, not used in the current studies) was performed. Lot 012390 contained no peroxide and results indicated a purity greater than 99%.

The purity of lot B081690RS was analyzed at the study laboratory by gas chromatography using a glass column packed with 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport. Results indicated a purity greater than 99% with no impurities greater than 0.1%.

Analysis for 2,6-di-*tert*-butyl-4-methylphenol (BHT), which is added to tetrahydrofuran as a stabilizer, was conducted by the analytical chemistry laboratory using gas chromatography with system A but with *p-tert*-butylphenol as the internal standard and with an isothermal oven temperature of 160° C. The content of BHT in lot WK8-6-86 was 0.032% ± 0.001%, lot L-107 contained 0.031% ± 0.001%, and lot 012390 contained 0.027% ± 0.000%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory. Gas chromatography was performed using system A. These studies indicated that tetrahydrofuran was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 25° C. To ensure stability, the bulk chemical was stored at room temperature in the original metal containers under a nitrogen blanket. Stability was monitored during the 14-week and 2-year studies using gas chromatography performed with system A. No degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

Diagrams of the tetrahydrofuran generation and delivery systems are shown in Figures H3 (14-week) and H4 (2-year). Tetrahydrofuran vapor was generated with a rotary evaporation system (Büchi Rotavapor, Model EL-131S, Büchi Laboratoriums Technik AG, Flavil, Switzerland). Tetrahydrofuran was pumped from the stainless steel bulk reservoir by a liquid micrometering pump into a rotating flask partially immersed in a bath of hot water (14-week studies) or hot oil (2-year studies). Tetrahydrofuran vapor passed from the flask into a chilled water condenser in which much of the vapor condensed and returned to the evaporator flask. Uncondensed vapor was carried to the top of the condenser column by a metered stream of nitrogen. Vapor temperature was monitored at the top of the condenser column by a temperature sensor. The saturation vapor pressure at the column exit temperature was calculated and used to determine the output (concentration of tetrahydrofuran and flow rate of saturated nitrogen) of the generator.

From the condensing column, the vapor entered a short distribution manifold from which individual delivery lines carried metered amounts of vapor to each exposure chamber. Flow to each chamber was regulated by vacuum pumps located at the chamber end of each delivery line. Within the generator cabinet, each delivery line was connected to the distribution manifold through a fine metering valve and flowmeter. Chamber concentration was adjusted by the metering valve and by adjustment of the pressure of compressed air to the vacuum pump.

A three-way valve, mounted in the line between the distribution manifold and each chamber, directed vapor to the exposure chamber exhaust until the generation system was stable. When equilibrium was reached, each valve was opened to allow the flow of vapor into the chamber. At each chamber location, the vapor was injected into the chamber inlet duct where it was further diluted with charcoal- and HEPA-filtered chamber air to achieve the desired exposure concentration.

Stainless-steel chambers designed at Battelle Northwest Laboratories were used for all studies (Hazleton 2000, Aberdeen, MD). The total volume for each chamber was 2.3 m^3; the active mixing volume of each chamber was 1.7 m^3. The chamber was designed so that uniform vapor concentrations could be maintained throughout the chamber when catch pans were in position. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that tetrahydrofuran vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

The chamber concentrations of tetrahydrofuran were monitored by an on-line gas chromatograph (Hewlett-Packard Model 5840, Hewlett-Packard, Palo Alto, CA) using a flame ionization detector and a 1% SP-1000 on 60/80 Carbopack B nickel column. Samples were drawn and analyzed from each exposure chamber, the control chamber, the exposure suite, an on-line standard, and a nitrogen blanket (14-week studies) or filtered air blank (2-year studies) approximately every 30 minutes using a 12-port sample valve.

The monitoring system was calibrated against gravimetrically prepared standards. The standards were related to the on-line monitor through quantitation analysis of grab samples collected from exposure chambers simultaneously sampled by an on-line gas chromatograph. The operation of the chamber monitor was checked throughout the day against an on-line standard (MG Industries Scientific Gases, Los Angeles, CA). The monitor calibration was verified by grab samples a minimum of once per month or when indicated by drift of 5% or greater in the measured value of the on-line standard; the grab samples were collected in bubblers containing dimethylformamide and analyzed by an off-line gas chromatograph. The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared tetrahydrofuran standards.

Summaries of the chamber concentrations during the studies are presented in Tables H1 and H2.

CHAMBER ATMOSPHERE CHARACTERIZATION

The times for the exposure concentrations to build up to 90% of the final exposure concentration (T_{90}) and to decay to 10% of the exposure concentration (T_{10}) were measured in all studies with and without animals present. At a chamber airflow rate of 15 air changes per hour, the theoretical value for both T_{90} and T_{10} is approximately 12.5 minutes; the T_{90} value chosen for all studies was 12 minutes. Actual T_{90} values ranged from 5 to 15 minutes in the 14-week studies, with and without animals in the chambers, and from 7 to 15 minutes without animals and from 8 to 18 minutes with animals in the 2-year studies. T_{10} values ranged from 7 to 10 minutes without animals and from 9 to 14 minutes with animals in the 14-week studies; in the 2-year studies, T_{10} values ranged from 9 to 13 minutes without animals and from 9 to 15 minutes with animals in the chambers.

The uniformity of tetrahydrofuran concentrations in the exposure chambers was measured before each study began, twice during the 14-week studies, and approximately every 3 months during the 2-year studies. The concentration was measured with and without animals present using the on-line gas chromatograph with the automatic 12-port sample valve disabled to allow continuous monitoring from a single input line. Uniformity of exposure concentrations in all chambers was acceptable.

The persistence of tetrahydrofuran in the 1,800 ppm exposure chamber, with and without animals present, after shutting off the system was monitored during the 2-year studies. The concentration of tetrahydrofuran in the exposure chamber fell to less than 1% of the beginning concentration within 30 minutes without animals present; with animals present, the time to decay to less than 1% of the initial concentration ranged

from 27 to 60 minutes. Tetrahydrofuran concentrations in the building exhaust and room air were also monitored during all studies.

Information supplied by the manufacturer indicated that all lots of tetrahydrofuran contained BHT as a stabilizer. BHT is less volatile than tetrahydrofuran and was expected to be depleted in the generated test atmosphere. BHT and peroxide concentrations were determined from samples collected from the generator reservoir for tetrahydrofuran stability analyses. BHT was analyzed with gas chromatography. Peroxide concentration in the generator flask was analyzed by iodometric titration with sodium thiosulfate to a colorimetric endpoint. Exposure chamber bubbler samples were tested for organic peroxides with a fluorescence detector (Perkin Elmer [14-week studies]; Hewlett Packard 1046A, Palo Alto, CA [2-year studies]) by the method of Kok *et al.*, (1986) using a tris(hydroxymethyl)aminomethane: *p*-hydroxyphenylacetic acid:horseradish peroxidase reagent. Samples were collected from the 66 and 5,000 ppm chambers, with and without animals present, during the 14-week studies and from the 200 and 1,800 ppm chambers and the control chambers, with animals present, during the 2-year studies. In the 14-week studies, generator flask samples contained 100 ppm BHT before exposures began; after 6 hours the content of BHT was 1,640 ppm; peroxide concentrations in the generator flask decreased from 14 ppm before exposure began to 11 ppm after 6 hours. No BHT or organic peroxides were observed in the exposure chambers in the 14-week studies. During the 2-year studies, the initial generator flask samples contained approximately 0.045% BHT; after 7 days, the generator flask content was approximately 0.381% BHT. Initial reservoir samples contained no peroxides; after 7 days, the reservoir samples had a peroxide content of approximately 12 ppm. For the generator flask samples, the initial peroxide content was approximately 3.1 ppm; after 7 days, the peroxide content was 3.7 ppm. These concentrations of peroxides were not considered significant. During the 2-year studies, no significant accumulation of peroxides was found.

During all studies, tetrahydrofuran was monitored for stability in the generator reservoir and exposure chambers by gas chromatography. Results indicated that tetrahydrofuran was stable in the generator reservoir. During the 2-year studies, grab samples were collected from the distribution line during the first and last hours of an exposure day and analyzed for tetrahydrofuran and BHT content by gas chromatography. Samples were also collected from the control, 200, and 1,800 ppm chambers and analyzed for volatile contaminants with gas chromatography-head space analysis. No contaminants or degradation products were found during the 14-week studies. No other contaminants or degradation products at concentrations greater than 0.3% were found in distribution lines or in 200 or 1,800 ppm exposure chamber samples during the 2-year studies. No enrichment of BHT was detected.

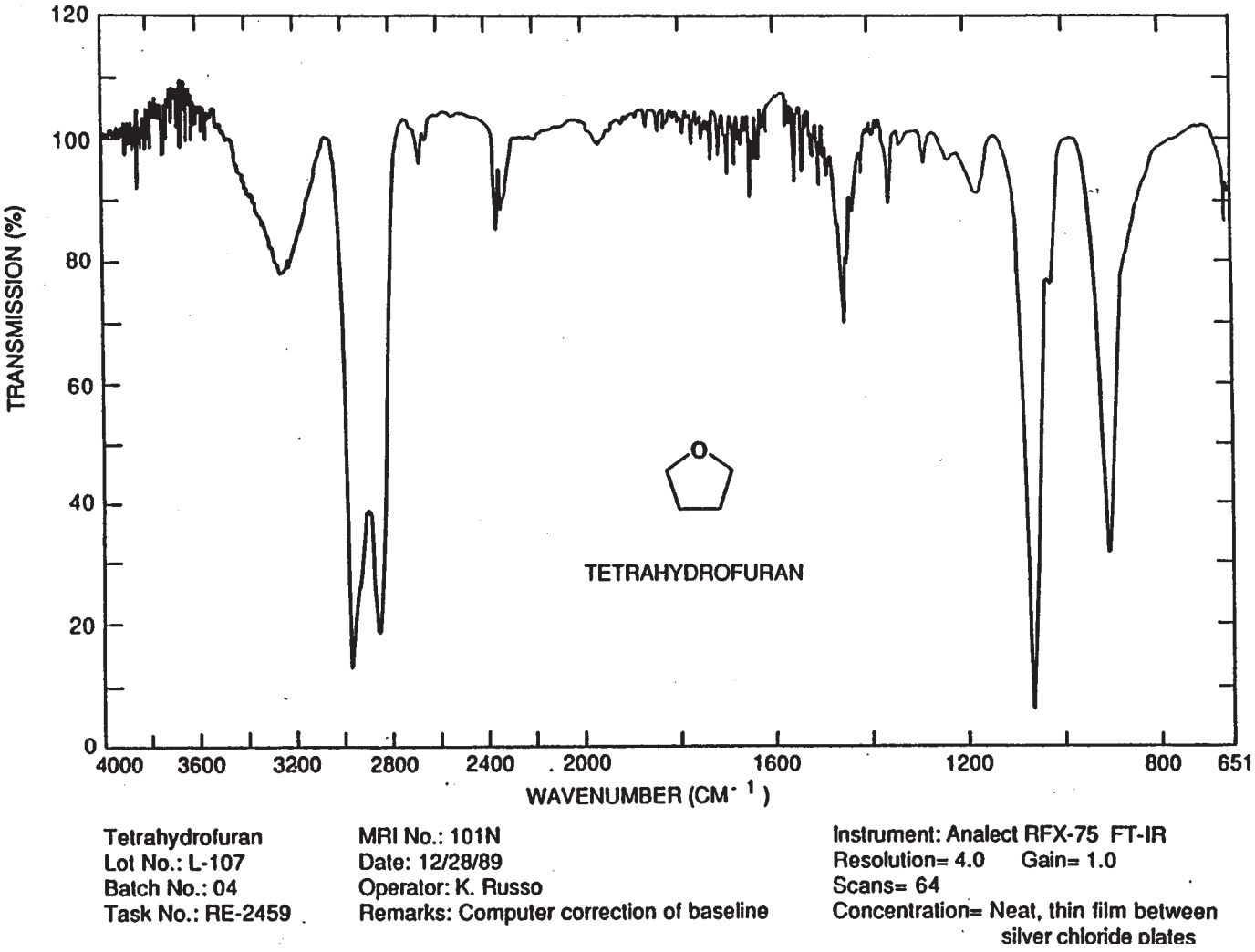

FIGURE H1
Infrared Absorption Spectrum of Tetrahydrofuran

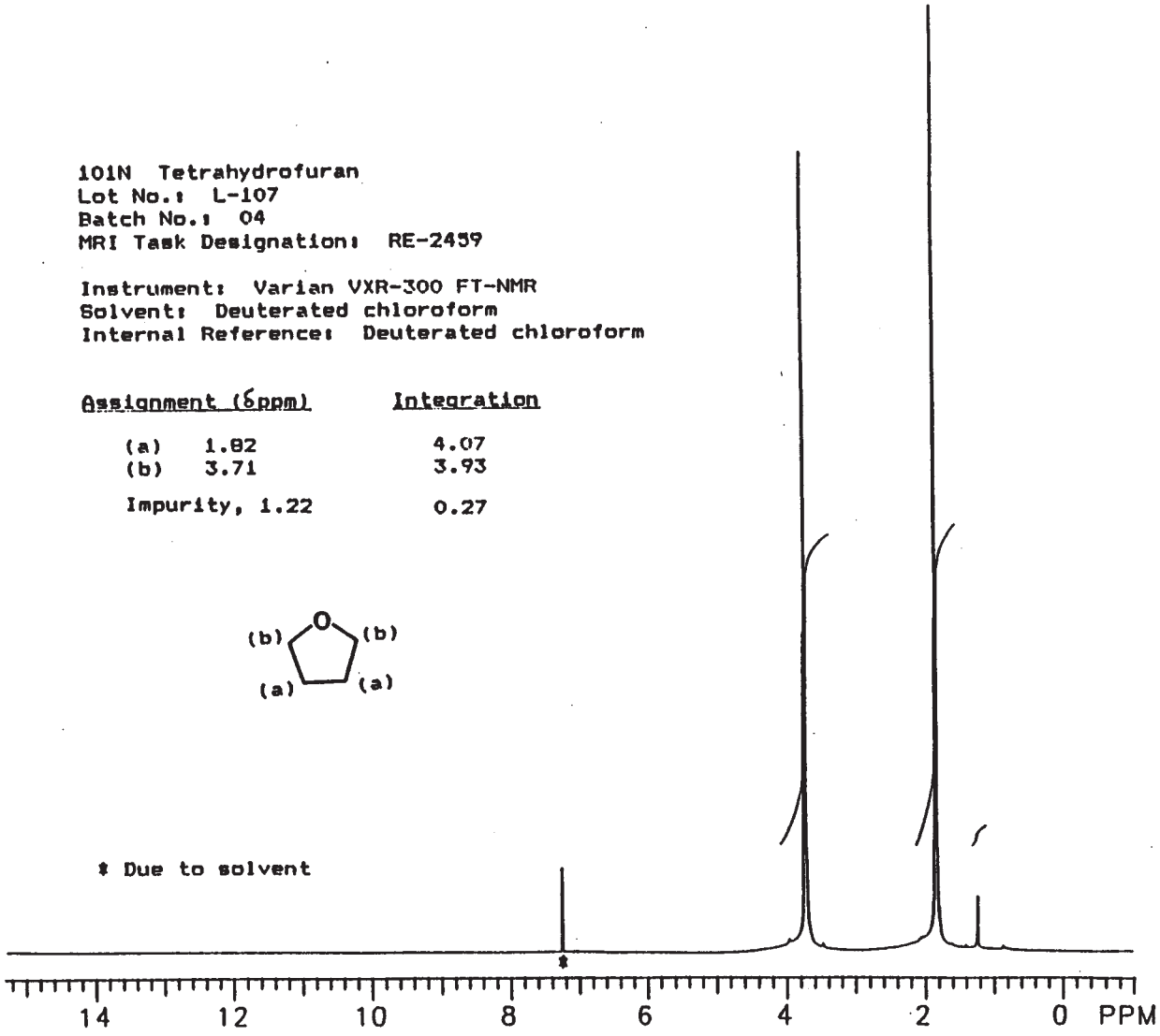

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Tetrahydrofuran

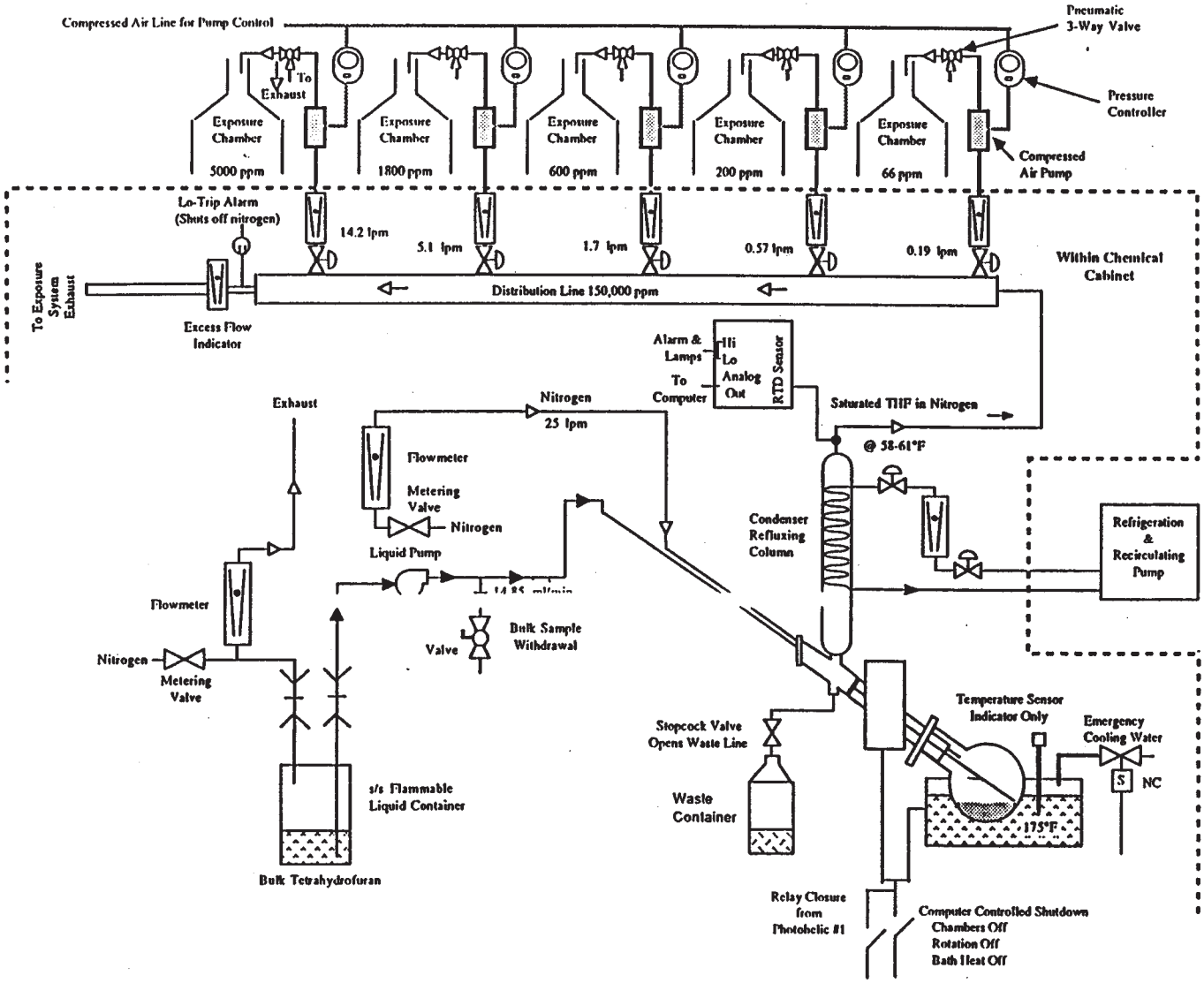

FIGURE H3
Tetrahydrofuran Vapor Generation and Delivery System for the 14-Week Studies

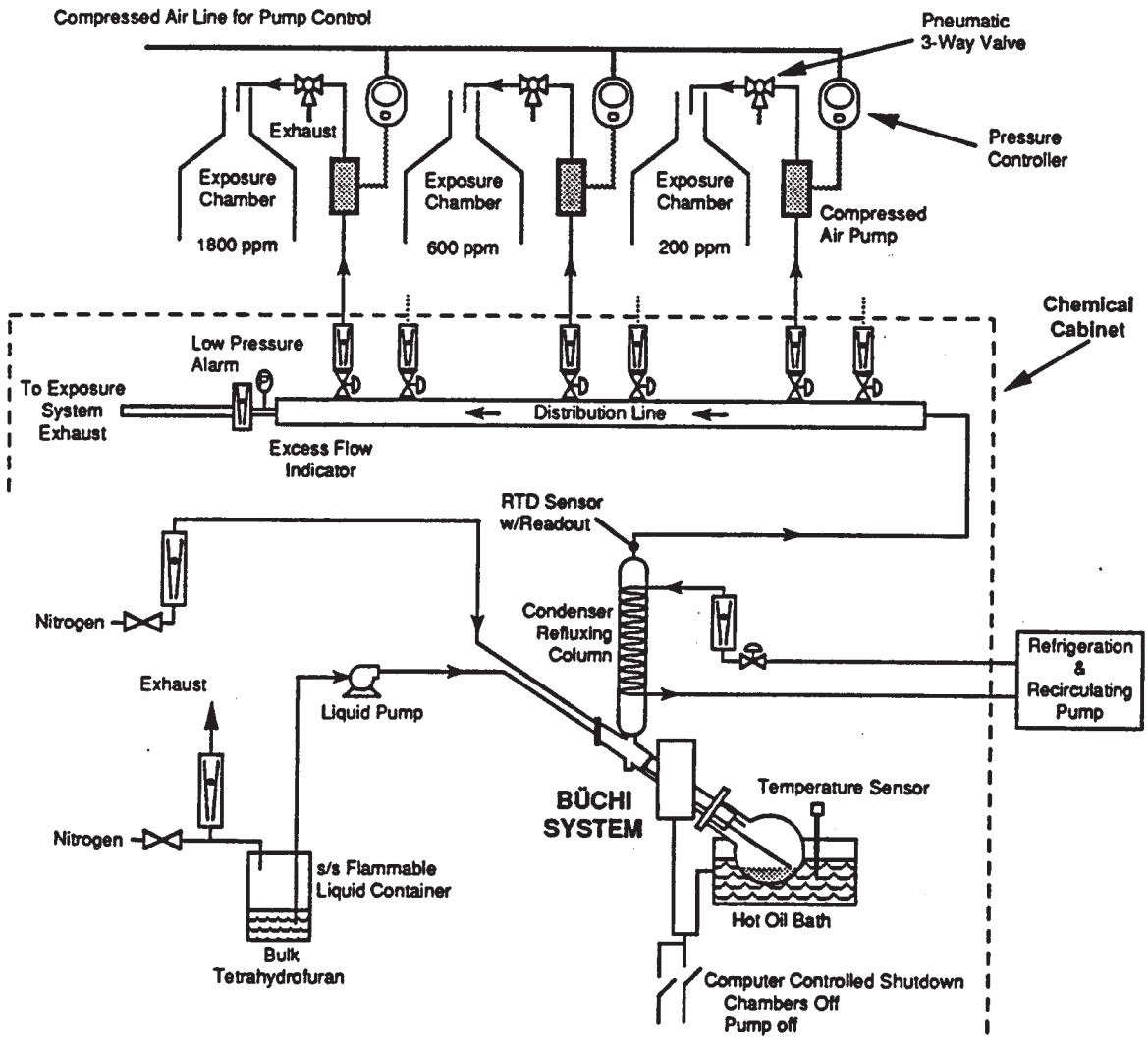

FIGURE H4
Tetrahydrofuran Vapor Generation and Delivery System for the 2-Year Studies

TABLE H1
Summary of Chamber Concentrations in the 14-Week Inhalation Studies of Tetrahydrofuran

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
66	817	66 ± 3
200	814	200 ± 9
600	810	600 ± 24
1,800	799	1,800 ± 74
5,000	785	4,970 ± 194
Mouse Chambers		
66	818	66 ± 3
200	815	200 ± 9
600	810	600 ± 24
1,800	799	1,800 ± 73
5,000	785	4,960 ± 193

[a] Mean ± standard deviation

TABLE H2
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Tetrahydrofuran

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
200	5,899	201 ± 10
600	5,606	599 ± 26
1,800	5,678	1,790 ± 74
Mouse Chambers		
200	5,791	199 ± 11
600	5,488	601 ± 26
1,800	5,622	1,790 ± 72

[a] Mean ± standard deviation

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

TABLE I1
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 I2
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 I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.38 ± 0.53	22.2 – 24.30	25
Crude fat (% by weight)	5.27 ± 0.14	5.00 – 5.60	25
Crude fiber (% by weight)	3.53 ± 0.41	2.60 – 4.30	25
Ash (% by weight)	6.39 ± 0.18	6.11 – 6.81	25
Amino Acids (% of total diet)			
Arginine	1.280 ± 0.083	1.110 – 1.390	11
Cystine	0.308 ± 0.071	0.181 – 0.400	11
Glycine	1.158 ± 0.048	1.060 – 1.220	11
Histidine	0.584 ± 0.027	0.531 – 0.630	11
Isoleucine	0.917 ± 0.033	0.867 – 0.965	11
Leucine	1.975 ± 0.051	1.850 – 2.040	11
Lysine	1.274 ± 0.049	1.200 – 1.370	11
Methionine	0.437 ± 0.109	0.306 – 0.699	11
Phenylalanine	0.999 ± 0.120	0.665 – 1.110	11
Threonine	0.904 ± 0.058	0.824 – 0.985	11
Tryptophan	0.218 ± 0.153	0.107 – 0.671	11
Tyrosine	0.685 ± 0.094	0.564 – 0.794	11
Valine	1.086 ± 0.055	0.962 – 1.170	11
Essential Fatty Acids (% of total diet)			
Linoleic	2.407 ± 0.227	1.830 – 2.570	10
Linolenic	0.259 ± 0.065	0.100 – 0.320	10
Vitamins			
Vitamin A (IU/kg)	6,531 ± 1,570	4,180 – 11,450	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	35.43 ± 8.98	22.5 – 48.90	11
Thiamine (ppm)	18.28 ± 1.51	15.0 – 21.0	25
Riboflavin (ppm)	7.83 ± 0.923	6.10 – 9.00	11
Niacin (ppm)	99.22 ± 24.27	65.0 – 150.0	11
Pantothenic acid (ppm)	30.55 ± 3.52	23.0 – 34.6	11
Pyridoxine (ppm)	9.11 ± 2.53	5.60 – 14.0	11
Folic acid (ppm)	2.46 ± 0.63	1.80 – 3.70	11
Biotin (ppm)	0.268 ± 0.047	0.190 – 0.354	11
Vitamin B_{12} (ppb)	40.5 ± 19.1	10.6 – 65.0	11
Choline (ppm)	2,991 ± 382	2,300 – 3,430	10
Minerals			
Calcium (%)	1.18 ± 0.10	1.00 – 1.49	25
Phosphorus (%)	0.93 ± 0.04	0.850 – 1.00	25
Potassium (%)	0.886 ± 0.063	0.772 – 0.971	9
Chloride (%)	0.529 ± 0.087	0.380 – 0.635	9
Sodium (%)	0.316 ± 0.033	0.258 – 0.371	11
Magnesium (%)	0.166 ± 0.010	0.148 – 0.181	11
Sulfur (%)	0.272 ± 0.059	0.208 – 0.420	10
Iron (ppm)	350.5 ± 87.3	255.0 – 523.0	11
Manganese (ppm)	92.48 ± 5.14	81.7 – 99.4	11
Zinc (ppm)	59.33 ± 10.2	46.1 – 81.6	11
Copper (ppm)	11.81 ± 2.50	8.09 – 15.4	11
Iodine (ppm)	3.54 ± 1.19	1.52 – 5.83	10
Chromium (ppm)	1.66 ± 0.46	0.85 – 2.09	11
Cobalt (ppm)	0.76 ± 0.23	0.49 – 1.15	7

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.36 ± 0.18	0.10 – 0.70	25
Cadmium (ppm)	0.10 ± 0.06	0.05 – 0.20	25
Lead (ppm)	0.29 ± 0.24	0.10 – 1.00	25
Mercury (ppm)[c]	0.02 ± 0.01	0.02 – 0.03	25
Selenium (ppm)	0.34 ± 0.12	0.05 – 0.60	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)[d]	12.85 ± 4.87	2.90 – 21.0	25
Nitrite nitrogen (ppm)[d]	0.22 ± 0.18	0.10 – 0.70	25
BHA (ppm)[e]	1.84 ± 1.95	1.00 –10.0	25
BHT (ppm)[e]	1.56 ± 1.58	1.0 – 8.00	25
Aerobic plate count (CFU/g)	67,888 ± 136,447	4,100 – 710,000	25
Coliform (MPN/g)	3 ± 0.2	3 – 4	25
Escherichia coli (MPN/g)	<3		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[f]	7.78 ± 2.52	4.80 – 16.50	25
N-Nitrosodimethylamine (ppb)[f]	5.85 ± 1.96	3.80 – 13.00	25
N-Nitrosopyrrolidine (ppb)[f]	1.92 ± 1.09	1.00 – 4.30	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.10		25
Estimated PCBs	<0.20		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.10		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.28 ± 0.26	0.05 – 1.00	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] CFU = colony forming units; MPN = most probable number; BHC = hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] All values except for the September 1991 milling date (0.03) were less than the detection limit. The detection limit is given as the mean.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX J
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 rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 14-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which the blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
14-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
2-Year Study	
ELISA	
Mycoplasma arthriditis	Study termination
Mycoplasma pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
PVM	Study termination
RCV/SDA	18 months and study termination
Hemagglutination Inhibition	
H-1	6, 12, and 18 months, study termination
KRV	6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE	
14-Week Study	
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis 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
Hemagglutination Inhibition	
K (papovavirus)	Study termination
Polyoma virus	Study termination
2-Year Study	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	12 months and study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus	6 months
Mouse adenoma virus-FL	12 and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
EDIM	6 and 18 months
GDVII	12 months
MVM	6 months
Mouse adenoma virus-FL	12 months
Reovirus 3	12 months
Hemagglutination Inhibition	
K	6, 12, and 18 months, study termination
MVM	12 and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table J1.

TABLE J1
Murine Virus Antibody Determinations for Rats and Mice in the 14-Week and 2-Year Studies of Tetrahydrofuran

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
14-Week Studies		
Rats		
Study termination	0/10	None positive
Mice		
Study termination	0/10	None positive
2-Year Studies		
Rats		
6 Months	0/10	None positive
12 Months	0/10	None positive
18 Months	0/10	None positive
Study termination	4/10	*M. arthritidis*[a]
Mice		
6 Months	0/10	None positive
12 Months	1/10	Reovirus 3
18 Months	0/9	None positive
Study termination	0/10	None positive

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been 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. athritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.