NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF TETRAFLUOROETHYLENE

(CAS NO. 116-14-3)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

April 1997

NTP TR 450

NIH Publication No. 97-3366

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.

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

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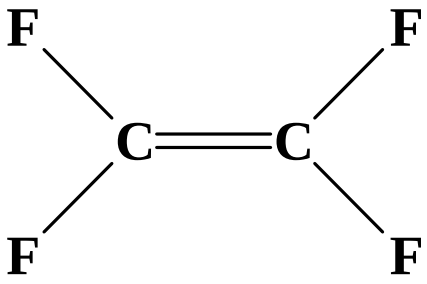
CONTENTS

ABSTRACT



TETRAFLUOROETHYLENE

CAS No. 116-14-3

Chemical Formula: C_2F_4 Molecular Weight: 100.02

Synonyms: Perfluoroethylene; tetrafluoroethene; 1,1,2,2-tetrafluoroethylene; TFE

Tetrafluoroethylene is used in the production of polytetrafluoroethylene (Teflon®) and other polymers. Tetrafluoroethylene was nominated by the National Cancer Institute for toxicity and carcinogenicity studies based on the potential for human exposure to the chemical due to the large production volume and on the lack of adequate data for tetrafluoroethylene in the literature. Male and female F344/N rats and B6C3F$_1$ mice were exposed to tetrafluoro ethylene (98% to 99% pure) by whole body inhalation exposure for 16 days, 13 weeks, or 2 years. Genetic toxicity studies were conducted in mouse peripheral blood erythrocytes.

16-DAY STUDY IN RATS

Groups of five male and five female F344/N rats were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week for a total of 12 exposures during a 16-day period. All rats survived to the end of the study. The final mean body weights and body weight gains of males and females exposed to 5,000 ppm were significantly less than those of the controls. The mean body weight gain of females exposed to 2,500 ppm was also significantly less than that of the controls. There were no exposure-related clinical findings in male or female rats. There were no significant differences in hematology parameters that were considered to be related to tetrafluoroethylene exposure. Absolute and relative kidney weights of all exposed groups of males were significantly greater than those of the controls, as were those of females in the 2,500 and 5,000 ppm groups. The absolute kidney weight of females exposed to 1,250 ppm was also significantly greater than that of the controls. The relative liver weights of all exposed groups of males and the absolute liver weights of males in the 625 and 2,500 ppm groups were significantly greater than those of the controls. Increased incidences of renal tubule degeneration occurred in males and females exposed to 625 ppm or greater; this lesion was located predominantly at the corticomedullary junction. The severity of degeneration increased with increasing exposure concentration and was slightly greater in males than females.

16-DAY STUDY IN MICE

Groups of five male and five female B6C3F$_1$ mice were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week for a total of 12 exposures during a 16-day period. All mice survived to the end of the study. Final mean body weights and body weight gains of all exposed groups of mice were similar to those of the controls. There were no exposure-related clinical findings in male or female mice. There were no significant differences in

hematology parameters that were considered to be related to tetrafluoroethylene exposure. The absolute and relative liver weights of females exposed to 5,000 ppm were significantly greater than those of the controls, as was the absolute kidney weight of females in that group and the absolute liver weight of females in the 2,500 ppm group. Renal tubule karyomegaly was observed in male and female mice in the 1,250, 2,500, and 5,000 ppm groups, and the severity of this lesion increased with increasing exposure concentration. Karyomegaly was located predominantly in the inner renal cortex.

13-WEEK STUDY IN RATS

Groups of 10 male and 9 or 10 female F344/N rats were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 13 weeks. All rats survived to the end of the study. The final mean body weight and body weight gain of males exposed to 5,000 ppm were significantly less than those of the controls, as was the mean body weight gain of females in this exposure group. There were no clinical findings attributed to exposure to tetrafluoroethylene. Exposure of rats to tetrafluoroethylene resulted in a concentration-dependent normocytic, normochromic, nonresponsive anemia consistent with a secondary hypoproliferative anemia. An exposure concentration-dependent proteinuria also occurred, consistent with renal tubule degeneration observed histopathologically. The absolute and relative liver weights of all exposed groups of males and of females in the 5,000 ppm group were significantly greater than those of the controls. The absolute and relative right kidney weights of males and females exposed to 1,250 ppm or greater and of females in the 625 ppm group were also significantly greater than those of the controls. There were no differences in sperm morphology or vaginal cytology parameters between control and exposed groups of rats. Incidences of renal tubule degeneration in males exposed to 625 ppm or greater and in females exposed to 2,500 or 5,000 ppm were significantly greater than those in the controls. Renal lesions were similar to those observed in the 16-day study and were located predominantly at the corticomedullary junction.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 13 weeks. All mice survived to the end of the study. Final mean body weights and body weight gains of all exposed groups of male and female mice were generally similar to those of the controls. There were no clinical findings that were considered to be related to tetrafluoroethylene exposure. Exposure of mice to tetrafluoroethylene resulted in a concentration-dependent normocytic, normochromic, nonresponsive anemia, consistent with a secondary hypoproliferative anemia, and in polyuria. Differences in sperm morphology parameters and estrous cycle lengths were not considered to be exposure related. Incidences of karyomegaly of the renal tubule epithelial cells in male and female mice exposed to 1,250 ppm or greater were significantly greater than those in the controls. Karyomegaly was similar to that observed in the 16-day study and was observed primarily in the inner renal cortex.

2-YEAR STUDY IN RATS

Groups of 60 male rats were exposed to 156, 312, or 625 ppm and groups of 60 female rats were exposed to 312, 625, or 1,250 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 104 weeks, with an observation period of 11 days following the final exposure. Ten male and ten female rats from each exposure group were evaluated at 15 months for organ weights and clinical pathology.

Survival, Body Weights, and Clinical Findings

Survival rates of males in the 625 ppm group and of all exposed groups of females were significantly less than those of the controls. Mean body weights of males exposed to 625 ppm were lower than those of the controls from week 81 until the end of the study, and the mean body weight of 1,250 ppm females was slightly lower than that of the controls at the end of the study. The only clinical finding associated with exposure to tetrafluoroethylene was opacity of the eyes in exposed groups of female rats; this change was observed microscopically as cataracts.

Hematology, Clinical Chemistry, and Urinalysis

At the 15-month interim evaluation, there were no differences in hematology, clinical chemistry, or urinalysis parameters that were considered to be related to tetrafluoroethylene exposure.

Pathology Findings

The absolute and relative kidney weights of males exposed to 625 ppm and females exposed to 1,250 ppm and the absolute kidney weight of females exposed to 625 ppm were significantly greater than those of the controls at the 15-month interim evaluation. At 15 months, renal tubule hyperplasia was observed in one male exposed to 312 ppm and one male and one female exposed to 625 ppm; oncocytic hyperplasia was observed in one female exposed to 1,250 ppm. At the end of the study, incidences of renal tubule adenoma were greater in males and females exposed to 312 ppm or greater than those in the controls. This exposure-related increase was confirmed by examination of step sections (extended evaluations). At the end of the study, the incidences of renal tubule hyperplasia in males exposed to 625 ppm and females exposed to 1,250 ppm were significantly greater than those in the controls. The incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in the extended evaluations and in the standard and extended evaluations (combined) in the 1,250 ppm female group and the 625 ppm male group were significantly greater than those in the controls, and the incidences occurred with significant positive trends. Oncocytic hyperplasia was observed at the end of the study in one male exposed to 312 ppm and in three females exposed to 1,250 ppm. At 15 months and at the end of the study, the incidences of renal tubule degeneration in all exposed groups of males and in females in the 625 and 1,250 ppm groups were greater than those in the controls. Renal tubule degeneration was similar to that observed in the 13-week study and was located predominantly at the corticomedullary junction. The severity of nephropathy generally increased with increasing exposure concentration in male rats at 15 months and 2 years.

The absolute and relative liver weights of females in the 1,250 ppm group and the absolute liver weight of females exposed to 625 ppm were significantly greater than those of the controls at the 15-month interim evaluation. At 2 years, the incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in males exposed to 312 ppm, the incidences of hepatocellular adenoma and adenoma or carcinoma (combined) in females in all exposed groups, and the incidences of hepatocellular carcinoma in females exposed to 312 or 625 ppm were significantly greater than those in the controls. Also at 2 years, the incidence of hemangiosarcoma in females exposed to 625 ppm was significantly greater than that in the controls. In all exposed groups of males, the incidences of clear cell foci at 15 months were greater than those in the controls; at 2 years, the incidences of eosinophilic foci in all exposed groups of males and the incidences of basophilic and mixed cell foci in males in the 312 and 625 ppm groups were greater than those in the controls. The incidences of mixed cell foci at 15 months in females exposed to 625 or 1,250 ppm and at 2 years in females exposed to 1,250 ppm were also significantly greater than those in the controls. At the end of the 2-year study, increased incidences of cystic degeneration occurred in the liver of all exposed groups of males, and increased incidences of hepatic angiectasis were observed in exposed groups of females.

Incidences of mononuclear cell leukemia in males exposed to 156 ppm and in all exposed groups of females were significantly greater than those in the controls.

Incidences of cataracts in females exposed to 1,250 ppm were greater than those in the controls at the end of the 2-year study.

At the end of the study, there were slight increases in the incidences of testicular interstitial cell adenoma in rats exposed to 312 or 625 ppm.

2-YEAR STUDY IN MICE

Groups of 58 male and 58 female B6C3F$_1$ mice were exposed to 0, 312, 625, or 1,250 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 95 to 96 weeks. Ten male and ten female mice from each exposure group were evaluated at 15 months for organ weights.

Survival, Body Weights, and Clinical Findings

The survival rates of all exposed groups of males and females were significantly less than those of the controls. Because of the reduced survival due to exposure-related liver neoplasms, the study was terminated during week 96. Mean body weights of exposed groups of males and females were generally similar to those of the controls, except at the end of the study, when they were somewhat less than those of the controls. There were no clinical findings related to tetrafluoroethylene exposure.

Pathology Findings

At the 15-month interim evaluation, there were no differences in absolute or relative kidney, liver, or lung weights between exposed and control groups of mice. At the end of the study, the incidences of multifocal coagulative necrosis of the liver were increased in males in the 625 and 1,250 ppm groups. Also at the end of the study, females in all exposed groups had greater incidences of hematopoietic cell proliferation in the liver than the controls. Angiectasis occurred in all exposed groups of males and females at 15 months and at the end of the study. At the 15-month interim evaluation, hemangiosarcomas were observed in three males exposed to 1,250 ppm and in one female exposed to 312 ppm. The incidences of hemangiosarcoma in all exposed groups of males and females at the end of the study were significantly greater than those in the controls and exceeded the historical chamber control ranges. Also at the end of the study, the incidences of hemangioma in males and females exposed to 312 ppm and in males exposed to 625 ppm were also significantly greater than those in the controls and exceeded the range in historical chamber controls. At 15 months, hepatocellular adenomas and carcinomas occurred in control males and all exposed groups of males and females. Females exposed to 625 or 1,250 ppm had significantly greater incidences of eosinophilic foci than the controls at the 15-month interim evaluation. At the end of the study, the incidences of eosinophilic foci in males exposed to 625 or 1,250 ppm and in females exposed to 312 or 625 ppm were significantly greater than those in the controls. In male and female mice, increased incidences of a variety of hepatocellular neoplasms, including adenomas, multiple adenomas, carcinomas, and multiple carcinomas, were considered related to tetrafluoroethylene exposure.

At the end of the study, the incidences of histiocytic sarcoma (all organs) in all exposed groups of males and females were significantly greater than those in the controls and exceeded the historical control ranges for all organs. The greatest incidences of histiocytic sarcomas were observed in the liver and lung, but these neoplasms were also observed in the spleen, lymph nodes, bone marrow, and kidney.

Significantly increased incidences of renal tubule dilatation (males) and karyomegaly (males and females), located predominantly in the inner cortex, were observed in mice exposed to 625 or 1,250 ppm at 15 months. At the end of the study, the increased incidences of dilatation and karyomegaly in all exposed groups of males and of karyomegaly in 1,250 ppm females were generally significant.

Incidences of hematopoietic cell proliferation in the spleen of all exposed groups of males and females were significantly greater than those in the controls at the end of the study. Additionally, the severity of this lesion increased with increasing exposure concentration.

GENETIC TOXICOLOGY

No increases in the frequency of micronucleated erythrocytes were observed in peripheral blood samples obtained from male and female mice at the end of the 13-week inhalation study of tetrafluoroethylene.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of tetrafluoroethylene in male F344/N rats based on increased incidences of renal tubule neoplasms (mainly adenomas) and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* of tetrafluoroethylene in female F344/N rats based on increased incidences of renal tubule neoplasms, liver hemangiosarcomas, hepatocellular neoplasms, and mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of tetrafluoroethylene in male and female B6C3F$_1$ mice based on increased incidences of liver hemangiomas and hemangiosarcomas, hepatocellular neoplasms, and histiocytic sarcomas.

Slight increases in the incidences of mononuclear cell leukemia and testicular interstitial cell adenomas in male rats may have been related to exposure to tetrafluoroethylene.

Exposure of rats to tetrafluoroethylene resulted in increased incidences of renal tubule hyperplasia and degeneration in males and females, increased severity of kidney nephropathy in males, and increased incidences of liver angiectasis and cataracts in females. Exposure of mice to tetrafluoroethylene resulted in increased incidences of hematopoietic cell proliferation of the liver in females, liver angiectasis in males and females, renal tubule dilatation in males, renal tubule karyomegaly in males and females, and splenic hematopoietic cell proliferation in males and females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure Concentrations	0, 156, 312, or 625 ppm	0, 312, 625, or 1,250 ppm	0, 312, 625, or 1,250 ppm	0, 312, 625, or 1,250 ppm
Body Weights	625 ppm group lower than controls	1,250 ppm group slightly lower than controls at end of study	Exposed groups lower than controls at end of study	Exposed groups lower than controls at end of study
Survival Rates	17/50, 12/50, 17/50, 1/50 (2 years)	28/50, 16/50, 15/50, 18/50 (2 years)	38/48, 11/48, 2/48, 1/48 (22 months)	36/48, 4/48, 6/48, 4/48 (22 months)
Nonneoplastic Effects	Kidney (renal tubule): hyperplasia (single sections - 1/50, 1/50, 1/50, 6/50; single and step sections - 7/50, 11/50, 7/50, 24/50); degeneration (2/50, 20/50, 50/50, 49/50); severity of nephropathy (2.3, 1.9, 2.7, 3.5)	Kidney (renal tubule): hyperplasia (single sections - 1/50, 3/50, 6/50, 12/50; single and step sections - 3/50, 6/50, 11/50, 25/50); degeneration (0/50, 0/50, 35/50, 46/50) Liver: angiectasis (0/50, 9/50, 9/50, 14/50) Eye: cataracts (15/50, 4/50, 10/50, 45/50)	Liver: angiectasis (0/48, 6/48, 10/48, 13/48) Kidney (renal tubule): dilatation (0/48, 4/48, 16/48, 36/48); karyomegaly (1/48, 2/48, 10/48, 28/48) Spleen: hematopoietic cell proliferation (14/48, 32/48, 41/46, 42/46)	Liver: hematopoietic cell proliferation (3/48, 19/48, 13/47, 15/47); angiectasis (1/48, 9/48, 6/47, 4/47) Kidney (renal tubule): karyomegaly (0/48, 0/48, 0/47, 38/48) Spleen: hematopoietic cell proliferation (18/48, 39/48, 41/46, 41/47)

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic Effects	Kidney (renal tubule): adenoma (single sections - 0/50, 0/50, 6/50, 3/50; single and step sections - 2/50, 4/50, 9/50, 13/50); carcinoma (single sections - 1/50, 0/50, 2/50, 0/50; single and step sections - 1/50, 1/50, 2/50, 0/50); adenoma or carcinoma (single sections - 1/50, 0/50, 6/50, 3/50; single and step sections - 3/50, 5/50, 9/50, 13/50) Liver: hepatocellular carcinoma (1/50, 1/50, 10/50, 3/50); hepatocellular adenoma or carcinoma (4/50, 7/50, 15/50, 8/50)	Kidney (renal tubule): adenoma (single sections - 0/50, 3/50, 1/50, 3/50; single and step sections - 0/50, 3/50, 3/50, 8/50); carcinoma (single sections - 0/50, 0/50, 0/50, 2/50; single and step sections - 0/50, 0/50, 0/50, 3/50); adenoma or carcinoma (single sections - 0/50, 3/50, 1/50, 5/50; single and step sections - 0/50, 3/50, 3/50, 10/50) Liver: hemangiosarcoma (0/50, 0/50, 5/50, 1/50); hepatocellular adenoma (0/50, 4/50, 5/50, 6/50); hepatocellular carcinoma (0/50, 4/50, 9/50, 2/50); hepatocellular adenoma or carcinoma (0/50, 7/50, 12/50, 8/50) Mononuclear cell leukemia: (16/50, 31/50, 23/50, 36/50)	Liver: hemangioma (0/48, 10/48, 5/48, 2/48); hemangiosarcoma (0/48, 21/48, 27/48, 37/48); hemangioma or hemangiosarcoma (0/48, 26/48, 30/48, 38/48); hepatocellular carcinoma (11/48, 20/48, 33/48, 26/48); hepatocellular adenoma or carcinoma (26/48, 34/48, 39/48, 35/48) Hematopoietic system (all organs): histiocytic sarcoma (0/48, 12/48, 7/48, 7/48)	Liver: hemangioma (0/48, 5/48, 2/47, 1/47); hemangiosarcoma (0/48, 27/48, 27/47, 34/47); hemangioma or hemangiosarcoma (0/48, 31/48, 28/47, 35/47); hepatocellular carcinoma (4/48, 28/48, 22/47, 20/47); hepatocellular adenoma or carcinoma (17/48, 33/48, 29/47, 28/47) Hematopoietic system (all organs): histiocytic sarcoma (1/48, 21/48, 19/47, 18/48)
Uncertain Findings	Mononuclear cell leukemia: (34/50, 43/50, 38/50, 31/50) Testis: interstitial cell adenoma (39/50, 40/50, 48/50, 47/50)	None	None	None
Level of Evidence of Carcinogenic Activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic Toxicology				
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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 tetrafluoroethylene on December 5, 1995, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

Arnold L. Brown, M.D., Chairperson
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Madison, WI

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St. Mary's Hospital and Medical Center
Cancer Research Institute
Grand Junction, CO

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

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* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 5 December 1995, the draft Technical Report on the toxicology and carcinogenesis studies of tetrafluoroethylene 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. J.H. Roycroft, NIEHS, introduced the toxicology and carcinogenesis studies of tetrafluoroethylene by describing the uses of the chemical, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in male and female rats and mice. Dr. R.C. Sills, NIEHS, presented data from ongoing molecular biology studies characterizing the H-*ras* codon 61 mutation spectra in hepatocellular neoplasms from control $B6C3F_1$ mice and mice exposed to tetrafluoroethylene for 2 years. Data were also presented comparing the mutation profiles of hepatocellular neoplasms from the current study with those from the NTP study of tetrachloroethylene. The proposed conclusions for the 2-year studies were *clear evidence of carcinogenic activity* in male and female F344/N rats and male and female $B6C3F_1$ mice.

Dr. Ryan, a principal reviewer, agreed with the proposed conclusions. She inquired as to whether short-burst, high exposures had been considered in the study design as being more similar to a typical occupational exposure. Dr. Roycroft replied that this regimen had not been considered; the 6-hour-per-day, 5-day-per-week design used was similar to continuous exposure in a workplace situation. Dr. Ryan asked whether there was information on the degree of human exposure encountered through spills or leaks. Dr. Roycroft noted that tetrafluoroethylene is produced and maintained in closed-capture systems, no occupational exposure limits have been established, and no information on spills or leaks has been found.

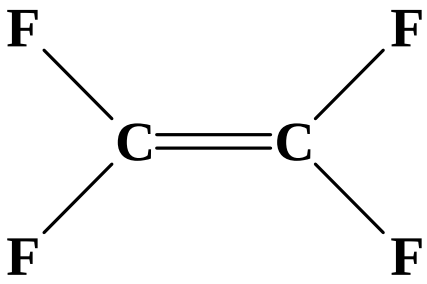
Dr. Carlson, the second principal reviewer, agreed with the proposed conclusions. He observed that the numbers of clinical pathology measurements appeared to be decreased from past reports and, in view of the types of lesions seen, wondered why. Dr. Roycroft responded that, in actuality, there were more mea-surements; in addition to standard time points and collections at 13 weeks, clinical pathology analyses were performed on animals killed at 15 months. Dr. Carlson said a sentence needed to be added to the Abstract regarding the reason for terminating the mouse study early. Dr. Roycroft agreed.

Dr. Reddy, the third principal reviewer, was unable to attend the meeting but had submitted his review, which Dr. L.G. Hart, NIEHS, read into the record. Dr. Reddy agreed with the proposed conclusions and found the report acceptable.

There was some discussion about the mixing of rats and mice in exposure chambers. Dr. Goldsworthy asked if hormonal alterations were seen. Dr. Roycroft said that hormone measurements were not made, but if a chemical to be studied was known to affect hormone levels, then separate housing might have to be considered. Dr. G.N. Rao, NIEHS, noted that rats and mice are produced in the same rooms so each species is accustomed to the other's presence; he pointed out that each inhalation chamber is by itself a room, and within the chamber, rats and mice are not side by side in cages, but rather in racks. This provides more efficient and economical use of available space. Dr. LeBoeuf commended the NTP for the molecular biology studies evaluating the H-*ras* activation profiles and noted the usefulness of such studies for risk assessment purposes.

Dr. Ryan moved that the Technical Report on tetrafluoroethylene be accepted with the revisions discussed and with the conclusions as written for male and female rats and male and female mice, *clear evidence of carcinogenic activity.* Dr. Carlson seconded the motion, which was accepted unanimously with seven votes.

INTRODUCTION



TETRAFLUOROETHYLENE

CAS No. 116-14-3

Chemical Formula: C_2F_4 Molecular Weight: 100.02

Synonyms: Perfluoroethylene; tetrafluoroethene; 1,1,2,2-tetrafluoroethylene; TFE

CHEMICAL AND PHYSICAL PROPERTIES

Tetrafluoroethylene is a colorless, odorless gas with a melting point of −142.5° C, a boiling point of −76.3° C, a specific gravity of 1.52 at −76° C, a vapor density of 3.87, and a vapor pressure of 428.4 mm Hg. It is insoluble in water. Tetrafluoroethylene is a highly flammable gas that reacts with oxidants and has a flash point of less than 0 ° C and an autoignition temperature of 188 ° C. The lower explosion limit of the chemical is 10% v/v and the upper explosion limit is 50% v/v. Tetrafluoroethylene can dimerize under appropriate temperature and pressure conditions to a stable perfluorocyclobutene and polymerizes easily in the absence of inhibitors or in the presence of heat or oxygen (IARC, 1979; Bretherick, 1985; Weast, 1985; NFPA, 1986; *Material Safety Data Sheet Collection*, 1993; HSDB, 1995).

PRODUCTION, USE, AND HUMAN EXPOSURE

Tetrafluoroethylene is generally produced by the pyrolysis of chlorodifluoromethane or trifluoromethane (IARC, 1979; Hawley, 1981; *Material Safety Data Sheet Collection*, 1993). Although tetrafluoroethylene was reported to the United States International Trade Commission for the year 1992, there was no estimate of the annual production (USITC, 1994). The most recent estimated United States annual production figure of 28 million pounds was reported in 1978. Virtually all of the tetrafluoroethylene produced in the United States is used in the synthesis of Teflon®, one of several polytetrafluoroethylene polymers (Kennedy, 1990). Because of its chemical properties, tetrafluoroethylene is produced and maintained in closed-capture systems. For this reason, human exposure would be primarily through leakage from these systems or through contact with one of several decomposition products of high-temperature processing or pyrolysis of Teflon® and other polymers (Kennedy, 1990). According to the National Occupational Exposure Survey, 14,963 male and 325 female workers were potentially exposed to tetrafluoroethylene from the years 1981 to 1983 (NIOSH, 1990). Currently, no occupational exposure limits have been established. There were no reports in the literature of the detection of tetrafluoroethylene in ambient air, drinking water, or wastewater, and the chemical is not known to occur naturally.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Dilley *et al*. (1974) reported the urinary excretion of fluoride ion following a 30-minute exposure of Sprague-Dawley rats to 3,500 ppm tetrafluoroethylene by inhalation. A significant increase in fluoride excretion occurred on days 6, 13, and 14 following exposure. Urinary creatinine, potassium, and volume were significantly increased following exposure to tetrafluoroethylene. Increased urinary fluoride was observed in male rats and hamsters exposed to 100 to 2,500 ppm tetrafluoroethylene by inhalation for 2 weeks; however, urinary fluoride concentrations returned to normal upon cessation of exposure (Kennedy, 1990). Male and female rats and hamsters exposed to 200 to 2,000 ppm tetrafluoroethylene by inhalation for 18 weeks displayed an exposure-related increase in urinary fluoride (Kennedy, 1990). Ding *et al.* (1980) exposed rabbits to 1,000 ppm tetrafluoroethylene for 60 minutes via a face mask and determined alveolar absorption to be 6.76%. Animals were evaluated during exposure and for a period of up to 75 minutes after exposure ended. The lung, bone, and kidney had the highest fluoride content of the sites examined.

As a part of an investigation of tetrafluoroethylene-induced nephrotoxicity, Odum and Green (1984) demonstrated that liver slices from Wistar rats metabolized tetrafluoroethylene to *S*-(1,1,2,2-tetrafluoroethyl)glutathione. The reaction was catalyzed by both microsomal and cytosolic glutathione *S*-transferases, with the rate of formation with microsomal fractions occurring at four times the rate with cytosol fractions. These same authors also identified the cysteinylglycine and cysteine conjugates of tetrafluoroethylene in bile from rats exposed to 6,000 ppm tetrafluoroethylene for 6 hours. Oral administration of the cysteine conjugate [*S*-(1,1,2,2--tetrafluoroethyl)- *L*-cysteine] to rats caused renal damage identical to that caused by tetrafluoroethylene. Cytochrome P_{450} oxidation did not appear to be involved in tetrafluoroethylene metabolism.

Cysteine conjugates of the nephrotoxins hexachlorobutadiene, tetrafluoroethylene, and hexafluoropropane, together with those of trichloroethylene and perchloroethylene, have been chemically synthesized, and a relationship between their structures, nephrotoxicity, and mutagenicity *in vitro* has been determined (Green and Odum, 1985). All of the conjugates had a marked effect on the uptake of both the organic anion *p*-aminohippuric acid and the cation tetraethylammonium bromide into rat kidney slices, suggesting activation of the conjugates in the slices to a toxic species which interferes with ion transport. This observation is consistent with the known nephrotoxicity of hexachlorobutadiene, tetrafluoroethylene, and hexafluoropropene *in vivo*. Each of the conjugates was found to be metabolized by rat kidney slices and by semi-purified rat kidney β-lyase to pyruvate, ammonia, and an unidentified reactive metabolite (postulated at that time to be a thiol). When semi-purified β-lyase was used, stoichiometric amounts of pyruvate and ammonia were produced. Although all of the conjugates were activated by β-lyase and had a similar effect on ion transport, their mutagenicity differed markedly. The conjugates of hexachlorobutadiene, trichloroethylene, and tetrachloroethylene were mutagenic in the Ames bacterial mutation assay when activated by rat kidney S9. Metabolic cofactors were not required, suggesting that activation was due to the enzyme β-lyase. In the same assay, conjugates of tetrafluoroethylene and hexafluoropropene were not mutagenic either in the presence or absence of rat kidney S9 and cofactors. With a limited number of cysteine conjugates, a clear distinction was identified between the conjugates of fluoroalkenes that were similarly nephrotoxic but not mutagenic. The mutagenicity of the cysteine conjugate of hexachlorobutadiene is consistent with the known renal carcinogenicity of this chemical.

Since the initial observations by Odum and Green (1984), a number of laboratories have investigated the *in vitro* and *in vivo* metabolism of nephrotoxic haloalkenes (including tetrafluoroethylene) and their cysteine conjugates in order to determine the mechanism of haloalkene-induced nephrotoxicity. The bioactivation of the haloalkenes likely begins with glutathione conjugation in the liver. These conjugates are primarily excreted via the bile in the small intestine, where biliary and intestinal peptidases degrade them to cysteine- *S*-conjugates which may be

reabsorbed from the small intestine. Glutathione conjugates released into the general circulation from the liver are hydrolyzed to the cysteine-*S*-conjugates by renal peptidases and are bioactivated by renal β-lyase to unstable, reactive thiols. Commandeur *et al*. (1988) administered tetrafluoroethylene-mercapturic acid intraperitoneally to Wistar rats at doses of 50 µmol/kg body weight or greater. After 48 hours, nephrotoxicity, but not liver toxicity, ensued, as evidenced by increased blood urea nitrogen, urinary protein and glucose, and relative kidney weights. Excretion of difluoroacetic acid was dose related, represented 10% of the dose of 50 µmol/kg body weight, and occurred primarily during the first 24 hours. Difluoroacetic acid, pyruvate, hydrogen sulfide, and thiosulfate were formed during *in vitro* metabolism of the tetrafluoroethylene-cysteine conjugate by rat renal cytosol. Difluoroacetic acid formation was inhibited by aminooxyacetic acid, a β-lyase inhibitor, which points to a β-lyase dependency for its formation. This suggests that the tetrafluoroethylene-cysteine conjugate is bioactivated to a significant extent to difluorothionacyl fluoride and is subsequently metabolized to difluoroacetic acid (Commandeur *et al*., 1988). Male Wistar rats were also injected with 50 µmol tetrafluoroethylene-cysteine conjugate/kg body weight. After 48 hours, 4% of the dose was excreted as the corresponding mercapturic acid. In order to evaluate the enzymatic activation or deactivation of various halogenated cysteine conjugates and mercapturic acids, rat liver and kidney cytosol (activation) and microsomes (deactivation) were incubated with the tetrafluoroethylene-cysteine conjugates and mercapturic acid or various chloro- and bromofluoro cysteine conjugates and mercapturic acids. Tetrafluoroethylene-cysteine conjugate incubated with β-lyase or tetrafluoroethylene-mercapturic acid with *N*-deacetylase demonstrated a greater activation activity with kidney cytosol than with liver. In addition, tetrafluoroethylene-cysteine conjugates and mercapturic acids demonstrated greater activity than chloro- or bromofluoro compounds. Deactivation as evidenced by *N*-acetyltransferase activity (microsomes) was greater with the chloro- and bromofluoro compounds than with tetrafluoroethylene conjugates or mercapturic acid. Deactivation activity was greatest with renal microsomes for both tetrafluoroethylene compounds (Commandeur *et al*., 1991). The same laboratory also demonstrated that when isolated proximal tubule cells from Wistar rat kidneys were incubated with 100 µmol of tetrafluoroethylene-cysteine conjugates or mercapturic acid and other chloro- and bromofluoro compounds, tetrafluoroethylene compounds were more toxic, as evidenced by their ability to inhibit α-methylglucose uptake by the cells (Boogaard *et al*., 1989). The cytotoxicity induced by both tetrafluoroethylene compounds was inhibited by aminooxyacetic acid; however, only the toxicity induced by tetrafluoroethylene-mercapturic acid could be inhibited by probenecid, suggesting that the two tetrafluoroethylene compounds are transported by a different carrier system. Tetrafluoroethylene cysteine accumulated in the proximal tubule cells on exposure to either tetrafluoroethylene-cysteine conjugate or tetrafluoroethylene-mercapturic acid (Boogaard *et al*., 1989). Commandeur *et al*. (1989) demonstrated that the tetrafluoroethylene-cysteine conjugate may be bioactivated in the rat kidney and, to a lesser extent, in the rat liver to electrophilic thioacylating reactive intermediates, probably thionacetyl fluorides, which are the putative reactive intermediates for tetrafluoroethylene-induced nephrotoxicity.

A number of studies have demonstrated that the tetrafluoroethylene-cysteine conjugate and tetrafluoroethylene-derived thionacetyl fluorides affect rat and rabbit kidney macromolecules. Using isolated rat kidney mitochondria, Hayden and Stevens (1990) demonstrated that tetrafluoroethylene-cysteine conjugate was a good substrate for the mitochondrial β-lyase, inhibited ADP-stimulated respiration (primarily stage III), was covalently bound to macromolecules (blocked by aminooxyacetic acid), and was metabolized by mitochondria. Rabbit renal proximal tubules incubated with 25 µmol tetrafluoroethylene-cysteine conjugate produced similar results, including a sevenfold increase in lipid peroxidation (Groves *et al*., 1993). Although the majority of binding in rat mitochondria is associated with the protein fraction, Hayden *et al*. (1992) have shown that significant binding occurs in the lipid fraction, and the major phospholipid adduct is the thioamide adduct of phosphatidylethanolamine.

Harris *et al*. (1992) administered 110 mmol tetrafluoroethylene-cysteine conjugate intraperito-

neally to male Fischer rats. After 1 hour, kidneys were removed, and cytosolic, microsomal, and mitochondrial fractions were obtained. The single, stable amino acid adduct formed with renal protein was *N*-(difluorothioacetyl)lysine. Urine taken from bladders at necropsy was analyzed for metabolites. Mercapturic acids, dihaloacetic acids, and inorganic fluoride were present, as in previously reported studies. In a similar experiment, Hayden *et al*. (1991a) intraperitoneally administered 30 mg tetrafluoroethylene-cysteine conjugate/kg body weight to male Sprague-Dawley rats. The resulting kidney toxicity showed a good correlation with metabolite binding in that difluorothioamide adducts and toxicity were localized to the medullary ray, which contains the S3C and S3M segments of the proximal tubule. Cell death occurred only in cells containing adducts.

Protein adducts such as *N*-acetyl-*N*-(difluorothionacetyl)lysine (Hayden *et al*., 1991b) from rat renal subcellular fractions and *N*-(difluorothionoacetyl)-*S*-(1,1,2,2-tetrafluoroethyl)- *L*-cysteine (Commandeur *et al*., 1989) from rat renal and liver subcellular fractions have been isolated. Bruschi *et al*. (1993) have demonstrated that as many as five mitochondrial proteins are modified following intraperitoneal injection of male F344/N rats with 30 mg tetrafluoroethylene-cysteine conjugate/kg body weight; modification also occurs at the time of formation of the *N*-acetyl-*N*-(difluorothionacetyl) lysine adduct. Two of the proteins have been identified as the heat shock proteins HSP60 (P1 protein) and HSP70-like protein (mortalin). HSP70 and HSP70 mRNA are increased in porcine renal epithelial cell cultures when tetrafluoroethylene-cysteine conjugate is added (Chen *et al*., 1992). Lock and Schnellmann (1990), using *in vitro* studies with rat renal mitochondrial or cytosolic preparations, have demonstrated that the addition of tetrafluoroethylene-cysteine conjugate inhibits lipoyl dehydrogenase and glutathione reductase activity, respectively.

Humans

No studies on the absorption, distribution, metabolism, or excretion of tetrafluoroethylene by humans were found in the available literature (National Library of Medicine, 1995).

TOXICITY

Experimental Animals

Sakharova and Tolgskaya (1977) reported LC_{50} values of 31,000 to 32,000 ppm for rats; 35,000 ppm for mice; and 28,000 ppm for guinea pigs following 4-hour inhalation exposures to tetrafluoroethylene. Kennedy (1990) reported a similar 4-hour LC_{50} of 28,500 ppm for hamsters. Zhemerdei (1958) reported that the lowest concentration of tetrafluoroethylene that caused mortality in rabbits was 40,000 ppm.

Odum and Green (1984) exposed male Wistar rats to tetrafluoroethylene for 6 hours at concentrations of 1,000, 2,000, 3,000, 4,000, and 6,000 ppm to evaluate the potential renal toxicity of the compound. Blood urea nitrogen values, urine volume and urinary excretion of glucose, and alkaline phosphatase and γ-glutamyltranspeptidase activities were significantly increased in rats exposed to 4,000 or 6,000 ppm. These changes are indicative of renal tubule damage. Histopathologic evaluations of the kidneys were conducted on rats in the control and 6,000 ppm groups. All exposed rats exhibited marked renal necrosis involving the pars recta of the proximal tubules. In addition, there were intertubule calcified deposits in the medulla. The no-observable-effect level for kidney toxicity was 2,000 ppm. As in previously discussed studies, oral exposure to tetrafluoroethylene-cysteine conjugate caused renal damage identical to that observed following exposure to tetrafluoroethylene via inhalation.

A number of industry-sponsored studies with tetrafluoroethylene have been conducted but not published. Kennedy (1990) has provided a brief review of some of these studies. Because few repeated-exposure studies with tetrafluoroethylene are presented in the available published literature, several of the studies are summarized here. Syrian hamsters and male Crl:CD rats were exposed to tetrafluoroethylene for 6 hours per day, 5 days per week, for 2 weeks at exposure concentrations of 0, 100, 500, 1,000, and 2,500 ppm. Some of the animals were evaluated at the end of the exposure period, and the remaining animals were evaluated following a 14-day recovery period. No clinical signs of toxicity were observed in either species. There were no significant differences in hamster

absolute or relative organ weights (liver or kidney) at either evaluation period. After the tenth exposure, absolute and relative kidney and liver weights were significantly increased in rats exposed to 2,500 ppm tetrafluoroethylene; however, following the recovery period, kidney and liver weights were similar to those of the control group. Exposure-related kidney lesions in rats exposed to 2,500 ppm were characterized by swelling of the tubular epithelial cells and dilation of the tubular lumen. Sparse cellular degeneration was observed and localized to the juxtamedullary cortex. No significant lesions were apparent following the 14-day recovery period. No significant histopathologic changes were observed in tetrafluoroethylene-exposed hamsters after the tenth exposure; however, following the 14-day recovery period, testicular atrophy was observed in the 2,500 ppm group. This effect consisted of degeneration and sloughing of germinal epithelial cells, resulting in an absence or reduction in the number of mature sperm in both the testes and epididymides, and the presence of degenerative germ cells sloughed into the lumen of the epididymal ducts. These effects were noted less frequently in animals exposed to lower concentrations.

Kennedy (1990) summarized the results of a study in which male and female rats and hamsters were exposed to 200, 600, or 2,000 ppm tetrafluoroethylene for 6 hours per day, 5 days per week, for 18 weeks. Hamsters appeared to be less affected than rats in that there was no reduction in the rate of weight gain in any exposed group of hamsters, while rats exposed to 2,000 ppm exhibited a reduction in the rate of weight gain. Additionally, toxic nephrosis associated with the straight portions of the proximal convoluted tubules was observed in rats exposed to 600 or 2,000 ppm tetrafluoroethylene. This was accompanied by increased urine volume and urine fluoride concentrations and decreased urine creatinine concentrations. The effects were more pronounced in female rats than in male rats. No effects on the kidneys of exposed groups of hamsters were observed; however, testicular atrophy similar to that reported in the 14-day study in male Syrian hamsters and Crl:CD rats was observed.

Although a number of animal studies have been performed with pyrolysis products of tetrafluoroethylene polymers, they are not reported here because these products are mixtures of a number of chemical vapors and particulates, and any observable effects cannot be solely attributed to the inhalation of tetra-fluoroethylene monomer.

Humans

Epidemiological studies relative to exposure to tetrafluoroethylene alone were not found in the literature (National Library of Medicine, 1995). Although monomeric tetrafluoroethylene is generally considered an irritant to the eyes and respiratory tract, there is a paucity of firm toxicologic data. There are considerable data in the literature on human exposure to pyrolysis products of tetrafluoroethylene polymers. However, those studies are not considered here because toxic effects from exposure to the polymer fumes cannot be attributed solely to inhalation of tetrafluoroethylene monomer. Following exposure to pyrolysis products of tetrafluoroethylene, influenza-like symptoms commonly referred to as "polymer-fume fever" do occur. The symptoms include fever, chills, headaches, dizziness, nausea, weakness, cough, and rigor-like shaking of the limbs (IARC, 1979; Gosselin *et al*., 1984; *Material Safety Data Sheet Collection*, 1993; *Patty's Industrial Hygiene and Toxicology*, 1994). The symptoms are transient if the oxygen supply to the subject is increased and the subject is removed from the contaminated environment.

S-(1,1,2,2-tetrafluoroethyl)-*L*-cysteine and other cysteine and glutathione conjugates such as *S*-(1,2-di-chlorovinyl)glutathione, *S*-(1,2-dichlorovinyl)-*L*-cysteine, *S*-(1,2,3,4,4-pentachlorobutadienyl)-*L*cysteine, and *S*-(2-chloro1,1,2-trifluoroethyl)-*L*-cysteine were found to be toxic to human proximal tubule cells in culture, as indicated by the release of lactate dehydrogenase (Chen *et al*., 1990). Aminooxyacetic acid protected the cells from the toxicity of all the conjugates and inhibited the covalent binding of the sulfur-containing metabolites to cellular macromolecules and thus prevented cell death.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No information on the reproductive or developmental toxicity of tetrafluoroethylene in

experimental animals or in humans was found in a search of the available literature (National Library of Medicine, 1995).

CARCINOGENICITY

No information on the carcinogenicity of tetrafluoroethylene in experimental animals or in humans was found in a search of the available literature (National Library of Medicine, 1995). Tetrachloroethylene, which is structurally similar to tetrafluoroethylene, produced hepatocellular carcinomas in male and female B6C3F$_1$ mice (NCI, 1977). Male mice were administered 450 or 900 mg tetrachloroethylene/kg body weight in corn oil by gavage for 11 weeks, then 550 or 1,100 mg/kg for 67 weeks. Female mice were administered 300 or 600 mg/kg tetrachloroethylene in corn oil by gavage for 11 weeks, then 400 or 800 mg/kg for 67 weeks. Exposure of male and female F344/N rats to 200 or 400 ppm tetrachloroeth-ylene by inhalation for 2 years resulted in increased incidences of renal tubule adenoma or adenocarcinoma in males and increased incidences of mononuclear cell leukemia in males all these tests were conducted with and without Aroclor-induced liver S9 enzymes.

STUDY RATIONALE

Tetrafluoroethylene was nominated to the NTP by the National Cancer Institute for testing following a review of related monomers and polymers. The nomination was based on the potential for human exposure to the chemical due to the large production volume and on the lack of adequate test data for tetrafluoroethylene. Inhalation was chosen as the route of exposure because human exposure occurs primarily via this route. Sixteen-day, 13-week, and 2-year whole body inhalation studies were performed in male and female F344/N rats and B6C3F$_1$ mice.

and females. (NTP, 1986). In the same inhalation study, mice exposed to 100 or 200 ppm for 2 years developed increased incidences of hepatocellular adenoma (males) and carcinoma (males and females).

GENETIC TOXICOLOGY

Kennedy (1990) reported that tetrafluoroethylene was not mutagenic in *Salmonella typhimurium* with or without metabolic activation.

Cysteine conjugates of tetrafluoroethylene were not mutagenic in the *Salmonella* assay, with or without rat kidney S9 (Green and Odum, 1985).

The structurally similar tetrachloroethylene was not mutagenic in *Salmonella* (Haworth *et al*., 1983), gave equivocal results in the mouse lymphoma mutagenicity assay with L5178Y mouse lymphoma cells (Myhr *et al*., 1990), and did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells (Galloway *et al*., 1987);

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TETRAFLUOROETHYLENE

Tetrafluoroethylene was obtained from SCM Specialty Chemicals (Gainesville, FL) in one lot (10271), which was used for the identity and purity analyses conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix I). Tetrafluoroethylene was also obtained from ICI Americas, Inc. (Bayonne, NJ), in five lots. The study laboratory assigned a lot number to each shipment of as many as 12 cylinders. Lot 12017-8 was used during the 16-day studies and during most of the 13-week studies; lot 12017-77 was used during the remainder of the 13-week studies; and lots 12438-6, 12438-79, and 12438-92 were used during the 2-year studies. Identity and purity analyses were also conducted by the study laboratory on each lot used during the studies. Reports on analyses performed in support of the tetrafluoroethylene studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

Each lot of the chemical, a colorless gas, was identified as tetrafluoroethylene by the analytical chemistry or study laboratory using infrared spectroscopy and the purity of each lot was determined by gas chromatography. Gas chromatography of lot 10271 indicated one major peak and one impurity with an area of 0.1% relative to the major peak. In addition, analysis for *d*-limonene, which is added to tetrafluoroethylene as a stabilizer, was conducted by the analytical chemistry laboratory using gas chromatography and indicated 0.03% ± 0.00% *d*-limonene. Gas chromatography conducted by the study laboratory for each cylinder of each lot used during the studies indicated that perfluorocyclobutane was present at concentrations less than or equal to 462 ppm (0.05%) for the 16-day studies and 2,604 ppm (0.26%) for the 13-week studies. During the 2-year studies, gas chromatography indicated peaks for perfluorocyclobutane with areas less than or equal to 1.21% relative to the major peak. Gas chromatography conducted by the study laboratory for each cylinder of each lot used during the 13-week studies indicated that *d*-limonene was present at concentrations less than or equal to 2,837 ppm (0.28%). During the 2-year studies, gas chromatography of lots 12438-6, 12438-79, and 12438-92 indicated peaks for *d*-limonene with areas less than or equal to 0.56% relative to the major peak. The manufacturer indicated that the following impurities were also present at concentrations less than or equal to 1.7 ppm: trifluoroethylene, methylene fluoride, vinyl fluoride, and vinylidene fluoride. The overall purity of lots 12017-8, 12017-77, and 12438-92 was determined to be greater than 99%. The overall purity of lots 12438-6 and 12438-79 was determined to be greater than 98%.

The manufacturer indicated that tetrafluoroethylene would be stable for up to 1 year when stored in the original containers at room temperature. To ensure stability, the bulk chemical was stored in the original metal cylinders at 10° to 22° C. Stability was monitored during the 13-week and 2-year studies using gas chromatography. The relative concentrations of perfluorocyclobutane were expected to increase due to the slow dimerization of tetrafluoroethylene; therefore, the gas cylinders were monitored for this dimer as well as for *d*-limonene during the 2-year studies. Two cylinders from lot 12438-6 contained higher concentrations of these compounds than canisters from the same lot that were analyzed earlier in the studies. One of these two cylinders, which contained 1.21% perfluorocyclobutane and 0.56% *d*-limonene, was replaced immediately after gas chromatographic analysis was performed; it is not known if the dimer formed in the canister due to degradation of tetrafluoroethylene or was present as an impurity at receipt. Stability was generally considered acceptable throughout the studies.

VAPOR GENERATION AND EXPOSURE SYSTEM

Because tetrafluoroethylene is a gas at room temperature, the generation and delivery system incorporated gas distribution under regulated pressure with individual adjustment and monitoring of the chemical flow

rate to each chamber. Tetrafluoroethylene was taken directly from the cylinder in which it was shipped and was metered to each exposure chamber. A sample line was included downstream from each gas cylinder. Stainless-steel chambers designed at Battelle Pacific Northwest Laboratories were used for all studies (Figure I3).

VAPOR CONCENTRATION MONITORING

The concentrations of tetrafluoroethylene were monitored using an on-line gas chromatograph, and samples were drawn and analyzed from each exposure chamber, the control chamber, the exposure suite, and an on-line standard. Summaries of the chamber concentrations during the studies are presented in Tables I1 through I3. The monthly mean exposure concentrations for the 2-year studies are presented in Figures I7 through I15; all were within 10% of the acceptable concentration range.

CHAMBER ATMOSPHERE CHARACTERIZATION

The time for the exposure concentration to build up to 90% of the final exposure concentration (T_{90}) used for all studies was 12 minutes. During the 16-day studies, T_{90} was approximately 12 minutes and T_{10} (the time for the exposure concentration to decay to 10% of the exposure concentration) was approximately 9 minutes with and without animals in the chambers. During the 13-week studies, T_{90} was 11 minutes with animals in the chambers and ranged from 11 to 14 minutes without animals; T_{10} ranged from 9 to 11 minutes with and without animals in the chambers. During the 2-year studies, T_{90} ranged from 8 to 10 minutes without animals in the chambers and from 10 to 16 minutes with animals present; T_{10} ranged from 7 to 9 minutes without animals and from 9 to 12 minutes with animals. The T_{90} value was not affected by the presence of animals.

Uniformity of tetrafluoroethylene concentration in the exposure chambers was measured using on-line gas chromatography before each of the studies, once during the 16-day and 13-week studies, and approximately every 3 months during the 2-year studies. Uniformity of exposure concentrations within each chamber was acceptable, and relative standard deviations were less than 5%.

The persistence of tetrafluoroethylene in the 1,250 ppm exposure chamber after shutting off the system was monitored without animals before the 2-year studies began and with animals present during the 2-year studies. The concentration of tetrafluoroethylene in the exposure chamber fell rapidly to less than 1% of the beginning concentration within 20 minutes. Tetrafluoroethylene concentrations in the building exhaust and room air were also monitored during all studies.

Information supplied by the manufacturer indicated that all cylinders contained *d*-limonene as a stabilizer. *d*-Limonene and perfluorocyclobutane are less volatile than tetrafluoroethylene and concentrate in the cylinder as the tetrafluoroethylene is removed. Cylinder usage was regulated to minimize concentrations of these chemicals in the exposure chambers; a maximum of 80% of the tetrafluoroethylene in each cylinder was used. Gas chromatography of chamber samples and cylinder headspace in used and unused cylinders was conducted for *d*-limonene and perfluorocyclobutane. The results indicated that tetrafluoroethylene was stable during generation and in the exposure chambers and that perfluorocyclobutane was not formed in significant quantities by the generation system.

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 11 days (rats) or 12 days (mice) and were approximately 6 weeks old on the first day of the studies. Groups of five male and five female rats and mice were exposed to tetrafluoroethylene at concentrations of 0, 312, 625, 1,250, 2,500, and 5,000 ppm. The animals were exposed for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 12 exposure days during a 16-day period. Feed was available *ad libitum* except during exposure periods, and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded two times during each exposure day for rats and mice. The animals were weighed on days 1, 8, and 15 and at

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

At the end of the 16-day studies, blood was collected from the retroorbital (rats) or supraorbital (mice) sinus for hematology analyses. Rats and mice were anesthetized with CO_2. Blood for hematology determinations was placed in tubes containing potassium EDTA as the anticoagulant. Analyses were performed with an Ortho ELT-8/ds hematology analyzer (Ortho Instruments; Westwood, MA). Leukocyte differential counts were determined by light microscopic examination of blood films stained with Wright-Giemsa. Reticulocyte counts were determined by light microscopy using smears stained supravitally with New Methylene Blue and a Miller disc for reticulocyte quantitation. Hematology parameters measured are listed in Table 1.

A necropsy was performed on all rats and mice. The brain, heart, left and right kidneys, liver, lung, right testis, and thymus were weighed. Histopathologic examinations were performed on all control and 5,000 ppm rats and mice. Selected organs were examined to a no-effect level in groups of animals exposed to lower concentrations of tetrafluoroethylene. Table 1 lists the tissues and organs examined.

13-WEEK STUDIES

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

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms, Inc. (Germantown, NY). On receipt, rats and mice were approximately 4 weeks old. Animals were quarantined for 12 days (rats) or 14 days (mice) and were approximately 6 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats and mice were exposed to tetrafluoroethylene at concentrations of 0, 312, 625, 1,250, 2,500, or 5,000 ppm. (One female rat assigned to the 2,500 ppm group was missexed and discarded at week 6.) The animals were exposed for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 13 weeks (excluding holidays). Feed was available *ad libitum* except during exposure periods, and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded once weekly for rats and mice. The animals were weighed prior to the start of the studies and weekly thereafter. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 13-week studies, blood was collected from the retroorbital (rats) or supraorbital (mice) sinus for hematology analyses. Rats and mice were anesthetized with CO_2. Hematology determinations were analyzed as described for the 16-day study. Fourteen days (rats) or 10 days (mice) before the end of the studies, rats and mice were placed in metabolism cages (with access to water but not food) for a 16-hour urine collection. Four days before the end of the studies, rats were again placed in metabolism cages and were deprived of water for 16 hours to determine urine concentrating ability; urine was expressed from the bladders of all rats, and urine was collected for the following 4 hours while water deprivation continued. Specific gravity was determined on an A/O refractometer; urine glucose was determined using an Abbott VP glucose oxidase methodology (Abbott Laboratories, Abbott Park, IL); urine protein was determined by a Coomassie blue reaction; and fluoride was measured using an ion-specific electrode. Hematology and urinalysis parameters measured are listed in Table 1.

At the end of the 13-week studies, samples were collected for sperm morphology and vaginal cytology evaluations on rats and mice exposed to 0, 312, 1,250, and 5,000 ppm. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1984). For 7 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells

were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm morphology, count, and motility. The right testis and right epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65 ° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all control and 5,000 ppm rats and mice and on selected organs from rats and mice exposed to lower concentrations. Table 1 lists the tissues and organs examined.

2-YEAR STUDIES

Study Design

Groups of 60 male rats were exposed to tetrafluoroethylene at concentrations of 0, 156, 312, and 625 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 104 weeks. Groups of 60 female rats and 58 male and female mice were exposed to tetrafluoroethylene at concentrations of 0, 312, 625, and 1,250 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 104 weeks (female rats) or 95 to 96 weeks (mice). Following the last day of exposure, rats were observed for approximately 11 days before necropsy. Ten male and ten female rats and mice from each group were evaluated at 15 months for alterations in hematology, clinical chemistry, and urinalysis parameters (rats only) and organ weights (rats and mice).

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Rats and mice were quarantined for 15 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 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 K).

Animal Maintenance

Rats and mice were housed individually. Feed was available *ad libitum* except during exposure periods, and water was available *ad libitum*. Chambers and cages were rotated weekly. Further details of animal maintenance are provided in Table 1. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded monthly until the last 13 weeks (rats) or 5 weeks (mice), when they were recorded twice monthly. Animals were weighed prior to the start of the studies, weekly for the first 13 weeks, and monthly thereafter, until the last 13 weeks (rats) or 5 weeks (mice), when they were weighed every 2 weeks.

Ten male and ten female rats and mice per exposure group were designated for interim evaluation at 15 months. Two weeks before the scheduled evaluation, designated rats were placed in metabolism cages for a 16-hour urine collection. One week later, male and female rats were again placed in metabolism cages for a urine concentrating study. Rats were deprived of water for 16 hours, and urine was expressed from the bladders of the animals; urine was then collected during the next 6 hours for a urine concentrating study.

At the 15-month interim evaluation, blood was taken from the retroorbital plexus of rats for hematology and clinical chemistry analyses. The methods used were those described for the 13-week studies, and parameters measured are listed in Table 1.

A complete necropsy and microscopic examination were performed on all rats and mice. At the 15-month interim evaluation, the right kidney, liver, and lung were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, imbedded 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. For extended evaluation of renal proliferative lesions, kidneys were step sectioned at 1 mm intervals, and six to ten additional sections were obtained from each kidney. 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 rat and mouse studies, a quality assessment pathologist reviewed the following organs: adrenal medulla, kidney, liver, and spleen (male rats); eye, kidney, liver, and spleen (female rats); kidney, liver, and spleen (male mice); and harderian gland, liver, and spleen (female mice).

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

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, 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

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

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

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

Analysis of Nonneoplastic Lesion Incidences

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

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparisons procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoa data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure levels.

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 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, 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 tetrafluoroethylene was assessed by testing the ability of the chemical to induce increases in the frequency of micronucleated erythrocytes in peripheral blood samples obtained from male and female mice at the end of the 13-week study. The protocol for this study and the results are given in Appendix E.

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

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Battelle Pacific Northwest Laboratories (Richland, WA)	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: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Taconic Farms, Inc. (Germantown, NY)	Simonsen Laboratories (Gilroy, CA)
Time Held Before Studies		
Rats: 11 days Mice: 12 days	Rats: 12 days Mice: 14 days	15 days
Average Age When Studies Began		
6 weeks	6 weeks	7 weeks
Date of First Exposure		
Rats: 30 September 1985 Mice: 1 October 1985	Rats: 25 March 1986 Mice: 27 March 1986	Rats: 23 June 1988 Mice: 9 June 1988
Duration of Exposure		
6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 days	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 13 weeks	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 104 weeks (rats) (followed by an observation period of approximately 11 days), or 95 to 96 weeks (mice)
Date of Last Exposure		
Rats: 15 October 1985 Mice: 16 October 1985	Rats: 24 June 1986 (males) 25 June 1986 (females) Mice: 26 June 1986 (males) 25 June 1985 (females)	Rats: 15-month interim evaluation 17-18 September 1989 terminal sacrifice 14 June 1990 Mice: 15-month interim evaluation 6-7 September 1989 terminal sacrifice 4-5 April 1990
Necropsy Dates		
Rats: 16 October 1985 Mice: 17 October 1985	Rats: 24 June 1986 (males) 25 June 1986 (females) Mice: 27 June 1986 (males) 26 June 1986 (females)	Rats: 15-month interim sacrifice 18-19 September 1989 terminal sacrifice 25 June 1990 (males) or 26-27 June 1990 (females) Mice: 15-month interim sacrifice 7-8 September 1989 terminal sacrifice 5 April 1990 (males) or 6 April 1990 (females)

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

16-Day Studies	13-Week Studies	2-Year Studies
Average Age at Necropsy		
8 weeks	19 weeks	Rats: 15-month interim evaluation - 71 weeks terminal sacrifice - 111-112 weeks Mice: 15-month interim evaluation - 72 weeks terminal sacrifice - 102 weeks
Size of Study Groups		
5 males and 5 females	10 males and 10 females (one rat assigned to the 2,500 ppm female group was determined to be missexed and was discarded during week 6)	15-Month interim evaluation: 10 males and 10 females Terminal sacrifice: 50 males and 50 females (rats) or 48 males and 48 females (mice)
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weight.	Same as 16-day studies	Same as 16-day studies
Animals per Cage		
1	1	1
Method of Animal Identification		
Toe clips and placement within cage unit	Same as 16-day studies	Rats: Tail tattoos and placement within cage unit Mice: Toe clips and placement within cage unit
Diet		
NIH-07 pelleted feed (Zeigler Brothers, Inc., Gardners, PA); available *ad libitum*, except during exposure periods	Same as 16-day studies	Same as 16-day studies
Maximum Storage Time for Feed		
120 days post-milling	Same as 16-day studies	Same as 16-day studies
Water		
Tap water (Richland municipal supply) via automatic watering system (Edstrom Industries; Waterford, WI); available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Cages		
Stainless steel (Hazleton Systems, Inc., Aberdeen, MD), changed weekly	Same as 16-day studies	Stainless steel (Lab Products, Inc., Harford Division, Aberdeen, Md), changed weekly
Bedding/Cage Board		
Techsorb®, Shepherd Specialty Papers, Inc. (Kalamazoo, MI), used during non-exposure periods, 7 days per week	Same as 16-day studies	Same as 16-day studies

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

16-Day Studies	13-Week Studies	2-Year Studies
Chamber Air Supply Filters		
Duct pre-filter, dual and single HEPA (American Air Filter, Louisville, KY); checked biannually	Same as 16-day studies	Single HEPA (Flanders Filters, Inc., San Rafael, CA) and charcoal (RSE, Inc., New Baltimore, MI); changed before the studies began and once yearly thereafter
Chambers		
Stainless steel (Hazleton Systems, Inc., Aberdeen, MD); changed weekly	Stainless steel (Hazleton Systems, Inc., Aberdeen, MD); changed weekly	Stainless steel (Lab Products, Inc., Harford Division, Aberdeen, MD); changed weekly
Chamber Environment		
Temperature: 22.3° – 23.2° C Relative humidity: 52.7% – 55.4% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 23.1° – 23.7° C Relative humidity: 56.1% – 60.5% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 24.1° – 24.5° C Relative humidity: 53% – 58% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour
Exposure Concentrations		
0, 312, 625, 1,250, 2,500, or 5,000 ppm	0, 312, 625, 1,250, 2,500, or 5,000 ppm	Rats: males - 0, 156, 312, or 625 ppm females - 0, 312, 625, or 1,250 ppm Mice: 0, 312, 625, or 1,250 ppm
Type and Frequency of Observation		
All animals were observed twice daily. Clinical findings were recorded two times each exposure day. All animals were weighed on days 1, 8, 15, and at necropsy.	All animals were observed twice daily. Clinical findings were recorded once weekly for rats and mice. The animals were weighed before the studies began and weekly thereafter.	All animals were observed twice daily. Clinical findings were recorded monthly until the last 13 weeks (rats) or 5 weeks (mice), when they were recorded twice monthly. Animals were weighed before the studies began, weekly for the first 13 weeks, and monthly thereafter, until the last 13 weeks (rats) or 5 weeks (mice) when they were weighed every 2 weeks.
Method of Sacrifice		
Anesthetization with sodium pentobarbital followed by exsanguination	Anesthetization with CO_2 followed by exsanguination	Anesthetization with CO_2 followed by exsanguination
Necropsy		
Necropsy performed on all animals. Organs weighed were brain, heart, left and right kidneys, liver, lung, right testis, and thymus.	Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. Organs weighed at the 15-month interim evaluation were the right kidney, liver, and lung.

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

16-Day Studies	13-Week Studies	2-Year Studies
Clinical Pathology		
Blood was collected from all animals from the retroorbital (rats) or supraorbital (mice) sinus for hematology analyses. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials	Blood was collected from all animals from the retroorbital (rats) or supraorbital (mice) sinus for hematology analyses. Fourteen days (rats) or 10 days (mice) before the end of the studies, animals were placed in metabolism cages (with access to water but not food) for a 16-hour urine collection. Four days before the end of the studies, rats were again placed in metabolism cages and were deprived of water for 16 hours; urine was expressed from the bladders of all rats, and urine was collected for the following 4 hours while water deprivation continued. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Urinalysis:*** fluoride, glucose, and protein concentrations; volume; and specific gravity	At the 15-month interim evaluation, blood was taken from the retroorbital plexus of rats for hematology and clinical chemistry analyses. Two weeks prior to the scheduled evaluation, designated rats were placed in metabolism cages for a 16-hour urine collection. One week prior to the evaluation, rats were again placed in metabolism cages and were deprived of water for 16 hours; urine was expressed from the bladders of all rats, and urine was collected for the following 6 hours while water deprivation continued. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, sodium, potassium, chloride, calcium, and phosphorus concentrations ***Urinalysis:*** glucose and protein concentrations; volume; and specific gravity
Histopathology		
Complete histopathology was performed on rats and mice exposed to 0 or 5,000 ppm. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, eye (if grossly abnormal), gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lungs, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, nose, ovaries, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, sternebrae (including marrow), stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Additionally, the kidney of all other exposed groups of male and female rats and mice was examined, as was the pancreas of male and female rats exposed to 2,500 ppm.	Complete histopathology was performed on rats and mice exposed to 0 or 5,000 ppm. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lungs, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, nose, ovaries, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, sternebrae (including marrow), stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Additionally, the following organs were examined in lower exposure groups: the kidney of all exposed groups of male and female rats and mice (except female rats exposed to 312 ppm); the cecum of 625 ppm male rats; the eye and mandibular lymph node of 2,500 ppm female rats; and the thymus and lung of 625 ppm male mice.	Complete histopathology was performed on all control and exposed rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, femur, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lungs, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, muscle (thigh), nose, oral cavity (larynx and pharynx), ovaries, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, sternebrae (including marrow), stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

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

16-Day Studies	13-Week Studies	2-Year Studies
Sperm Morphology and Vaginal Cytology		
None	At terminal sacrifice, sperm samples were collected from all male animals in the 0, 312, 1,250, and 5,000 ppm groups for sperm morphology evaluations. The parameters evaluated included sperm morphology, concentration, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal samples were collected for up to 7 consecutive days prior to the end of the studies from all females exposed to 0, 312, 1,250, or 5,000 ppm for vaginal cytology evaluations. The parameters evaluated included the relative frequency of estrous stages and estrous cycle length.	None

RESULTS

RATS

16-DAY STUDY

All rats survived to the end of the study (Table 2). The final mean body weights and body weight gains of males and females exposed to 5,000 ppm were significantly less than those of the controls. The mean body weight gain of females exposed to 2,500 ppm was also significantly less than that of the control group. There were no exposure-related clinical findings in male or female rats.

There were no significant differences in hematology parameters that were considered to be related to tetrafluoroethylene exposure (Table G1). Absolute and relative left and right kidney weights of all exposed groups of males were significantly greater than those of the controls (Table F1), as were those of females in the 2,500 and 5,000 ppm groups. The absolute left and right kidney weight of females exposed to 1,250 ppm was also significantly greater than that of the controls. All exposed groups of males had significantly greater relative liver weights than the controls; males in the 625 and 2,500 ppm groups also had greater absolute liver weights than the controls. Other organ weight differences were not considered to be related to chemical exposure.

TABLE 2
Survival and Body Weights of Rats in the 16-Day Inhalation Study of Tetrafluoroethylene

Exposure Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	120 ± 3	167 ± 4	48 ± 1	
312	5/5	121 ± 2	176 ± 4	55 ± 3	105
625	5/5	122 ± 1	172 ± 3	50 ± 3	103
1,250	5/5	119 ± 1	165 ± 1	46 ± 1	99
2,500	5/5	119 ± 1	162 ± 2	43 ± 2	96
5,000	5/5	116 ± 2	143 ± 3**	27 ± 2**	86
Female					
0	5/5	98 ± 1	126 ± 3	28 ± 2	
312	5/5	104 ± 2*	131 ± 2	27 ± 2	104
625	5/5	97 ± 2	125 ± 3	28 ± 2	99
1,250	5/5	103 ± 1	131 ± 3	28 ± 3	104
2,500	5/5	100 ± 2	119 ± 4	19 ± 3*	94
5,000	5/5	99 ± 1	113 ± 2*	14 ± 1**	89

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Increased incidences of renal tubule degeneration occurred in males and females exposed to 625 ppm or greater (Table 3). The severity of these lesions increased with increasing exposure concentration and was slightly greater in males than in females. Renal lesions occurred predominantly in the inner cortical tubular epithelial cells at the junction of the cortex and medulla. Degeneration was characterized by inner cortical tubules that contained lumenal debris and were lined by cells with vacuolated or eosinophilic cytoplasm. Other tubule epithelial cells had occasional dark pyknotic nuclei and shrunken, eosinophilic cytoplasm. Associated with renal tubule degeneration was regeneration of renal cortical tubule epithelium, characterized by epithelial cells with basophilic cytoplasm, enlarged vesicular nuclei, and slightly increased numbers of mitotic figures. The increased kidney weights were associated with the renal lesions. Histopathologic examination revealed no chemical-related lesions in the livers of exposed male or female rats.

Exposure Concentration Selection Rationale: Based on the lack of overt toxicity following exposure of male and female rats to 5,000 ppm for 16 days, the 13-week exposure concentrations selected were 0, 312, 625, 1,250, 2,500, and 5,000 ppm.

TABLE 3
Incidences of Nonneoplastic Lesions of the Kidney in Rats in the 16-Day Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
Number Examined Microscopically	5	5	5	5	5	5
Renal Tubule, Degeneration[a]	0	0	5** (1.0)[b]	5** (1.4)	5** (2.0)	5** (3.0)
Female						
Number Examined Microscopically	5	5	5	5	5	5
Renal Tubule, Degeneration	0	0	3 (1.0)	5** (1.2)	5** (1.8)	5** (3.2)

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

13-WEEK STUDY

All rats survived to the end of the study (Table 4); one rat in the 2,500 ppm female group was missexed and was removed from the study. The final mean body weight and body weight gain of males and the mean body weight gain of females exposed to 5,000 ppm were significantly less than those of the controls. There were no clinical findings attributed to exposure to tetrafluoroethylene.

The hematology and clinical chemistry data for rats in the 13-week study are presented in Table G2. Exposure to tetrafluoroethylene caused a concentration-dependent anemia, evidenced by decreased hematocrit values, hemoglobin concentrations, and erythrocyte counts in all exposed groups of males and in females exposed to 5,000 ppm. There were no changes in the mean cell volume values of exposed groups of rats, indicating the erythrocytes were normocytic. There were minimal decreases of the mean cell hemoglobin concentration in males exposed to 1,250 ppm or greater; this did not occur in exposed female rats. Decreases in mean cell hemoglobin concentrations without alterations in mean cell volumes have been related to the early stages of iron deficiency. Because the mean cell hemoglobin concentration values of exposed groups of male rats were well within a normal physiological range and no changes occurred in exposed groups of females, the significance of the mean cell hemoglobin concentration alterations was considered questionable and the erythrocytes were characterized as normochromic. There were no increases in reticulocyte counts to indicate a bone marrow response to the anemia. Therefore, the anemia would be characterized as normocytic, normochromic, and nonresponsive. Normocytic, normochromic, nonresponsive anemias have been related to selective suppression of erythropoiesis in a variety of disorders and may be due to decreased erythropoietin

TABLE 4
Survival and Body Weights of Rats in the 13-Week Inhalation Study of Tetrafluoroethylene

Exposure Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	116 ± 3	328 ± 5	212 ± 3	
312	10/10	117 ± 2	337 ± 5	220 ± 4	103
625	10/10	115 ± 2	339 ± 4	225 ± 3	103
1,250	10/10	114 ± 2	330 ± 4	216 ± 4	101
2,500	10/10	113 ± 2	327 ± 4	214 ± 4	100
5,000	10/10	115 ± 3	299 ± 6**	184 ± 4**	91
Female					
0	10/10	91 ± 2	185 ± 6	94 ± 4	
312	10/10	97 ± 3	196 ± 3	99 ± 3	106
625	10/10	93 ± 2	195 ± 5	102 ± 5	105
1,250	10/10	95 ± 2	192 ± 4	97 ± 3	104
2,500	9/9	89 ± 4	177 ± 7	88 ± 4	95
5,000	10/10	94 ± 2	174 ± 4	80 ± 3*	94

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

elaboration, bone marrow suppression, or defective iron metabolism.

A concentration-dependent proteinuria occurred in all exposed groups of male rats and in females exposed to 2,500 or 5,000 ppm. Proteinuria could be related to glomerular or renal tubule injury and is consistent with the renal tubule degeneration observed histopathologically. However, the renal injury did not appear to affect the ability of the kidney to concentrate the urine, as evidenced by appropriate increases in urine specific gravity in response to a water concentration test. There was a concentration-dependent increase of urinary fluoride excretion in all exposed groups of male and female rats, consistent with metabolism and excretion of tetrafluoroethylene. A possible polyuria, evidenced by increased 16-hour urine volumes, occurred in males in the 5,000 ppm group and in all exposed groups of females.

The absolute and relative liver weights of all exposed groups of males and of females in the 5,000 ppm group were significantly greater than those of the controls (Table F2). The absolute and relative right kidney weights of males and females exposed to 1,250 ppm or greater and of females in the 625 ppm group were also significantly greater than those of the controls. The absolute and relative heart weights of males exposed to 1,250, 2,500, or 5,000 ppm were generally significantly greater than those of the controls. Other organ weight differences were not considered to be related to chemical exposure.

There were no differences in sperm morphology parameters or in the length of estrous cycles between control and exposed groups of rats (Tables H1 and H2).

Incidences of renal tubule degeneration in males exposed to 625 ppm or greater and in females exposed to 2,500 or 5,000 ppm were significantly greater than those in the controls (Table 5). The renal lesions, which were similar to those observed in the 16-day study, increased in severity with exposure concentration and were slightly more severe in males than females. Renal lesions were observed at the junction of the cortex and medulla and involved inner cortical tubules. Degeneration was characterized by inner cortical tubules that were dilated, contained lumenal debris, and had occasional pyknotic nuclei. Associated with degeneration was regeneration, characterized by renal tubule epithelial cells that were lined by cells with basophilic cytoplasm having pleomorphic

TABLE 5
Incidences of Nonneoplastic Lesions of the Kidney in Rats in the 13-Week Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
Number Examined Microscopically	10	10	10	10	10	10
Renal Tubule, Degeneration[a]	0	0	10** (1.0)[b]	10** (1.0)	10** (2.0)	10** (2.0)
Female						
Number Examined Microscopically	10	—[c]	10	10	9	10
Renal Tubule, Degeneration	0		0	0	9** (1.0)	10** (2.0)

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

nuclei with large, prominent nucleoli, a slightly increased number of mitotic figures, and varying degrees of karyomegaly. The increased kidney weights were associated with the renal lesions. Histopathologically, there were no chemical-related lesions in the livers of male or female rats exposed to tetrafluoroethylene.

Exposure Concentration Selection Rationale: Exposure concentrations for the 2-year rat study in males were based on kidney effects. Although the severity and incidence of kidney lesions were identical for male rats exposed to 625 or 1,250 ppm, the absolute and relative kidney weights of males exposed to 1,250 ppm were significantly greater than those of the controls. Therefore, the highest exposure concentration selected was 625 ppm, which was expected to cause minimal toxicity in the kidney following 2 years of exposure.

Although kidney effects were the main toxicologic consideration for exposure concentration selection in the 2-year study in female rats, the highest exposure concentration was selected, in part, based on the number of chambers to be used in this inhalation study. When possible in inhalation studies, males and females of a species for each concentration are housed in the same chamber. When it is obvious that the same exposure concentration will cause more severe effects in one sex of the same species, space is sought in chambers housing the other species. In the present study, concentrations selected for the 2-year mouse study were 312, 625, and 1,250 ppm. At the time of selection of concentrations for the mouse study, it was believed that female rats could tolerate exposure to 2,500 ppm with minimal toxic effects. However, it was decided that an additional chamber solely for female rats could not be justified economically; therefore, female rats were housed in the same chambers as mice. In addition, because of the increased absolute and relative kidney weights of females exposed to 625 ppm or greater (even in the absence of histopathologic effects), it was believed that toxicity might occur at 625 or 1,250 ppm. Therefore, because there was additional space in the mouse chambers, 1,250 ppm was selected as the highest exposure concentration for the 2-year study in female rats.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 1). The survival rates of males in the 625 ppm group and of all exposed groups of females were significantly less than those of the controls.

Body Weights and Clinical Findings

Mean body weights of males exposed to 625 ppm were lower than those of the controls from week 81 until the end of the study; the mean body weights of males exposed to 156 or 312 ppm and of females exposed to 312 or 625 ppm were similar to those of the controls throughout the study (Figure 2 and Tables 7 and 8). Mean body weights of females exposed to 1,250 ppm were slightly lower than those of the controls at the end of the study; the final mean body weight of this group was 91% that of the controls. The only clinical finding associated with exposure to tetrafluoroethylene was opacity of one or both eyes in exposed groups of female rats; this change was observed microscopically as cataracts.

Hematology, Clinical Chemistry, and Urinalysis

At the 15-month interim evaluation, no differences in hematology, clinical chemistry, or urinalysis parameters were considered to be related to tetrafluoroethylene exposure (Table G3).

TABLE 6
Survival of Rats in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	156 ppm	312 ppm	625 ppm
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Moribund	27	34	32	48
Natural deaths	6	4	1	1
Animals surviving to study termination	17	12	17	1
Percent probability of survival at end of study[b]	34	24	34	2
Mean survival (days)[c]	665	644	665	609
Survival analyses[d]	P<0.001	P=0.216	P=0.829	P<0.001

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental death[a]	0	0	0	1
Moribund	21	33	31	25
Natural deaths	1	1	4	6
Animals surviving to study termination	28	16[e]	15	18
Percent probability of survival at end of study	56	32	30	37
Mean survival (days)	694	642	651	620
Survival analyses	P=0.034	P=0.008	P=0.007	P=0.014

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

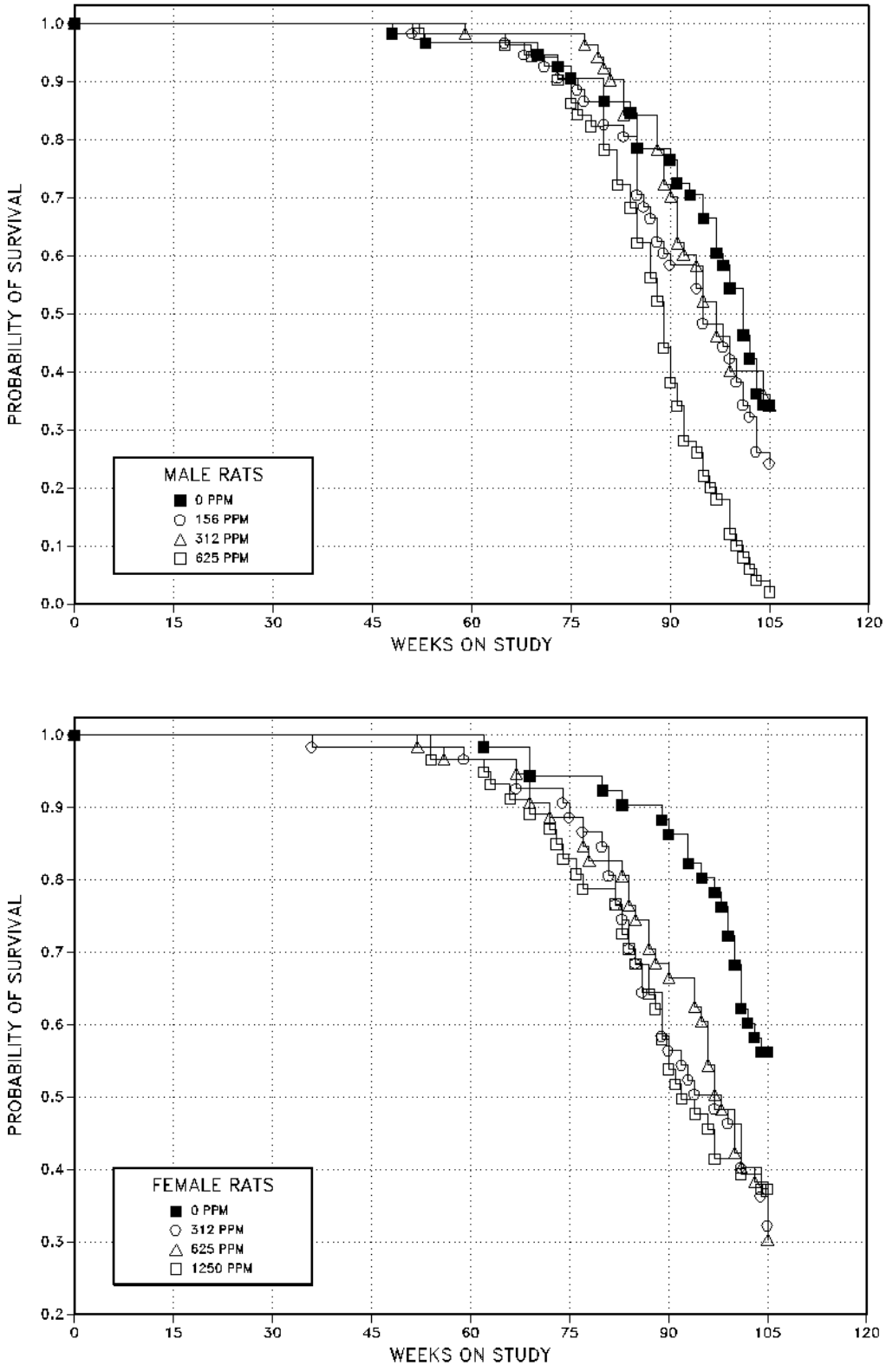


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Tetrafluoroethylene by Inhalation for 2 Years

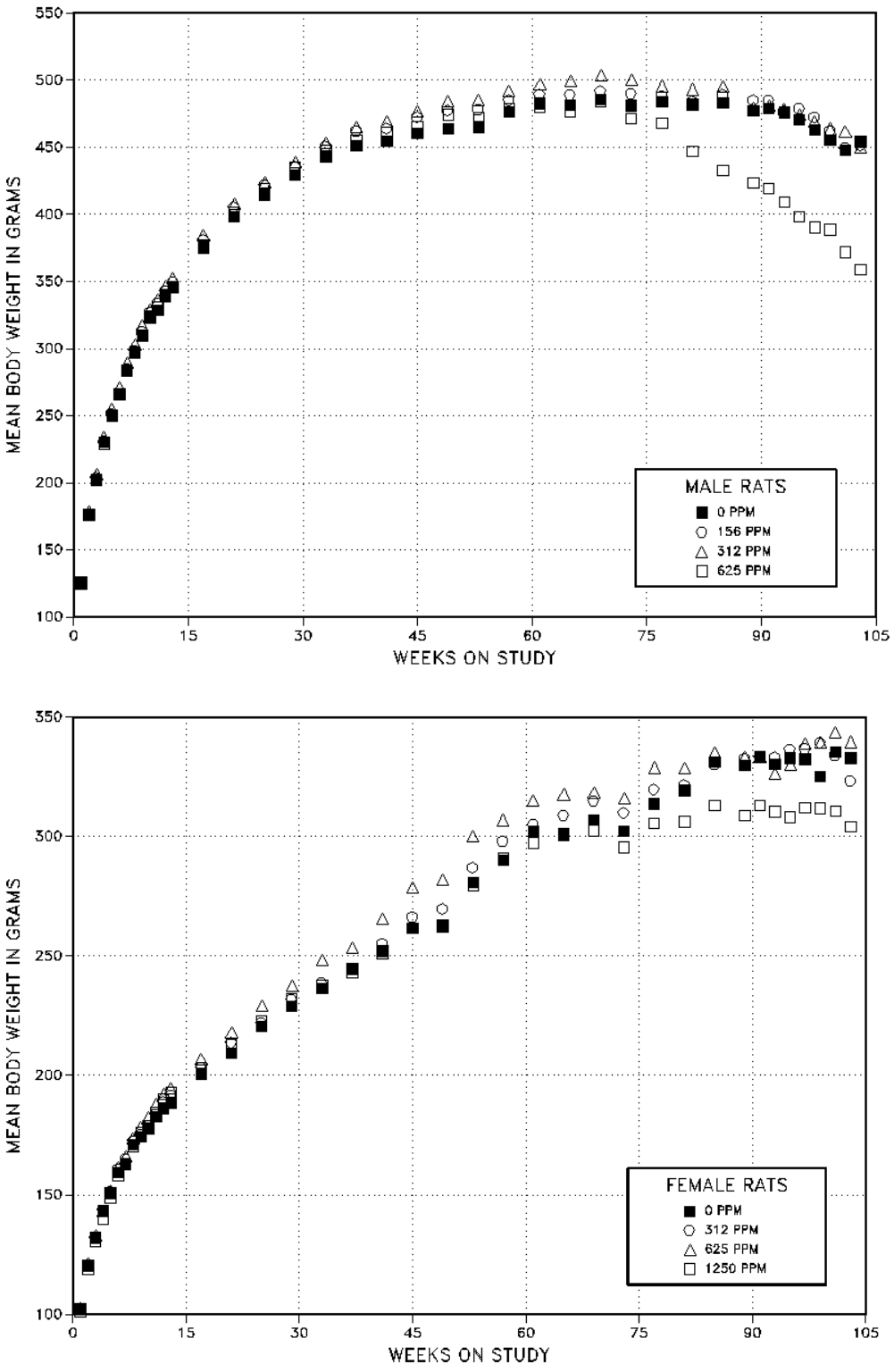


FIGURE 2
Growth Curves for Male and Female Rats Administered Tetrafluoroethylene by Inhalation for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene

Weeks on Study	0 ppm		156 ppm			312 ppm			625 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	126	60	126	100	60	126	100	60	125	99	60
2	176	60	177	101	60	179	102	60	176	100	60
3	203	60	204	101	60	207	102	60	202	100	60
4	230	60	231	100	60	234	102	60	229	100	60
5	250	60	251	100	60	255	102	60	250	100	60
6	267	60	267	100	60	271	102	60	266	100	60
7	284	60	285	100	60	289	102	60	283	100	60
8	298	60	299	100	60	303	102	60	297	100	60
9	310	60	312	101	60	317	102	60	310	100	60
10	324	60	327	101	60	329	102	60	323	100	60
11	329	60	334	102	60	336	102	60	331	101	60
12	339	60	343	101	60	347	102	60	340	100	60
13	346	60	350	101	60	353	102	60	346	100	60
17	375	60	381	102	60	384	103	60	377	101	60
21	398	60	406	102	60	408	103	60	402	101	60
25	415	60	422	102	60	424	102	60	420	101	60
29	430	60	436	101	60	439	102	60	436	101	60
33	443	60	451	102	60	454	102	60	448	101	60
37	451	60	462	102	60	465	103	60	456	101	60
41	455	60	464	102	60	469	103	60	461	101	60
45	461	60	473	103	60	477	104	60	465	101	60
49	464	59	478	103	60	484	104	60	475	102	60
53	465	59	478	103	59	485	104	60	472	101	59
57	476	58	485	102	59	492	103	60	479	101	59
61	483	58	489	101	59	497	103	59	480	99	59
65[a]	482	48	489	102	48	499	104	49	477	99	49
69	486	48	492	101	47	504	104	49	484	100	47
73	481	47	490	102	45	501	104	49	472	98	47
77	484	45	488	101	43	496	102	49	468	97	42
81	482	43	485	101	41	493	102	45	447	93	39
85	483	41	490	101	38	495	103	42	433	90	33
89	477	39	485	102	30	479	100	36	423	89	22
91	479	36	485	101	29	481	101	31	419	88	17
93	476	35	477	100	29	478	101	30	409	86	14
95	471	34	479	102	26	475	101	28	399	85	11
97	463	31	473	102	24	469	101	23	390	84	9
99	456	27	462	102	21	464	102	21	389	85	6
101	448	24	449	100	17	462	103	20	372	83	4
103	454	19	452	99	13	450	99	20	359	79	3
Mean for weeks											
1-13	268		270	101		273	102		268	100	
14-52	432		441	102		445	103		438	101	
53-103	473		479	101		484	102		434	92	

[a] Interim evaluation occurred during week 65.

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene

Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 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	102	60	102	100	60	102	100	60	101	99	60
2	121	60	121	100	60	121	101	60	119	99	59
3	132	60	132	100	60	133	101	60	130	99	59
4	143	60	144	100	60	143	100	60	140	98	59
5	151	60	151	101	60	152	101	60	149	99	59
6	159	60	161	101	60	161	101	60	158	99	59
7	163	60	165	101	60	166	102	60	163	100	59
8	171	60	173	101	60	174	101	60	170	100	59
9	174	60	175	101	60	178	102	60	176	101	59
10	178	60	179	101	60	183	103	60	179	101	59
11	183	60	184	101	60	188	103	60	185	101	59
12	186	60	189	102	60	192	103	60	190	102	59
13	189	60	192	102	60	195	103	60	193	102	59
17	201	60	203	101	60	207	103	60	203	101	59
21	209	60	214	102	60	218	104	60	213	102	59
25	220	60	222	101	60	229	104	60	223	101	59
29	229	60	232	101	60	238	104	60	232	101	59
33	236	60	239	101	60	248	105	60	238	101	59
37	245	60	245	100	59	253	104	60	243	99	59
41	252	60	255	101	59	265	105	60	251	100	59
45	262	60	266	102	59	279	106	60	262	100	59
49	263	60	270	103	59	282	107	60	262	100	59
53	281	60	287	102	59	300	107	59	279	100	59
57	290	60	298	103	59	307	106	58	291	100	57
61	302	60	305	101	58	315	104	58	297	98	57
65[a]	301	59	309	103	58	318	106	58	300	100	55
69	307	48	315	103	46	318	104	45	303	99	43
73	302	47	310	103	46	316	105	44	296	98	42
77	314	47	320	102	44	329	105	42	305	97	39
81	319	46	322	101	40	328	103	41	306	96	38
85	331	45	330	100	35	335	101	37	313	95	34
89	330	44	333	101	29	333	101	34	309	94	28
91	333	43	333	100	28	333	100	33	313	94	25
93	330	41	333	101	26	326	99	33	310	94	24
95	333	40	336	101	25	330	99	31	308	93	23
97	332	39	337	101	24	339	102	25	312	94	21
99	325	38	339	104	23	339	104	24	312	96	20
101	336	33	334	100	21	344	102	20	311	93	19
103	333	30	323	97	20	340	102	19	304	91	19
Mean for weeks											
1-13	158		159	101		161	102		158	100	
14-52	235		238	101		247	105		236	100	
53-103	318		321	101		326	103		304	96	

[a] Interim evaluation occurred during week 65.

Pathology and Statistical Analyses

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

Absolute and relative lung weights of exposed groups of rats were similar to those of the controls at the 15-month interim evaluation (Table F3), and no lung lesions related to tetrafluoroethylene exposure occurred.

Kidney: At the 15-month interim evaluation, the absolute and relative right kidney weights of males exposed to 625 ppm and females exposed to 1,250 ppm were significantly greater than those of the controls (Table F3). Additionally, the absolute kidney weight of females exposed to 625 ppm and the relative kidney weight of males exposed to 312 ppm were significantly greater than those of the controls.

At 15 months, renal tubule hyperplasia was observed in one male exposed to 312 ppm and in one male exposed to 625 ppm. At the end of the study, the incidences of renal tubule hyperplasia in males exposed to 625 ppm and of renal tubule adenoma in males exposed to 312 ppm were significantly greater than those in the controls (Tables 9, A3, and A5). The combined incidence of renal tubule adenoma or carcinoma in males exposed to 312 or 625 ppm exceeded the range in historical controls from 2-year NTP inhalation studies (Tables 9 and A4a).

At 15 months, renal tubule hyperplasia was observed in one female exposed to 625 ppm. At the end of the study, the incidence of renal tubule hyperplasia in females in the 1,250 ppm group was significantly greater than that in the controls (Tables 9 and B5); the incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in females exposed to 1,250 ppm were also greater than those in the controls (Tables 9 and B3), and the incidences occurred with significant trends. The incidences of renal tubule adenoma or carcinoma (combined) in females exposed to 312 or 1,250 ppm exceeded the range in historical controls (Tables 9 and A4a).

Initially, a single hematoxylin- and eosin-stained section of each kidney was prepared. Primarily because of the increased incidences of renal tubule hyperplasia, adenomas, and carcinomas that were observed in some groups in the standard evaluation of the 2-year studies, additional step sections of kidney were prepared from the remaining formalin-fixed tissues of interim evaluation and 2-year study rats. Six to ten additional kidney sections taken at 1-mm intervals were prepared for each male and female. Additional males and females with focal hyperplasia or adenomas and one 156 ppm male with a carcinoma were identified among rats exposed for 2 years. The incidences of these proliferative lesions in standard and extended evaluations are presented in Table 9.

At the 2-year extended evaluations and combined standard and extended evaluations, males in the 625 ppm group and females in the 1,250 ppm group had significantly greater incidences of renal tubule hyperplasia, renal tubule adenoma, and renal tubule adenoma or carcinoma (combined) than the controls (Tables 9 and A3). In the combined standard and extended evaluations, the incidences of renal tubule hyperplasia in females exposed to 625 ppm and renal tubule adenoma in males exposed to 312 ppm were also significantly greater than those in the controls. The incidences renal tubule adenoma in females and of renal tubule adenoma or carcinoma (combined) in males and females occurred with significant positive trends in the extended and combined standard and extended evaluations.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	156 ppm	312 ppm	625 ppm
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Single Sections (Standard Evaluation)				
Nephropathy[a]	10 (1.8)[b]	10 (1.8)	10 (1.6)	10 (2.4)
Renal Tubule, Degeneration	1 (1.0)	8** (1.0)	10** (2.0)	10** (3.0)
Renal Tubule, Hyperplasia	0	0	1 (1.0)	1 (1.0)
Renal Tubule, Carcinoma	0	0	0	1
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	0	0	1 (1.0)	0
2-Year Study				
Number Examined Microscopically	50	50	50	50
Single Sections (Standard Evaluation)				
Nephropathy	49 (2.3)	50 (1.9)	50 (2.7)	50 (3.5)
Renal Tubule, Degeneration	2 (1.0)	20** (1.1)	50** (2.3)	49** (3.6)
Renal Tubule, Hyperplasia	1 (1.0)	1 (1.0)	1 (4.0)	6* (1.3)
Renal Tubule, Hyperplasia, Oncocytic	0	0	1 (1.0)	0
Renal Tubule, Adenoma	0	0	6*	3
Renal Tubule, Carcinoma	1	0	2	0
Renal Tubule, Adenoma or Carcinoma[c]	1	0	6	3
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	7	10	7	18**
Renal Tubule, Adenoma	2	4	3	11**
Renal Tubule, Carcinoma	0	1	0	0
Renal Tubule, Adenoma or Carcinoma	2	5	3	11**
Single and Step Sections (Combined)				
Renal Tubule, Hyperplasia	7	11	7	24**
Renal Tubule, Adenoma	2	4	9*	13**
Renal Tubule, Carcinoma	1	1	2	0
Renal Tubule, Adenoma or Carcinoma	3	5	9	13**

(continued)

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Inhalation Study of Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Single Sections (Standard Evaluation)				
Nephropathy	8 (1.0)	9 (1.0)	9 (1.2)	10 (1.0)
Renal Tubule, Degeneration	0	0	10** (2.0)	10** (2.6)
Renal Tubule, Hyperplasia	0	0	1 (1.0)	0
Renal Tubule, Hyperplasia, Oncocytic	0	0	0	1 (1.0)
Renal Tubule, Adenoma	0	0	0	1
Mixed Tumor, Malignant	0	0	0	1
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	0	1	0	4*
Renal Tubule, Adenoma	0	0	0	2
2-Year Study				
Number Examined Microscopically	50	50	50	50
Single Sections (Standard Evaluation)				
Nephropathy	48 (1.7)	46 (1.5)	48 (1.7)	47 (2.0)
Renal Tubule, Degeneration	0	0	35** (1.3)	46** (2.0)
Renal Tubule, Hyperplasia	1 (2.0)	3 (1.7)	6 (1.2)	12** (1.8)
Renal Tubule, Hyperplasia, Oncocytic	0	0	0	3 (1.0)
Renal Tubule, Adenoma	0	3	1	3
Renal Tubule, Carcinoma	0	0	0	2
Renal Tubule, Adenoma or Carcinoma[d]	0	3	1	5**
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	2	3	7	17**
Renal Tubule, Adenoma	0	0	2	5*
Renal Tubule, Carcinoma	0	0	0	1
Renal Tubule, Adenoma or Carcinoma	0	0	2	5*
Single Sections and Step Sections (Combined)				
Renal Tubule, Hyperplasia	3	6	11*	25**
Renal Tubule, Adenoma	0	3	3	8**
Renal Tubule, Carcinoma	0	0	0	3
Renal Tubule, Adenoma or Carcinoma	0	3	3	10**

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesion in affected animals: 1=minimal; 2=mild; 3=moderate; 4=marked
[c] Historical incidence for 2-year NTP inhalation studies with chamber control groups at all labs (mean ± standard deviation): 6/652 (0.9% ± 1.3%); range, 0%-4%. Historical incidence for 2-year NTP inhalation studies with chamber control groups at Battelle Pacific Northwest Laboratories: 5/347 (1.4% ± 1.5%); range, 0%-4%
[d] Historical incidence at all labs: 2/650 (0.3% ± 0.8%); range, 0%-2%. Historical incidence at Battelle Pacific Northwest Laboratories: 2/346 (0.6% ± 1.0%); range, 0%-2%

Renal tubule hyperplasia, as defined in the present study, was distinguished from regenerative epithelial changes commonly seen as a part of nephropathy and was considered a preneoplastic lesion. Renal tubule hyperplasia, adenoma, and carcinoma constitute a morphologic continuum. Hyperplasia was generally a focal, minimal to mild lesion consisting of tubules that were dilated to 1.5 to 2 times the normal diameter and were lined by increased numbers of tubule epithelial cells, which partially or totally filled the tubule lumen (Plate 1). Cells within hyperplastic lesions varied slightly in size and sometimes stained more basophilic than normal cells, but otherwise appeared similar to normal tubule epithelial cells. Renal tubule adenomas were larger, discrete lesions, ranging from greater than five tubule diameters to 1 mm or more in size (Plate 2). Cells within adenomas were mildly to moderately pleomorphic, sometimes had vacuolated cytoplasm, and tended to form complex patterns, particularly microtubular structures. Renal tubule carcinomas were differentiated from adenomas in that they usually were larger and less discrete and had a more prominent vascular supply and more anaplasia and cellular atypia (Plate 3). Renal tubule cell carcinoma was characterized by vesiculate nuclei with prominent nucleoli and increased numbers of mitotic figures (Plate 4).

Oncocytic hyperplasia was observed at the end of the study in one male exposed to 312 ppm and in three females exposed to 1,250 ppm (Tables 9, A5, and B5). This lesion was characterized by individual tubules or small clusters of tubules that were somewhat dilated and totally filled by large polygonal cells with abundant brightly eosinophilic granular cytoplasm and small, centrally located, basophilic nuclei (oncocytes). These lesions are thought to arise from the distal tubule epithelium.

At 15 months and at the end of the study, the incidences of renal tubule degeneration in all exposed groups of males and in females in the 625 and 1,250 ppm groups were greater than those in the controls (Tables 9, A5, and B5). Renal tubule degeneration was similar to that observed in the 13-week study. Degeneration was characterized by dilatation of renal tubule epithelial cells and was located predominantly at the corticomedullary junction (Plates 5 and 6). Dilated tubules sometimes contained eosinophilic debris and/or proteinaceous fluid in their lumens. The tubules were lined by flattened to cuboidal epithelium (Plate 6) and often had both basophilic and eosinophilic cells lining adjacent areas of the same tubule. At 15 months, renal tubule degeneration was easily detected; however, in the 2-year study, it was sometimes obscured by the presence of concurrent nephropathy. The location of the renal tubule degeneration at the corticomedullary junction was the primary feature which distinguished this lesion from chronic progressive nephropathy. Also lacking in tetrafluoroethylene-induced renal tubule degeneration, but present in chronic progressive nephropathy, were thickened basement membranes, interstitial fibrosis, inflammatory infiltrates, and prominent protein casts in dilated tubules throughout the cortex and medulla.

The severity of nephropathy generally increased with increasing exposure concentration in male and female rats at 15 months and 2 years, although the increase in exposed female rats was not as pronounced. These increases were observed at the end of the 2-year study in males exposed to 312 or 625 ppm and in females exposed to 1,250 ppm.

Liver: The absolute and relative liver weights of females in the 1,250 ppm group and the absolute liver weight of females exposed to 625 ppm were significantly greater than those of the controls at the 15-month interim evaluation (Table F3). At 15 months, all exposed groups of males had significantly greater incidences of clear cell foci than the controls; females exposed to 625 or 1,250 ppm had significantly greater incidences of mixed cell foci than the controls (Tables 10, A5, and B5). At the end of the study, the incidences of eosinophilic foci in all exposed groups of males and of mixed cell foci and basophilic foci in males exposed to 312 or 625 ppm were significantly greater than those in the controls, as was the incidence of mixed cell foci in females exposed to 1,250 ppm. The incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in males exposed to 312 ppm were significantly greater than those in the controls at the end of the study (Tables 10 and A3). At 2 years, the incidences of hepatocellular adenoma and adenoma or carcinoma (combined) in all exposed groups of females were significantly greater than those in the controls, and the incidences occurred with significant positive trends (Tables 10 and B3). Additionally, females exposed to 312 or 625 ppm had significantly

greater incidences of hepatocellular carcinoma than the controls at 2 years. The combined incidence of hepatocellular neoplasms in each exposed group of males and females exceeded the historical control ranges in chamber controls from 2-year NTP inhalation studies (Tables 10, A4b, and B4b). Also at 2 years, the incidence of hemangiosarcoma in females exposed to 625 ppm was significantly greater than in the controls. The incidence of liver hemangiosarcoma in 625 ppm females exceeded the historical range for hemangiosarcomas in all organs in control female rats from NTP 2-year inhalation studies (Table 10), and liver hemangiosarcomas have not been observed in historical control females.

Hepatocellular foci are considered potential preneoplastic lesions. Hepatocellular foci were relatively discrete aggregates of often enlarged hepatocytes, and the lobular pattern of the liver was generally retained. Hepatocellular adenomas consisted of nodules of hepatocytes which compressed adjacent hepatic parenchyma and lacked the normal lobular and sinusoidal pattern (Plate 7). Hepatocellular carcinomas consisted of solid sheets of hepatocytes or trabeculae, three or more cells thick (Plate 8). Neoplastic hepatocytes were anaplastic, with prominent nuclei containing one or more nucleoli and variable amounts of cytoplasm. Hemangiosarcomas were malignant vascular neoplasms characterized by irregular, vascular spaces filled with erythrocytes (Plate 9) and lined by variable numbers of pleomorphic endothelial

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	156 ppm	312 ppm	625 ppm
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Basophilic Focus[a]	6	4	7	4
Clear Cell Focus	4	10**	9*	10**
Cystic Degeneration	0	1	3	0
Eosinophilic Focus	1	0	0	1
Mixed Cell Focus	0	2	2	2
Hepatocellular Adenoma	0	0	1	0
Hepatocellular Carcinoma	0	0	0	1
2-Year Study				
Number Examined Microscopically	50	50	50	50
Basophilic Focus	22	19	33*	29**
Clear Cell Focus	7	8	11	3
Eosinophilic Focus	3	18**	22**	19**
Cystic Degeneration	17	39**	35**	32**
Mixed Cell Focus	5	5	16**	13**
Hepatocellular Adenoma	3	6	8	5
Hepatocellular Carcinoma	1	1	10**	3
Hepatocellular Adenoma or Carcinoma[b]				
Overall rate[c]	4/50 (8%)	7/50 (14%)	15/50 (30%)	8/50 (16%)
Adjusted rate[d]	16.3%	34.4%	62.1%	100.0%
Terminal rate[e]	2/17 (12%)	3/12 (25%)	9/17 (53%)	1/1 (100%)
First incidence (days)	624	600	617	572
Logistic regression test[f]	P=0.025	P=0.223	P=0.003	P=0.112

(continued)

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Inhalation Study of Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Angiectasis	0	1	0	0
Basophilic Focus	9	9	10	10
Clear Cell Focus	0	2	3	3
Eosinophilic Focus	0	5*	2	0
Mixed Cell Focus	0	1	6**	4*
2-Year Study				
Number Examined Microscopically	50	50	50	50
Angiectasis	0	9**	9**	14**
Basophilic Focus	41	38	41	37
Clear Cell Focus	10	3	12	9
Eosinophilic Focus	1	4	5*	4
Mixed Cell Focus	12	14	16	18*
Hepatocellular Adenoma	0	4*	5**	6**
Hepatocellular Carcinoma	0	4*	9**	2
Hepatocellular Adenoma or Carcinoma[g]				
Overall rate	0/50 (0%)	7/50 (14%)	12/50 (24%)	8/50 (16%)
Adjusted rate	0.0%	36.3%	65.4%	37.8%
Terminal rate	0/28 (0%)	5/16 (31%)	9/15 (60%)	5/18 (28%)
First incidence (days)	—[h]	583	668	677
Logistic regression test	P=0.001	P=0.002	P<0.001	P<0.001
Hemangiosarcoma[i]				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	19.5%	5.0%
Terminal rate	0/28 (0%)	0/16 (0%)	0/15 (0%)	0/18 (0%)
First incidence (days)	—	—	589	703
Logistic regression test	P=0.182	—	P=0.025	P=0.435

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Historical incidence for 2-year NTP inhalation studies with chamber control groups at all labs (mean ± standard deviation): 28/653 (4.3% ± 2.9%); range, 2%-9%. Historical incidence for 2-year NTP inhalation studies with chamber control groups at Battelle Pacific Northwest Laboratories: 11/347 (3.2% ± 2.3%); range, 2%-8%
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[g] Historical incidence at all labs: 10/650 (1.5% ± 2.0%); range, 0%-6%. Historical incidence at Battelle Pacific Northwest Laboratories: 7/346 (2.0% ± 2.3%); range, 0%-6%
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for all organs at all labs: 2/653 (0.3% ± 0.8%); range, 0%-2% (incidence in liver: 0/650)

cells. Occasionally, hemangiosarcomas metastasized to the lung.

At the end of the 2-year study, increased incidences of hepatic cystic degeneration occurred in all exposed groups of males, and increased incidences of hepatic angiectasis were observed in exposed groups of females (Tables 10, A5, and B5). Cystic degeneration was characterized by multifocal dilated areas with cysts containing fluid, fibrin, and/or erythrocytes; these lesions occur spontaneously in aging rats at low incidences but are common following chemical exposure to a hepatocarcinogen. Hepatic angiectasis was characterized by multifocal, dilated, blood-filled sinusoids with prominent lining endothelial cells; these lesions are sometimes associated with hepatocellular neoplasms.

Mononuclear Cell Leukemia: Incidences of mononuclear cell leukemia in males exposed to 156 ppm and in all exposed groups of females were significantly greater than those in the controls (Tables 11, A3, and B3), and the incidences occurred with significant positive trends in males and females. The incidence of this neoplasm in male controls exceeded the historical range for all types of leukemia in 2-year NTP inhalation studies (Tables 11 and A4c), as did the incidences in males exposed to 156 or 312 ppm. However, the incidence in females exposed to 0 ppm was within the historical control range (Tables 11 and B4c), and the incidences in females exposed to 312 or 1,250 ppm exceeded that range.

Eye: The incidence of cataracts in females exposed to 1,250 ppm was greater than that in the controls at the end of the 2-year study (0 ppm, 15/50; 312 ppm, 4/50; 625 ppm, 10/50; 1,250 ppm, 45/50; Table B5). Cataracts were characterized by a disruption of the normal organization of lens filters, with swelling, vacuolization, and mineralization.

Testis: At the end of the study, there was a slight increase in the incidences of interstitial cell adenoma in rats exposed to 312 or 625 ppm (39/50, 40/50, 48/50, 47/50; Table A3). At 15 months, there were no increases in the incidences of interstitial cell hyperplasia or adenoma. Interstitial cell hyperplasia and adenomas are very common in F344/N rats, and nearly all rats will develop such proliferative lesions if allowed to complete their natural life span. It is uncertain whether the slightly increased incidences of interstitial cell adenoma were related to tetrafluoroethylene exposure, although the control incidence is within the historical control range for 2-year NTP inhalation studies with chamber controls (450/655; mean ± standard deviation, 68.7% ± 8.7%; range, 54%-83%).

Mammary Gland: At 2 years, the incidences of fibroadenoma in the mammary gland of exposed female rats were decreased (22/50, 11/50, 9/50, 7/50; Table B3). Fibroadenomas are the most common benign neoplasm of the mammary gland in the female F344/N rat. In other studies, decreases in the incidence of this neoplasm have been associated with decreases in body weights; however, in the present study, the decreases are not related to body weight changes. The biological significance of these decreased incidences is uncertain.

TABLE 11
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	156 ppm	312 ppm	625 ppm
Male				
Mononuclear Cell Leukemia (All Organs)[a]				
Overall rate[b]	34/50 (68%)	43/50 (86%)	38/50 (76%)	31/50 (62%)
Adjusted rate[c]	81.5%	95.3%	91.9%	100.0%
Terminal rate[d]	10/17 (59%)	10/12 (83%)	14/17 (82%)	1/1 (100%)
First incidence (days)	509	351	413	509
Life table test[e]	P<0.001	P=0.016	P=0.231	P<0.001
Logistic regression test[e]	P=0.064N	P=0.020	P=0.254	P=0.079N
	0 ppm	**312 ppm**	**625 ppm**	**1,250 ppm**
Female				
Mononuclear Cell Leukemia (All Organs)[f]				
Overall rate	16/50 (32%)	31/50 (62%)	23/50 (46%)	36/50 (72%)
Adjusted rate	43.7%	76.5%	65.1%	82.6%
Terminal rate	8/28 (29%)	7/16 (44%)	6/15 (40%)	11/18 (61%)
First incidence (days)	621	468	469	372
Life table test	P<0.001	P<0.001	P=0.008	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.105	P<0.001

[a] Historical incidence for 2-year NTP inhalation studies with chamber control groups at all labs (mean ± standard deviation): 356/655 (54.4% ± 8.8%); range, 34%-66%. Historical incidence for 2-year NTP inhalation studies with chamber control groups at Battelle Pacific Northwest Laboratories: 195/348 (56.0% ± 8.7%); range, 38%-66%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these neoplasms as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[f] Historical incidence at all labs: 262/653 (40.1% ± 7.2%); range, 30%-54%. Historical incidence at Battelle Pacific Northwest Laboratories: 146/348 (42.0% ± 7.2%); range, 30%-54%

MICE

16-DAY STUDY

All mice survived to the end of the study (Table 12). Final mean body weights and body weight gains of all exposed groups of mice were similar to those of the controls. There were no exposure-related clinical findings in male or female mice.

There were no significant differences in hematology parameters that were considered to be related to tetrafluoroethylene exposure (Table G4). The absolute and relative liver weights of females exposed to 5,000 ppm were significantly greater than those of the controls, as were the absolute kidney weight of females in that group and the absolute liver weight of females in the 2,500 ppm group (Table F4). Other differences in organ weights were not considered to be related to chemical exposure.

Renal tubule karyomegaly was observed in male mice exposed to 1,250 or greater, in females in the 2,500 and 5,000 ppm groups, and in one female exposed to 1,250 ppm; the severity of this lesion increased with increasing exposure concentration (Table 13). Karyomegaly of renal tubule cells was observed primarily in the inner renal cortex and was characterized by nuclei that were enlarged, pleomorphic, and vesicular and that had prominent nucleoli. In the areas with karyomegaly, individual tubule epithelial cells had pyknotic nuclei consistent with minimal to mild scattered necrosis.

Exposure Concentration Selection Rationale: Based on the lack of overt toxicity following exposure of mice to 5,000 ppm for 16 days, exposure concentrations selected for the 13-week study were 0, 312, 625, 1,250, 2,500, and 5,000 ppm.

TABLE 12
Survival and Body Weights of Mice in the 16-Day Inhalation Study of Tetrafluoroethylene

Exposure Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	22.4 ± 0.3	25.3 ± 0.2	3.0 ± 0.3	
312	5/5	22.6 ± 0.7	25.5 ± 0.7	2.9 ± 0.3	101
625	5/5	22.2 ± 0.5	24.8 ± 0.6	2.6 ± 0.4	98
1,250	5/5	21.5 ± 0.7	24.8 ± 1.2	3.4 ± 0.6	98
2,500	5/5	21.8 ± 0.7	25.7 ± 0.5	3.9 ± 0.2	102
5,000	5/5	21.8 ± 1.0	25.2 ± 1.0	3.4 ± 0.3	100
Female					
0	5/5	18.8 ± 0.7	20.8 ± 0.6	2.0 ± 0.6	
312	5/5	18.8 ± 1.2	20.8 ± 1.1	2.0 ± 0.3	100
625	5/5	18.8 ± 0.3	20.9 ± 0.3	2.1 ± 0.1	101
1,250	5/5	18.2 ± 1.0	21.0 ± 0.8	2.7 ± 0.5	101
2,500	5/5	18.9 ± 0.6	21.5 ± 0.7	2.6 ± 0.5	104
5,000	5/5	18.2 ± 0.4	21.3 ± 0.6	3.1 ± 0.5	103

[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group were not significant by Williams' or Dunnett's test.

TABLE 13
Incidences of Kidney Lesions in Mice in the 16-Day Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
Number Examined Microscopically	5	5	5	5	5	5
Renal Tubule, Karyomegaly[a]	0	0	0	5** (1.0)[b]	5** (1.2)	5** (2.4)
Female						
Number Examined Microscopically	5	5	5	5	5	5
Renal Tubule, Karyomegaly	0	0	0	1 (1.0)	5** (2.0)	5** (3.0)

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

13-WEEK STUDY

All mice survived to the end of the study (Table 14). Males in the 1,250, 2,500, and 5,000 ppm groups had significantly lower initial mean body weights than the controls; however, final mean body weights and body weight gains of all exposed groups of male and female mice were generally similar to those of the controls. There were no clinical findings that were considered related to tetrafluoroethylene exposure.

The hematology and urinalysis data for mice in the 13-week inhalation study of tetrafluoroethylene are presented in Table G5. A normocytic, normochromic, nonresponsive anemia, similar to that observed in the 13-week rat study, occurred in males exposed to 2,500 ppm and in males and females in the 5,000 ppm groups. The anemia was evidenced by minimal decreases of hematocrit values, hemoglobin concentrations, and erythrocyte counts. There were no alterations of mean cell volume or mean cell hemoglobin concentration; thus, the erythrocytes were normocytic and normochromic. The lack of a bone marrow response was evidenced by the absence of an increase in reticulocyte counts.

A concentration-dependent polyuria, evidenced by increased 16-hour urine volumes, occurred in male and female mice exposed to 2,500 or 5,000 ppm. The increased urine volumes were accompanied by decreased urine specific gravity values; these findings are consistent with increased water consumption or lack of urine concentrating ability of the kidney. There was a concentration-dependent increase of urinary fluoride excretion in all exposed groups of male and female mice, consistent with metabolism and excretion of tetrafluoroethylene. No biologically significant differences in organ weights were observed.

TABLE 14
Survival and Body Weights of Mice in the 13-Week Inhalation Study of Tetrafluoroethylene

Exposure Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	25.5 ± 0.3	33.6 ± 0.6	8.2 ± 0.5	
312	10/10	24.9 ± 0.3	32.4 ± 0.3	7.4 ± 0.3	96
625	10/10	25.0 ± 0.4	33.6 ± 0.7	8.6 ± 0.5	100
1,250	10/10	24.0 ± 0.2**	33.3 ± 0.6	9.3 ± 0.4	99
2,500	10/10	24.8 ± 0.2**	32.6 ± 0.3	7.9 ± 0.4	97
5,000	10/10	24.0 ± 0.2**	31.6 ± 0.5*	7.6 ± 0.4	94
Female					
0	10/10	20.2 ± 0.3	28.8 ± 0.8	8.7 ± 0.7	
312	10/10	20.0 ± 0.2	28.5 ± 0.7	8.4 ± 0.6	99
625	10/10	20.1 ± 0.4	27.8 ± 0.9	7.7 ± 0.8	96
1,250	10/10	19.7 ± 0.1	27.5 ± 0.6	7.8 ± 0.6	95
2,500	10/10	19.9 ± 0.2	27.8 ± 0.7	7.9 ± 0.6	96
5,000	10/10	19.9 ± 0.1	26.3 ± 0.4	6.4 ± 0.4	91

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Differences in sperm morphology parameters and estrous cycle length were not considered to be related to chemical administration (Tables H3 and H4).

Incidences of karyomegaly of the renal tubule epithelial cells in male and female mice exposed to 1,250 ppm or greater were significantly greater than those in the controls (Table 15). As in the 16-day study, the renal changes were observed primarily in the inner renal cortex. Karyomegaly was characterized by nuclei that were enlarged, pleomorphic, and vesicular and had large, hyperchromatic, prominent nucleoli. In areas of karyomegaly, there was minimal cytomegaly and scattered necrosis of individual tubule epithelial cells. The severity of the kidney lesions was slightly more pronounced in males than in females.

Exposure Concentration Selection Rationale: Based on the incidence and severity of kidney lesions in male and female mice exposed to 2,500 or 5,000 ppm tetrafluoroethylene, the absence of kidney lesions in mice exposed to 625 ppm, and the absence of kidney weight effects in exposed groups of mice, exposure concentrations selected for the 2-year mouse study were 312, 625, and 1,250 ppm. The highest concentration (1,250 ppm) was expected to cause minimal toxicity in the 2-year study.

TABLE 15
Incidences of Nonneoplastic Lesions of the Kidney in Mice in the 13-Week Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
Number Examined Microscopically	10	10	10	10	10	10
Karyomegaly[a]	0	0	0	10** (2.8)[b]	10** (2.8)	10** (3.0)
Female						
Number Examined Microscopically	10	10	10	10	10	10
Karyomegaly	0	0	0	10** (1.8)	10** (2.8)	10** (2.2)

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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 16 and in the Kaplan-Meier survival curves (Figure 3). The survival rates of all exposed groups of males and females were significantly less than those of the controls. Because of the reduced survival, the study was terminated during week 96.

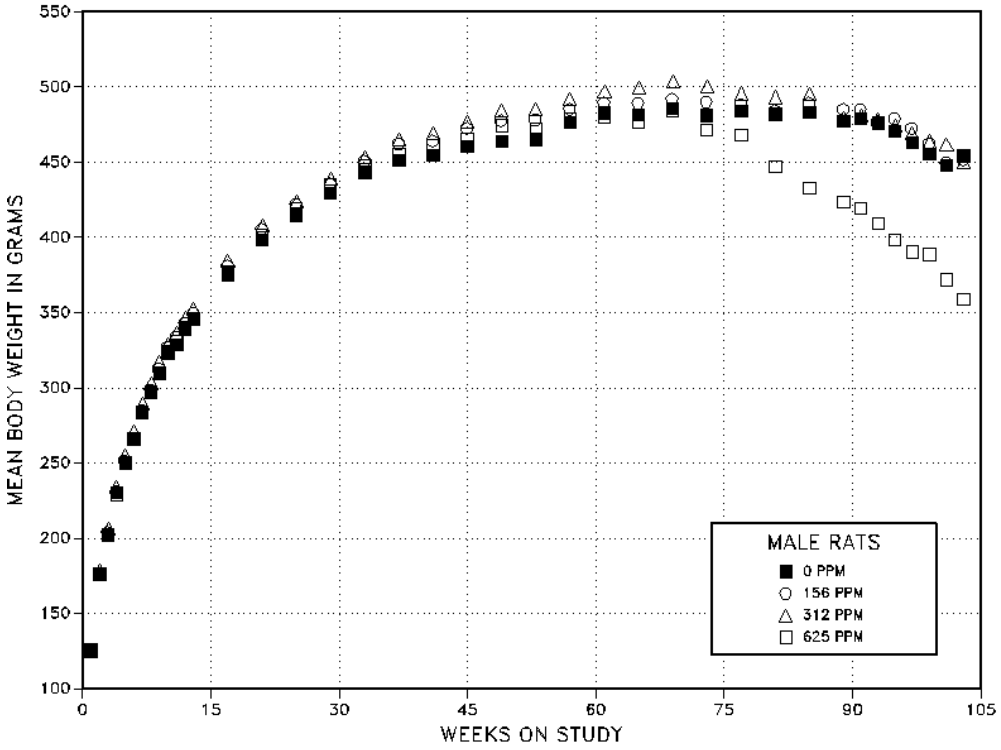
Body Weights and Clinical Findings

Mean body weights of exposed groups were generally similar to those of the controls except at the end of the study, when they were somewhat lower; however, the number of exposed mice surviving at the end of the study was considerably less than the number of controls surviving (Tables 17 and 18 and Figure 4). There were no clinical findings related to tetrafluoroethylene exposure.

TABLE 16
Survival of Mice in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Animals initially in study	58	58	58	58
15-Month interim evaluation[a]	10	10	10	10
Moribund	6	24	26	27
Natural deaths	4	13	20	20
Animals surviving to study termination	38	11	2	1
Percent probability of survival at end of study[b]	79	23	4	2
Mean survival (days)[c]	647	561	554	548
Survival analyses[d]	P<0.001	P<0.001	P<0.001	P<0.001
Female				
Animals initially in study	58	58	58	58
15-Month interim evaluation[a]	10	10	10	10
Accidental death[a]	0	0	1	0
Moribund	8	28	26	27
Natural deaths	4	16	15	17
Animals surviving to study termination	36	4	6	4
Percent probability of survival at end of study	75	8	13	8
Mean survival (days)	643	597	587	560
Survival analyses	P<0.001	P<0.001	P<0.001	P<0.001

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



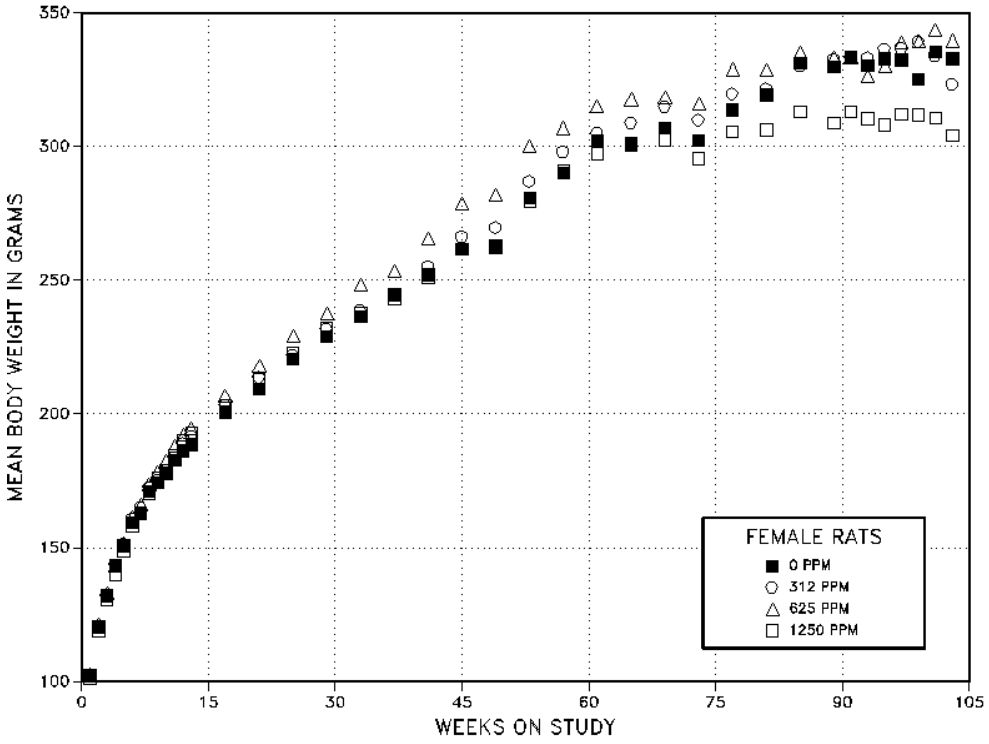


FIGURE 2
Growth Curves for Male and Female Rats Administered Tetrafluoroethylene by Inhalation for 2 Years

TABLE 17
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene

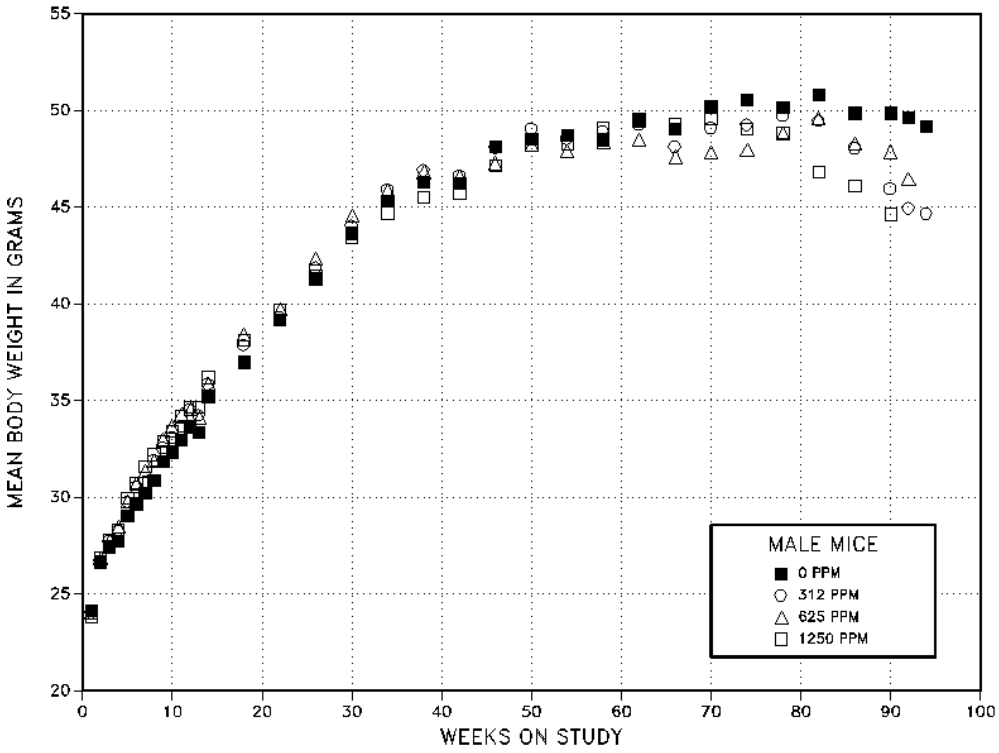
Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.1	58	24.0	100	58	24.0	100	58	23.8	99	58
2	26.6	58	26.7	100	58	26.9	101	58	26.9	101	57
3	27.4	58	27.7	101	58	27.7	101	58	27.8	102	57
4	27.7	58	28.2	102	58	28.5	103	58	28.3	102	57
5	29.0	58	29.8	103	58	29.8	103	58	29.9	103	57
6	29.7	58	30.5	103	58	30.7	103	58	30.7	103	57
7	30.2	58	30.8	102	58	31.3	104	58	31.6	105	57
8	30.9	58	31.9	103	57	31.9	103	58	32.2	104	57
9	31.8	58	32.6	103	57	33.0	104	58	32.9	104	57
10	32.3	58	33.1	103	57	33.6	104	58	33.4	103	57
11	32.9	58	33.7	102	57	34.3	104	58	34.2	104	57
12	33.6	58	34.5	103	55	34.6	103	58	34.6	103	57
13	33.4	58	34.2	102	55	34.1	102	58	34.7	104	57
14	35.2	58	35.9	102	55	35.8	102	58	36.2	103	57
18	37.0	58	37.9	102	55	38.4	104	58	38.1	103	57
22	39.1	58	39.3	101	55	39.7	102	58	39.7	102	57
26	41.3	58	41.9	102	55	42.3	102	58	41.5	101	57
30	43.6	58	44.0	101	55	44.5	102	58	43.4	100	57
34	45.3	58	45.9	101	55	45.8	101	58	44.7	99	57
38	46.3	58	46.9	101	55	46.8	101	58	45.5	98	56
42	46.2	58	46.6	101	55	46.6	101	58	45.7	99	56
46	48.1	58	48.1	100	55	47.3	98	58	47.1	98	55
50	48.5	58	49.0	101	55	48.2	99	58	48.2	99	55
54	48.7	58	48.5	100	55	47.9	98	56	48.2	99	54
58	48.4	58	48.9	101	55	48.3	100	56	49.1	101	53
62	49.5	58	49.3	100	55	48.5	98	54	49.4	100	53
66[a]	49.0	47	48.1	98	45	47.6	97	41	49.3	101	43
70	50.2	46	49.1	98	43	47.8	95	40	49.5	99	41
74	50.5	46	49.3	98	40	47.9	95	37	49.0	97	41
78	50.1	45	49.7	99	33	48.8	97	28	48.8	97	34
82	50.8	44	49.5	97	29	49.6	98	22	46.8	92	26
86	49.8	42	48.0	96	23	48.3	97	16	46.1	93	18
90	49.9	41	45.9	92	17	47.9	96	9	44.6	89	7
92	49.6	40	44.9	91	15	46.5	94	6			
94	49.2	38	44.7	91	12						
Mean for weeks											
1-13	30.0		30.6	102		30.8	103		30.8	103	
14-52	43.1		43.6	101		43.5	101		43.0	100	
53-94	49.6		48.0	97		48.1	97		48.1	97	

[a] Interim evaluation occurred during week 66.

TABLE 18
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene

Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 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	19.3	58	19.2	100	58	19.1	99	58	19.2	100	58
2	21.6	58	21.7	101	58	21.6	100	58	21.6	100	58
3	22.2	58	22.3	101	58	22.2	100	58	21.8	98	58
4	22.6	58	22.4	99	58	22.5	100	58	22.6	100	58
5	23.9	58	24.0	100	58	23.9	100	58	24.1	101	58
6	24.4	58	24.8	102	58	24.6	101	58	24.8	102	58
7	25.1	58	25.0	100	58	25.3	101	58	25.1	100	58
8	25.3	58	25.7	102	58	25.6	101	58	25.4	100	58
9	26.2	58	26.2	100	58	26.4	101	58	26.3	100	58
10	26.8	58	26.9	100	58	26.9	100	58	26.8	100	58
11	27.1	58	27.3	101	58	27.5	102	58	27.3	101	58
12	27.3	58	28.1	103	58	27.5	101	58	27.6	101	58
13	27.8	58	27.9	100	58	27.5	99	58	27.7	100	58
14	29.2	58	29.4	101	58	29.6	101	58	29.1	100	58
18	30.7	58	30.9	101	58	32.2	105	58	30.5	99	58
22	34.3	58	34.0	99	58	34.6	101	58	33.3	97	56
26	36.2	58	36.6	101	58	37.1	103	58	34.4	95	56
30	38.0	58	39.0	103	58	39.7	105	58	37.0	97	56
34	40.2	58	40.5	101	58	41.9	104	58	38.3	95	56
38	41.7	58	42.6	102	58	43.7	105	58	39.8	95	56
42	43.1	58	43.4	101	58	44.1	102	58	41.8	97	56
46	45.0	58	45.2	100	58	46.0	102	58	44.0	98	56
50	45.7	58	46.0	101	58	47.2	103	58	44.2	97	56
54	47.1	58	47.7	101	58	48.7	103	58	45.8	97	55
58	48.0	57	49.6	103	58	49.8	104	58	47.3	99	55
62	51.0	57	51.3	101	58	52.1	102	58	49.5	97	55
66[a]	50.9	47	50.6	99	44	51.1	100	48	48.8	96	45
70	51.8	47	50.7	98	44	50.9	98	43	49.1	95	42
74	51.6	46	50.4	98	43	49.8	97	40	48.7	94	39
78	51.9	45	51.8	100	38	51.6	99	35	49.5	95	35
82	52.0	44	50.7	98	35	49.4	95	31	48.3	93	28
86	50.7	41	48.8	96	32	50.0	99	22	47.1	93	17
90	49.6	38	45.7	92	20	48.2	97	18	41.4	84	10
92	50.9	37	43.8	86	14	49.2	97	13	41.3	81	7
94	50.5	37				50.8	101	7	40.1	79	4
Mean for weeks											
1-13	24.6		24.7	100		24.7	100		24.6	100	
14-52	38.4		38.8	101		39.6	103		37.2	97	
53-94	50.5		49.2	97		50.1	99		46.4	92	

[a] Interim evaluation occurred during week 66.



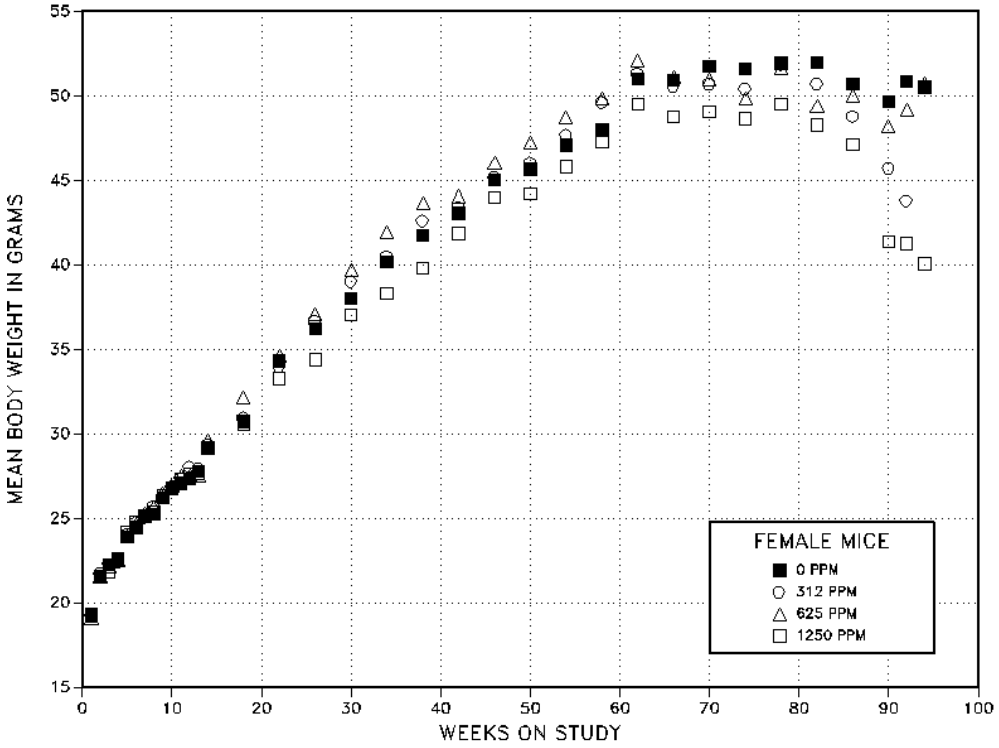


FIGURE 4
Growth Curves for Male and Female Mice Administered Tetrafluoroethylene by Inhalation for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of histiocytic sarcoma and of neoplasms and/or nonneoplastic lesions of the liver, kidney, and spleen. 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.

At the 15-month interim evaluation, absolute and relative lung weights of exposed groups of mice were similar to those of the controls (Table F6), and no lung lesions related to tetrafluoroethylene exposure occurred.

Liver: At the 15-month interim evaluation, absolute and relative liver weights of exposed groups of mice were similar to those of the controls (Table F6). At 15 months and at the end of the study, vascular neoplasms and nonneoplastic lesions occurred in the livers of exposed male and female mice. At the 15-month interim evaluation, hemangiosarcomas occurred in three males exposed to 1,250 ppm and in one female exposed to 312 ppm (Tables 19, C1, and D1). At the end of the study, the incidences of hemangioma in males and females exposed to 312 ppm and in males exposed to 625 ppm were significantly greater than those in the controls (Tables 19, C3, and D3); the incidences of hemangioma in all exposed groups of males and in females exposed to 312 or 625 ppm exceeded the range in historical chamber controls from 2-year NTP inhalation studies (Tables 19, C4a, and D4a). The incidences of hemangiosarcoma in all exposed groups of males and females were significantly greater than those in the controls and exceeded the historical control ranges. The incidences occurred with a significant positive trend in males and females. Multiple hemangiomas occurred in all exposed groups of males and females except females in the 1,250 ppm group, and multiple hemangiosarcomas occurred in all exposed groups of males and females.

Hemangiomas are benign, vascular neoplasms characterized by dilated vascular spaces (Plate 10), with an increase in the number of neoplastic endothelial cells (Plate 11). Hemangiosarcomas are malignant vascular neoplasms characterized by large, irregular, cavernous spaces filled with erythrocytes and masses of fibrin (Plate 12) and lined by variable numbers of pleomorphic endothelial cells which form fronds, solid sheets (Plate 13), or vascular channels around and within extensive areas of thrombosis and necrosis. Although there were high incidences of hepatic hemangiosarcomas in all groups of exposed mice, incidences of this neoplasm in other organs were low. Hemangiosarcomas were observed in the lung, mesentery, pancreas, ovary, bone marrow, and subcutaneous tissues of a few mice exposed to tetrafluoroethylene, and all of these mice had hepatic hemangiosarcomas. It was not clear whether the few extra-hepatic hemangiosarcomas were metastases or whether they arose concomitantly in extra-hepatic sites. There were no hemangiosarcomas in the liver or in other organs of control mice.

At 15 months and at the end of the studies, increased incidences of angiectasis occurred in all exposed groups of males and females (Tables 19, C5, and D5). Angiectasis is characterized by dilated vascular spaces of sinusoids in which the endothelial cells are normal in morphology and number, and the lesion is commonly observed following exposure to a hepatocarcinogen.

At 15 months, hepatocellular adenomas and carcinomas occurred in all control and exposed groups of males, but only in exposed groups of females (Tables 19, C1, and D1). Additionally, the incidences of eosinophilic foci were significantly greater in females exposed to 625 or 1,250 ppm than in the controls (Tables 19 and D5). At the end of the study, the incidence of hepatocellular adenoma in females exposed to 625 ppm was significantly greater than that in the controls and exceeded the historical control range from 2-year NTP inhalation studies. Multiple hepatocellular adenomas occurred in all control and exposed groups of males and females, and the incidences in exposed females were significantly

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Angiectasis[a]	0	1	5*	2
Eosinophilic Focus	0	0	3	0
Necrosis, Coagulative, Multifocal	1	1	0	1
Hemangiosarcoma	0	0	0	3
Hepatocellular Adenoma	6	2	4	1
Hepatocellular Adenoma, Multiple	1	0	2	0
Hepatocellular Carcinoma	2	4	2	2
2-Year Study				
Number Examined Microscopically	48	48	48	48
Angiectasis	0	6**	10**	13**
Eosinophilic Focus	1	6	7*	7*
Necrosis, Coagulative, Multifocal	4	3	13*	11*
Hemangioma[b]	0	10**	5*	2
Hemangioma, Multiple	0	7**	2	1
Hemangiosarcoma[c]	0	21**	27**	37**
Hemangiosarcoma, Multiple	0	16**	17**	18**
Hemangioma or Hemangiosarcoma	0	26**	30**	38**
Hepatocellular Adenoma	17	17	12	20
Hepatocellular Adenoma, Multiple	6	6	7	7
Hepatocellular Carcinoma	11	20**	33**	26**
Hepatocellular Carcinoma, Multiple	4	9**	9**	6*
Hepatocellular Adenoma or Carcinoma[d]	26	34**	39**	35**

(continued)

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Angiectasis	0	4*	2	1
Eosinophilic Focus	0	1	4*	5*
Hemangiosarcoma	0	1	0	0
Hepatocellular Adenoma	0	2	3	2
Hepatocellular Adenoma, Multiple	0	0	0	1
Hepatocellular Carcinoma	0	3	1	3
2-Year Study				
Number Examined Microscopically	48	48	47	47
Angiectasis	1	9*	6	4
Eosinophilic Focus	5	13*	12**	7
Hematopoietic Cell Proliferation	3	19**	13	15**
Hemangioma[e]	0	5*	2	1
Hemangioma, Multiple	0	1	1	0
Hemangiosarcoma[f]	0	27**	27**	34**
Hemangiosarcoma, Multiple	0	8**	12**	15**
Hemangioma or Hemangiosarcoma	0	31**	28**	35**
Hepatocellular Adenoma	15	17	20*	15
Hepatocellular Adenoma, Multiple	1	7**	9**	7**
Hepatocellular Carcinoma	4	28**	22**	20**
Hepatocellular Carcinoma, Multiple	0	5**	7**	7**
Hepatocellular Adenoma or Carcinoma[g]	17	33**	29**	28**

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation), the logistic regression test (2-year study, nonneoplastic lesions and benign neoplasms), or the life table test (2-year study malignant neoplasms and combined incidences, benign and malignant)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Historical incidence for 2-year NTP inhalation studies with chamber control groups at all labs (mean ± standard deviation): 2/947 (0.2% ± 0.7%); range, 0%-2%. Historical incidence for 2-year NTP inhalation studies with chamber control groups at Battelle Pacific Northwest Laboratories: 1/448 (0.2% ± 0.7%); range, 0%-2%
[c] Historical incidence at all labs: 12/947 (1.3% ± 1.7%); range, 0%-6%. Historical incidence at Battelle Pacific Northwest Laboratories: 2/448 (0.5% ± 0.9%); range, 0%-2%
[d] Historical incidence at all labs: 358/947 (37.8% ± 12.5%); range, 11%-60%. Historical incidence at Battelle Pacific Northwest Laboratories: 186/448 (41.5% ± 9.2%); range, 30%-60%
[e] Historical incidence at all labs: 1/937 (0.1% ± 0.5%); range, 0%-2%. Historical incidence at Battelle Pacific Northwest Laboratories: 0/446
[f] Historical incidence at all labs: 5/937 (0.5% ± 1.0%); range, 0%-3%. Historical incidence at Battelle Pacific Northwest Laboratories: 2/446 (0.5% ± 0.9%); range, 0%-2%
[g] Historical incidence at all labs: 200/937 (21.3% ± 11.9%); range, 3%-54%. Historical incidence at Battelle Pacific Northwest Laboratories: 95/446 (21.3% ± 14.8%); range, 6%-54%

increased compared to the controls. The incidences of hepatocellular carcinoma in all exposed groups of males and females were significantly greater than those in the controls and exceeded the historical control ranges (Tables 19, C4a, and D4a).

Multiple hepatocellular carcinomas occurred in all groups of males, including controls. However, in female mice, multiple hepatocellular carcinomas were observed only in the exposed groups. The combined incidences of hepatocellular adenomas and carcinomas in exposed males and females were significantly greater than those in the controls and exceeded the historical control ranges. The incidences in males and females occurred with significant positive trends. Hepatocellular adenomas consisted of nodules of hepatocytes that compressed adjacent liver parenchyma and lacked the normal lobular and sinusoidal pattern (Plate 14). Hepatocellular carcinomas consisted of solid sheets of hepatocytes or trabeculae, three or more cells thick (Plate 15). Neoplastic hepatocytes were anaplastic, with prominent nuclei containing one or more nucleoli and variable amounts of cytoplasm. Frequently, carcinomas had multiple foci of necrosis, hemorrhage, and thrombi. Also at the end of the study, females exposed to 312 or 625 ppm had significantly greater incidences of eosinophilic foci than the controls (Tables 19 and D5).

At 15 months, coagulative multifocal necrosis of the liver occurred in one control male, one male exposed to 312 ppm, and one male exposed to 1,250 ppm (Tables 19 and C5). At the end of the study, incidences of coagulative multifocal necrosis were significantly greater in males exposed to 625 or 1,250 ppm than in the controls. Also at the end of the study, all exposed groups of females had greater incidences of hematopoietic cell proliferation of the liver than the controls, and the increases in females exposed to 312 or 1,250 ppm were significant (Tables 19 and D5). Both coagulative multifocal necrosis and hematopoietic cell proliferation are often associated with malignant neoplasms in the liver of mice.

Hematopoietic System: At the end of the study, the incidences of histiocytic sarcoma (all organs) in all exposed groups of males and females were significantly greater than those in the controls (Tables 20, C3, and D3). The incidences of histiocytic sarcoma in all exposed groups of male and female mice exceeded the historical control ranges for all organs (Tables 20, C4b, and D4b). Although the incidences of this neoplasm were increased in exposed groups of males and females, females had higher incidences than males. The highest incidences of histiocytic sarcoma were observed in the liver and lung, and lower incidences were observed in the spleen, lymph nodes, bone marrow, and kidney. The neoplastic histiocytic cells infiltrated the liver diffusely, but sometimes formed nodular patterns (Plate 16). Marked variations in the size and shape of the neoplastic cells and nuclei and the high cytoplasmic-to-nuclear ratio were distinguishing characteristics. Neoplastic cells had abundant eosinophilic cytoplasm, and nuclei were hyperchromatic and sometimes bean shaped (Plate 17). Occasional giant cells were present. In the lung, marked perivascular infiltrates of neoplastic histiocytic cells were observed, and neoplastic cells were also present in vascular spaces. Many mice with histiocytic sarcomas had cytoplasmic eosinophilic droplets in renal tubule epithelial cells; this is consistent with other studies in which an association between renal tubule hyaline droplet and lysozyme accumulation in mice with histiocytic sarcomas has been demonstrated.

TABLE 20
Incidences of Histiocytic Sarcoma in Mice in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Liver[a] 0/48 (0%)	12/48 (25%)	7/48 (15%)	7/48 (15%)	
Lung	0/48 (0%)	7/48 (15%)	4/48 (8%)	3/48 (6%)
Spleen	0/48 (0%)	2/48 (4%)	1/46 (2%)	2/46 (4%)
Mesenteric Lymph Node	0/47 (0%)	4/42 (10%)	1/41 (2%)	2/40 (5%)
Bone Marrow	0/48 (0%)	1/48 (2%)	1/47 (2%)	2/47 (4%)
Kidney	0/48 (0%)	3/48 (6%)	3/48 (6%)	2/48 (4%)
All Organs[b]				
Overall rate[a]	0/48 (0%)	12/48 (25%)	7/48 (15%)	7/48 (15%)
Adjusted rate[c]	0.0%	47.8%	35.1%	65.8%
Terminal rate[d]	0/38 (0%)	1/11 (9%)	0/2 (0%)	0/1 (0%)
First incidence (days)	—[f]	513	415	527
Life table test[e]	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test[e]	P=0.100	P<0.001	P=0.039	P=0.004
Female				
Liver	1/48 (2%)	21/48 (44%)	19/47 (40%)	18/47 (38%)
Lung	1/48 (2%)	16/48 (33%)	13/47 (28%)	13/47 (28%)
Uterus	1/48 (2%)	0/48 (0%)	0/45 (0%)	0/47 (0%)
Spleen	1/48 (2%)	7/48 (15%)	8/46 (17%)	9/47 (19%)
Mesenteric Lymph Node	1/43 (2%)	6/40 (15%)	7/41 (17%)	6/43 (14%)
Bone Marrow	0/48 (0%)	6/48 (13%)	5/46 (11%)	4/47 (9%)
Kidney	1/48 (2%)	7/48 (15%)	4/47 (9%)	3/47 (6%)
All Organs[g]				
Overall rate	1/48 (2%)	21/48 (44%)	19/47 (40%)	18/48 (38%)
Adjusted rate	2.1%	77.6%	51.3%	78.2%
Terminal rate	0/36 (0%)	1/4 (25%)	0/6 (0%)	1/4 (25%)
First incidence (days)	400	429	457	484
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.015	P<0.001	P<0.001	P<0.001

[a] Number of animals with neoplasm per number of animals examined microscopically
[b] Historical incidence for 2-year NTP inhalation studies with chamber control groups at all labs (mean ± standard deviation): 6/950 (0.6% ± 1.2%); range, 0%-4%. Historical incidence for 2-year NTP inhalation studies with chamber controls at Battelle Pacific Northwest Laboratories: 2/450 (0.4% ± 0.9%); range, 0%-2%.
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence at all labs: 26/941 (2.8% ± 3.1%); range, 0%-10%. Historical incidence at Battelle Pacific Northwest Laboratories: 14/447 (3.1% ± 3.0%); range, 0%-8%

Kidney: At the 15-month interim evaluation, absolute and relative kidney weights of exposed groups of male and female mice were similar to those of the controls (Table F6). Significantly increased incidences of renal tubule dilatation and karyomegaly were observed in male mice exposed to 625 or 1,250 ppm at 15 months (Tables 21 and C5). At the end of the study, the increased incidences of these lesions in exposed groups of males were generally significant. These increased incidences were considered to be related to exposure to tetrafluoroethylene. The severity of renal tubule dilatation was slightly increased at the end of the study in males exposed to 1,250 ppm. Karyomegaly was similar to that observed in the 13-week study and was most prominent in the inner renal cortex (Plates 18 and 19). Dilated renal tubules were filled with eosinophilic amorphous material and were lined by flattened epithelium (Plates 20 and 21). Karyomegaly in renal tubule cells was characterized by nuclei that were enlarged, pleomorphic, and vesicular and had large, prominent, hyperchromatic nucleoli (Plate 20). At 15 months, karyomegaly was present in females exposed to 625 or 1,250 ppm, but at the end of the study, this lesion was observed only in females in the 1,250 ppm group. Tubule dilatation was not present in female mice at 15 months or at the end of the study. At the interim evaluation, tubule changes were more clearly

TABLE 21
Incidences of Nonneoplastic Lesions of the Kidney in Mice in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Renal Tubule, Dilatation[a]	0	0	6** (1.0)[b]	10** (1.2)
Renal Tubule, Karyomegaly	0	0	4* (1.0)	10** (1.0)
2-Year Study				
Number Examined Microscopically	48	48	48	48
Renal Tubule, Dilatation	0	4** (1.0)	16** (1.0)	36** (1.4)
Renal Tubule, Karyomegaly	1 (1.0)	2 (1.0)	10** (1.0)	28** (1.0)
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Renal Tubule, Karyomegaly[c]	0	0	10** (1.0)	10** (2.0)
2-Year Study				
Number Examined Microscopically	48	48	47	48
Renal Tubule, Karyomegaly[c]	0	0	0	38** (1.8)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesion in affected mice: 1=minimal; 2=mild; 3=moderate; 4=severe
[c] Results of a special review

defined; however, by the end of the study, the changes were sometimes obscured by concurrent age-related background lesions (i.e., inflammation). Karyomegaly was located in the tubules in the inner renal cortex.

Spleen: Incidences of hematopoietic cell proliferation in all exposed groups of males and females were significantly greater than those in the controls at the end of the study (Tables 22, C5, and D5). Additionally, the severity of this lesion increased with increasing exposure concentration. Hematopoietic cell proliferation was frequently associated with the presence of malignant neoplasms in the livers of affected mice.

GENETIC TOXICOLOGY

No increases in the frequency of micronucleated normochromatic erythrocytes were observed in peripheral blood samples obtained from male and female mice at the end of the 13-week inhalation study of tetrafluoroethylene (Table E1).

TABLE 22
Incidences of Nonneoplastic Lesions of the Spleen in Mice in the 2-Year Inhalation Study of Tetrafluoroethylene

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Hematopoietic Cell Proliferation[a]	2 (2.0)[b]	4 (2.0)	5 (1.6)	3 (1.7)
2-Year Study				
Number Examined Microscopically	48	48	46	46
Hematopoietic Cell Proliferation	14 (2.1)	32* (2.7)	41** (2.9)	42** (3.0)
Female				
15-Month Interim Evaluation				
Number Examined Microscopically	10	10	10	10
Hematopoietic Cell Proliferation	2 (1.5)	4 (1.8)	4 (1.5)	3 (2.0)
2-Year Study				
Number Examined Microscopically	48	48	46	47
Hematopoietic Cell Proliferation	18 (2.1)	39** (2.8)	41** (2.9)	41** (2.9)

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

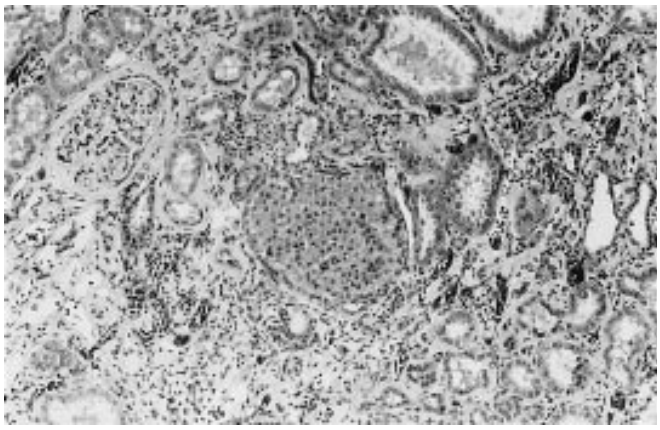


PLATE 1
Kidney of a male F344/N rat exposed to 312 ppm tetrafluoroethylene by inhalation for 2 years. Hyperplasia is focal. Note that the renal tubule is lined by increased numbers of tubule epithelial cells, which totally fill the tubule lumen. H&E; 33×

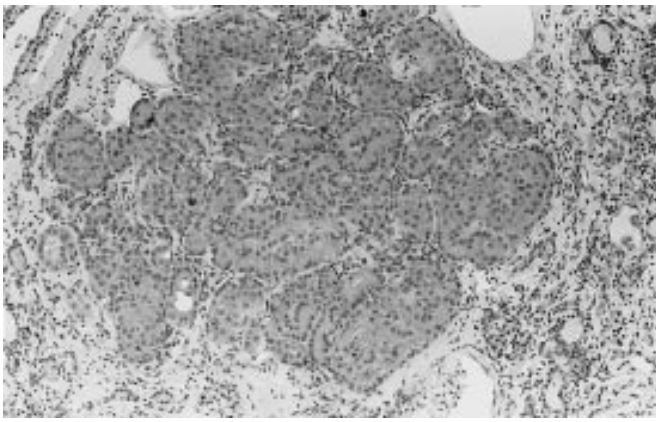


PLATE 2
Renal tubule adenoma in the kidney of a male F344/N rat exposed to 625 ppm tetrafluoroethylene by inhalation for 2 years. Note the adenoma is greater than five renal tubules in diameter and neoplastic cells are mildly pleomorphic and tend to form irregular clusters. H&E; 33×

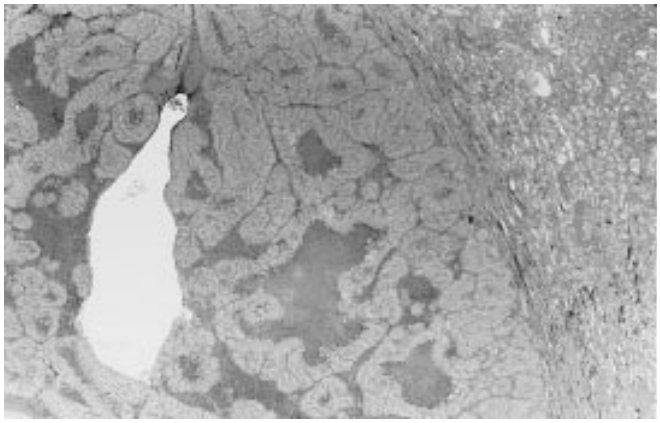


PLATE 3
Renal tubule carcinoma in the kidney of a female F344/N rat exposed to 1,250 ppm tetrafluoroethylene by inhalation for 2 years. Note the carcinoma is much larger, less discrete, and has a more prominent vascular supply than the adenoma in Plate 2. H&E; 6.6×

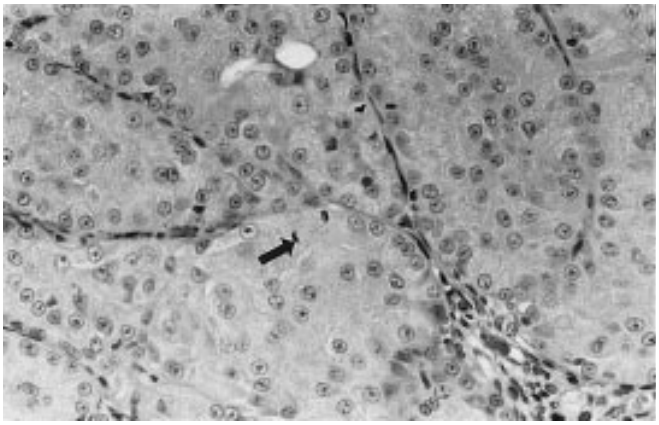


PLATE 4
Higher magnification of Plate 3. Note neoplastic cells are arranged in irregular clusters and are characterized by vesiculate nuclei with prominent nucleoli and increased mitotic figures (arrow). H&E; 100×

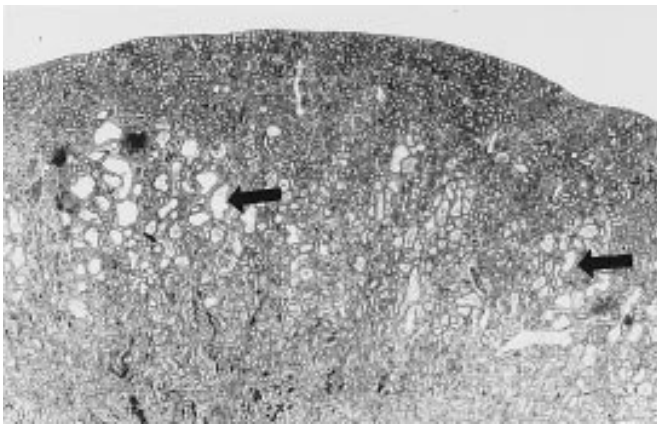


PLATE 5
Renal tubule degeneration (arrows) in a male F344/N rat exposed to 625 ppm tetrafluoroethylene by inhalation for 2 years. Degeneration is characterized by dilatation of renal tubules in the cortex near the corticomedullary junction, with or without eosinophilic debris and/or proteinaceous fluid in their lumens. H&E; 5×

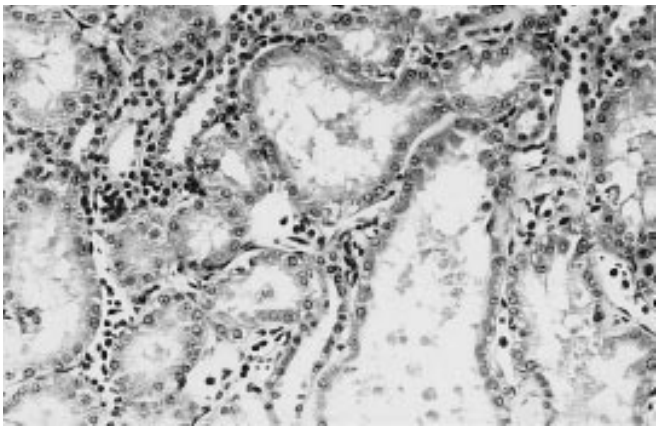


PLATE 6
Higher magnification of Plate 5 at the corticomedullary junction. Degeneration is characterized by dilatation of renal tubules with or without eosinophilic debris and/or proteinaceous fluid in their lumens. The renal tubules are lined by cuboidal epithelium. H&E; 66×

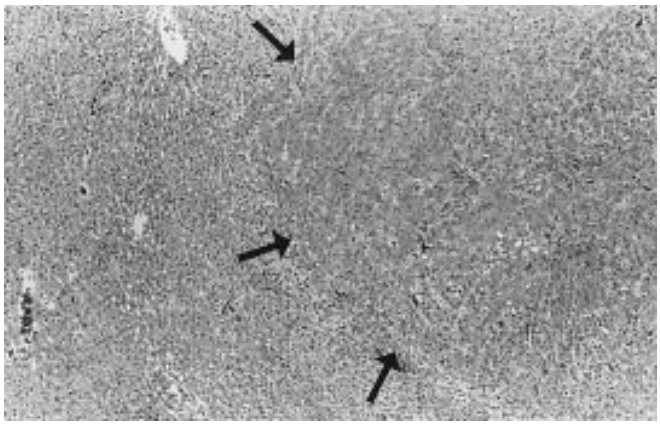


PLATE 7
Hepatocellular adenoma in the liver of a female F344/N rat exposed to 312 ppm tetrafluoroethylene by inhalation for 2 years. Note the hepatocellular adenoma caused compression of the adjacent liver parenchyma (arrows), and the adenoma lacks normal lobular architecture. H&E; 16×

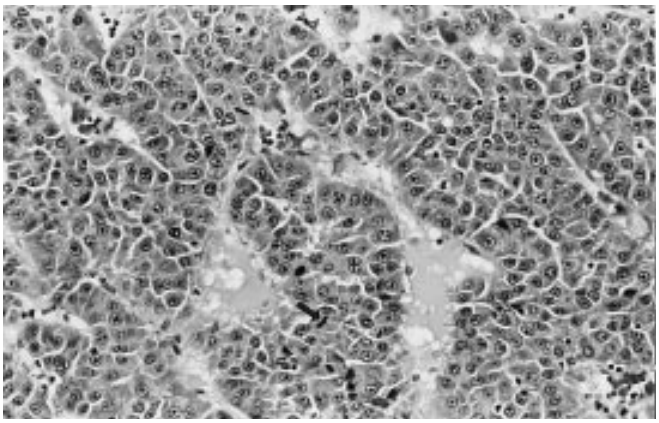


PLATE 8
Hepatocellular carcinoma from a male F344/N rat exposed to 312 ppm tetrafluoroethylene by inhalation for 2 years. The high magnification shows the trabecular pattern, three or more cells thick. Note the prominent mitotic figures (arrow). H&E; 66×

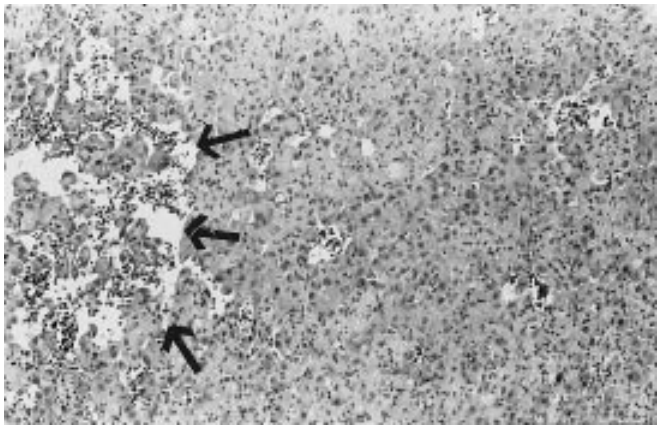


PLATE 9
Hemangiosarcoma in the liver of a female F344/N rat exposed to 625 ppm tetrafluoroethylene by inhalation for 2 years. Note the irregular, vascular spaces (arrow) containing variable numbers of erythrocytes. This hemangiosarcoma metastasized to the lung. H&E; 33×

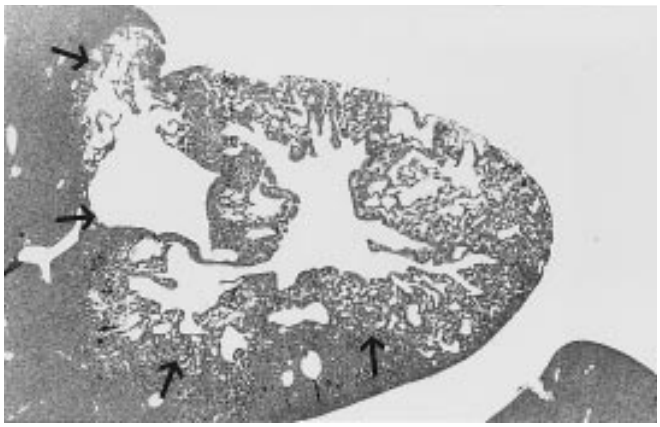


PLATE 10
Hemangioma (arrows) in the liver (L) of a male B6C3F$_1$ mouse exposed to 312 ppm tetrafluoroethylene by inhalation for 2 years. H&E; 6.6×

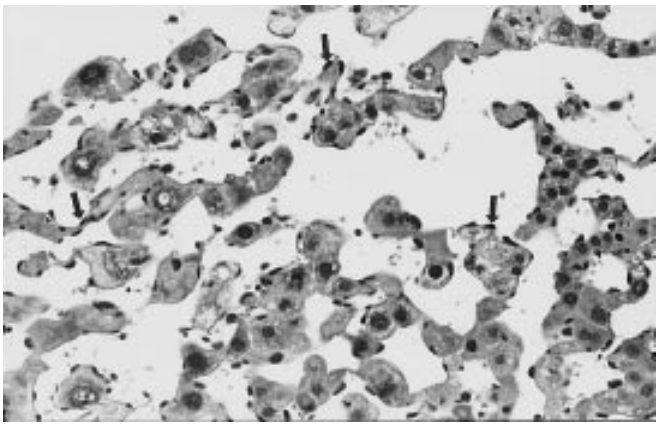


PLATE 11
Higher magnification of Plate 10 showing the dilated sinusoids with an increased number of neoplastic endothelial cells (arrows). H&E; 66×

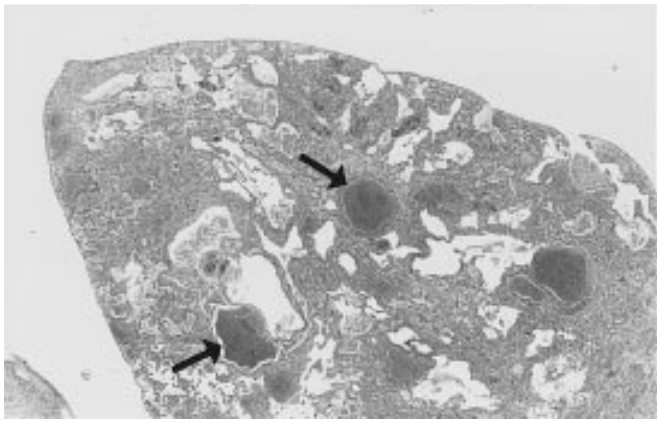


PLATE 12
Hemangiosarcoma in the liver of a male B6C3F$_1$ mouse exposed to 1,250 ppm tetrafluoroethylene by inhalation for 2 years. Note the large, irregular, cavernous spaces filled with erythrocytes (arrows). H&E; 5×

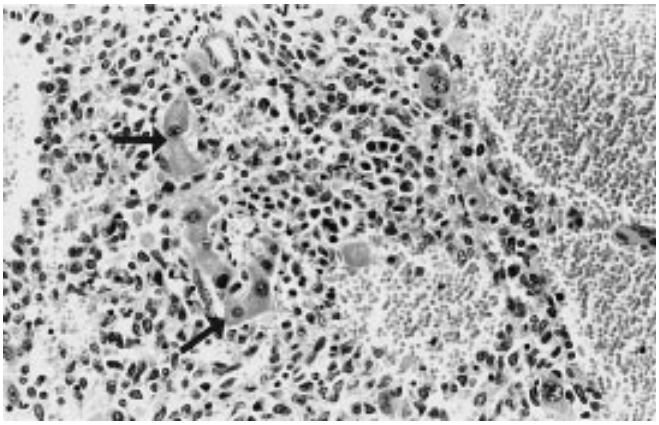


PLATE 13
Higher magnification of Plate 12, showing sheets of anaplastic, pleomorphic, endothelial cells that efface the liver parenchyma with only a few hepatocytes remaining (arrows). H&E; 80×

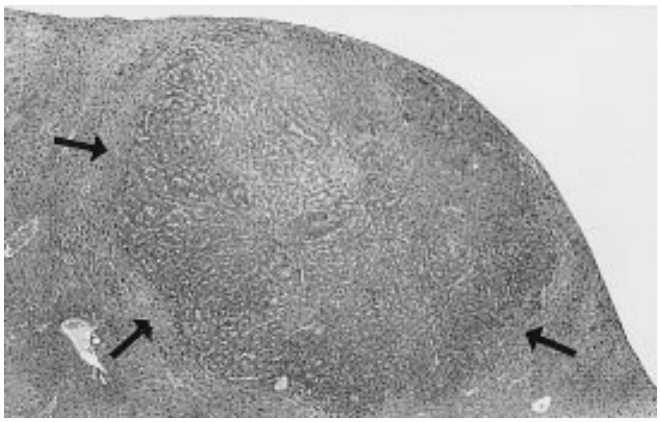


PLATE 14
Hepatocellular adenoma in the liver of a male B6C3F$_1$ mouse exposed to 1,250 ppm tetrafluoroethylene by inhalation for 2 years. Note the hepatocellular adenoma caused compression of the adjacent liver parenchyma (arrows), and the adenoma lacks normal lobular architecture. H&E; 10×

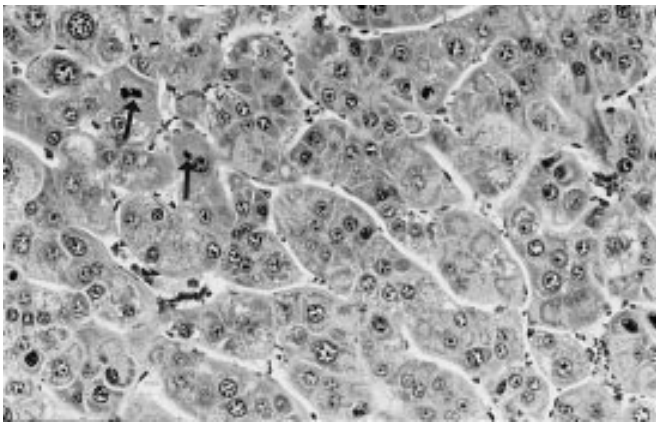


PLATE 15
Hepatocellular carcinoma from a male B6C3F$_1$ mouse exposed to 1,250 ppm tetrafluoroethylene by inhalation for 2 years. The high magnification shows the trabecular pattern, three or more cells thick. Note the prominent mitotic figures (arrows). H&E; 80×

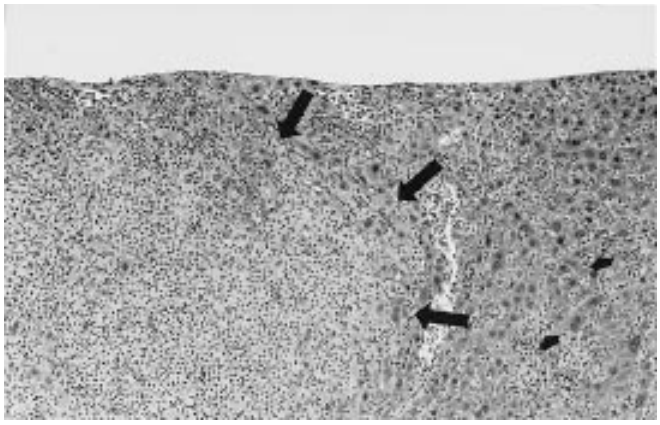


PLATE 16
Histiocytic sarcoma in the liver of a male B6C3F$_1$ mouse exposed to 1,250 ppm tetrafluoroethylene by inhalation for 2 years. Note the nodular (arrows) and infiltrative (arrowheads) nature of the neoplastic cells between hepatic plates. H&E; 25×

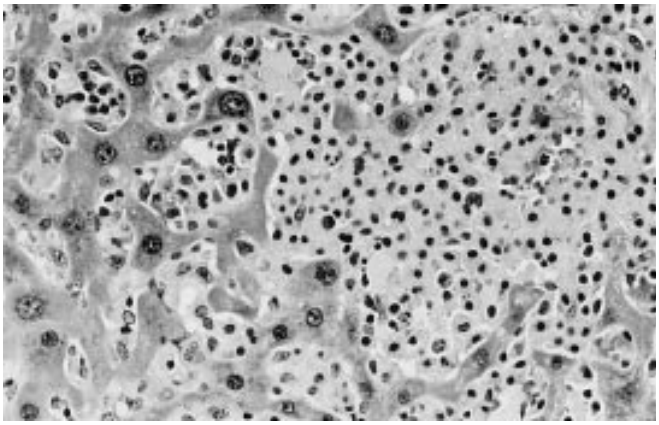


PLATE 17
Higher magnification of Plate 16. Note the neoplastic cells have abundant eosinophilic cytoplasm and nuclei are hyperchromatic and sometimes bean-shaped. H&E; 100×

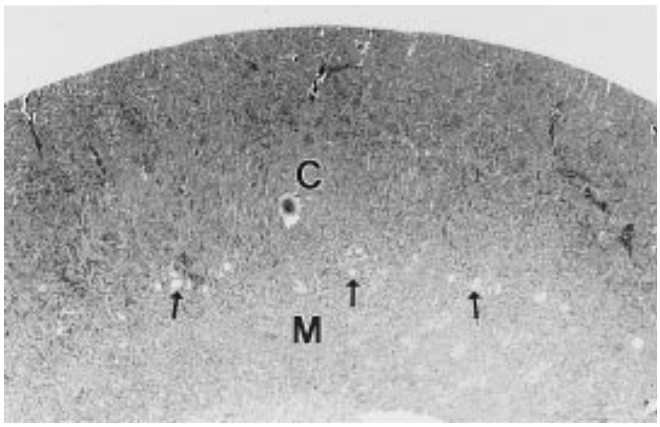


PLATE 18
Kidney of a male B6C3F$_1$ mouse exposed to 1,250 ppm tetrafluoroethylene for 2 years. Compare to kidney from a control mouse in Plate 19. Renal tubule dilatation (arrows) and karyomegaly were most prominent at the junction between the cortex (C) and medulla (M). H&E; 5×

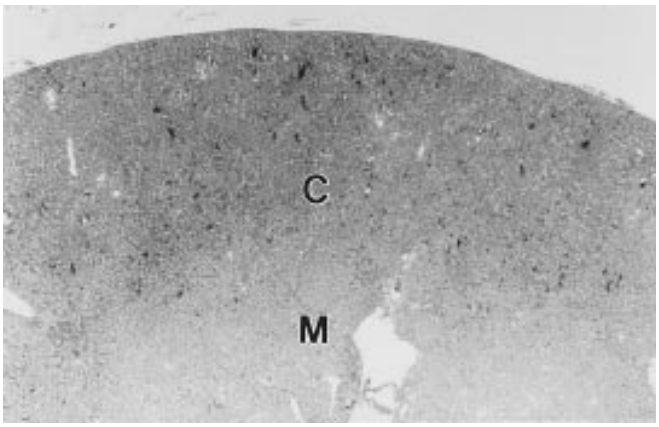


PLATE 19
Kidney from a male B6C3F$_1$ mouse exposed to filtered air for 2 years. Note the lack of tubular dilatation at the junction between the cortex (C) and medulla (M). H&E; 5×

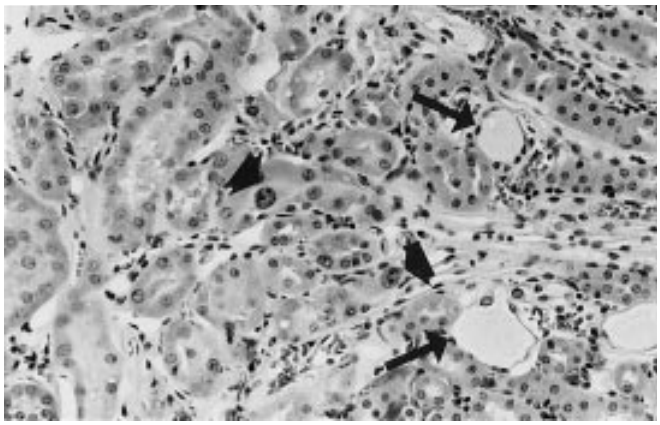


PLATE 20
Higher magnification of Plate 18 at the corticomedullary junction. Note the dilated renal tubules are filled with eosinophilic amorphous material and lined by flattened epithelium (arrows). Karyomegaly in renal tubule cells was characterized by nuclei that were enlarged and had prominent nucleoli (arrowhead). Compare with kidney from a control mouse in Plate 21. H&E; 66×

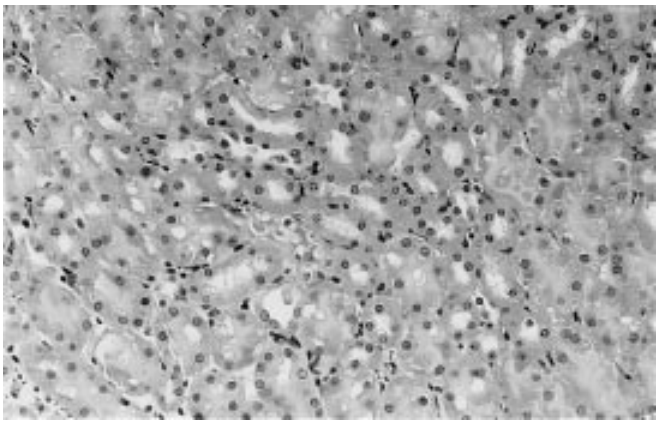


PLATE 21
Higher magnification of Plate 19. Note the lack of tubular dilatation and karyomegaly. H&E; 66×

DISCUSSION AND CONCLUSIONS

Tetrafluoroethylene was evaluated for toxicity and carcinogenicity in 16-day, 13-week, and 2-year studies in male and female F344/N rats and B6C3F$_1$ mice, with whole body inhalation as the route of exposure.

In the 16-day studies, there were no exposure-related deaths, clinical findings, or effects on hematologic parameters. Mean body weights of male and female rats exposed to 5,000 ppm were lower than those of the controls. Absolute kidney weights of all exposed groups of male rats, female rats exposed to 1,250 ppm, and female mice exposed to 5,000 ppm were greater than those of controls. Relative liver weights of all exposed groups of male rats and of female mice exposed to 5,000 ppm were also greater than those of the controls; however, there were no histopathologic effects in the liver. There were exposure concentration-related effects on the kidneys of exposed rats and mice, although the effects were different between the species. In rats, the kidney lesion (renal tubule degeneration) was located predominantly in the inner cortical tubule epithelial cells at the junction of the cortex and medulla and was observed in male and female rats exposed to 625 ppm or greater. This lesion has been observed previously in rats exposed to tetrafluoroethylene and other halogenated compounds and is well documented in the literature. In mice, the lesion was characterized as renal tubule karyomegaly; however, it was also located primarily in the inner renal cortex.

In the 13-week studies, there were no exposure-related deaths or clinical findings. Mean body weight gains of male and female rats exposed to 5,000 ppm were marginally reduced. Although there were no treatment-related lesions in the livers of exposed rats or mice, absolute and relative liver weights of female rats exposed to 5,000 ppm and all exposed groups of male rats were significantly increased. Absolute and relative kidney weights of male rats exposed to 1,250 ppm or greater and females exposed to 625 ppm or greater were significantly increased. Absolute and relative kidney weights of exposed mice were not significantly different from those of the controls.

Exposure concentration-related renal lesions similar to those observed in the 16-day study were observed in male rats exposed to 625 ppm or greater and in female rats in the 2,500 and 5,000 ppm groups. These lesions were considered mild at most. As with exposed rats, mice exposed to 1,250 ppm or greater in the 13-week study also developed kidney lesions similar to those observed in mice at 16 days, and these lesions were slightly more severe in males than in females. A concentration-related proteinuria occurred in all exposed groups of rats with kidney lesions. Proteinuria could be related to either glomerular or proximal tubule renal injury and, in the present study, would be consistent with the renal tubule degeneration observed morphologically. Polyuria occurred in exposed mice and probably in rats and could be related to a variety of conditions, including overdrinking, osmotic diuresis, damage to the proximal and/or distal portions of the renal tubule, and alterations of metabolism or kidney response to antidiuretic hormone (Finco, 1989). Based on an appropriate response to a water concentration test (rats only), the ability of the kidney to concentrate the urine was not compromised, indicating that the pituitarykidney ADH axis was intact and that there was no medullary washout (which could occur with conditions such as long-term overhydration or hyperadrenocorticism). Therefore, the renal damage observed morphologically, although different for rats and mice, would appear to involve primarily the proximal convoluted tubules.

An exposure concentration-dependent normocytic, normochromic, nonresponsive anemia occurred in exposed rats and mice in the 13-week studies. Normocytic, normochromic, nonresponsive anemias have been related to selective suppression of erythropoiesis in a variety of chronic disorders and may be related to decreased erythropoietin elaboration, bone marrow suppression, or defective iron metabolism (Jain, 1986). Because there was histopathologic evidence of exposure concentration-dependent renal lesions in male and female rats and mice, the anemia would be consistent with a secondary hypoproliferative

anemia, possibly related to altered erythropoietin production/metabolism in the kidney.

In the 2-year study, survival was reduced in male rats exposed to 625 ppm and in all exposed female rats. Mean body weights of exposed rats were generally similar to those of the controls until the end of the study, at which time mean body weights were lower in males in the 625 ppm group and females in the 1,250 ppm group than in the controls. These reductions reflected the mean body weights of a very small number of surviving rats. The only exposure-related clinical finding was eye opacity in female rats, which upon histological examination was determined to be cataracts. At the 15-month interim evaluation, relative kidney weights of male rats exposed to 312 or 625 ppm and absolute kidney and liver weights of females exposed to 625 or 1,250 ppm were significantly greater than those of the controls.

The renal toxicity noted in male and female rats in the 13-week study was exacerbated in the 2-year study in that exposure to tetrafluoroethylene caused increased incidences of neoplasms and nonneoplastic lesions of the kidney in rats. As in the 13-week studies, renal tubule degeneration was associated with the proximal tubules at the corticomedullary junction, and the incidence was significantly increased at 15 months and 2 years. The only difference between the two time points was that the renal lesions were generally more severe and more numerous after 2 years.

Additional sections of the kidney were taken to further evaluate the renal proliferative effects. These sections did detect additional proliferative lesions and generally confirmed the findings of the single sections. Exposure to tetrafluoroethylene caused significantly increased incidences of hyperplasia at 15 months and 2 years in male and female rats. In the combined extended and standard evaluations, the incidences of renal tubule adenoma or carcinoma (combined) were significantly increased, with positive trends in exposed males and females. Because these neoplasms, which are considered uncommon, occurred consistently and because the incidences increased with increasing exposure concentration, the neoplasms are considered to have been caused by tetrafluoroethylene exposure. Similarly, increased incidences of renal tubule hyperplasia, adenoma, and carcinoma in male rats have been reported following inhalation exposure to 200 and 400 ppm tetrachloroethylene, a structurally related compound (NTP, 1986). In addition, incidences of karyomegaly were significantly increased in male and female rats exposed to tetrachloroethylene.

Considerable effort has been expended in the past 10 years investigating the mechanism of tetrafluoroethylene-induced renal proximal tubule toxicity, primarily in rats (Odum and Green, 1984; Boogaard *et al.*, 1989; Commandeur *et al.*, 1989; Hayden *et al.*, 1991a,b), and that induced by other halogenated compounds. Tetrafluoroethylene is conjugated in the liver with glutathione and subsequently excreted via the bile to the small intestine, where biliary and intestinal peptidases degrade them to cysteine-*S*-conjugates which may be reabsorbed from the small intestine. Glutathione conjugates released into the general circulation from the liver are also hydrolyzed to cysteine-*S*-conjugates by renal peptidases, where they are bioactivated by renal β-lyase to unstable reactive thiols. The tetrafluoroethylene cysteine conjugate, *S*-(1,1,2,2-tetrafluoroethyl)-*L*-cysteine, and tetrafluoroethylene mercapturic acid have been shown to cause renal damage *in vivo* identical to that caused by tetrafluoroethylene and to have greater enzyme activation activity than several chlorinated or brominated compounds; additionally, exposure to these compounds causes their accumulation in the proximal tubule cells (Commandeur *et al.*, 1989). Like tetrafluoroethylene, they are not mutagenic. The tetrafluoroethylene cysteine conjugate has also been shown to cause death to cultured human proximal tubule cells, as indicated by the release of lactate dehydrogenase. Toxicity and binding to macromolecules in human renal cells can be prevented with aminooxyacetic acid, a known β-lyase inhibitor; this process has also been demonstrated for rat renal cells (Chen *et al.*, 1990). In rats, the cysteine conjugate is further bioactivated in the kidney and, to a lesser extent, in the liver to a difluorothionacetyl fluoride, the putative reactive metabolite for tetrafluoroethylene-induced nephrotoxicity. The thionacetyl fluorides cause mitochondrial dysfunction by inhibiting adenosine diphosphate-stimulated respiration, increasing lipid peroxidation, modifying mitochondrial proteins (HSP60 and HSP70), and inhibiting lipoyl dehydrogenase; by binding to macromolecules; and by forming protein and phospholipid adducts. The difluorothioamide adduct has been shown to cause nephrotoxicity in the

proximal tubule. Considering the similarity in effects and location of renal lesions in the present 2-year inhalation studies and the metabolism and toxicity studies reported in the literature, similar metabolites and common mechanisms may be involved in the carcinogenic response in the kidney of tetrafluoroethylene-exposed animals.

Although no liver lesions were observed in the 13-week studies, exposure to tetrafluoroethylene for 2 years caused increased incidences of nonneoplastic lesions and uncommon neoplasms of the liver in rats; these neoplasms include hemangiosarcomas, which have not been observed previously in chamber control rats from 2-year NTP inhalation studies. Hepatocellular foci (including clear cell, eosinophilic, and mixed cell) were observed in rats at the 15-month interim evaluation. At 2 years, the incidences of eosinophilic and mixed cell foci were significantly increased in exposed male rats and slightly increased in exposed female rats. At 15 months, one male exposed to 312 ppm had a hepatocellular adenoma and one male exposed to 625 ppm had a hepatocellular carcinoma. At the end of the 2-year study, male rats in the 312 ppm group had significantly increased incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined); in females, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) in all exposed groups and the incidences of hepatocellular carcinoma in the 312 and 625 ppm groups were significantly greater than those in the controls. There were no adenomas or carcinomas in control females. The incidences of hepatocellular adenoma or carcinoma (combined) occurred with positive trends in exposed males and females, even though the 8% incidence in the control male rats in the present study exceeds the previous highest incidence of 4% for inhalation chamber controls. The fact that fewer hepatocellular neoplasms occurred in male and female rats exposed to the highest concentrations (625 ppm for males, 1,250 ppm for females) than in rats exposed to lower concentrations may be a result of reduced survival. Also, the highest exposure concentration for males was half that for females.

Exposure to tetrafluoroethylene also caused hemangiosarcomas of the liver in female rats. These uncommon liver neoplasms have not been observed previously in male or female chamber controls from 2-year NTP inhalation studies or in untreated controls by any oral route of exposure. Hepatic angiectasis, characterized by multifocal, dilated, blood-filled sinusoids with prominent lining endothelial cells, was observed in exposed groups of female rats. This lesion is sometimes associated with hepatocellular neoplasms. Cystic degeneration of the liver occurs at a low incidence in aging rats; however, following exposure of rats to hepatocarcinogens, the incidence has been shown to be increased. In fact, the incidences of cystic degeneration in exposed groups of male rats were significantly greater than the control group incidence.

The incidence of mononuclear cell leukemia in male rats exposed to 156 ppm was significantly greater than in controls. In males, interpretation of the increased incidence of mononuclear cell leukemia is complicated by reduced survival in rats exposed to 625 ppm and the fact that the control incidence exceeded the previous historical chamber control range. The incidence of mononuclear cell leukemia in male rats exposed to 312 ppm, although not significantly greater than that in the control group, also exceeded the previous historical range. Whether this response in male rats was caused by tetrafluoroethylene exposure is uncertain. However, there was a significant increase in the incidence of mononuclear cell leukemia in all exposed groups of female rats. The incidence of mononuclear cell leukemia in female controls from the present study was within the historical control range. The increased incidence of mononuclear cell leukemia in female rats is considered to have been caused by exposure to tetrafluoroethylene. Exposure to tetrachloroethylene for 2 years (NTP, 1986) also caused an increase in the incidence of mononuclear cell leukemia in male and female F344/N rats exposed to 200 or 400 ppm.

At 15 months, there were no increases in the incidence of interstitial adenoma or interstitial cell hyperplasia. At the end of the 2-year study, there was a slight but statistically significant increase in the incidence of interstitial cell adenoma in the testes of rats exposed to 312 or 625 ppm. It is uncertain whether these increased incidences of adenomas were due to tetrafluoroethylene exposure; however, there was a similar slight but significant increase in the incidence of interstitial cell adenomas in F344/N rats exposed to 200 or 400 ppm tetrachloroethylene for 2 years (NTP, 1986).

Exposure to tetrafluoroethylene for 2 years caused a significant increase in the incidence of cataracts in female rats exposed to 1,250 ppm. The lesion was characterized by a disruption of the normal organization of lens fibers, with swelling, vacuolization, and mineralization.

In the 2-year mouse study, survival was reduced in all exposed male and female mice to the extent that the study was terminated at week 96. The reduction in survival was considered to be the result of exposure-related neoplasms of the liver. Mean body weights of exposed mice were generally similar to those of controls except at the end of the study, where survival was significantly decreased.

As observed in the 2-year rat study, exposure of mice to tetrafluoroethylene caused significant increases in the incidences of nonneoplastic lesions and uncommon neoplasms of the liver in mice at 15 months and 2 years. Exposure to tetrafluoroethylene caused hemangiomas in the liver of male and female mice, and multiple hemangiomas were observed in males and females. These uncommon neoplasms were not observed in control mice. Hemangiosarcomas caused by exposure to tetrafluoroethylene were observed as early as 15 months in males in the 1,250 ppm group and females in the 312 ppm group. Hemangiosarcomas occurred with statistically significant incidences and with a positive trend in all groups of exposed males and females. The incidences of multiple hemangiosarcomas were significant in all exposed groups of males and females. In a few males and females, the hemangiosarcomas metastasized to the lung. Hemangiosarcomas were not observed in male or female control mice. The incidences of hemangioma or hemangiosarcoma (combined) were also highly significant and occurred with a positive trend for exposed groups of males and females. Hemangiomas and hemangiosarcomas are uncommon neo-plasms in mice in studies using such routes as feed or dosed water, and the historical incidences of these neoplasms in untreated mice from 2-year NTP feed and dosed water studies are similar to those for inhalation chamber control mice. The rarity of these neoplasms further accentuates the striking results of the present study. These uncommon neoplasms probably had a significant effect on the survival of mice in the present study.

Although exposure to 100 or 200 ppm tetrachloroethylene for 2 years caused increased incidences of hepatocellular adenoma and carcinoma in male and female mice, there were no exposure-related increases in hemangioma or hemangiosarcoma incidences (NTP, 1986). However, chronic inhalation exposure to vinyl chloride (chloroethylene) has caused hemangiosarcomas and hepatocellular adenomas and carcinomas in several strains of rats, mice, and hamsters (IARC, 1979, 1987). More importantly, a number of epidemiologic studies have shown that workers exposed to vinyl chloride have higher mortality rates and a high incidence of neoplasms in the liver, brain, lung, and lymphatic and hematopoietic systems, all attributed to vinyl chloride exposure. Neoplasms observed in the liver of these workers include hemangiosarcomas and hepatocellular adenomas and carcinomas. Liver neoplasms caused by vinyl chloride exposure in laboratory animals and humans are similar to those observed in rats and mice exposed to tetrafluoroethylene.

Angiectasis, eosinophilic foci, and coagulative multifocal necrosis of the liver were observed at 15 months and were significantly increased in incidence and severity at 2 years. The incidences of hepatocellular adenoma or carcinoma (combined) were increased in all exposed groups of male mice and were significantly greater in all exposed groups of female mice than in the control group. Many animals had multiple adenomas or carcinomas. In all exposed groups, the incidences of multiple adenomas and multiple carcinomas in female mice and multiple carcinomas in male mice were significantly increased. A number of the carcinomas in exposed males and females, but only one carcinoma in each of the male and female control groups, metastasized to the lung. Incidences of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) in control male and female mice were within the historical ranges in chamber control mice from 2-year NTP inhalation studies. The increased incidences of these neoplasms in exposed male and female mice were considered to be exposure related. A low frequency (15%) of H-*ras* codon 61 mutations was observed in tetrafluoroethylene-induced hepatocellular neoplasms when compared to the frequency in neoplasms in controls (59%) or in spontaneous liver neoplasms of B6C3F$_1$ mice (56%) (Appendix L). This frequency is similar to that detected in liver neoplasms in B6C3 F$_1$ mice exposed to

tetrachloroethylene (24%) (Anna *et al*., 1994). Although a few neoplasms in the tetrachloroethylene study were found to have a K-*ras* mutation, none were found in neoplasms in the tetrafluoroethylene study. These data indicate that these two hepatocellular carcinogens induce liver neoplasms via a *ras*-independent pathway.

The incidence of histiocytic sarcoma was markedly increased in exposed male mice and significantly increased in all female mice, although not in an exposure concentration-related manner. Among mice with any histiocytic sarcomas, histiocytic sarcomas were present in the liver of all animals and in the lung of many animals. The spleen, lymph nodes, bone marrow, and kidney were also affected. Combined with the hepatocellular adenomas and carcinomas, hemangiomas, and hemangiosarcomas, the presence of histiocytic sarcomas in exposed mice compromised liver function, ultimately leading to the death of the mice.

In the 13-week mouse study, renal tubule karyomegaly, accompanied by a polyuria, occurred in male and female mice exposed to 1,250 ppm or greater and was the only consideration for exposure concentration selection for the 2-year study. Although there were no kidney neoplasms in exposed groups of mice as were observed in the 2-year rat study, there were significantly increased incidences of renal tubule dilatation in exposed males and renal tubule karyomegaly, located in the tubules in the inner cortex, in males and females. These lesions were observed at 15 months as well as at the end of the study. In general, only the incidences of these lesions increased over the course of the study, while the severities remained essentially unchanged; in fact, the severity of karyomegaly was similar to that observed in the 13-week study at the same exposure concentration. Although these lesions were observed in all exposed groups of males at the end of the study, incidences of karyomegaly were observed only in 1,250 ppm females; however, this group had a high incidence. As in the 13-week study, males were affected more than females, and the increased incidences of both nonneoplastic lesions were considered to be related to exposure to tetrafluoroethylene. The effect of tetrafluoroethylene exposure on the kidney of mice is very similar to the effects of exposure to 100 or 200 ppm tetrachloroethylene for 2 years (NTP, 1986), in that tetrachloroethylene caused increased incidences of karyomegaly in male and female mice without causing increased incidences of kidney neoplasms.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of tetrafluoroethylene in male F344/N rats based on increased incidences of renal tubule neoplasms (mainly adenomas) and hepatocellular neo-plasms. There was *clear evidence of carcinogenic activity* of tetrafluoroethylene in female F344/N rats based on increased incidences of renal tubule neoplasms, liver hemangiosarcomas, hepatocellular neoplasms, and mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of tetrafluoroethylene in male and female $B6C3F_1$ mice based on increased incidences of liver hemangiomas and hemangiosarcomas, hepatocellular neoplasms, and histiocytic sarcomas.

Slight increases in the incidences of mononuclear cell leukemia and testicular interstitial cell adenomas in male rats may have been related to exposure to tetrafluoroethylene.

Exposure of rats to tetrafluoroethylene resulted in increased incidences of renal tubule hyperplasia and degeneration in males and females, increased severity of kidney nephropathy in males, and increased incidences of liver angiectasis and cataracts in females. Exposure of mice to tetrafluoroethylene resulted in increased incidences of hematopoietic cell proliferation of the liver in females, liver angiectasis in males and females, renal tubule dilatation in males, renal tubule karyomegaly in males and females, and splenic hematopoietic cell proliferation in males and females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

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

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

	0 ppm	156 ppm	312 ppm	625 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	27	34	32	48
Natural deaths	6	4	1	1
Survivors				
Terminal sacrifice	17	12	17	1
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Polyp adenomatous		1 (10%)		
Intestine small, duodenum	(10)	(10)	(10)	(10)
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma				1 (10%)
Hepatocellular adenoma			1 (10%)	
Mesentery	(2)		(2)	(4)
Endocrine System				
Pituitary gland	(10)	(9)	(10)	(10)
Pars distalis, adenoma	2 (20%)	3 (33%)	1 (10%)	4 (40%)
Pars distalis, adenoma, multiple	1 (10%)			
Pars intermedia, adenoma	1 (10%)			
Thyroid gland	(10)	(10)	(10)	(10)
Follicular cell, adenoma	1 (10%)			
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Preputial gland	(10)	(10)	(10)	(10)
Carcinoma	1 (10%)			
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	7 (70%)	5 (50%)	10 (100%)	9 (90%)
Interstitial cell, adenoma	2 (20%)	2 (20%)		1 (10%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Subcutaneous tissue, sarcoma			1 (10%)	
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar carcinoma	1 (10%)			

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

	0 ppm	156 ppm	312 ppm	625 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Renal tubule, carcinoma				1 (10%)
Urinary bladder	(10)	(10)	(10)	(10)
Transitional epithelium, papilloma		1 (10%)		
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear				1 (10%)
Mesothelioma malignant				1 (10%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Intestine small, jejunum	(48)	(47)	(49)	(50)
Intestine small, ileum	(49)	(49)	(50)	(50)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)	1 (2%)	10 (20%)	3 (6%)
Hepatocellular adenoma	2 (4%)	3 (6%)	5 (10%)	4 (8%)
Hepatocellular adenoma, multiple	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Hepatocholangioma		1 (2%)		
Mesentery	(15)	(11)	(18)	(14)
Hepatocellular carcinoma, metastatic, liver				1 (7%)
Pancreas	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Acinus, adenoma		2 (4%)	1 (2%)	1 (2%)
Pharynx	(1)			
Palate, squamous cell carcinoma	1 (100%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Tongue	(1)	(1)		(1)
Squamous cell papilloma	1 (100%)	1 (100%)		

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

	0 ppm	156 ppm	312 ppm	625 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma NOS		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			2 (4%)	
Adrenal medulla	(50)	(50)	(50)	(50)
Ganglioneuroma				1 (2%)
Pheochromocytoma malignant	2 (4%)		1 (2%)	
Pheochromocytoma complex		1 (2%)		
Pheochromocytoma benign	15 (30%)	8 (16%)	8 (16%)	6 (12%)
Bilateral, pheochromocytoma benign	4 (8%)	3 (6%)	1 (2%)	4 (8%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Carcinoma	1 (2%)	5 (10%)	1 (2%)	1 (2%)
Parathyroid gland	(50)	(50)	(50)	(49)
Pituitary gland	(50)	(49)	(49)	(49)
Pars distalis, adenoma	39 (78%)	37 (76%)	35 (71%)	23 (47%)
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	7 (14%)	8 (16%)	5 (10%)	4 (8%)
C-cell, carcinoma	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Follicular cell, adenoma	1 (2%)		1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(49)
Adenoma	1 (2%)	3 (6%)	5 (10%)	2 (4%)
Carcinoma	3 (6%)	3 (6%)	1 (2%)	4 (8%)
Bilateral, carcinoma			1 (2%)	
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	35 (70%)	37 (74%)	40 (80%)	42 (84%)
Interstitial cell, adenoma	4 (8%)	3 (6%)	8 (16%)	5 (10%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(11)	(17)	(16)	(17)
Lymph node, bronchial	(45)	(50)	(46)	(47)
Lymph node, mandibular	(50)	(49)	(49)	(46)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Lymph node, mediastinal	(49)	(47)	(48)	(46)
Spleen	(50)	(50)	(50)	(50)
Thymus	(49)	(47)	(47)	(45)

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

	0 ppm	156 ppm	312 ppm	625 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(33)	(36)	(41)	(34)
Adenoma				1 (3%)
Carcinoma		1 (3%)	1 (2%)	
Fibroadenoma	2 (6%)	2 (6%)	2 (5%)	1 (3%)
Skin	(49)	(50)	(50)	(50)
Basosquamous tumor benign	2 (4%)			1 (2%)
Keratoacanthoma	3 (6%)		1 (2%)	1 (2%)
Squamous cell carcinoma	1 (2%)		1 (2%)	
Squamous cell papilloma	1 (2%)			1 (2%)
Subcutaneous tissue, fibroma	3 (6%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, neurofibroma	1 (2%)		1 (2%)	
Subcutaneous tissue, neurofibrosarcoma			1 (2%)	
Subcutaneous tissue, sarcoma				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meningioma NOS			1 (2%)	
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	2 (4%)	1 (2%)
Carcinoma, metastatic, kidney	1 (2%)			
Chordoma, metastatic, uncertain primary site		1 (2%)		1 (2%)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland			(1)	
Carcinoma			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Bilateral, renal tubule, adenoma			1 (2%)	
Renal tubule, adenoma			5 (10%)	3 (6%)
Renal tubule, carcinoma	1 (2%)		2 (4%)	
Transitional epithelium, papilloma				1 (2%)
Urinary bladder	(49)	(50)	(50)	(50)
Transitional epithelium, papilloma		3 (6%)		

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

	0 ppm	156 ppm	312 ppm	625 ppm
2-Year Study (continued)				
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Leukemia mononuclear	34 (68%)	43 (86%)	38 (76%)	31 (62%)
Mesothelioma malignant	5 (10%)	1 (2%)	2 (4%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	10	9	10	10
2-Year study	49	49	50	49
Total primary neoplasms				
15-Month interim evaluation	16	12	13	18
2-Year study	177	175	194	149
Total animals with benign neoplasms				
15-Month interim evaluation	10	9	10	10
2-Year study	49	48	50	49
Total benign neoplasms				
15-Month interim evaluation	14	12	12	14
2-Year study	126	117	127	106
Total animals with malignant neoplasms				
15-Month interim evaluation	2		1	4
2-Year study	39	46	48	35
Total malignant neoplasms				
15-Month interim evaluation	2		1	4
2-Year study	51	57	66	43
Total animals with metastatic neoplasms				
2-Year study	1	1	1	2
Total metastatic neoplasms				
2-Year study	1	1	1	3
Total animals with malignant neoplasms of uncertain primary site				
2-Year study		1		1
Total animals with uncertain neoplasms-benign or malignant				
2-Year study		1	1	
Total uncertain neoplasms				
2-Year study		1	1	

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 0 ppm

Number of Days on Study	3 3 6	3 7 1	4 8 9	5 0 9	5 2 5	5 5 5	5 5 9	5 8 8	5 9 1	5 9 3	5 9 4	6 2 4	6 3 2	6 3 5	6 4 9	6 5 9	6 6 4	6 7 4	7 7 7	7 7 9	8 6	9 0	9 1	7 1	0 2
Carcass ID Number	0 2 0	0 5 2	0 5 6	0 1 3	0 5 0	0 3 0	0 5 3	0 2 8	0 4 3	0 5 9	0 4 8	0 4 4	0 0 7	0 2 3	0 5 4	0 0 6	0 4 7	0 1 6	0 2 6	0 4 1	0 3 6	0 4	0 2 7	0 3 3	0 3 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma												X													
Hepatocellular adenoma													X												
Hepatocellular adenoma, multiple																									
Mesentery			+													+						+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																						+			
Palate, squamous cell carcinoma																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Tooth		+									+														
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign								X		X					X		X			X	X		X		X
Bilateral, pheochromocytoma benign																								X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																						X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X	X			X			X	X		X	X	X	X		X	X	X		X	X	X	X
Pars intermedia, adenoma																					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
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 A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 0 ppm (continued)

Number of Days on Study	7 0 5	7 0 7	7 0 8	7 0 9	7 1 5	7 1 6	7 2 1	7 2 7	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 4 6	0 1 2	0 3 7	0 1 1	0 2 5	0 2 4	0 0 9	0 2 1	0 0 1	0 0 3	0 0 8	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 9	0 3 1	0 3 2	0 3 9	0 4 0	0 4 2	0 4 5	0 5 1	0 5 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma									X																	2
Hepatocellular adenoma, multiple												X														1
Mesentery		+		+			+			+		+		+		+	+	+			+		+	+		15
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Palate, squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																					+					1
Squamous cell papilloma																					X					1
Tooth																										2
Cardiovascular System																										
Blood vessel							+																			1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant					X													X								2
Pheochromocytoma benign					X								X	X	X						X	X			X	15
Bilateral, pheochromocytoma benign	X					X	X																			4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																	X		X						3
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	X		39
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X		X	X	X							X		X						X					7
C-cell, carcinoma										X					X											2
Follicular cell, adenoma				X																						1
General Body System																										
None																										

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

Number of Days on Study	3 3 4 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 7 7 3 7 8 0 2 5 5 8 9 9 9 2 3 3 4 5 6 7 7 7 8 9 9 0 6 1 9 9 5 5 9 8 1 3 4 4 2 5 9 9 4 4 7 7 9 6 0 1 1 2
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2 5 5 1 5 3 5 2 4 5 4 4 0 2 5 0 4 1 2 4 3 0 2 3 3 0 2 6 3 0 0 3 8 3 9 8 4 7 3 4 6 7 6 6 1 6 4 7 7 4
Genital System	
Epididymis	+ +
Preputial gland	+ +
Adenoma	
Carcinoma	
Prostate	+ +
Seminal vesicle	+ +
Testes	+ +
Bilateral, interstitial cell, adenoma	X X X X X X X X X X X X X X X X X X X X X
Interstitial cell, adenoma	X
Hematopoietic System	
Blood	
Bone marrow	+ +
Lymph node	+ + + + + + + + + + + + + + + + +
Lymph node, bronchial	+ + + + + M + + + + + + M + + M + + + + + + + + +
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ +
Lymph node, mediastinal	+ + + + + + + + + + + + + + M + + + + + + + + + +
Spleen	+ +
Thymus	+ + + + + + + + + + + + + + + + M + + + + + + + +
Integumentary System	
Mammary gland	M + + M M + M + + + + + + + + M + + + M + + M + + +
Fibroadenoma	
Skin	+ M + + + + +
Basosquamous tumor benign	
Keratoacanthoma	X
Squamous cell carcinoma	
Squamous cell papilloma	
Subcutaneous tissue, fibroma	X X
Subcutaneous tissue, neurofibroma	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Larynx	+ +
Lung	+ +
Carcinoma, metastatic, kidney	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+ +

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

Number of Days on Study	7 0 5	7 0 7	7 0 8	7 0 9	7 1 5	7 1 6	7 2 1	7 2 7	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 4 6	0 1 2	0 3 7	0 1 1	0 2 5	0 2 4	0 0 9	0 2 1	0 0 1	0 0 3	0 0 8	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 9	0 3 1	0 3 2	0 3 9	0 4 0	0 4 2	0 4 5	0 5 1	0 5 7	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Carcinoma			X								X			X												3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X	X			X		X	X	X	X	X	X			X	X	X	X	X		X	X	35
Interstitial cell, adenoma			X			X			X																	4
Hematopoietic System																										
Blood	+																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+			+							+											+			11
Lymph node, bronchial	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	M	+	+	M	+	M	+	M	M	+	M	M	+	+	+	+	M	M	33
Fibroadenoma					X									X												2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor benign							X										X									2
Keratoacanthoma															X							X				3
Squamous cell carcinoma								X																		1
Squamous cell papilloma						X																				1
Subcutaneous tissue, fibroma																		X								3
Subcutaneous tissue, neurofibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45

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

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

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

Number of Days on Study	7 0 5	7 0 7	7 0 8	7 0 9	7 1 5	7 1 6	7 2 1	7 2 7	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 4 6	0 1 2	0 3 7	0 1 1	0 2 5	0 2 4	0 0 9	0 2 1	0 0 1	0 0 3	0 0 8	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 9	0 3 1	0 3 2	0 3 9	0 4 0	0 4 2	0 4 5	0 5 1	0 5 7	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X	X		X	X		X	X	X		X		X	X			X	X	X			34
Mesothelioma malignant										X																5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 156 ppm

Number of Days on Study	3 5 1	4 5 0	4 7 0	4 9 4	5 0 9	5 2 9	5 3 3	5 5 5	5 5 5	5 8 1	5 8 9	5 9 2	5 9 4	5 9 4	5 9 4	6 0 0	6 0 4	6 1 2	6 1 6	6 2 1	6 2 7	6 5 2	6 5 3	6 5 9	6 6 4
Carcass ID Number	1 7 3	1 5 0	1 5 3	1 4 6	1 4 1	1 3 7	1 5 2	1 2 8	1 4 4	1 3 9	1 6 0	1 7 8	1 2 9	1 3 0	1 3 4	1 6 1	1 4 3	1 6 7	1 6 4	1 3 1	1 2 7	1 6 2	1 2 2	1 3 6	1 3 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																						X			
Hepatocellular adenoma																X	X								
Hepatocellular adenoma, multiple																									
Hepatocholangioma																									
Mesentery							+					+		+			+						+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Tooth																				+					
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS												X													
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex																									
Pheochromocytoma benign															X		X	X					X		
Bilateral, pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									X
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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		X
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma				X											X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 156 ppm (continued)

Number of Days on Study	6 6 4	6 8 1	6 8 6	6 9 1	6 9 8	7 0 0	7 0 2	7 0 5	7 1 1	7 1 5	7 1 6	7 1 6	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 5 5	1 3 2	1 4 7	1 6 5	1 3 5	1 7 6	1 7 2	1 6 9	1 6 3	1 7 9	1 3 3	1 3 8	1 7 0	1 2 1	1 2 5	1 2 6	1 4 9	1 5 1	1 5 7	1 5 9	1 6 6	1 6 8	1 7 4	1 7 7	1 8 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma	X																									3
Hepatocellular adenoma, multiple															X						X	X				3
Hepatocholangioma																				X						1
Mesentery								+		+				+		+	+					+				11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma					X											X										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																							+			1
Squamous cell papilloma																							X			1
Tooth				+																						2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma NOS																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex														X												1
Pheochromocytoma benign		X											X						X			X				8
Bilateral, pheochromocytoma benign						X					X															3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Carcinoma						X																	X	X	X	5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X		X	X	X		X		X	X	X	X	X	X	X	X			X	X	X	X		37
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X									X		X								X		8
C-cell, carcinoma																		X								1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X					X		X		3
Carcinoma								X																		3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 156 ppm (continued)

Number of Days on Study	3 5 1	4 5 0	4 7 0	4 9 4	5 0 9	5 2 9	5 3 3	5 5 5	5 5 5	5 8 1	5 8 9	5 9 2	5 9 4	5 9 4	5 9 4	6 0 0	6 0 4	6 1 2	6 1 6	6 2 1	6 2 7	6 5 2	6 5 3	6 5 9	6 6 4
Carcass ID Number	1 7 3	1 5 0	1 5 3	1 4 6	1 4 1	1 3 7	1 5 2	1 2 8	1 4 4	1 3 9	1 6 0	1 7 8	1 2 9	1 3 0	1 4 8	1 6 1	1 4 3	1 6 7	1 6 4	1 3 1	1 2 7	1 6 2	1 2 2	1 3 6	1 3 4
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X			X		X	X	X	X	X	X		X	X	X	X		X	X	X	X		X
Interstitial cell, adenoma							X																		
Hematopoietic System																									
Blood									+																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+					+	+	+		+				+	+			+	+				+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	M	+	+	+	+	M	+	M	M	+	M	+	M	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Chordoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																X									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X		X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 156 ppm (continued)

Number of Days on Study	6 6 4	6 8 1	6 8 6	6 9 1	6 9 8	7 0 0	7 0 2	7 0 5	7 1 1	7 1 5	7 1 6	7 1 6	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 1 5 5	1 3 2	1 4 7	1 6 5	1 3 5	1 7 6	1 7 2	1 6 9	1 6 3	1 7 9	1 3 3	1 3 8	1 7 0	1 2 1	1 2 5	1 2 6	1 4 9	1 5 1	1 5 7	1 5 9	1 6 6	1 6 8	1 7 4	1 7 7	1 8 0	Total Tissues/ Tumors
Genital System (continued)																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X		X	X	X		X	X		X	X	X	X	X	X	X		37
Interstitial cell, adenoma														X			X									3
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+					+	+			+	+		+										+			17
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	M	M	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	36
Carcinoma					X																					1
Fibroadenoma					X																	X				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma								X																		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma					X																					1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				1
Chordoma, metastatic, uncertain primary site					X																				1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	42
Harderian gland																						+				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma			X																						X	3
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	43
Mesothelioma malignant	X																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm

Number of Days on Study	4 1 3	5 3 8	5 4 7	5 5 9	5 6 4	5 7 5	5 7 6	5 8 1	6 1 4	6 1 4	6 1 6	6 1 7	6 1 7	6 2 1	6 2 7	6 3 1	6 3 2	6 3 2	6 3 5	6 3 8	6 5 8	6 6 3	6 6 4	6 6 4	6 7 4
Carcass ID Number	1 9 6	2 1 9	2 2 2	2 2 9	2 1 3	1 9 5	1 8 9	1 9 8	2 2 0	2 3 8	1 9 2	1 8 1	1 8 7	1 8 7	2 0 7	2 2 5	2 0 6	1 9 4	2 2 4	2 2 7	2 3 5	2 1 8	2 0 3	2 0 4	2 3 4	1 9 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma												X				X						X	X		
Hepatocellular adenoma																				X					
Hepatocellular adenoma, multiple																									
Mesentery	+	+			+			+	+	+			+							+	+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel																								+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								X	
Pheochromocytoma benign							X	X					X											X	
Bilateral, pheochromocytoma benign																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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				
Follicular cell, adenoma																								X	
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X		X										X											X
Carcinoma		X																							
Bilateral, carcinoma																		X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	6 7 4	6 7 7	6 8 8	6 9 1	6 9 3	7 2 3	7 2 6	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 2 8	1 8 6	1 9 1	2 1 7	2 1 2	2 3 7	1 8 8	2 0 5	1 8 2	1 8 5	1 9 0	1 9 7	2 0 0	2 0 1	2 0 2	2 0 8	2 1 1	2 1 4	2 1 5	2 1 6	2 2 3	2 2 6	2 3 0	2 3 1	2 3 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma								X			X		X	X					X						X	10
Hepatocellular adenoma											X			X	X										X	5
Hepatocellular adenoma, multiple												X					X			X						3
Mesentery		+		+				+	+	+			+			+							+	+		18
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																	+									1
Cardiovascular System																										
Blood vessel							+																+			3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X			X																						2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign											X					X	X					X				8
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Carcinoma										X																1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	35
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X		X											X	X										5
C-cell, carcinoma			X							X				X												4
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											5
Carcinoma																										1
Bilateral, carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	4 1 3	5 3 8	5 4 7	5 5 9	5 6 4	5 7 5	5 7 6	5 8 1	6 1 4	6 1 4	6 1 6	6 1 7	6 1 7	6 2 1	6 2 7	6 3 1	6 3 2	6 3 2	6 3 5	6 3 8	6 5 8	6 6 3	6 6 4	6 6 4	6 7 4
Carcass ID Number	1 9 6	2 1 9	2 2 2	2 2 9	2 1 3	1 9 5	1 8 9	1 9 8	2 2 0	2 3 8	1 9 2	1 8 1	1 8 7	1 0 7	2 2 5	2 0 6	1 9 4	2 2 4	2 2 7	2 3 5	2 1 8	2 0 3	2 0 4	2 3 4	1 9 3
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X			X		X	X	X	X	X	X	X	X				X			X	X	X	X
Interstitial cell, adenoma	X				X											X	X	X		X	X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+								+	+	+			+			+		+	+					
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+
Carcinoma															X										
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma						X																			
Squamous cell carcinoma																									
Subcutaneous tissue, fibrosarcoma																							X		
Subcutaneous tissue, hemangiosarcoma							X																		
Subcutaneous tissue, neurofibroma																									
Subcutaneous tissue, neurofibrosarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma NOS																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									
Carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	6 7 4	6 7 7	6 8 8	6 9 1	6 9 3	7 2 3	7 2 6	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 2 8	1 8 6	1 9 1	2 1 7	2 1 2	2 3 7	1 8 8	2 0 5	1 8 2	1 8 5	1 9 0	1 9 7	2 0 0	2 0 1	2 0 2	2 0 8	2 1 1	2 1 4	2 1 5	2 1 6	2 2 3	2 2 6	2 3 0	2 3 1	2 3 3	Total Tissues/ Tumors
Genital System (continued)																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma																X										8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+			+	+						+	+						+			+			+	16
Lymph node, bronchial	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	41
Carcinoma																										1
Fibroadenoma									X															X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Squamous cell carcinoma								X																		1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, neurofibroma																							X			1
Subcutaneous tissue, neurofibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																							+			1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma NOS												X														1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				2
Hepatocellular carcinoma, metastatic, liver											X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Zymbal's gland																									+	1
Carcinoma																									X	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	6 7 4	6 7 7	6 8 8	6 9 1	6 9 3	7 2 3	7 2 6	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 2 8	1 8 6	1 9 1	2 1 7	2 1 2	2 3 7	1 8 8	2 0 5	1 8 2	1 8 5	1 9 0	1 9 7	2 0 0	2 0 1	2 0 2	2 0 8	2 1 1	2 1 4	2 1 5	2 1 6	2 2 3	2 2 6	2 3 0	2 3 1	2 3 3	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, renal tubule, adenoma																										1
Renal tubule, adenoma																				X			X	X		5
Renal tubule, carcinoma																							X			2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X		X	X		X	X	38
Mesothelioma malignant	X								X																	2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	6 1 7	6 1 7	6 2 1	6 2 6	6 2 6	6 3 0	6 3 2	6 3 2	6 3 9	6 3 9	6 3 9	6 5 2	6 6 3	6 6 3	6 6 8	6 7 4	6 8 8	6 8 8	6 9 1	6 9 5	7 0 2	7 1 2	7 2 1	7 3 0	7 3 3	
Carcass ID Number	3 1 2	3 5 0	3 1 4	3 5 4	3 5 8	3 2 0	3 2 3	3 3 4	3 0 9	3 1 5	3 2 7	3 4 5	3 0 4	3 5 6	3 4 2	3 3 2	3 2 5	3 2 6	3 3 6	3 1 9	3 5 7	3 3 5	3 1 1	3 2 1	3 2 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X								X									3
Hepatocellular adenoma													X												X	4
Hepatocellular adenoma, multiple																										1
Mesentery			+	+					+		+	+								+	+		+		+	14
Hepatocellular carcinoma, metastatic, liver									X																	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver									X																	1
Acinus, adenoma						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																		+								1
Tooth																										2
Cardiovascular System																										
Blood vessel						+		+		+	+				+		+			+		+		+		12
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma																										1
Pheochromocytoma benign								X	X		X				X											6
Bilateral, pheochromocytoma benign																X	X			X						4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																X						2
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Pars distalis, adenoma		X			X	X	X		X	X	X			X		X	X		X	X		X	X			23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X	X				X												4
C-cell, carcinoma	X																									1
General Body System																										
Tissue NOS																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	3 6 1	4 5 5	4 8 1	5 0 9	5 1 0	5 2 3	5 2 5	5 3 1	5 4 4	5 5 5	5 5 9	5 7 1	5 7 2	5 7 2	5 8 3	5 8 6	5 9 0	5 9 3	5 9 4	6 0 3	6 0 4	6 0 8	6 1 1	6 1 6	6 1 7
Carcass ID Number	3 4 4 3	3 1 3	3 4 9	3 1 8	3 3 9	3 1 0	3 0 7	3 2 9	3 0 2	3 5 9	3 0 5	3 0 6	3 3 0	3 4 8	3 6 0	3 0 3	3 3 3	3 3 8	3 0 1	3 5 5	3 4 6	3 3 7	3 4 0	3 2 8	3 0 8
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Carcinoma			X														X				X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X			X
Interstitial cell, adenoma			X											X	X									X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+		+			+						+		+	+		
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	M	M	M	+	M	M	M	+	+	+	+	M	+	+	+	M	M	+	M	+	+	+	+
Adenoma						X																			
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma												X													
Subcutaneous tissue, fibrosarcoma							X																		
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Chordoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye									+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	6 1 7	6 1 7	6 2 1	6 2 6	6 2 6	6 3 0	6 3 2	6 3 2	6 3 9	6 3 9	6 3 9	6 5 2	6 6 3	6 6 3	6 6 8	6 7 4	6 8 8	6 8 8	6 9 1	6 9 5	7 0 2	7 1 2	7 2 1	7 3 0	7 3 3	
Carcass ID Number	3 1 2	3 5 0	3 1 4	3 5 4	3 5 8	3 2 0	3 2 3	3 3 4	3 0 9	3 1 5	3 2 7	3 4 5	3 0 4	3 5 6	3 4 2	3 3 2	3 2 5	3 2 6	3 3 6	3 1 9	3 5 7	3 3 5	3 1 1	3 2 1	3 2 4	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X																									2
Carcinoma										X																4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	42
Interstitial cell, adenoma		X																								5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+	+		+			+	+	+		+	+			+				+					17
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	34
Adenoma																										1
Fibroadenoma															X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign		X																								1
Keratoacanthoma							X																			1
Squamous cell papilloma	X																									1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Chordoma, metastatic, uncertain primary site																X									1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	6 1 7	6 1 7	6 2 1	6 2 6	6 2 6	6 3 0	6 3 2	6 3 2	6 3 9	6 3 9	6 3 9	6 5 2	6 6 3	6 6 3	6 6 8	6 7 4	6 8 8	6 8 8	6 9 1	6 9 5	7 0 2	7 1 2	7 2 1	7 3 0	7 3 3	
Carcass ID Number	3 1 2	3 5 0	3 1 4	3 5 4	3 5 8	3 2 0	3 2 3	3 3 4	3 0 9	3 1 5	3 2 7	3 4 5	3 0 4	3 5 6	3 4 2	3 3 2	3 2 5	3 2 6	3 3 6	3 1 9	3 5 7	3 3 5	3 1 1	3 2 1	3 2 4	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X		X														X								3
Transitional epithelium, papilloma												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	31
Mesothelioma malignant																										1

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

	0 ppm	156 ppm	312 ppm	625 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	19/50 (38%)	11/50 (22%)	9/50 (18%)	10/50 (20%)
Adjusted rate[b]	60.0%	44.2%	33.4%	52.8%
Terminal rate[c]	6/17 (35%)	2/12 (17%)	4/17 (24%)	0/1 (0%)
First incidence (days)	588	594	576	481
Life table test[d]	P=0.282	P=0.280N	P=0.058N	P=0.083
Logistic regression test[d]	P=0.108N	P=0.090N	P=0.024N	P=0.180N
Cochran-Armitage test[d]	P=0.040N			
Fisher exact test[d]		P=0.063N	P=0.022N	P=0.038N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	20/50 (40%)	12/50 (24%)	9/50 (18%)	10/50 (20%)
Adjusted rate	63.6%	49.8%	33.4%	52.8%
Terminal rate	7/17 (41%)	3/12 (25%)	4/17 (24%)	0/1 (0%)
First incidence (days)	588	594	576	481
Life table test	P=0.331	P=0.305N	P=0.039N	P=0.087
Logistic regression test	P=0.078N	P=0.123N	P=0.015N	P=0.151N
Cochran-Armitage test	P=0.023N			
Fisher exact test		P=0.066N	P=0.013N	P=0.024N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	6/50 (12%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	25.7%	18.4%
Terminal rate	0/17 (0%)	0/12 (0%)	3/17 (18%)	0/1 (0%)
First incidence (days)	—[e]	—	627	617
Life table test	P<0.001	—	P=0.015	P=0.032
Logistic regression test	P=0.015	—	P=0.015	P=0.097
Cochran-Armitage test	P=0.047			
Fisher exact test		—	P=0.013	P=0.121
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)	11/50 (22%)
Adjusted rate	10.8%	24.9%	10.2%	85.3%
Terminal rate	1/17 (6%)	2/12 (17%)	0/17 (0%)	0/1 (0%)
First incidence (days)	721	555	614	572
Life table test	P<0.001	P=0.217	P=0.506	P<0.001
Logistic regression test	P<0.001	P=0.259	P=0.492	P<0.001
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.339	P=0.500	P=0.007
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	2/50 (4%)	4/50 (8%)	9/50 (18%)	13/50 (26%)
Adjusted rate	10.8%	24.9%	33.3%	87.7%
Terminal rate	1/17 (6%)	2/12 (17%)	3/17 (18%)	0/1 (0%)
First incidence (days)	721	555	614	572
Life table test	P<0.001	P=0.217	P=0.029	P<0.001
Logistic regression test	P<0.001	P=0.259	P=0.024	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.339	P=0.026	P=0.002

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

	0 ppm	156 ppm	312 ppm	625 ppm
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	1/50 (2%)	0/50 (0%)	6/50 (12%)	3/50 (6%)
Adjusted rate	2.8%	0.0%	25.7%	18.4%
Terminal rate	0/17 (0%)	0/12 (0%)	3/17 (18%)	0/1 (0%)
First incidence (days)	649	—	627	617
Life table test	P=0.004	P=0.543N	P=0.049	P=0.094
Logistic regression test	P=0.052	P=0.497N	P=0.055	P=0.270
Cochran-Armitage test	P=0.114			
Fisher exact test		P=0.500N	P=0.056	P=0.309
Kidney (Renal Tubule): Adenoma or Carcinoma (Step Sections)				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	11/50 (22%)
Adjusted rate	10.8%	28.4%	10.2%	85.3%
Terminal rate	1/17 (6%)	2/12 (17%)	0/17 (0%)	0/1 (0%)
First incidence (days)	721	555	614	572
Life table test	P<0.001	P=0.123	P=0.506	P<0.001
Logistic regression test	P<0.001	P=0.151	P=0.492	P<0.001
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.218	P=0.500	P=0.007
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	3/50 (6%)	5/50 (10%)	9/50 (18%)	13/50 (26%)
Adjusted rate	13.3%	28.4%	33.3%	87.7%
Terminal rate	1/17 (6%)	2/12 (17%)	3/17 (18%)	0/1 (0%)
First incidence (days)	649	555	614	572
Life table test	P<0.001	P=0.224	P=0.060	P<0.001
Logistic regression test	P<0.001	P=0.281	P=0.057	P<0.001
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.357	P=0.061	P=0.006
Liver: Hepatocellular Adenoma				
Overall rate	3/50 (6%)	6/50 (12%)	8/50 (16%)	5/50 (10%)
Adjusted rate	14.1%	32.0%	43.1%	100.0%
Terminal rate	2/17 (12%)	3/12 (25%)	7/17 (41%)	1/1 (100%)
First incidence (days)	632	600	638	572
Life table test	P=0.004	P=0.127	P=0.082	P=0.018
Logistic regression test	P=0.103	P=0.193	P=0.065	P=0.240
Cochran-Armitage test	P=0.352			
Fisher exact test		P=0.243	P=0.100	P=0.357
Liver: Hepatocellular Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	10/50 (20%)	3/50 (6%)
Adjusted rate	2.6%	3.4%	41.3%	18.8%
Terminal rate	0/17 (0%)	0/12 (0%)	5/17 (29%)	0/1 (0%)
First incidence (days)	624	652	617	590
Life table test	P=0.003	P=0.710	P=0.005	P=0.113
Logistic regression test	P=0.053	P=0.756N	P=0.004	P=0.301
Cochran-Armitage test	P=0.149			
Fisher exact test		P=0.753N	P=0.004	P=0.309

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

	0 ppm	156 ppm	312 ppm	625 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	4/50 (8%)	7/50 (14%)	15/50 (30%)	8/50 (16%)
Adjusted rate	16.3%	34.4%	62.1%	100.0%
Terminal rate	2/17 (12%)	3/12 (25%)	9/17 (53%)	1/1 (100%)
First incidence (days)	624	600	617	572
Life table test	P<0.001	P=0.137	P=0.004	P=0.003
Logistic regression test	P=0.025	P=0.223	P=0.003	P=0.112
Cochran-Armitage test	P=0.140			
Fisher exact test		P=0.262	P=0.005	P=0.178
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	10.4%	12.7%	14.2%	11.1%
Terminal rate	1/17 (6%)	1/12 (8%)	2/17 (12%)	0/1 (0%)
First incidence (days)	715	698	627	523
Life table test	P=0.117	P=0.580	P=0.491	P=0.229
Logistic regression test	P=0.386	P=0.598	P=0.463	P=0.631
Cochran-Armitage test	P=0.569			
Fisher exact test		P=0.691N	P=0.500	P=0.691N
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	15.3%	5.6%	5.9%	20.5%
Terminal rate	2/17 (12%)	0/12 (0%)	1/17 (6%)	0/1 (0%)
First incidence (days)	705	705	733 (T)	626
Life table test	P=0.248	P=0.433N	P=0.324N	P=0.182
Logistic regression test	P=0.463	P=0.400N	P=0.339N	P=0.521
Cochran-Armitage test	P=0.475N			
Fisher exact test		P=0.309N	P=0.309N	P=0.500N
Pancreatic Islets: Carcinoma				
Overall rate	1/50 (2%)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rate	3.4%	31.5%	5.9%	3.0%
Terminal rate	0/17 (0%)	3/12 (25%)	1/17 (6%)	0/1 (0%)
First incidence (days)	690	664	733 (T)	593
Life table test	P=0.432	P=0.049	P=0.730	P=0.587
Logistic regression test	P=0.550N	P=0.059	P=0.744	P=0.768
Cochran-Armitage test	P=0.313N			
Fisher exact test		P=0.102	P=0.753N	P=0.753N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	6/50 (12%)	2/50 (4%)	3/50 (6%)
Adjusted rate	18.2%	35.3%	11.8%	22.9%
Terminal rate	2/17 (12%)	3/12 (25%)	2/17 (12%)	0/1 (0%)
First incidence (days)	690	664	733 (T)	593
Life table test	P=0.202	P=0.192	P=0.375N	P=0.144
Logistic regression test	P=0.525	P=0.228	P=0.387N	P=0.553
Cochran-Armitage test	P=0.278N			
Fisher exact test		P=0.370	P=0.339N	P=0.500N

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

	0 ppm	156 ppm	312 ppm	625 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	39/50 (78%)	37/49 (76%)	35/49 (71%)	23/49 (47%)
Adjusted rate	94.9%	91.1%	84.5%	86.1%
Terminal rate	15/17 (88%)	9/12 (75%)	10/16 (63%)	0/0
First incidence (days)	336	351	559	361
Life table test	P=0.042	P=0.213	P=0.514N	P=0.003
Logistic regression test	P=0.002N	P=0.500N	P=0.290N	P=0.014N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.478N	P=0.301N	P=0.001N
Preputial Gland: Adenoma				
Overall rate	1/50 (2%)	3/50 (6%)	5/50 (10%)	2/49 (4%)
Adjusted rate	5.9%	25.0%	15.6%	6.0%
Terminal rate	1/17 (6%)	3/12 (25%)	1/17 (6%)	0/1 (0%)
First incidence (days)	733 (T)	733 (T)	538	523
Life table test	P=0.099	P=0.182	P=0.104	P=0.228
Logistic regression test	P=0.393	P=0.182	P=0.099	P=0.523
Cochran-Armitage test	P=0.428			
Fisher exact test		P=0.309	P=0.102	P=0.492
Preputial Gland: Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	4/49 (8%)
Adjusted rate	15.6%	10.0%	4.9%	13.9%
Terminal rate	2/17 (12%)	0/12 (0%)	0/17 (0%)	0/1 (0%)
First incidence (days)	708	494	538	481
Life table test	P=0.152	P=0.552	P=0.515N	P=0.077
Logistic regression test	P=0.481	P=0.656	P=0.500N	P=0.471
Cochran-Armitage test	P=0.409			
Fisher exact test		P=0.661N	P=0.500N	P=0.489
Preputial Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	6/50 (12%)	6/50 (12%)	6/49 (12%)
Adjusted rate	21.2%	32.5%	18.1%	19.0%
Terminal rate	3/17 (18%)	3/12 (25%)	1/17 (6%)	0/1 (0%)
First incidence (days)	708	494	538	481
Life table test	P=0.035	P=0.211	P=0.350	P=0.023
Logistic regression test	P=0.355	P=0.295	P=0.369	P=0.354
Cochran-Armitage test	P=0.337			
Fisher exact test		P=0.370	P=0.370	P=0.357
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adjusted rate	14.7%	0.0%	2.2%	5.3%
Terminal rate	2/17 (12%)	0/12 (0%)	0/17 (0%)	0/1 (0%)
First incidence (days)	686	—	575	632
Life table test	P=0.579N	P=0.184N	P=0.326N	P=0.598
Logistic regression test	P=0.356N	P=0.165N	P=0.309N	P=0.609N
Cochran-Armitage test	P=0.296N			
Fisher exact test		P=0.121N	P=0.309N	P=0.309N

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

	0 ppm	156 ppm	312 ppm	625 ppm
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	4/50 (8%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Adjusted rate	19.0%	0.0%	2.2%	8.9%
Terminal rate	2/17 (12%)	0/12 (0%)	0/17 (0%)	0/1 (0%)
First incidence (days)	686	—	575	617
Life table test	P=0.525	P=0.112N	P=0.197N	P=0.375
Logistic regression test	P=0.452N	P=0.095N	P=0.186N	P=0.629N
Cochran-Armitage test	P=0.373N			
Fisher exact test		P=0.059N	P=0.181N	P=0.339N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adjusted rate	23.5%	0.0%	7.7%	8.9%
Terminal rate	2/17 (12%)	0/12 (0%)	0/17 (0%)	0/1 (0%)
First incidence (days)	686	—	575	617
Life table test	P=0.552	P=0.071N	P=0.233N	P=0.421
Logistic regression test	P=0.401N	P=0.056N	P=0.236N	P=0.550N
Cochran-Armitage test	P=0.263N			
Fisher exact test		P=0.028N	P=0.218N	P=0.218N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Benign Basosquamous Tumor, or Squamous Cell Carcinoma				
Overall rate	7/50 (14%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	32.3%	0.0%	7.7%	12.6%
Terminal rate	3/17 (18%)	0/12 (0%)	0/17 (0%)	0/1 (0%)
First incidence (days)	686	—	575	617
Life table test	P=0.527	P=0.029N	P=0.092N	P=0.301
Logistic regression test	P=0.369N	P=0.019N	P=0.095N	P=0.529N
Cochran-Armitage test	P=0.211N			
Fisher exact test		P=0.006N	P=0.080N	P=0.159N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	11.3%	5.6%	0.0%	2.6%
Terminal rate	1/17 (6%)	0/12 (0%)	0/17 (0%)	0/1 (0%)
First incidence (days)	635	705	—	571
Life table test	P=0.430N	P=0.420N	P=0.150N	P=0.700N
Logistic regression test	P=0.224N	P=0.343N	P=0.122N	P=0.346N
Cochran-Armitage test	P=0.200N			
Fisher exact test		P=0.309N	P=0.121N	P=0.309N
Testes: Adenoma				
Overall rate	39/50 (78%)	40/50 (80%)	48/50 (96%)	47/50 (94%)
Adjusted rate	92.5%	97.3%	100.0%	100.0%
Terminal rate	14/17 (82%)	11/12 (92%)	17/17 (100%)	1/1 (100%)
First incidence (days)	489	470	413	418
Life table test	P<0.001	P=0.101	P=0.081	P<0.001
Logistic regression test	P<0.001	P=0.361	P=0.009	P=0.003
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.500	P=0.007	P=0.020

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

	0 ppm	156 ppm	312 ppm	625 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/50 (14%)	8/50 (16%)	5/50 (10%)	4/50 (8%)
Adjusted rate	31.8%	37.3%	21.6%	20.6%
Terminal rate	3/17 (18%)	3/12 (25%)	2/17 (12%)	0/1 (0%)
First incidence (days)	707	533	631	571
Life table test	P=0.283	P=0.286	P=0.437N	P=0.128
Logistic regression test	P=0.348N	P=0.386	P=0.438N	P=0.636
Cochran-Armitage test	P=0.152N			
Fisher exact test		P=0.500	P=0.380N	P=0.262N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	11.8%	8.3%	18.4%	3.8%
Terminal rate	2/17 (12%)	1/12 (8%)	2/17 (12%)	0/1 (0%)
First incidence (days)	733 (T)	733 (T)	658	617
Life table test	P=0.204	P=0.623N	P=0.307	P=0.508
Logistic regression test	P=0.403	P=0.623N	P=0.291	P=0.754
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.500N	P=0.339	P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	9/50 (18%)	9/50 (18%)	5/50 (10%)
Adjusted rate	36.7%	44.3%	37.2%	23.7%
Terminal rate	4/17 (24%)	4/12 (33%)	4/17 (24%)	0/1 (0%)
First incidence (days)	707	533	631	571
Life table test	P=0.105	P=0.263	P=0.433	P=0.073
Logistic regression test	P=0.530N	P=0.357	P=0.420	P=0.577
Cochran-Armitage test	P=0.204N			
Fisher exact test		P=0.500	P=0.500	P=0.277N
Urinary Bladder: Papilloma				
Overall rate	0/49 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	14.8%	0.0%	0.0%
Terminal rate	0/17 (0%)	1/12 (8%)	0/17 (0%)	0/1 (0%)
First incidence (days)	—	600	—	—
Life table test	P=0.509N	P=0.085	—	—
Logistic regression test	P=0.354N	P=0.113	—	—
Cochran-Armitage test	P=0.308N			
Fisher exact test		P=0.125	—	—
All Organs: Mononuclear Cell Leukemia				
Overall rate	34/50 (68%)	43/50 (86%)	38/50 (76%)	31/50 (62%)
Adjusted rate	81.5%	95.3%	91.9%	100.0%
Terminal rate	10/17 (59%)	10/12 (83%)	14/17 (82%)	1/1 (100%)
First incidence (days)	509	351	413	509
Life table test	P<0.001	P=0.016	P=0.231	P<0.001
Logistic regression test	P=0.064N	P=0.020	P=0.254	P=0.079N
Cochran-Armitage test	P=0.108N			
Fisher exact test		P=0.028	P=0.252	P=0.338N

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

	0 ppm	156 ppm	312 ppm	625 ppm
All Organs: Malignant Mesothelioma				
Overall rate	5/50 (10%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	15.0%	3.8%	9.5%	2.3%
Terminal rate	1/17 (6%)	0/12 (0%)	1/17 (6%)	0/1 (0%)
First incidence (days)	489	664	674	525
Life table test	P=0.248N	P=0.154N	P=0.253N	P=0.278N
Logistic regression test	P=0.076N	P=0.089N	P=0.222N	P=0.062N
Cochran-Armitage test	P=0.093N			
Fisher exact test		P=0.102N	P=0.218N	P=0.102N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	48/50 (96%)	50/50 (100%)	49/50 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	17/17 (100%)	12/12 (100%)	17/17 (100%)	1/1 (100%)
First incidence (days)	336	351	413	361
Life table test	P<0.001	P=0.130	P=0.365	P<0.001
Logistic regression test	P=0.460	P=0.529N	P=0.894	P=0.759N
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.500N	P=0.500	P=0.753N
All Organs: Malignant Neoplasms				
Overall rate	39/50 (78%)	46/50 (92%)	48/50 (96%)	35/50 (70%)
Adjusted rate	87.9%	97.8%	98.0%	100.0%
Terminal rate	12/17 (71%)	11/12 (92%)	16/17 (94%)	1/1 (100%)
First incidence (days)	489	351	413	481
Life table test	P<0.001	P=0.025	P=0.087	P<0.001
Logistic regression test	P=0.035N	P=0.030	P=0.009	P=0.042N
Cochran-Armitage test	P=0.075N			
Fisher exact test		P=0.045	P=0.007	P=0.247N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	17/17 (100%)	12/12 (100%)	17/17 (100%)	1/1 (100%)
First incidence (days)	336	351	413	361
Life table test	P<0.001	P=0.105	P=0.365	P<0.001
Logistic regression test	P=0.655N	P=0.769N	P=0.894	P=0.759N
Cochran-Armitage test	P=0.617			
Fisher exact test		P=0.753N	P=0.500	P=0.753N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, pancreatic islets, pituitary gland, preputial gland, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table 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 A4a
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			
o-Chlorobenzalmalononitrile (CS-2)	1/50	0/50	1/50
Acetonitrile	1/48	0/48	1/48
α-Chloroacetophenone	1/49	0/49	1/49
Epinephrine Hydrochloride	0/50	0/50	0/50
Ethyl Chloride	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 A4b
Historical Incidence of Hepatocellular 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			
o-Chlorobenzalmalononitrile (CS-2)	2/50	2/50	4/50
Acetonitrile	0/48	1/48	1/48
α-Chloroacetophenone	1/49	0/49	1/49
Epinephrine Hydrochloride	1/50	0/50	1/50
Ethyl Chloride	0/50	1/50	1/50
Hexachlorocyclopentadiene	1/50	0/50	1/50
Ozone	2/50	0/50	2/50
Total	7/347 (2.0%)	4/347 (1.2%)	11/347 (3.2%)
Standard deviation	1.6%	1.6%	2.3%
Range	0%-4%	0%-4%	2%-8%
Overall Historical Incidence			
Total	20/653 (3.1%)	8/653 (1.2%)	28/653 (4.3%)
Standard deviation	2.8%	1.5%	2.9%
Range	0%-8%	0%-4%	2%-9%

[a] Data as of 12 May 1995

TABLE A4c
Historical Incidence of Mononuclear Cell Leukemia in Chamber Control Male F344/N Rats [a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
o-Chlorobenzalmalononitrile (CS-2)	29/50
Acetonitrile	29/48
α-Chloroacetophenone	29/50
Epinephrine Hydrochloride	19/50
Ethyl Chloride	33/50
Hexachlorocyclopentadiene	29/50
Ozone	27/50
Total	195/348 (56.0%)
Standard deviation	8.7%
Range	38%-66%
Overall Historical Incidence	
Total	356/655 (54.4%)
Standard deviation	8.8%
Range	34%-66%

[a] Data as of 12 May 1995; includes data for lymphocytic, monocytic, and undifferentiated cell type leukemias

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

	0 ppm	156 ppm	312 ppm	625 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	27	34	32	48
Natural deaths	6	4	1	1
Survivors				
Terminal sacrifice	17	12	17	1
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)	(10)	(10)	(10)
Fibrosis				1 (10%)
Liver	(10)	(10)	(10)	(10)
Basophilic focus	6 (60%)	4 (40%)	7 (70%)	4 (40%)
Clear cell focus	4 (40%)	10 (100%)	9 (90%)	10 (100%)
Degeneration, cystic		1 (10%)	3 (30%)	
Eosinophilic focus	1 (10%)			1 (10%)
Hepatodiaphragmatic nodule	1 (10%)		1 (10%)	1 (10%)
Mixed cell focus		2 (20%)	2 (20%)	2 (20%)
Regeneration				1 (10%)
Bile duct, hyperplasia	7 (70%)	9 (90%)	6 (60%)	3 (30%)
Serosa, fibrosis			1 (10%)	
Mesentery	(2)		(2)	(4)
Fat, hemorrhage	1 (50%)			
Fat, necrosis	1 (50%)		2 (100%)	3 (75%)
Pancreas	(10)	(10)	(10)	(10)
Basophilic focus			2 (20%)	
Hyperplasia			1 (10%)	
Acinus, atrophy	4 (40%)	7 (70%)	2 (20%)	4 (40%)
Stomach, glandular	(10)	(10)	(10)	(10)
Mineralization	1 (10%)			
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)	2 (20%)	1 (10%)	2 (20%)
Adrenal medulla	(10)	(10)	(10)	(10)
Hyperplasia	3 (30%)			1 (10%)
Pituitary gland	(10)	(9)	(10)	(10)
Pars distalis, hyperplasia	6 (60%)	3 (33%)	4 (40%)	7 (70%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia	4 (40%)	6 (60%)	5 (50%)	6 (60%)

[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 Tetrafluoroethylene (continued)

	0 ppm	156 ppm	312 ppm	625 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Inflammation, chronic active	3 (30%)	8 (80%)	7 (70%)	6 (60%)
Testes	(10)	(10)	(10)	(10)
Atrophy		1 (10%)		
Interstitial cell, hyperplasia	2 (20%)	4 (40%)		1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hyperplasia, reticulum cell	1 (10%)		1 (10%)	
Lymph node, mandibular	(10)	(8)	(10)	(10)
Hemorrhage	1 (10%)			
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)			
Lymph node, mediastinal	(10)	(10)	(10)	(10)
Hemorrhage	2 (20%)	1 (10%)	2 (20%)	1 (10%)
Spleen	(10)	(10)	(10)	(10)
Developmental malformation	2 (20%)		1 (10%)	
Capsule, fibrosis			1 (10%)	
Integumentary System				
Mammary gland	(5)	(7)	(4)	(5)
Galactocele				1 (20%)
Skin	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)	1 (10%)	
Respiratory System				
Larynx	(10)	(10)	(10)	(10)
Inflammation, chronic active	4 (40%)	5 (50%)	5 (50%)	7 (70%)
Metaplasia, squamous			1 (10%)	
Mineralization	6 (60%)	8 (80%)	8 (80%)	9 (90%)
Lung	(10)	(10)	(10)	(10)
Hemorrhage	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Metaplasia, osseous				1 (10%)
Alveolar epithelium, hyperplasia	1 (10%)	2 (20%)	3 (30%)	
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Cyst		1 (10%)		
Nephropathy	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Renal tubule, degeneration	1 (10%)	8 (80%)	10 (100%)	10 (100%)
Renal tubule, hyperplasia			1 (10%)	1 (10%)

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

	0 ppm	156 ppm	312 ppm	625 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Mineralization	1 (2%)		2 (4%)	1 (2%)
Parasite metazoan	2 (4%)	1 (2%)		3 (6%)
Intestine large, rectum	(49)	(50)	(50)	(50)
Parasite metazoan	3 (6%)	1 (2%)		2 (4%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)		
Parasite metazoan		2 (4%)	1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)
Necrosis	1 (2%)			
Intestine small, ileum	(49)	(49)	(50)	(50)
Inflammation, chronic active		1 (2%)		1 (2%)
Mineralization				1 (2%)
Peyer's patch, inflammation, granulomatous				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis		3 (6%)	2 (4%)	3 (6%)
Basophilic focus	22 (44%)	19 (38%)	33 (66%)	29 (58%)
Clear cell focus	7 (14%)	8 (16%)	11 (22%)	3 (6%)
Congestion				1 (2%)
Cyst				1 (2%)
Degeneration, cystic	17 (34%)	39 (78%)	35 (70%)	32 (64%)
Eosinophilic focus	3 (6%)	18 (36%)	22 (44%)	19 (38%)
Fatty change	5 (10%)	3 (6%)	4 (8%)	5 (10%)
Fibrosis				1 (2%)
Hepatodiaphragmatic nodule	2 (4%)	2 (4%)	3 (6%)	4 (8%)
Hyperplasia				1 (2%)
Mineralization				1 (2%)
Mixed cell focus	5 (10%)	5 (10%)	16 (32%)	13 (26%)
Necrosis, focal			1 (2%)	
Regeneration	3 (6%)	4 (8%)	1 (2%)	
Thrombosis			1 (2%)	
Bile duct, hyperplasia	44 (88%)	43 (86%)	44 (88%)	42 (84%)
Centrilobular, necrosis	3 (6%)	1 (2%)	1 (2%)	
Mesentery	(15)	(11)	(18)	(14)
Inflammation, suppurative	2 (13%)			
Fat, hemorrhage	1 (7%)		3 (17%)	1 (7%)
Fat, necrosis	11 (73%)	11 (100%)	16 (89%)	12 (86%)

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

	0 ppm	156 ppm	312 ppm	625 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Basophilic focus		4 (8%)	1 (2%)	4 (8%)
Hyperplasia	3 (6%)	1 (2%)	3 (6%)	
Acinus, atrophy	32 (64%)	25 (50%)	31 (62%)	20 (40%)
Duct, concretion	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Acanthosis	2 (4%)	1 (2%)	2 (4%)	5 (10%)
Diverticulum	2 (4%)	1 (2%)	2 (4%)	
Infiltration cellular, mast cell	1 (2%)		1 (2%)	
Mineralization	1 (2%)		2 (4%)	3 (6%)
Necrosis	6 (12%)	4 (8%)	1 (2%)	6 (12%)
Stomach, glandular	(50)	(50)	(50)	(50)
Mineralization	1 (2%)	3 (6%)	4 (8%)	13 (26%)
Necrosis	5 (10%)	3 (6%)		3 (6%)
Tongue	(1)	(1)		(1)
Epithelium, hyperplasia				1 (100%)
Tooth	(2)	(2)	(1)	(2)
Dysplasia	2 (100%)	2 (100%)	1 (100%)	2 (100%)
Cardiovascular System				
Blood vessel	(1)		(3)	(12)
Mineralization	1 (100%)		2 (67%)	3 (25%)
Aorta, mineralization	1 (100%)		3 (100%)	12 (100%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	46 (92%)	44 (88%)	43 (86%)	48 (96%)
Mineralization	1 (2%)		2 (4%)	4 (8%)
Atrium, thrombosis	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia	16 (32%)	13 (26%)	21 (42%)	17 (34%)
Hypertrophy	4 (8%)	4 (8%)	5 (10%)	4 (8%)
Vacuolization cytoplasmic	2 (4%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	21 (42%)	21 (42%)	23 (46%)	26 (52%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)			1 (2%)
Parathyroid gland	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)	3 (6%)	7 (14%)	25 (51%)
Pituitary gland	(50)	(49)	(49)	(49)
Thrombosis		1 (2%)		
Pars distalis, angiectasis			1 (2%)	
Pars distalis, hyperplasia	4 (8%)	3 (6%)	4 (8%)	8 (16%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	22 (44%)	24 (48%)	35 (70%)	20 (40%)
Follicular cell, hyperplasia	2 (4%)			2 (4%)
General Body System				
None				

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

	0 ppm	156 ppm	312 ppm	625 ppm
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm			1 (2%)	
Thrombosis		1 (2%)		
Preputial gland	(50)	(50)	(50)	(49)
Hyperplasia		1 (2%)	1 (2%)	
Inflammation, chronic active	10 (20%)	8 (16%)	10 (20%)	14 (29%)
Inflammation, granulomatous	1 (2%)			
Duct, ectasia	1 (2%)		1 (2%)	
Prostate	(50)	(50)	(50)	(50)
Inflammation, chronic active	2 (4%)	1 (2%)		
Inflammation, suppurative			1 (2%)	
Seminal vesicle	(50)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Mineralization			2 (4%)	1 (2%)
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	2 (4%)	2 (4%)	
Interstitial cell, hyperplasia	8 (16%)	10 (20%)	6 (12%)	8 (16%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Thrombosis	1 (2%)			
Lymph node	(11)	(17)	(16)	(17)
Iliac, pigmentation				1 (6%)
Lumbar, hemorrhage				2 (12%)
Pancreatic, edema				1 (6%)
Renal, edema				2 (12%)
Renal, hemorrhage				1 (6%)
Renal, pigmentation				1 (6%)
Lymph node, bronchial	(45)	(50)	(46)	(47)
Hemorrhage				1 (2%)
Lymph node, mandibular	(50)	(49)	(49)	(46)
Hemorrhage		2 (4%)		
Infiltration cellular, plasma cell	2 (4%)		5 (10%)	2 (4%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Edema		1 (2%)		
Hemorrhage		1 (2%)		2 (4%)
Lymph node, mediastinal	(49)	(47)	(48)	(46)
Hemorrhage	3 (6%)	1 (2%)		3 (7%)
Inflammation, granulomatous		1 (2%)	1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Congestion		1 (2%)		
Developmental malformation	2 (4%)	3 (6%)	1 (2%)	4 (8%)
Fibrosis	9 (18%)	14 (28%)	11 (22%)	6 (12%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, lipocyte		1 (2%)		
Capsule, fibrosis	1 (2%)		1 (2%)	
Thymus	(49)	(47)	(47)	(45)
Hemorrhage	1 (2%)			

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

	0 ppm	156 ppm	312 ppm	625 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(33)	(36)	(41)	(34)
Galactocele	1 (3%)		1 (2%)	
Inflammation, chronic active	1 (3%)	1 (3%)		
Skin	(49)	(50)	(50)	(50)
Acanthosis				1 (2%)
Fibrosis	1 (2%)			
Hemorrhage			1 (2%)	
Hyperkeratosis	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic active	9 (18%)	4 (8%)	4 (8%)	4 (8%)
Necrosis				1 (2%)
Prepuce, edema	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	1 (2%)	1 (2%)	1 (2%)	
Cranium, fibrous osteodystrophy	1 (2%)	1 (2%)	3 (6%)	17 (34%)
Femur, fibrous osteodystrophy	1 (2%)	1 (2%)	3 (6%)	19 (38%)
Sternum, developmental malformation			1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	12 (24%)	11 (22%)	9 (18%)	6 (12%)
Hemorrhage		1 (2%)	1 (2%)	
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Inflammation, chronic active	10 (20%)	9 (18%)	8 (16%)	12 (24%)
Metaplasia, squamous	1 (2%)	1 (2%)	1 (2%)	
Mineralization	36 (72%)	38 (76%)	36 (72%)	33 (66%)
Lung	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Hemorrhage	9 (18%)	5 (10%)	3 (6%)	8 (16%)
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)	1 (2%)	3 (6%)	12 (24%)
Thrombosis	1 (2%)			1 (2%)
Alveolar epithelium, hyperplasia	5 (10%)	4 (8%)	3 (6%)	3 (6%)
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	5 (10%)	3 (6%)	4 (8%)	7 (14%)
Thrombosis	2 (4%)			1 (2%)
Nasolacrimal duct, inflammation, chronic active				1 (2%)
Olfactory epithelium, degeneration				1 (2%)
Respiratory epithelium, hyperplasia	1 (2%)			
Respiratory epithelium, metaplasia, squamous	2 (4%)			
Trachea	(50)	(50)	(50)	(50)
Metaplasia, squamous	1 (2%)			1 (2%)
Mineralization	1 (2%)		2 (4%)	1 (2%)

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

	0 ppm	156 ppm	312 ppm	625 ppm
2-Year Study (continued)				
Special Senses System				
Eye	(45)	(42)	(48)	(42)
Cataract	3 (7%)		4 (8%)	
Degeneration		1 (2%)	4 (8%)	
Cornea, inflammation, chronic active		1 (2%)		4 (10%)
Cornea, mineralization	1 (2%)		2 (4%)	7 (17%)
Retina, atrophy	3 (7%)	2 (5%)	5 (10%)	2 (5%)
Harderian gland		(1)		
Hypertrophy		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Developmental malformation				1 (2%)
Infarct		3 (6%)		
Mineralization		1 (2%)	3 (6%)	4 (8%)
Nephropathy	49 (98%)	50 (100%)	50 (100%)	50 (100%)
Pelvis, dilatation			1 (2%)	
Renal tubule, degeneration	2 (4%)	20 (40%)	50 (100%)	49 (98%)
Renal tubule, hyperplasia	1 (2%)	1 (2%)	1 (2%)	6 (12%)
Renal tubule, hyperplasia, oncocytic			1 (2%)	
Urinary bladder	(49)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, suppurative			1 (2%)	
Transitional epithelium, hyperplasia		1 (2%)		

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

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death				1
Moribund	21	33	31	25
Natural deaths	1	1	4	6
Survivors				
Died last week of study		1		
Terminal sacrifice	28	15	15	18
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma	1 (10%)	2 (20%)	1 (10%)	
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Adenoma		1 (10%)		
Carcinoma		1 (10%)		
Uterus	(10)	(10)	(10)	(10)
Polyp stromal			2 (20%)	1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Histiocytic sarcoma	1 (10%)			
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Fibroadenoma				1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Histiocytic sarcoma, metastatic, bone marrow	1 (10%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mixed tumor malignant				1 (10%)
Renal tubule, adenoma				1 (10%)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Histiocytic sarcoma	1 (10%)			

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(49)	(50)
Intestine large, rectum	(50)	(50)	(49)	(50)
Sarcoma stromal, metastatic, uterus		1 (2%)		
Intestine large, cecum	(50)	(50)	(49)	(50)
Hemangiosarcoma, metastatic, liver				1 (2%)
Intestine small, duodenum	(49)	(50)	(49)	(50)
Intestine small, jejunum	(50)	(50)	(47)	(49)
Hemangiosarcoma, metastatic, liver				1 (2%)
Intestine small, ileum	(50)	(49)	(48)	(49)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma			5 (10%)	1 (2%)
Hepatocellular carcinoma		4 (8%)	6 (12%)	2 (4%)
Hepatocellular carcinoma, multiple			3 (6%)	
Hepatocellular adenoma		3 (6%)	4 (8%)	5 (10%)
Hepatocellular adenoma, multiple		1 (2%)	1 (2%)	1 (2%)
Sarcoma			1 (2%)	
Mesentery	(6)	(4)	(4)	(6)
Leiomyosarcoma, metastatic, uterus	1 (17%)			
Pancreas	(50)	(50)	(49)	(50)
Salivary glands	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Stomach, forestomach	(50)	(50)	(48)	(50)
Squamous cell carcinoma	1 (2%)			
Stomach, glandular	(50)	(50)	(49)	(50)
Hemangiosarcoma, metastatic, liver				1 (2%)
Tongue	(2)		(2)	(1)
Squamous cell papilloma	2 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma NOS	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, liver			1 (2%)	
Leiomyosarcoma, metastatic, uterus	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	4 (8%)	1 (2%)	2 (4%)	5 (10%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma			1 (2%)	
Carcinoma		1 (2%)		
Parathyroid gland	(48)	(49)	(49)	(47)
Adenoma	1 (2%)			
Pituitary gland	(50)	(50)	(49)	(50)
Pars distalis, adenoma	43 (86%)	34 (68%)	36 (73%)	34 (68%)
Pars distalis, carcinoma		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	5 (10%)	9 (18%)	5 (10%)	2 (4%)
C-cell, carcinoma	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Follicular cell, carcinoma		1 (2%)		
General Body System				
Tissue NOS				(1)
Abdominal, fat, hemangiosarcoma, metastatic, tissue NOS				1 (100%)
Genital System				
Clitoral gland	(49)	(49)	(50)	(48)
Adenoma	6 (12%)	6 (12%)	2 (4%)	
Carcinoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Granulosa-theca tumor benign			1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)	1 (2%)		
Polyp stromal	5 (10%)	4 (8%)	4 (8%)	5 (10%)
Polyp stromal, multiple	1 (2%)	1 (2%)		
Sarcoma stromal		1 (2%)		1 (2%)
Vagina	(1)		(1)	(1)
Polyp	1 (100%)			1 (100%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Lymph node	(3)	(7)	(7)	(13)
Iliac, osteosarcoma, metastatic, bone				1 (8%)
Lymph node, bronchial	(50)	(50)	(50)	(48)
Lymph node, mandibular	(48)	(49)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Leiomyosarcoma, metastatic, uterus	1 (2%)			
Lymph node, mediastinal	(49)	(49)	(49)	(45)
Spleen	(50)	(50)	(49)	(50)
Thymus	(47)	(48)	(49)	(48)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Carcinoma	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Carcinoma, multiple			1 (2%)	
Fibroadenoma	17 (34%)	10 (20%)	8 (16%)	5 (10%)
Fibroadenoma, multiple	5 (10%)	1 (2%)	1 (2%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Basosquamous tumor malignant			1 (2%)	1 (2%)
Keratoacanthoma	2 (4%)			1 (2%)
Squamous cell papilloma			1 (2%)	1 (2%)
Subcutaneous tissue, fibroma		1 (2%)		
Subcutaneous tissue, neurofibroma				1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Vertebra, osteosarcoma				1 (2%)
Vertebra, sarcoma	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma NOS		1 (2%)		1 (2%)
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)		
Carcinoma, metastatic, mammary gland			1 (2%)	
Carcinoma, metastatic, pituitary gland		1 (2%)		
Carcinoma, metastatic, thyroid gland		1 (2%)		1 (2%)
Hemangiosarcoma, metastatic, liver			3 (6%)	
Hepatocellular carcinoma, metastatic, liver			2 (4%)	
Leiomyosarcoma, metastatic, uterus	1 (2%)			
Osteosarcoma, metastatic, bone				1 (2%)
Sarcoma, metastatic, bone	1 (2%)			
Sarcoma, metastatic, liver			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Zymbal's gland			(1)	(1)
Adenoma			1 (100%)	

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Leiomyosarcoma, metastatic, uterus	1 (2%)			
Renal tubule, adenoma		3 (6%)	1 (2%)	3 (6%)
Renal tubule, carcinoma				2 (4%)
Urinary bladder	(49)	(50)	(50)	(49)
Sarcoma stromal, metastatic, uterus		1 (2%)		
Transitional epithelium, papilloma			2 (4%)	
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	16 (32%)	31 (62%)	23 (46%)	36 (72%)
Mesothelioma malignant		1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	4	3	3
2-Year study	49	50	49	48
Total primary neoplasms				
15-Month interim evaluation	2	4	3	4
2-Year study	121	123	121	118
Total animals with benign neoplasms				
15-Month interim evaluation	1	3	3	3
2-Year study	46	43	43	40
Total benign neoplasms				
15-Month interim evaluation	1	3	3	3
2-Year study	93	75	72	68
Total animals with malignant neoplasms				
15-Month interim evaluation	1	1		1
2-Year study	21	41	35	42
Total malignant neoplasms				
15-Month interim evaluation	1	1		1
2-Year study	27	47	49	49
Total animals with metastatic neoplasms				
15-Month interim evaluation	1			
2-Year study	2	3	8	3
Total metastatic neoplasms				
15-Month interim evaluation	1			
2-Year study	6	4	9	7
Total animals with uncertain neoplasms-benign or malignant				
2-Year study	1	1		1
Total uncertain neoplasms				
2-Year study	1	1		1

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 0 ppm

Number of Days on Study	4 3 3	4 8 1	4 8 1	5 5 4	5 8 1	6 2 1	6 2 6	6 4 8	6 4 9	6 6 3	6 7 7	6 8 5	6 9 2	6 9 3	6 9 8	6 9 9	7 0 2	7 0 7	7 0 7	7 1 4	7 2 1	7 2 6	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 0 2	0 7 3	1 1 5	1 0 7	1 1 2	1 2 0	0 9 9	0 9 3	0 9 2	0 7 1	1 1 7	0 8 0	0 8 3	0 6 3	0 9 4	0 7 0	0 9 5	0 6 7	1 1 8	0 1 6	1 1 3	0 9 8	0 6 1	0 6 2	0 6 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery									+		+					+				+					
Leiomyosarcoma, metastatic, uterus									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																					+				
Squamous cell papilloma																					X				
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign															X						X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X	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										
C-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 B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 0 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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 6 5	0 6 8	0 7 2	0 7 6	0 7 9	0 8 2	0 8 4	0 8 5	0 8 8	0 8 9	0 9 0	0 9 1	0 9 6	0 9 7	1 0 0	1 0 1	1 0 4	1 0 5	1 0 8	1 0 9	1 1 0	1 1 1	1 1 4	1 1 6	1 1 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+	+																					6
Leiomyosarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																									X	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+																							2
Squamous cell papilloma			X																							2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma NOS					X																					1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X									X															4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
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	X	X	43
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X									X					X				X						5
C-cell, carcinoma													X										X			2
General Body System																										
None																										

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

Number of Days on Study	4 3 3	4 8 1	4 8 1	5 5 4	5 8 1	6 2 1	6 2 6	6 4 8	6 4 9	6 6 3	6 7 7	6 8 5	6 9 2	6 9 3	6 9 8	6 9 9	7 0 2	7 0 7	7 0 7	7 1 4	7 2 1	7 2 6	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 0 2	0 7 3	1 1 5	1 0 7	1 1 2	1 2 0	0 9 9	0 9 3	0 9 2	0 7 1	1 1 7	0 8 0	0 8 3	0 6 3	0 9 4	0 7 0	0 9 5	0 6 7	1 1 8	0 6 6	1 1 3	0 9 8	0 6 1	0 6 2	0 6 4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma								X								X									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma									X																
Polyp stromal							X																	X	X
Polyp stromal, multiple																									
Vagina									+																
Polyp									X																
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node											+			+	+										
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus									X																
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma														X		X									
Fibroadenoma		X	X					X					X			X			X		X		X		X
Fibroadenoma, multiple									X								X	X		X				X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								X	
Subcutaneous tissue, sarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, sarcoma	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus									X																
Sarcoma, metastatic, bone	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																				+					
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 4	7 4 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 6 5	0 6 8	0 7 2	0 7 6	0 7 9	0 8 2	0 8 4	0 8 5	0 8 8	0 8 9	0 9 0	0 9 1	0 9 6	0 9 7	1 0 0	1 0 1	1 0 4	1 0 5	1 0 8	1 0 9	1 1 0	1 1 1	1 1 4	1 1 6	1 1 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X					X						X					X								6
Carcinoma															X											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal							X																		X	5
Polyp stromal, multiple											X															1
Vagina																										1
Polyp																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																			X							1
Lymph node																										3
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Carcinoma															X											3
Fibroadenoma	X		X		X			X	X					X	X					X						17
Fibroadenoma, multiple																										5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																			X							2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Sarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	4 3 3	4 8 1	4 8 1	5 5 4	5 8 1	6 2 1	6 2 6	6 4 8	6 4 9	6 6 3	6 7 7	6 8 5	6 9 2	6 9 3	6 9 8	6 9 9	7 0 2	7 0 7	7 0 7	7 1 4	7 2 1	7 2 6	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 0 2	0 7 3	1 1 5	1 0 7	1 1 2	1 2 0	0 9 9	0 9 3	0 9 2	0 7 1	1 1 7	0 8 0	0 8 3	0 6 3	0 9 4	0 7 0	0 9 5	0 6 7	1 1 8	0 6 6	1 1 3	0 1 9	0 6 1	0 6 2	0 6 4
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus									X																
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
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 Tetrafluoroethylene: 0 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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 6 5	0 6 8	0 7 2	0 7 6	0 7 9	0 8 2	0 8 4	0 8 5	0 8 8	0 8 9	0 9 0	0 9 1	0 9 6	0 9 7	1 0 0	1 0 1	1 0 4	1 0 5	1 0 8	1 0 9	1 1 0	1 1 1	1 1 4	1 1 6	1 1 9	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																			X							1
Leukemia mononuclear		X	X		X								X			X			X		X				X	16

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	6 7 5	6 9 1	7 0 1	7 0 4	7 0 7	7 2 2	7 2 3	7 3 0	7 3 0	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 5 3	2 6 0	2 9 3	2 4 5	2 9 5	2 4 2	2 5 9	2 6 6	2 8 5	2 9 4	4 3	2 5 7	2 6 3	2 6 8	2 7 3	2 7 5	2 7 7	2 8 0	2 8 2	2 8 3	2 8 4	2 8 6	2 9 6	2 9 8	2 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma												X					X							X		4
Hepatocellular adenoma					X								X				X									3
Hepatocellular adenoma, multiple																		X								1
Mesentery								+																		4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X	X		X	X	X	X	X		X	X	X	X	X				X	X	X	X	X	34
Pars distalis, carcinoma																				X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X	X		X		X	X	X										X							9
C-cell, carcinoma														X												2
Follicular cell, carcinoma																X										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X							X						X			X	X	6
Carcinoma																						X				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal		X														X	X				X					4
Polyp stromal, multiple																										1
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	2 4 7	4 1 3	4 6 8	4 6 8	5 1 7	5 2 3	5 3 7	5 5 7	5 6 5	5 6 5	5 7 4	5 7 4	5 8 1	5 8 3	5 8 8	5 9 4	5 9 7	6 0 0	6 1 7	6 1 8	6 1 8	6 2 5	6 3 8	6 4 9	6 5 3
Carcass ID Number	2 9 2	2 7 2	2 5 2	2 8 8	2 4 8	2 7 9	2 5 5	2 7 6	2 5 0	2 7 1	2 4 4	2 6 5	2 9 0	2 9 1	2 8 1	2 5 4	2 7 4	2 6 9	2 8 7	2 6 1	2 6 7	2 7 0	2 5 8	2 9 7	3 0 0
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+							+									+	
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X												
Fibroadenoma			X						X		X	X							X						
Fibroadenoma, multiple																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, sarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS	X																								
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, pituitary gland																									
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																							X		
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X			X	X			X	X	X	X		X	X	X	X	X	X		X	X
Mesothelioma malignant		X																							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	6 7 5	6 9 1	7 0 1	7 0 4	7 0 7	7 2 2	7 2 3	7 3 0	7 3 0	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 5 3	2 6 0	2 9 3	2 4 5	2 9 5	2 4 2	2 5 9	2 5 6	2 8 5	2 9 4	2 4 3	2 5 7	2 6 3	2 6 8	2 7 3	2 7 5	2 7 7	2 8 0	2 8 2	2 8 3	2 8 4	2 8 6	2 9 6	2 9 8	2 9 9	Total Tissues/ Tumors
Hematopoietic System																										
Blood				+																						1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+					+											+				+			7
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma												X		X		X			X					X		10
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma											X															1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma NOS																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																					X					1
Carcinoma, metastatic, pituitary gland																				X						1
Carcinoma, metastatic, thyroid gland														X												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland												+														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma								X			X															3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X	X	X	X	X	X	X	X		X				X	X	X	X						31
Mesothelioma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm

Number of Days on Study	3 6 3	3 8 7	4 6 9	4 7 7	4 7 8	5 0 4	5 3 4	5 3 6	5 4 4	5 8 1	5 8 7	5 8 7	5 8 9	6 0 7	6 0 8	6 1 1	6 2 5	6 5 2	6 5 3	6 6 4	6 6 8	6 6 8	6 7 2	6 7 4	6 7 7
Carcass ID Number	4 0 3	3 6 9	3 7 9	4 1 0	3 8 5	3 7 3	3 6 5	3 7 7	4 1 1	4 1 9	3 9 2	4 0 0	4 1 2	3 6 2	3 7 4	4 0 4	3 9 6	4 1 5	3 6 1	4 0 1	3 6 4	3 8 4	3 9 4	4 1 4	3 9 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X										X		
Hepatocellular carcinoma																						X			
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Sarcoma																									
Mesentery			+																					+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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							X						
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																							X		
Hepatocellular carcinoma, metastatic, liver																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Vagina						+																			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm
(continued)

Number of Days on Study	6 8 5	6 9 8	6 9 8	6 9 9	7 0 2	7 1 6	7 2 9	7 3 3	7 3 3	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 8 8	3 7 5	3 8 1	3 7 0	3 8 2	4 0 8	4 1 8	3 6 6	3 9 3	4 1 7	3 6 3	3 6 8	3 7 1	3 7 6	3 8 0	3 8 3	3 8 6	3 8 7	3 9 0	3 9 1	3 9 7	3 9 9	4 0 5	4 0 6	4 2 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X				X		X																	5
Hepatocellular carcinoma							X		X						X			X							X	6
Hepatocellular carcinoma, multiple																	X			X			X			3
Hepatocellular adenoma														X				X	X				X			4
Hepatocellular adenoma, multiple																								X		1
Sarcoma						X																				1
Mesentery																		+	+							4
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue		+													+											2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver									X																	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																				X						2
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X				X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	36
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X										X	X						5
C-cell, carcinoma												X			X					X						3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																X		2
Carcinoma									X																	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor benign																										1
Hepatocellular carcinoma, metastatic, liver																	X									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X	X									X			X									4
Vagina																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm
(continued)

Number of Days on Study	3 6 3	3 8 7	4 6 9	4 7 7	4 7 8	5 0 4	5 3 4	5 3 6	5 4 4	5 8 1	5 8 7	5 8 7	5 8 9	6 0 7	6 0 8	6 1 1	6 2 5	6 5 2	6 5 3	6 6 4	6 6 8	6 6 8	6 7 2	6 7 4	6 7 7
Carcass ID Number	4 0 3	3 6 9	3 7 9	4 1 0	3 8 5	3 7 3	3 6 5	3 7 7	4 1 1	4 1 9	3 9 2	4 0 0	4 1 2	4 2 2	3 6 2	4 0 4	3 9 6	4 1 5	3 6 1	4 0 1	3 6 4	3 8 4	3 9 4	4 1 4	3 9 8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+									+					+				+				
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																X					X				
Carcinoma, multiple																									
Fibroadenoma							X		X													X		X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant																									
Squamous cell papilloma																									
Subcutaneous tissue, sarcoma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, mammary gland																X									
Hemangiosarcoma, metastatic, liver													X										X		
Hepatocellular carcinoma, metastatic, liver																						X			
Sarcoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									X
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Tetrafluoroethylene: 625 ppm
(continued)

Number of Days on Study	6 8 5	6 9 8	6 9 8	6 9 9	7 0 2	7 1 6	7 2 9	7 3 3	7 3 3	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 4 0	7 4 0	7 4 2	
Carcass ID Number	3 8 8	3 7 5	3 8 1	3 7 0	3 8 2	4 0 8	4 1 8	3 6 6	3 9 3	4 1 7	3 6 3	3 6 8	3 7 1	3 7 6	3 8 0	3 8 3	3 8 6	3 8 7	3 9 0	3 9 1	3 9 7	3 9 9	4 0 5	4 0 6	4 2 0	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+						+																	7
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																						1
Carcinoma																	X										3
Carcinoma, multiple																		X									1
Fibroadenoma						X											X			X			X				8
Fibroadenoma, multiple																						X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant					X																						1
Squamous cell papilloma																X											1
Subcutaneous tissue, sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																								X			1
Carcinoma, metastatic, mammary gland																											1
Hemangiosarcoma, metastatic, liver							X																				3
Hepatocellular carcinoma, metastatic, liver																	X										2
Sarcoma, metastatic, liver						X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland											+																1
Adenoma											X																1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																								X			2
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X						X	X			X	X		X			X			X				23

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm

Number of Days on Study	0 0 6	3 7 2	3 7 8	4 3 3	4 3 9	4 6 1	4 8 1	5 0 4	5 0 9	5 1 8	5 3 1	5 3 8	5 7 2	5 7 6	5 7 9	5 8 3	5 9 4	6 0 3	6 0 8	6 1 0	6 2 1	6 2 1	6 2 4	6 2 8	6 3 5
Carcass ID Number	4 6 4	4 7 7	4 5 2	4 4 6	4 6 5	4 3 5	4 3 2	4 7 6	4 5 1	4 5 3	4 5 6	4 7 1	4 3 6	4 2 8	4 2 4	4 6 0	4 6 8	4 3 9	4 6 6	4 6 2	4 6 1	4 6 3	4 4 7	4 8 0	4 5 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Mesentery				+	+					+							+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																				X				X	X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				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																									
Tissue NOS																									
Abdominal, fat, hemangiosarcoma, metastatic, tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Carcinoma																				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X								X								X				
Sarcoma stromal																				X					
Vagina																				+					
Polyp																				X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

Number of Days on Study	6 3 9	6 5 3	6 6 8	6 7 7	6 7 8	7 0 3	7 2 7	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 2 2	4 2 1	4 7 3	4 4 3	4 4 4	4 3 1	4 4 5	4 2 3	4 2 5	4 2 7	4 3 0	4 3 7	4 3 8	4 4 1	4 4 2	4 4 8	4 4 9	4 5 0	4 5 5	4 6 7	4 6 9	4 7 0	4 7 2	4 7 4	4 7 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver		X																								1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, liver		X																								1
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Hepatocellular carcinoma																				X			X			2
Hepatocellular adenoma				X	X			X	X													X				5
Hepatocellular adenoma, multiple																									X	1
Mesentery									+										+							6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver		X																								1
Tongue																					+					1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																				X					X	5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	34
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X																		2
C-cell, carcinoma																X		X								2
General Body System																										
Tissue NOS		+																								1
Abdominal, fat, hemangiosarcoma, metastatic, tissue NOS		X																								1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																				X						2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal								X															X			5
Sarcoma stromal																										1
Vagina																										1
Polyp																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

Number of Days on Study	0 0 6	3 7 2	3 7 8	4 3 3	4 3 9	4 6 1	4 8 1	5 0 4	5 0 9	5 1 8	5 3 1	5 3 8	5 7 2	5 7 6	5 7 9	5 8 3	5 9 4	6 0 3	6 0 8	6 1 0	6 2 1	6 2 1	6 2 4	6 2 8	6 3 5
Carcass ID Number	4 6 4	4 7 7	4 5 2	4 4 6	4 6 5	4 3 5	4 3 2	4 7 6	4 5 1	4 5 3	4 5 6	4 7 1	4 3 6	4 2 8	4 2 4	4 6 0	4 6 8	4 3 9	4 6 6	4 6 2	4 6 1	4 6 3	4 4 7	4 8 0	4 5 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+							+		+		+					+				+	+	+	
Iliac, osteosarcoma, metastatic, bone											X														
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Fibroadenoma								X																	
Fibroadenoma, multiple											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant																									
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, neurofibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS			X																						
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Osteosarcoma, metastatic, bone											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X	X		X	X		X	X	X	X	X	X	X	X		X	X	X	X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

Number of Days on Study	6 3 9	6 5 3	6 6 8	6 7 7	6 7 8	7 0 3	7 2 7	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 2 2	4 2 1	4 7 3	4 4 3	4 4 4	4 3 1	4 4 5	4 2 3	4 2 5	4 2 7	4 3 0	4 3 7	4 3 8	4 4 1	4 4 2	4 4 8	4 4 9	4 5 0	4 5 5	4 6 7	4 6 9	4 7 0	4 7 2	4 7 4	4 7 9	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+		+	+						+											+	13
Iliac, osteosarcoma, metastatic, bone																									1
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X													1
Carcinoma																		X							1
Fibroadenoma						X												X				X	X		5
Fibroadenoma, multiple				X																					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant																								X	1
Keratoacanthoma																			X						1
Squamous cell papilloma								X																	1
Subcutaneous tissue, neurofibroma															X										1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma NOS																									1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																		X							1
Osteosarcoma, metastatic, bone																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																		+							1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma								X							X									X		3
Renal tubule, carcinoma														X			X								2
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X	X		X		X		X	X	X		X		X	X			X	X	X		X	36

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/50 (8%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rate[b]	12.7%	3.2%	9.6%	20.4%
Terminal rate[c]	2/28 (7%)	0/16 (0%)	1/15 (7%)	2/18 (11%)
First incidence (days)	698	618	653	610
Life table test[d]	P=0.136	P=0.347N	P=0.577N	P=0.239
Logistic regression test[d]	P=0.188	P=0.247N	P=0.461N	P=0.354
Cochran-Armitage test[d]	P=0.273			
Fisher exact test[d]		P=0.181N	P=0.339N	P=0.500
Clitoral Gland: Adenoma				
Overall rate	6/49 (12%)	6/49 (12%)	2/50 (4%)	0/48 (0%)
Adjusted rate	18.7%	31.4%	11.9%	0.0%
Terminal rate	4/28 (14%)	4/16 (25%)	1/15 (7%)	0/18 (0%)
First incidence (days)	648	617	733	—[e]
Life table test	P=0.029N	P=0.263	P=0.365N	P=0.062N
Logistic regression test	P=0.020N	P=0.382	P=0.242N	P=0.046N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.620N	P=0.128N	P=0.014N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	7/49 (14%)	7/49 (14%)	4/50 (8%)	2/48 (4%)
Adjusted rate	22.1%	37.1%	19.5%	8.6%
Terminal rate	5/28 (18%)	5/16 (31%)	1/15 (7%)	1/18 (6%)
First incidence (days)	648	617	625	610
Life table test	P=0.152N	P=0.223	P=0.594N	P=0.243N
Logistic regression test	P=0.114N	P=0.333	P=0.412N	P=0.180N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=0.613N	P=0.251N	P=0.084N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	13.7%	3.3%	16.7%
Terminal rate	0/28 (0%)	1/16 (6%)	0/15 (0%)	3/18 (17%)
First incidence (days)	—	574	668	734(T)
Life table test	P=0.095	P=0.066	P=0.443	P=0.054
Logistic regression test	P=0.099	P=0.100	P=0.505	P=0.054
Cochran-Armitage test	P=0.165			
Fisher exact test		P=0.121	P=0.500	P=0.121
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted rate	0.0%	0.0%	11.9%	23.0%
Terminal rate	0/28 (0%)	0/16 (0%)	1/15 (7%)	3/18 (17%)
First incidence (days)	—	—	733	628
Life table test	P<0.001	—	P=0.133	P=0.008
Logistic regression test	P<0.001	—	P=0.143	P=0.013
Cochran-Armitage test	P=0.003			
Fisher exact test		—	P=0.247	P=0.028

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	0/50 (0%)	3/50 (6%)	3/50 (6%)	8/50 (16%)
Adjusted rate	0.0%	13.7%	14.8%	38.4%
Terminal rate	0/28 (0%)	1/16 (6%)	1/15 (7%)	6/18 (33%)
First incidence (days)	—	574	668	628
Life table test	P<0.001	P=0.066	P=0.057	P<0.001
Logistic regression test	P<0.001	P=0.100	P=0.076	P<0.001
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.121	P=0.121	P=0.003
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	5/50 (10%)
Adjusted rate	0.0%	13.7%	3.3%	27.8%
Terminal rate	0/28 (0%)	1/16 (6%)	0/15 (0%)	5/18 (28%)
First incidence (days)	—	574	668	734 (T)
Life table test	P=0.012	P=0.066	P=0.443	P=0.007
Logistic regression test	P=0.010	P=0.100	P=0.505	P=0.007
Cochran-Armitage test	P=0.029			
Fisher exact test		P=0.121	P=0.500	P=0.028
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	0/50 (0%)	3/50 (6%)	3/50 (6%)	10/50 (20%)
Adjusted rate	0.0%	13.7%	14.8%	48.8%
Terminal rate	0/28 (0%)	1/16 (6%)	1/15 (7%)	8/18 (44%)
First incidence (days)	—	574	668	628
Life table test	P<0.001	P=0.066	P=0.057	P<0.001
Logistic regression test	P<0.001	P=0.100	P=0.076	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.121	P=0.121	P<0.001
Liver: Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	19.5%	5.0%
Terminal rate	0/28 (0%)	0/16 (0%)	0/15 (0%)	0/18 (0%)
First incidence (days)	—	—	589	703
Life table test	P=0.143	—	P=0.013	P=0.400
Logistic regression test	P=0.182	—	P=0.025	P=0.435
Cochran-Armitage test	P=0.242			
Fisher exact test		—	P=0.028	P=0.500
Liver: Hepatocellular Adenoma				
Overall rate	0/50 (0%)	4/50 (8%)	5/50 (10%)	6/50 (12%)
Adjusted rate	0.0%	22.6%	33.3%	28.2%
Terminal rate	0/28 (0%)	3/16 (19%)	5/15 (33%)	3/18 (17%)
First incidence (days)	—	707	734 (T)	677
Life table test	P=0.006	P=0.017	P=0.003	P=0.003
Logistic regression test	P=0.004	P=0.020	P=0.003	P=0.003
Cochran-Armitage test	P=0.026			
Fisher exact test		P=0.059	P=0.028	P=0.013

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	0/50 (0%)	4/50 (8%)	9/50 (18%)	2/50 (4%)
Adjusted rate	0.0%	20.9%	48.1%	11.1%
Terminal rate	0/28 (0%)	3/16 (19%)	6/15 (40%)	2/18 (11%)
First incidence (days)	—	583	668	734 (T)
Life table test	P=0.146	P=0.020	P<0.001	P=0.147
Logistic regression test	P=0.128	P=0.037	P<0.001	P=0.147
Cochran-Armitage test	P=0.309			
Fisher exact test		P=0.059	P=0.001	P=0.247
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	0/50 (0%)	7/50 (14%)	12/50 (24%)	8/50 (16%)
Adjusted rate	0.0%	36.3%	65.4%	37.8%
Terminal rate	0/28 (0%)	5/16 (31%)	9/15 (60%)	5/18 (28%)
First incidence (days)	—	583	668	677
Life table test	P=0.002	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.001	P=0.002	P<0.001	P<0.001
Cochran-Armitage test	P=0.020			
Fisher exact test		P=0.006	P<0.001	P=0.003
Mammary Gland: Fibroadenoma				
Overall rate	22/50 (44%)	11/50 (22%)	9/50 (18%)	7/50 (14%)
Adjusted rate	55.2%	41.8%	38.1%	28.0%
Terminal rate	11/28 (39%)	5/16 (31%)	4/15 (27%)	3/18 (17%)
First incidence (days)	481	468	534	504
Life table test	P=0.033N	P=0.277N	P=0.162N	P=0.055N
Logistic regression test	P=0.003N	P=0.024N	P=0.009N	P=0.004N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.016N	P=0.004N	P<0.001N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	23/50 (46%)	11/50 (22%)	10/50 (20%)	8/50 (16%)
Adjusted rate	57.8%	41.8%	41.1%	32.8%
Terminal rate	12/28 (43%)	5/16 (31%)	4/15 (27%)	4/18 (22%)
First incidence (days)	481	468	534	504
Life table test	P=0.050N	P=0.232N	P=0.196N	P=0.068N
Logistic regression test	P=0.005N	P=0.016N	P=0.011N	P=0.006N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.010N	P=0.005N	P=0.001N
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	8.9%	2.6%	18.6%	5.6%
Terminal rate	1/28 (4%)	0/16 (0%)	2/15 (13%)	1/18 (6%)
First incidence (days)	693	581	611	734 (T)
Life table test	P=0.523N	P=0.461N	P=0.262	P=0.501N
Logistic regression test	P=0.431N	P=0.318N	P=0.421	P=0.461N
Cochran-Armitage test	P=0.343N			
Fisher exact test		P=0.309N	P=0.500	P=0.309N

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	5/50 (10%)	2/50 (4%)
Adjusted rate	12.2%	2.6%	22.5%	11.1%
Terminal rate	2/28 (7%)	0/16 (0%)	2/15 (13%)	2/18 (11%)
First incidence (days)	693	581	611	734 (T)
Life table test	P=0.522	P=0.336N	P=0.226	P=0.575N
Logistic regression test	P=0.558N	P=0.213N	P=0.389	P=0.565N
Cochran-Armitage test	P=0.420N			
Fisher exact test		P=0.181N	P=0.500	P=0.339N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	24/50 (48%)	12/50 (24%)	13/50 (26%)	8/50 (16%)
Adjusted rate	59.0%	43.3%	49.8%	32.8%
Terminal rate	12/28 (43%)	5/16 (31%)	5/15 (33%)	4/18 (22%)
First incidence (days)	481	468	534	504
Life table test	P=0.050N	P=0.260N	P=0.386N	P=0.054N
Logistic regression test	P=0.004N	P=0.016N	P=0.037N	P=0.004N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.011N	P=0.019N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	43/50 (86%)	34/50 (68%)	36/49 (73%)	34/50 (68%)
Adjusted rate	93.4%	88.4%	94.0%	88.9%
Terminal rate	25/28 (89%)	12/16 (75%)	13/15 (87%)	14/18 (78%)
First incidence (days)	481	413	387	433
Life table test	P=0.177	P=0.156	P=0.074	P=0.164
Logistic regression test	P=0.270N	P=0.112N	P=0.253N	P=0.251N
Cochran-Armitage test	P=0.063N			
Fisher exact test		P=0.028N	P=0.096N	P=0.028N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	43/50 (86%)	35/50 (70%)	36/49 (73%)	34/50 (68%)
Adjusted rate	93.4%	91.3%	94.0%	88.9%
Terminal rate	25/28 (89%)	13/16 (81%)	13/15 (87%)	14/18 (78%)
First incidence (days)	481	413	387	433
Life table test	P=0.186	P=0.112	P=0.074	P=0.164
Logistic regression test	P=0.248N	P=0.176N	P=0.253N	P=0.251N
Cochran-Armitage test	P=0.052N			
Fisher exact test		P=0.045N	P=0.096N	P=0.028N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Malignant Basosquamous Tumor				
Overall rate	2/50 (4%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	7.1%	0.0%	11.1%	16.7%
Terminal rate	2/28 (7%)	0/16 (0%)	1/15 (7%)	3/18 (17%)
First incidence (days)	734 (T)	—	702	734 (T)
Life table test	P=0.136	P=0.368N	P=0.470	P=0.301
Logistic regression test	P=0.120	P=0.368N	P=0.550	P=0.301
Cochran-Armitage test	P=0.237			
Fisher exact test		P=0.247N	P=0.691N	P=0.500

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/50 (10%)	9/50 (18%)	5/50 (10%)	2/50 (4%)
Adjusted rate	16.7%	35.0%	22.7%	8.2%
Terminal rate	4/28 (14%)	1/16 (6%)	2/15 (13%)	1/18 (6%)
First incidence (days)	698	523	587	579
Life table test	P=0.265N	P=0.044	P=0.316	P=0.420N
Logistic regression test	P=0.169N	P=0.084	P=0.487	P=0.370N
Cochran-Armitage test	P=0.086N			
Fisher exact test		P=0.194	P=0.630N	P=0.218N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	7.1%	8.2%	20.0%	11.1%
Terminal rate	2/28 (7%)	1/16 (6%)	3/15 (20%)	2/18 (11%)
First incidence (days)	734 (T)	468	734 (T)	734 (T)
Life table test	P=0.406	P=0.536	P=0.228	P=0.528
Logistic regression test	P=0.427	P=0.701N	P=0.228	P=0.528
Cochran-Armitage test	P=0.569			
Fisher exact test		P=0.691N	P=0.500	P=0.691N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/50 (14%)	11/50 (22%)	7/50 (14%)	4/50 (8%)
Adjusted rate	23.6%	40.6%	34.6%	19.0%
Terminal rate	6/28 (21%)	2/16 (13%)	4/15 (27%)	3/18 (17%)
First incidence (days)	698	468	587	579
Life table test	P=0.365N	P=0.041	P=0.215	P=0.548N
Logistic regression test	P=0.253N	P=0.110	P=0.386	P=0.543N
Cochran-Armitage test	P=0.117N			
Fisher exact test		P=0.218	P=0.613N	P=0.262N
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted rate	19.7%	24.2%	21.2%	18.2%
Terminal rate	5/28 (18%)	3/16 (19%)	2/15 (13%)	2/18 (11%)
First incidence (days)	626	583	699	439
Life table test	P=0.432	P=0.405	P=0.538	P=0.489
Logistic regression test	P=0.552	P=0.569	P=0.564N	P=0.568N
Cochran-Armitage test	P=0.437N			
Fisher exact test		P=0.500N	P=0.370N	P=0.500N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	6/50 (12%)	6/50 (12%)	4/50 (8%)	6/50 (12%)
Adjusted rate	19.7%	26.9%	21.2%	20.8%
Terminal rate	5/28 (18%)	3/16 (19%)	2/15 (13%)	2/18 (11%)
First incidence (days)	626	583	699	439
Life table test	P=0.328	P=0.270	P=0.538	P=0.348
Logistic regression test	P=0.468	P=0.456	P=0.564N	P=0.582
Cochran-Armitage test	P=0.530N			
Fisher exact test		P=0.620N	P=0.370N	P=0.620N

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	19.5%	5.0%
Terminal rate	0/28 (0%)	0/16 (0%)	0/15 (0%)	0/18 (0%)
First incidence (days)	—	—	589	703
Life table test	P=0.143	—	P=0.013	P=0.400
Logistic regression test	P=0.182	—	P=0.025	P=0.435
Cochran-Armitage test	P=0.242			
Fisher exact test		—	P=0.028	P=0.500
All Organs: Mononuclear Cell Leukemia				
Overall rate	16/50 (32%)	31/50 (62%)	23/50 (46%)	36/50 (72%)
Adjusted rate	43.7%	76.5%	65.1%	82.6%
Terminal rate	8/28 (29%)	7/16 (44%)	6/15 (40%)	11/18 (61%)
First incidence (days)	621	468	469	372
Life table test	P<0.001	P<0.001	P=0.008	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.105	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.002	P=0.109	P<0.001
All Organs: Benign Neoplasms				
Overall rate	46/50 (92%)	43/50 (86%)	43/50 (86%)	40/50 (80%)
Adjusted rate	95.8%	97.6%	100.0%	95.1%
Terminal rate	26/28 (93%)	15/16 (94%)	15/15 (100%)	16/18 (89%)
First incidence (days)	481	413	387	433
Life table test	P=0.080	P=0.016	P=0.013	P=0.057
Logistic regression test	P=0.305N	P=0.546N	P=0.499N	P=0.360N
Cochran-Armitage test	P=0.065N			
Fisher exact test		P=0.262N	P=0.262N	P=0.074N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	41/50 (82%)	35/50 (70%)	42/50 (84%)
Adjusted rate	52.7%	93.0%	84.0%	91.1%
Terminal rate	10/28 (36%)	13/16 (81%)	9/15 (60%)	14/18 (78%)
First incidence (days)	433	413	387	372
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.005	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P=0.004	P<0.001

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	50/50 (100%)	49/50 (98%)	48/50 (96%)
Adjusted rate	98.0%	100.0%	100.0%	98.0%
Terminal rate	27/28 (96%)	16/16 (100%)	15/15 (100%)	17/18 (94%)
First incidence (days)	433	247	387	372
Life table test	P=0.021	P=0.003	P=0.004	P=0.009
Logistic regression test	P=0.526N	P=0.612	P=0.629	P=0.748
Cochran-Armitage test	P=0.247N			
Fisher exact test		P=0.500	P=0.753N	P=0.500N

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

TABLE B4a
Historical Incidence of Renal Tubule Neoplasms in Chamber Control Female F344/N Rats [a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile (CS-2)	0/49	0/49	0/49
Acetonitrile	0/48	0/48	0/48
α-Chloroacetophenone	0/49	0/49	0/49
Epinephrine Hydrochloride	0/50	0/50	0/50
Ethyl Chloride	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	1/50	1/50
Ozone	1/50	0/50	1/50
Total	1/346 (0.3%)	1/346 (0.3%)	2/346 (0.6%)
Standard deviation	0.8%	0.8%	1.0%
Range	0%-2%	0%-2%	0%-2%
Overall Historical Incidence			
Total	1/650 (0.2%)	1/650 (0.2%)	2/650 (0.3%)
Standard deviation	0.6%	0.6%	0.8%
Range	0%-2%	0%-2%	0%-2%

[a] Data as of 12 May 1995

TABLE B4b
Historical Incidence of Liver Neoplasms in Chamber Control Female F344/N Rats [a]

Study	Incidence in Controls			
	Hemangiosarcoma	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories				
o-Chlorobenzalmalononitrile (CS-2)	0/49	3/49	0/49	3/49
Acetonitrile	0/48	0/48	0/48	0/48
α-Chloroacetophenone	0/49	0/49	0/49	0/49
Epinephrine Hydrochloride	0/50	2/50	0/50	2/50
Ethyl Chloride	0/50	0/50	1/50	1/50
Hexachlorocyclopentadiene	0/50	1/50	0/50	1/50
Ozone	0/50	0/50	0/50	0/50
Total	0/346	6/346 (1.7%)	1/346 (0.3%)	7/346 (2.0%)
Standard deviation		2.4%	0.8%	2.3%
Range		0%-6%	0%-2%	0%-6%
Overall Historical Incidence				
Total	0/650	9/650 (1.4%)	1/650 (0.2%)	10/650 (1.5%)
Standard deviation		2.1%	0.6%	2.0%
Range		0%-6%	0%-2%	0%-6%

[a] Data as of 12 May 1995

TABLE B4c
Historical Incidence of Mononuclear Cell Leukemia in Chamber Control Female F344/N Rats [a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
o-Chlorobenzalmalononitrile (CS-2)	24/50
Acetonitrile	18/48
α-Chloroacetophenone	27/50
Epinephrine Hydrochloride	24/50
Ethyl Chloride	20/50
Hexachlorocyclopentadiene	16/50
Ozone	17/50
Total	146/348 (42.0%)
Standard deviation	8.2%
Range	32%-54%
Overall Historical Incidence	
Total	262/653 (40.1%)
Standard deviation	7.2%
Range	30%-54%

[a] Data as of 12 May 1995; includes data for lymphocytic, monocytic, and undifferentiated cell type leukemias

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death				1
Moribund	21	33	31	25
Natural deaths	1	1	4	6
Survivors				
Died last week of study		1		
Terminal sacrifice	28	15	15	18
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Angiectasis		1 (10%)		
Basophilic focus	9 (90%)	9 (90%)	10 (100%)	10 (100%)
Clear cell focus		2 (20%)	3 (30%)	3 (30%)
Eosinophilic focus		5 (50%)	2 (20%)	
Hepatodiaphragmatic nodule		2 (20%)		1 (10%)
Mixed cell focus		1 (10%)	6 (60%)	4 (40%)
Bile duct, hyperplasia	1 (10%)			
Mesentery	(2)	(2)	(3)	(1)
Fat, necrosis	2 (100%)	2 (100%)	3 (100%)	1 (100%)
Pancreas	(10)	(10)	(10)	(10)
Metaplasia, hepatocyte				2 (20%)
Acinus, atrophy	3 (30%)	1 (10%)	2 (20%)	3 (30%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Acanthosis			1 (10%)	
Ulcer			1 (10%)	
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy	8 (80%)	10 (100%)	9 (90%)	10 (100%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)	1 (10%)	1 (10%)	2 (20%)
Hypertrophy	2 (20%)			
Parathyroid gland	(10)	(10)	(10)	(10)
Hyperplasia				1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, hyperplasia	6 (60%)	5 (50%)	8 (80%)	7 (70%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia	9 (90%)	7 (70%)	9 (90%)	9 (90%)

[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 Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)		1 (10%)	
Ovary	(10)	(10)	(10)	(10)
Cyst		1 (10%)	1 (10%)	
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hyperplasia, reticulum cell	2 (20%)	2 (20%)	3 (30%)	2 (20%)
Lymph node		(1)		
Renal, hemorrhage		1 (100%)		
Lymph node, mediastinal	(8)	(10)	(10)	(9)
Hemorrhage	3 (38%)	2 (20%)	1 (10%)	
Spleen	(10)	(10)	(10)	(10)
Developmental malformation		1 (10%)		
Respiratory System				
Larynx	(10)	(10)	(10)	(10)
Inflammation, chronic active	2 (20%)	3 (30%)	5 (50%)	3 (30%)
Metaplasia, squamous		2 (20%)	1 (10%)	1 (10%)
Mineralization	7 (70%)	6 (60%)	10 (100%)	10 (100%)
Lung	(10)	(10)	(10)	(10)
Hemorrhage	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Infiltration cellular, histiocyte	1 (10%)	1 (10%)	3 (30%)	1 (10%)
Inflammation, chronic active			1 (10%)	
Alveolar epithelium, hyperplasia	1 (10%)	1 (10%)	2 (20%)	
Nose	(10)	(10)	(10)	(10)
Inflammation, chronic active				1 (10%)
Special Senses System				
Eye	(1)			
Cataract	1 (100%)			
Retina, atrophy	1 (100%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	8 (80%)	9 (90%)	9 (90%)	10 (100%)
Renal tubule, degeneration			10 (100%)	10 (100%)
Renal tubule, hyperplasia			1 (10%)	
Renal tubule, hyperplasia, oncocytic				1 (10%)
Urinary bladder	(10)	(10)	(10)	(10)
Transitional epithelium, hyperplasia				1 (10%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(49)	(50)
Cyst			1 (2%)	
Parasite metazoan	4 (8%)	5 (10%)	3 (6%)	3 (6%)
Intestine large, rectum	(50)	(50)	(49)	(50)
Diverticulum	1 (2%)			
Parasite metazoan	5 (10%)	2 (4%)	2 (4%)	6 (12%)
Intestine large, cecum	(50)	(50)	(49)	(50)
Diverticulum	1 (2%)			
Fibrosis				1 (2%)
Infiltration cellular, eosinophil	1 (2%)			
Parasite metazoan	1 (2%)	1 (2%)		4 (8%)
Intestine small, duodenum	(49)	(50)	(49)	(50)
Necrosis			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis		9 (18%)	9 (18%)	14 (28%)
Basophilic focus	41 (82%)	38 (76%)	41 (82%)	37 (74%)
Clear cell focus	10 (20%)	3 (6%)	12 (24%)	9 (18%)
Degeneration, cystic	1 (2%)	4 (8%)	1 (2%)	3 (6%)
Embolus bacterial				1 (2%)
Eosinophilic focus	1 (2%)	4 (8%)	5 (10%)	4 (8%)
Fatty change	15 (30%)	20 (40%)	17 (34%)	10 (20%)
Hepatodiaphragmatic nodule	3 (6%)	5 (10%)	10 (20%)	5 (10%)
Mitotic alteration			1 (2%)	
Mixed cell focus	12 (24%)	14 (28%)	16 (32%)	18 (36%)
Necrosis, focal	1 (2%)		2 (4%)	
Regeneration	1 (2%)	2 (4%)	3 (6%)	8 (16%)
Bile duct, hyperplasia	9 (18%)	18 (36%)	12 (24%)	18 (36%)
Centrilobular, necrosis			2 (4%)	2 (4%)
Mesentery	(6)	(4)	(4)	(6)
Polyarteritis	1 (17%)		1 (25%)	
Fat, necrosis	4 (67%)	4 (100%)	4 (100%)	4 (67%)
Pancreas	(50)	(50)	(49)	(50)
Basophilic focus	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia	1 (2%)			
Metaplasia		1 (2%)		
Acinus, atrophy	15 (30%)	14 (28%)	9 (18%)	9 (18%)
Pharynx		(1)		
Palate, hyperplasia		1 (100%)		

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(48)	(50)
Acanthosis	4 (8%)	4 (8%)	1 (2%)	1 (2%)
Diverticulum		1 (2%)		
Inflammation, suppurative			1 (2%)	
Mineralization		1 (2%)		
Necrosis	5 (10%)	4 (8%)		
Stomach, glandular	(50)	(50)	(49)	(50)
Mineralization	1 (2%)		1 (2%)	2 (4%)
Necrosis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Tongue	(2)		(2)	(1)
Hyperplasia, squamous			1 (50%)	
Epithelium, hyperplasia			1 (50%)	1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	41 (82%)	40 (80%)	40 (80%)	33 (66%)
Embolus bacterial				1 (2%)
Polyarteritis	1 (2%)			
Atrium, thrombosis	1 (2%)	2 (4%)		1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Embolus bacterial				1 (2%)
Fibrosis		1 (2%)		
Hyperplasia	18 (36%)	11 (22%)	16 (32%)	22 (44%)
Hypertrophy	4 (8%)	4 (8%)	3 (6%)	5 (10%)
Metaplasia, osseous			1 (2%)	
Necrosis			1 (2%)	
Vacuolization cytoplasmic	5 (10%)	3 (6%)	4 (8%)	3 (6%)
Adrenal medulla	(50)	(50)	(50)	(50)
Embolus bacterial				1 (2%)
Hyperplasia	6 (12%)	9 (18%)	3 (6%)	8 (16%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia		1 (2%)		
Pituitary gland	(50)	(50)	(49)	(50)
Pars distalis, angiectasis	1 (2%)			
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	4 (8%)	8 (16%)	8 (16%)	13 (26%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	48 (96%)	40 (80%)	41 (82%)	38 (76%)
Follicular cell, hyperplasia	2 (4%)		1 (2%)	
General Body System				
None				

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Genital System				
Clitoral gland	(49)	(49)	(50)	(48)
Dilatation	1 (2%)			
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic active	2 (4%)	4 (8%)	7 (14%)	2 (4%)
Duct, ectasia	1 (2%)			
Ovary	(50)	(50)	(50)	(50)
Cyst	4 (8%)	3 (6%)	2 (4%)	2 (4%)
Uterus	(50)	(50)	(50)	(50)
Cyst	1 (2%)			1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia, reticulum cell				1 (2%)
Myelofibrosis		3 (6%)	1 (2%)	
Lymph node	(3)	(7)	(7)	(13)
Lumbar, pigmentation		1 (14%)		
Renal, hemorrhage	1 (33%)		1 (14%)	2 (15%)
Lymph node, bronchial	(50)	(50)	(50)	(48)
Hemorrhage			2 (4%)	
Lymph node, mandibular	(48)	(49)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)		
Infiltration cellular, plasma cell			3 (6%)	2 (4%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Embolus bacterial				1 (2%)
Hemorrhage		1 (2%)	1 (2%)	
Lymph node, mediastinal	(49)	(49)	(49)	(45)
Hemorrhage	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Spleen	(50)	(50)	(49)	(50)
Angiectasis			1 (2%)	1 (2%)
Fibrosis	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hematopoietic cell proliferation			1 (2%)	
Infiltration cellular, lipocyte		2 (4%)		
Thymus	(47)	(48)	(49)	(48)
Cyst				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Hyperplasia, focal		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic active		2 (4%)	4 (8%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	6 (12%)	14 (28%)	8 (16%)	3 (6%)
Tibia, fracture				1 (2%)
Turbinate, fracture				1 (2%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	30 (60%)	23 (46%)	20 (40%)	19 (38%)
Embolus bacterial				1 (2%)
Hemorrhage		2 (4%)		
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Inflammation, chronic active	13 (26%)	14 (28%)	14 (28%)	21 (42%)
Metaplasia, squamous	2 (4%)	1 (2%)	2 (4%)	4 (8%)
Mineralization	31 (62%)	29 (58%)	31 (62%)	30 (60%)
Lung	(50)	(50)	(50)	(50)
Hemorrhage	17 (34%)	8 (16%)	12 (24%)	5 (10%)
Infiltration cellular, lymphocyte	1 (2%)			
Infiltration cellular, histiocyte	2 (4%)			2 (4%)
Inflammation, chronic active	2 (4%)	3 (6%)		1 (2%)
Metaplasia, osseous				1 (2%)
Alveolar epithelium, hyperplasia	8 (16%)	4 (8%)	9 (18%)	6 (12%)
Mediastinum, polyarteritis	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		
Inflammation, suppurative	1 (2%)	2 (4%)	3 (6%)	5 (10%)
Thrombosis				1 (2%)
Nares, inflammation, chronic active				1 (2%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)			
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Cataract	15 (30%)	4 (8%)	10 (20%)	45 (90%)
Degeneration	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Hemorrhage	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Cornea, inflammation, chronic active	1 (2%)	2 (4%)		
Cornea, mineralization	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Retina, atrophy	21 (42%)	11 (22%)	15 (30%)	21 (42%)
Retina, degeneration	33 (66%)	23 (46%)	14 (28%)	13 (26%)
Harderian gland		(1)		
Inflammation, chronic active		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Embolus bacterial				1 (2%)
Hyperplasia, atypical				1 (2%)
Nephropathy	48 (96%)	46 (92%)	48 (96%)	47 (94%)
Papilla, necrosis		1 (2%)		
Pelvis, dilatation		1 (2%)		1 (2%)
Renal tubule, degeneration			35 (70%)	46 (92%)
Renal tubule, hyperplasia	1 (2%)	3 (6%)	6 (12%)	12 (24%)
Renal tubule, hyperplasia, oncocytic				3 (6%)
Urinary bladder	(49)	(50)	(50)	(49)
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)		

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

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	58	58	58	58
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	6	24	26	27
Natural deaths	4	13	20	20
Survivors				
Terminal sacrifice	38	11	2	1
Animals examined microscopically	58	58	58	58
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hemangiosarcoma				3 (30%)
Hepatocellular carcinoma	2 (20%)	4 (40%)	2 (20%)	2 (20%)
Hepatocellular adenoma	5 (50%)	2 (20%)	2 (20%)	1 (10%)
Hepatocellular adenoma, multiple	1 (10%)		2 (20%)	
Histiocytic sarcoma				1 (10%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Squamous cell papilloma			1 (10%)	
Hematopoietic System				
Thymus	(8)	(9)	(10)	(9)
Thymoma NOS		1 (11%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)			1 (10%)
Hepatocellular carcinoma, metastatic, liver	1 (10%)		1 (10%)	
Histiocytic sarcoma				1 (10%)
Special Senses System				
Harderian gland	(1)	(2)		(1)
Adenoma	1 (100%)	2 (100%)		1 (100%)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Histiocytic sarcoma				1 (10%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				
2-Year Study				
Alimentary System				
Liver	(48)	(48)	(48)	(48)
Carcinoma, metastatic, harderian gland				1 (2%)
Carcinoma, metastatic, lung		1 (2%)		
Hemangioma		3 (6%)	3 (6%)	1 (2%)
Hemangioma, multiple		7 (15%)	2 (4%)	1 (2%)
Hemangiosarcoma		5 (10%)	10 (21%)	19 (40%)
Hemangiosarcoma, multiple		16 (33%)	17 (35%)	18 (38%)
Hepatocellular carcinoma	7 (15%)	11 (23%)	24 (50%)	20 (42%)
Hepatocellular carcinoma, multiple	4 (8%)	9 (19%)	9 (19%)	6 (13%)
Hepatocellular adenoma	11 (23%)	11 (23%)	5 (10%)	13 (27%)
Hepatocellular adenoma, multiple	6 (13%)	6 (13%)	7 (15%)	7 (15%)
Histiocytic sarcoma		12 (25%)	7 (15%)	7 (15%)
Mesentery	(2)	(3)	(2)	(7)
Carcinoma, metastatic, lung		1 (33%)		
Hemangioma				1 (14%)
Hemangiosarcoma				1 (14%)
Hepatocellular carcinoma, metastatic, liver				1 (14%)
Histiocytic sarcoma			1 (50%)	
Pancreas	(48)	(48)	(46)	(45)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Stomach, forestomach	(48)	(48)	(46)	(46)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	2 (4%)	1 (2%)		1 (2%)
Cardiovascular System				
Heart	(48)	(48)	(48)	(48)
Carcinoma, metastatic, lung		1 (2%)		1 (2%)
Endocrine System				
Adrenal cortex	(48)	(48)	(47)	(48)
Adenoma	1 (2%)		1 (2%)	
Islets, pancreatic	(48)	(48)	(46)	(45)
Adenoma				1 (2%)
Thyroid gland	(48)	(48)	(47)	(47)
Follicular cell, adenoma		3 (6%)		
Follicular cell, carcinoma		1 (2%)		

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
General Body System				
Tissue NOS	(1)	(2)	(2)	
Carcinoma, metastatic, lung		1 (50%)		
Hemangioma		1 (50%)		
Genital System				
Epididymis	(48)	(48)	(48)	(48)
Leiomyoma				1 (2%)
Leiomyosarcoma		1 (2%)		
Hematopoietic System				
Bone marrow	(48)	(48)	(47)	(47)
Hemangioma			1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)	2 (4%)
Lymph node	(3)	(1)	(2)	
Renal, histiocytic sarcoma		1 (100%)	1 (50%)	
Lymph node, bronchial	(36)	(36)	(35)	(26)
Histiocytic sarcoma		3 (8%)		1 (4%)
Lymph node, mandibular	(36)	(34)	(32)	(34)
Histiocytic sarcoma		2 (6%)	1 (3%)	
Lymph node, mesenteric	(47)	(42)	(41)	(40)
Histiocytic sarcoma		4 (10%)	1 (2%)	2 (5%)
Lymph node, mediastinal	(30)	(34)	(32)	(29)
Carcinoma, metastatic, lung		1 (3%)		1 (3%)
Histiocytic sarcoma		2 (6%)		1 (3%)
Spleen	(48)	(48)	(46)	(46)
Hemangiosarcoma	2 (4%)			
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Thymus	(43)	(40)	(34)	(37)
Histiocytic sarcoma				1 (3%)
Integumentary System				
Skin	(48)	(48)	(48)	(48)
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma			1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(48)	(48)	(48)	(48)
Carcinoma, metastatic, harderian gland				1 (2%)
Skeletal muscle				(1)
Carcinoma, metastatic, lung				1 (100%)
Nervous System				
Brain	(48)	(48)	(48)	(48)
Carcinoma, metastatic, harderian gland				1 (2%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(48)	(48)	(48)	(48)
Alveolar/bronchiolar adenoma	9 (19%)	7 (15%)	12 (25%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	4 (8%)	3 (6%)	1 (2%)
Carcinoma		1 (2%)		1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			1 (2%)
Hemangiosarcoma, metastatic, liver			2 (4%)	2 (4%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	7 (15%)	14 (29%)	8 (17%)
Histiocytic sarcoma		7 (15%)	4 (8%)	3 (6%)
Nose	(48)	(47)	(46)	(47)
Carcinoma, metastatic, harderian gland	1 (2%)			
Special Senses System				
Harderian gland	(6)	(8)	(5)	(6)
Adenoma	5 (83%)	7 (88%)	4 (80%)	4 (67%)
Carcinoma	1 (17%)	1 (13%)		1 (17%)
Urinary System				
Kidney	(48)	(48)	(48)	(48)
Carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma		3 (6%)	3 (6%)	2 (4%)
Urinary bladder	(48)	(43)	(43)	(42)
Systemic Lesions				
Multiple organs	(48)	(48)	(48)	(48)
Histiocytic sarcoma		12 (25%)	7 (15%)	7 (15%)
Lymphoma malignant mixed	2 (4%)	1 (2%)		1 (2%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	6	7	6	6
2-Year study	37	44	48	46
Total primary neoplasms				
15-Month interim evaluation	10	9	7	9
2-Year study	53	110	107	112
Total animals with benign neoplasms				
15-Month interim evaluation	6	4	4	3
2-Year study	26	30	27	27
Total benign neoplasms				
15-Month interim evaluation	8	4	5	3
2-Year study	35	48	36	35
Total animals with malignant neoplasms				
15-Month interim evaluation	2	4	2	4
2-Year study	16	39	47	46
Total malignant neoplasms				
15-Month interim evaluation	2	4	2	6
2-Year study	18	62	71	77
Total animals with metastatic neoplasms				
15-Month interim evaluation	1		1	
2-Year study	2	8	14	11
Total metastatic neoplasms				
15-Month interim evaluation	1		1	
2-Year study	3	12	17	20
Total animals with uncertain neoplasms-benign or malignant				
15-Month interim evaluation		1		
Total uncertain neoplasms				
15-Month interim evaluation		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 Tetrafluoroethylene: 0 ppm

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

+: 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 Tetrafluoroethylene: 0 ppm (continued)

Number of Days on Study	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 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 6	6 6 6	6 6 6	6 6 6	6 6 6	6 6 6	6 6 6	6 6 6	
Carcass ID Number	0 2 6	0 2 7	0 2 9	0 3 0	0 3 1	0 3 4	0 3 5	0 3 6	0 3 8	0 3 9	0 4 0	0 4 4	0 4 5	0 4 7	0 4 9	0 5 0	0 5 1	0 5 2	0 5 3	0 5 5	0 5 6	0 5 7	0 5 8	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma																								7
Hepatocellular carcinoma, multiple				X					X												X			4
Hepatocellular adenoma								X			X		X	X	X	X			X					11
Hepatocellular adenoma, multiple	X											X												6
Mesentery									+															2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																X								2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																								2
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	M	M	+	+	+	M	+	+	M	+	+	M	M	M	+	+	+	+	M	+	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																								
Tissue NOS																						+		1
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																+								3
Lymph node, bronchial	+	M	+	M	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	36
Lymph node, mandibular	M	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	36

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

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

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

Number of Days on Study	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 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 6	6 6 6	6 6 6	6 6 6	6 6 6	6 6 6	6 6 6	6 6 6	
Carcass ID Number	0 2 6	0 2 7	0 2 9	0 3 0	0 3 1	0 3 4	0 3 5	0 3 6	0 3 8	0 3 9	0 4 0	0 4 4	0 4 5	0 4 7	0 4 9	0 5 0	0 5 1	0 5 2	0 5 3	0 5 5	0 5 6	0 5 7	0 5 8	Total Tissues/ Tumors
Hematopoietic System (continued)																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	M	+	M	M	+	M	M	M	M	+	+	M	M	M	+	+	+	M	+	+	+	+	M	30
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma		X												X										2
Thymus	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma			X										X		X							X		9
Alveolar/bronchiolar adenoma, multiple							X																	1
Alveolar/bronchiolar carcinoma																								2
Carcinoma, metastatic, harderian gland																								1
Hepatocellular carcinoma, metastatic, liver				X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, harderian gland																								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																								
Ear																								1
Harderian gland															+							+		6
Adenoma															X							X		5
Carcinoma																								1
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																								2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	5 9 9	6 0 0	6 1 4	6 1 4	6 1 6	6 2 5	6 3 1	6 3 7	6 4 6	6 4 6	6 4 9	6 6 0	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 6 6	6 6 6	6 6 6	6 6 6	
Carcass ID Number	1 6 5	1 3 0	1 1 8	1 4 3	1 3 7	1 4 2	1 4 0	1 4 7	1 1 7	1 5 3	1 2 9	1 3 3	1 2 1	1 2 6	1 2 8	1 4 4	1 4 5	1 4 6	1 5 7	1 6 0	1 6 1	1 6 4	1 6 7	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, lung																								1
Hemangioma		X																						3
Hemangioma, multiple			X	X							X				X	X		X					X	7
Hemangiosarcoma														X	X	X							X	5
Hemangiosarcoma, multiple	X		X	X		X	X	X					X						X	X	X	X		16
Hepatocellular carcinoma				X					X					X										11
Hepatocellular carcinoma, multiple							X			X		X									X		X	9
Hepatocellular adenoma							X					X	X	X	X		X	X				X		11
Hepatocellular adenoma, multiple	X				X			X			X								X	X				6
Histiocytic sarcoma		X		X		X	X	X	X		X								X					12
Mesentery																		+		+				3
Carcinoma, metastatic, lung																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth														+										2
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, lung																								1
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	M	M	M	+	+	+	+	+	M	M	M	M	M	+	M	+	+	+	+	M	+	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma								X								X					X			3
Follicular cell, carcinoma													X											1
General Body System																								
Tissue NOS																							+	2
Carcinoma, metastatic, lung																								1
Hemangioma																							X	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	0 4 4	0 7 5	0 7 7	4 6 2	4 6 3	4 9 5	5 0 8	5 0 9	5 1 3	5 2 2	5 3 7	5 3 7	5 3 7	5 4 1	5 4 1	5 4 1	5 5 1	5 5 2	5 6 6	6 6 9	7 3 3	8 6	9 0	9 3	9 3
Carcass ID Number	1 3 5	1 3 1	1 5 8	1 5 1	1 6 9	1 7 2	1 5 5	1 2 0	1 5 9	1 3 8	1 5 0	1 6 3	1 6 6	1 2 4	1 2 5	1 2 7	1 2 3	1 5 6	1 6 2	1 3 6	1 3 2	1 5 4	1 7 3	1 4 9	1 5 2
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																							X		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node																									
Renal, histiocytic sarcoma																									
Lymph node, bronchial	M	M	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	M	+
Histiocytic sarcoma														X											
Lymph node, mandibular	+	M	+	M	+	M	M	+	+	+	M	+	+	+	+	M	M	M	+	+	+	+	+	M	I
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	I	M
Histiocytic sarcoma														X											
Lymph node, mediastinal	+	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M
Carcinoma, metastatic, lung																						X			
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	M	+	+	+	+	+	+	M	+	+	M	I	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	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X		X													
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma													X												
Carcinoma																						X			
Hepatocellular carcinoma, metastatic, liver				X		X	X						X			X		X				X		
Histiocytic sarcoma									X					X					X						
Nose	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	5 9 9	6 0 0	6 1 4	6 1 4	6 1 6	6 2 5	6 3 1	6 3 7	6 4 6	6 4 6	6 4 9	6 6 0	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 6 6	6 6 6	6 6 6	
Carcass ID Number	1 6 5	1 3 0	1 1 8	1 4 3	1 3 7	1 4 2	1 4 0	1 4 7	1 1 7	1 5 3	1 2 9	1 3 3	1 2 1	1 2 6	1 2 8	1 4 4	1 4 5	1 4 6	1 5 7	1 6 0	1 6 1	1 6 4	1 6 7	Total Tissues/ Tumors
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma																								1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma									X															1
Lymph node									+															1
Renal, histiocytic sarcoma									X															1
Lymph node, bronchial	+	+	I	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	M	36
Histiocytic sarcoma		X							X															3
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	34
Histiocytic sarcoma		X							X															2
Lymph node, mesenteric	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	42
Histiocytic sarcoma		X					X		X															4
Lymph node, mediastinal	M	+	+	+	M	+	+	+	+	+	M	+	M	+	+	M	+	M	+	M	+	+	+	34
Carcinoma, metastatic, lung																								1
Histiocytic sarcoma		X							X															2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma		X							X															2
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	40
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, hemangioma																								1
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma		X				X											X				X	X		7
Alveolar/bronchiolar adenoma, multiple								X																1
Alveolar/bronchiolar carcinoma										X				X									X	4
Carcinoma																								1
Hepatocellular carcinoma, metastatic, liver																								7
Histiocytic sarcoma							X	X	X		X													7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm (continued)

Number of Days on Study	5 9 9	6 0 0	6 1 4	6 1 4	6 1 6	6 2 5	6 3 1	6 3 7	6 4 6	6 4 6	6 4 9	6 6 0	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 6 6	6 6 6	6 6 6	
Carcass ID Number	1 6 5	1 3 0	1 1 8	1 4 3	1 3 7	1 4 2	1 4 0	1 4 7	1 1 7	1 5 3	1 2 9	1 3 3	1 2 1	1 2 6	1 2 8	1 4 4	1 4 5	1 4 6	1 5 7	1 6 0	1 6 1	1 6 4	1 6 7	Total Tissues/ Tumors
Special Senses System																								
Eye					+																			1
Harderian gland	+			+	+			+							+				+		+			8
Adenoma	X			X	X			X											X		X			7
Carcinoma															X									1
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma							X		X															3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma		X		X		X	X	X	X		X								X					12
Lymphoma malignant mixed			X																					1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	5 6 9	5 7 3	5 8 6	5 8 9	5 8 9	5 9 3	5 9 7	6 0 0	6 0 7	6 0 8	6 0 8	6 1 5	6 1 6	6 1 8	6 3 1	6 3 2	6 3 9	6 4 6	6 4 9	6 5 3	6 5 7	6 6 6	6 6 6	
Carcass ID Number	2 4 9	2 5 3	2 8 8	2 3 6	2 6 5	2 6 6	2 4 8	2 8 0	2 7 4	2 6 7	2 7 1	2 7 7	2 6 3	2 5 4	2 3 8	2 8 9	2 5 7	2 9 0	2 7 3	2 4 3	2 6 0	2 4 6	2 4 7	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	M	+	A	A	+	+	+	+	+	+	+	31
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	41
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	A	+	M	A	+	+	+	+	+	+	+	36
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	34
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	34
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	35
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma												X												3
Hemangioma, multiple						X																X		2
Hemangiosarcoma	X		X	X		X		X								X	X	X						10
Hemangiosarcoma, multiple		X			X		X		X		X		X		X				X	X	X		X	17
Hepatocellular carcinoma	X				X										X	X	X		X			X		24
Hepatocellular carcinoma, multiple											X	X		X				X			X			9
Hepatocellular adenoma	X					X					X												X	5
Hepatocellular adenoma, multiple							X	X	X															7
Histiocytic sarcoma			X	X						X								X						7
Mesentery											+													2
Histiocytic sarcoma																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Tooth							+						+											4
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma														X										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	+	+	+	M	M	+	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	M	+	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
General Body System																								
Tissue NOS																								2
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	46
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	3 6 3	3 6 8	4 1 5	4 2 0	4 3 3	4 4 6	4 4 7	4 8 4	4 8 5	4 9 7	5 0 9	5 1 6	5 1 7	5 1 8	5 1 8	5 3 1	5 3 9	5 4 1	5 4 1	5 4 1	5 4 7	5 4 8	5 4 8	5 5 1	5 5 4
Carcass ID Number	2 7 8	2 8 2	2 5 5	2 6 2	2 5 8	2 8 7	2 5 9	2 6 1	2 3 4	2 4 1	2 7 9	2 6 4	2 4 4	2 8 1	2 8 6	2 5 6	2 3 3	2 4 0	2 5 0	2 8 4	2 7 6	2 5 1	2 7 0	2 4 2	2 5 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Hemangioma																		X							
Histiocytic sarcoma							X																		
Lymph node																									
Renal, histiocytic sarcoma																									
Lymph node, bronchial	A	M	M	+	+	+	M	+	+	+	+	+	+	+	I	+	+	M	M	+	+	M	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	M	M	+	M	+	+	+
Histiocytic sarcoma							X																		
Lymph node, mesenteric	A	+	+	+	+	+	M	+	+	+	A	+	+	+	M	M	+	+	+	+	A	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mediastinal	A	+	+	+	+	+	M	I	+	+	M	I	M	M	M	+	M	+	+	+	+	M	+	M	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Histiocytic sarcoma							X																		
Thymus	A	M	+	+	+	M	M	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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		
Hemangiosarcoma, metastatic, liver																		X							
Hepatocellular carcinoma, metastatic, liver			X		X					X	X		X					X		X		X	X		
Histiocytic sarcoma							X								X										
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Special Senses System																									
Eye							+												+						
Harderian gland							+	+											+						+
Adenoma							X												X						X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	5 6 9	5 7 3	5 8 6	5 8 9	5 8 9	5 9 3	5 9 7	6 0 0	6 0 7	6 0 8	6 0 8	6 1 5	6 1 6	6 1 8	6 3 1	6 3 2	6 3 9	6 4 6	6 4 9	6 5 3	6 5 7	6 6 6	6 6 6	
Carcass ID Number	2 4 9	2 5 3	2 8 8	2 3 6	2 6 5	2 6 6	2 4 8	2 8 0	2 7 4	2 6 7	2 7 1	2 7 7	2 6 3	2 5 4	2 3 8	2 8 9	2 5 7	2 9 0	2 7 3	2 4 3	2 6 0	2 4 6	2 4 7	Total Tissues/ Tumors
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma																								1
Histiocytic sarcoma																								1
Lymph node	+			+																				2
Renal, histiocytic sarcoma				X																				1
Lymph node, bronchial	+	+	+	M	M	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	35
Lymph node, mandibular	M	I	I	+	M	+	+	+	M	M	+	+	+	M	+	+	+	I	M	+	+	+	+	32
Histiocytic sarcoma																								1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	41
Histiocytic sarcoma			X																					1
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	M	32
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																								1
Thymus	+	+	+	+	+	+	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	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, hemangiosarcoma			X																					1
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma					X				X		X	X				X		X						12
Alveolar/bronchiolar adenoma, multiple																							X	1
Alveolar/bronchiolar carcinoma																				X	X			3
Hemangiosarcoma, metastatic, liver	X																							2
Hepatocellular carcinoma, metastatic, liver	X													X		X	X				X			14
Histiocytic sarcoma			X	X																				4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Special Senses System																								
Eye																								2
Harderian gland			+																					5
Adenoma			X																					4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm (continued)

Number of Days on Study	5 6 9	5 7 3	5 8 6	5 8 9	5 8 9	5 9 3	5 9 7	6 0 0	6 0 7	6 0 8	6 0 8	6 1 5	6 1 6	6 1 8	6 3 1	6 3 2	6 3 9	6 4 6	6 4 9	6 5 3	6 5 7	6 6 6	6 6 6	
Carcass ID Number	2 4 9	2 5 3	2 8 8	2 3 6	2 6 5	2 6 6	2 4 8	2 8 0	2 7 4	2 6 7	2 7 1	2 7 7	2 6 3	2 5 4	2 3 8	2 8 9	2 5 7	2 9 0	2 7 3	2 4 3	2 6 0	2 4 6	2 4 7	Total Tissues/ Tumors
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma, metastatic, liver																								1
Histiocytic sarcoma			X							X														3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	43
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma			X	X						X								X						7

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm

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

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

Number of Days on Study	5 8 3	5 8 5	5 8 6	5 8 6	5 8 9	5 9 9	6 0 0	6 0 0	6 0 6	6 0 8	6 0 8	6 0 8	6 1 0	6 1 3	6 1 3	6 2 3	6 2 9	6 3 0	6 3 1	6 4 3	6 4 6	6 5 4	6 6 6	
Carcass ID Number	3 5 9	3 8 9	3 8 0	3 9 9	3 6 5	3 6 7	3 6 3	3 7 5	4 0 5	3 5 7	3 6 4	3 8 1	3 8 6	3 6 6	3 7 4	3 7 8	3 6 9	3 8 2	4 0 6	4 4 9	3 9 2	4 0 0	3 6 1	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	A	+	A	+	M	+	+	+	M	M	+	M	+	+	A	+	A	+	27
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	36
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	A	+	34
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	36
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, harderian gland																								1
Hemangioma												X												1
Hemangioma, multiple						X																		1
Hemangiosarcoma					X					X	X		X				X						X	19
Hemangiosarcoma, multiple	X	X		X			X	X	X			X		X	X	X		X	X	X	X	X		18
Hepatocellular carcinoma			X			X		X	X		X	X		X	X	X	X	X						20
Hepatocellular carcinoma, multiple		X																					X	6
Hepatocellular adenoma		X	X	X					X		X		X		X		X							13
Hepatocellular adenoma, multiple										X				X		X								7
Histiocytic sarcoma						X													X	X	X			7
Mesentery							+							+				+			+		+	7
Hemangioma																		X						1
Hemangiosarcoma																								1
Hepatocellular carcinoma, metastatic, liver																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hepatocellular carcinoma, metastatic, liver															X									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell carcinoma													X											1
Squamous cell papilloma																							X	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Tooth												+						+				+		7
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, lung									X															1
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																								1
Parathyroid gland	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	M	M	+	39
Pituitary gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
General Body System																								
None																								

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

Number of Days on Study	0 5 9	2 5 9	3 1 5	3 5 6	4 0 1	4 6 5	4 8 3	5 1 8	5 2 7	5 2 7	5 3 6	5 4 1	5 4 1	5 4 1	5 4 3	5 4 4	5 4 8	5 4 8	5 5 1	5 5 9	6 3	6 5 4	7 5	7 5 8
Carcass ID Number	4 0 3	3 7 1	3 9 1	3 5 2	3 9 0	3 9 3	3 5 4	3 7 3	3 8 7	3 9 5	4 0 2	3 6 0	3 8 3	4 0 1	3 5 5	3 7 9	3 7 0	3 8 4	3 7 6	3 7 7	3 7 2	4 0 4	3 9 8	3 9 7	3 9 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																								X	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Seminal vesicle	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																X
Lymph node, bronchial	M	M	+	M	M	A	M	+	M	+	+	M	+	M	M	M	+	M	M	+	I	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mandibular	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	M	+	M	M	A	+	+	+	M
Histiocytic sarcoma																									
Lymph node, mediastinal	M	+	+	+	+	M	+	+	M	+	I	+	+	M	+	M	M	M	M	+	M	+	+	+	+
Carcinoma, metastatic, lung																									
Histiocytic sarcoma																									
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Histiocytic sarcoma									X																X
Thymus	+	+	+	M	+	A	M	+	+	+	+	+	M	+	+	M	+	+	M	M	+	+	+	+	+
Histiocytic sarcoma									X																
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland										X															
Skeletal muscle																									
Carcinoma, metastatic, lung																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland										X															

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

Number of Days on Study	5 8 3	5 8 5	5 8 6	5 8 6	5 8 9	5 9 9	6 0 0	6 0 0	6 0 6	6 0 8	6 0 8	6 0 8	6 1 0	6 1 3	6 1 3	6 2 3	6 2 9	6 3 0	6 3 1	6 4 3	6 4 6	6 5 4	6 6 6	
Carcass ID Number	3 5 9	3 8 9	3 8 0	3 9 9	3 6 5	3 6 7	3 6 3	3 7 5	4 0 5	3 5 7	3 6 4	3 8 1	3 8 6	3 6 6	3 7 4	3 7 8	3 6 9	3 8 2	4 0 6	4 4 9	3 9 2	3 0 0	3 0 1	Total Tissues/ Tumors
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																								1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																								2
Lymph node, bronchial	M	I	+	M	+	+	+	M	+	M	M	+	+	+	+	I	+	+	M	+	+	+	+	26
Histiocytic sarcoma																				X				1
Lymph node, mandibular	M	M	M	+	M	+	+	+	+	+	M	M	+	+	+	M	+	+	+	M	+	M	+	34
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	40
Histiocytic sarcoma																			X	X				2
Lymph node, mediastinal	+	+	+	+	+	+	M	M	+	+	M	M	+	M	+	+	I	M	M	+	+	M	+	29
Carcinoma, metastatic, lung									X															1
Histiocytic sarcoma																				X				1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																								2
Thymus	+	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	37
Histiocytic sarcoma																								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	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, hemangiosarcoma											X													1
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, harderian gland																								1
Skeletal muscle									+															1
Carcinoma, metastatic, lung									X															1
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, harderian gland																								1

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

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

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

Number of Days on Study	5 8 3	5 8 5	5 8 6	5 8 6	5 8 9	5 9 9	6 0 0	6 0 0	6 0 6	6 0 8	6 0 8	6 0 8	6 1 0	6 1 3	6 1 3	6 2 3	6 2 9	6 3 0	6 3 1	6 4 3	6 4 6	6 5 4	6 6 6	
Carcass ID Number	3 5 9	3 8 9	3 8 0	3 9 9	3 6 5	3 6 7	3 6 3	3 7 5	4 0 5	3 5 7	3 6 4	3 8 1	3 8 6	3 6 6	3 7 4	3 7 8	3 6 9	3 8 2	4 0 6	4 4 9	3 9 2	3 4 0	3 6 1	Total Tissues/ Tumors
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma							X					X												3
Alveolar/bronchiolar adenoma, multiple						X																		2
Alveolar/bronchiolar carcinoma																	X							1
Carcinoma									X															1
Carcinoma, metastatic, harderian gland																								1
Hemangiosarcoma, metastatic, liver																				X				2
Hepatocellular carcinoma, metastatic, liver															X			X					X	8
Histiocytic sarcoma																			X	X				3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Special Senses System																								
Ear									+															1
Harderian gland					+							+						+						6
Adenoma					X													X						4
Carcinoma																								1
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, lung									X															1
Histiocytic sarcoma																								2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma						X													X	X	X			7
Lymphoma malignant mixed																X								1

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	5/48 (10%)	7/48 (15%)	4/48 (8%)	4/48 (8%)
Adjusted rate[b]	12.6%	35.3%	13.8%	24.7%
Terminal rate[c]	4/38 (11%)	2/11 (18%)	0/2 (0%)	0/1 (0%)
First incidence (days)	597	463	447	465
Life table test[d]	P=0.047	P=0.022	P=0.100	P=0.052
Logistic regression test[d]	P=0.381N	P=0.239	P=0.481N	P=0.545N
Cochran-Armitage test[d]	P=0.316N			
Fisher exact test[d]		P=0.379	P=0.500N	P=0.500N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	6/48 (13%)	8/48 (17%)	4/48 (8%)	5/48 (10%)
Adjusted rate	14.6%	42.5%	13.8%	26.6%
Terminal rate	4/38 (11%)	3/11 (27%)	0/2 (0%)	0/1 (0%)
First incidence (days)	597	463	447	465
Life table test	P=0.033	P=0.016	P=0.166	P=0.058
Logistic regression test	P=0.389N	P=0.230	P=0.319N	P=0.487N
Cochran-Armitage test	P=0.312N			
Fisher exact test		P=0.387	P=0.370N	P=0.500N
Liver: Hemangioma				
Overall rate	0/48 (0%)	10/48 (21%)	5/48 (10%)	2/48 (4%)
Adjusted rate	0.0%	53.2%	60.1%	12.3%
Terminal rate	0/38 (0%)	4/11 (36%)	1/2 (50%)	0/1 (0%)
First incidence (days)	—[e]	590	548	599
Life table test	P=0.012	P<0.001	P<0.001	P=0.066
Logistic regression test	P=0.289N	P<0.001	P=0.015	P=0.188
Cochran-Armitage test	P=0.448N			
Fisher exact test		P<0.001	P=0.028	P=0.247
Liver: Hemangiosarcoma				
Overall rate	0/48 (0%)	21/48 (44%)	27/48 (56%)	37/48 (77%)
Adjusted rate	0.0%	89.3%	95.6%	100.0%
Terminal rate	0/38 (0%)	9/11 (82%)	1/2 (50%)	1/1 (100%)
First incidence (days)	—	522	497	401
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hemangioma or Hemangiosarcoma				
Overall rate	0/48 (0%)	26/48 (54%)	30/48 (63%)	38/48 (79%)
Adjusted rate	0.0%	95.7%	100.0%	100.0%
Terminal rate	0/38 (0%)	10/11 (91%)	2/2 (100%)	1/1 (100%)
First incidence (days)	—	522	497	401
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Liver: Hepatocellular Adenoma				
Overall rate	17/48 (35%)	17/48 (35%)	12/48 (25%)	20/48 (42%)
Adjusted rate	42.1%	83.5%	70.3%	71.3%
Terminal rate	15/38 (39%)	8/11 (73%)	1/2 (50%)	0/1 (0%)
First incidence (days)	452	566	485	401
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.043	P=0.059	P=0.444N	P=0.181
Cochran-Armitage test	P=0.322			
Fisher exact test		P=0.584N	P=0.187N	P=0.338
Liver: Hepatocellular Carcinoma				
Overall rate	11/48 (23%)	20/48 (42%)	33/48 (69%)	26/48 (54%)
Adjusted rate	24.4%	63.4%	94.3%	100.0%
Terminal rate	5/38 (13%)	3/11 (27%)	1/2 (50%)	1/1 (100%)
First incidence (days)	475	462	363	315
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.150	P=0.056	P=0.055	P=0.245
Cochran-Armitage test	P=0.001			
Fisher exact test		P=0.040	P<0.001	P=0.002
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	26/48 (54%)	34/48 (71%)	39/48 (81%)	35/48 (73%)
Adjusted rate	57.4%	96.8%	100.0%	100.0%
Terminal rate	19/38 (50%)	10/11 (91%)	2/2 (100%)	1/1 (100%)
First incidence (days)	452	462	363	315
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.236	P=0.015	P=0.289	P=0.550N
Cochran-Armitage test	P=0.040			
Fisher exact test		P=0.070	P=0.004	P=0.045
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	10/48 (21%)	8/48 (17%)	13/48 (27%)	5/48 (10%)
Adjusted rate	24.7%	41.7%	76.8%	23.1%
Terminal rate	8/38 (21%)	3/11 (27%)	1/2 (50%)	0/1 (0%)
First incidence (days)	475	522	433	548
Life table test	P=0.007	P=0.079	P<0.001	P=0.042
Logistic regression test	P=0.297N	P=0.597	P=0.324	P=0.344N
Cochran-Armitage test	P=0.159N			
Fisher exact test		P=0.397N	P=0.317	P=0.130N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/48 (4%)	5/48 (10%)	3/48 (6%)	2/48 (4%)
Adjusted rate	5.3%	28.4%	51.9%	20.0%
Terminal rate	2/38 (5%)	2/11 (18%)	0/2 (0%)	0/1 (0%)
First incidence (days)	666 (T)	537	548	606
Life table test	P=0.014	P=0.015	P=0.004	P=0.043
Logistic regression test	P=0.355	P=0.103	P=0.150	P=0.330
Cochran-Armitage test	P=0.420N			
Fisher exact test		P=0.218	P=0.500	P=0.692N

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	12/48 (25%)	13/48 (27%)	16/48 (33%)	7/48 (15%)
Adjusted rate	29.7%	61.8%	88.8%	38.5%
Terminal rate	10/38 (26%)	5/11 (45%)	1/2 (50%)	0/1 (0%)
First incidence (days)	475	522	433	548
Life table test	P<0.001	P=0.003	P<0.001	P=0.004
Logistic regression test	P=0.383N	P=0.218	P=0.136	P=0.537N
Cochran-Armitage test	P=0.130N			
Fisher exact test		P=0.500	P=0.250	P=0.153N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/48 (0%)	3/48 (6%)	0/47 (0%)	0/47 (0%)
Adjusted rate	0.0%	23.3%	0.0%	0.0%
Terminal rate	0/38 (0%)	2/11 (18%)	0/2 (0%)	0/1 (0%)
First incidence (days)	—	637	—	—
Life table test	P=0.345	P=0.008	—	—
Logistic regression test	P=0.590	P=0.020	—	—
Cochran-Armitage test	P=0.316N			
Fisher exact test		P=0.121	—	—
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	0/48 (0%)	4/48 (8%)	0/47 (0%)	0/47 (0%)
Adjusted rate	0.0%	31.8%	0.0%	0.0%
Terminal rate	0/38 (0%)	3/11 (27%)	0/2 (0%)	0/1 (0%)
First incidence (days)	—	637	—	—
Life table test	P=0.228	P=0.001	—	—
Logistic regression test	P=0.478	P=0.004	—	—
Cochran-Armitage test	P=0.252N			
Fisher exact test		P=0.059	—	—
All Organs: Hemangioma				
Overall rate	0/48 (0%)	11/48 (23%)	6/48 (13%)	3/48 (6%)
Adjusted rate	0.0%	54.7%	61.3%	26.9%
Terminal rate	0/38 (0%)	4/11 (36%)	1/2 (50%)	0/1 (0%)
First incidence (days)	—	566	541	599
Life table test	P=0.005	P<0.001	P<0.001	P=0.005
Logistic regression test	P=0.311N	P<0.001	P=0.011	P=0.057
Cochran-Armitage test	P=0.563N			
Fisher exact test		P<0.001	P=0.013	P=0.121
All Organs: Hemangiosarcoma				
Overall rate	2/48 (4%)	21/48 (44%)	27/48 (56%)	37/48 (77%)
Adjusted rate	5.3%	89.3%	95.6%	100.0%
Terminal rate	2/38 (5%)	9/11 (82%)	1/2 (50%)	1/1 (100%)
First incidence (days)	666 (T)	522	497	401
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/48 (4%)	27/48 (56%)	30/48 (63%)	38/48 (79%)
Adjusted rate	5.3%	95.8%	100.0%	100.0%
Terminal rate	2/38 (5%)	10/11 (91%)	2/2 (100%)	1/1 (100%)
First incidence (days)	666 (T)	522	497	401
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Histiocytic Sarcoma				
Overall rate	0/48 (0%)	12/48 (25%)	7/48 (15%)	7/48 (15%)
Adjusted rate	0.0%	47.8%	35.1%	65.8%
Terminal rate	0/38 (0%)	1/11 (9%)	0/2 (0%)	0/1 (0%)
First incidence (days)	—	513	415	527
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.100	P<0.001	P=0.039	P=0.004
Cochran-Armitage test	P=0.143			
Fisher exact test		P<0.001	P=0.006	P=0.006
All Organs: Benign Neoplasms				
Overall rate	26/48 (54%)	30/48 (63%)	27/48 (56%)	27/48 (56%)
Adjusted rate	61.6%	100.0%	100.0%	100.0%
Terminal rate	22/38 (58%)	11/11 (100%)	2/2 (100%)	1/1 (100%)
First incidence (days)	452	463	433	401
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.135	P=0.015	P=0.329	P=0.179
Cochran-Armitage test	P=0.520N			
Fisher exact test		P=0.267	P=0.500	P=0.500
All Organs: Malignant Neoplasms				
Overall rate	16/48 (33%)	39/48 (81%)	47/48 (98%)	46/48 (96%)
Adjusted rate	34.6%	94.9%	100.0%	100.0%
Terminal rate	8/38 (21%)	9/11 (82%)	2/2 (100%)	1/1 (100%)
First incidence (days)	475	462	363	315
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/48 (77%)	44/48 (92%)	48/48 (100%)	46/48 (96%)
Adjusted rate	78.6%	100.0%	100.0%	100.0%
Terminal rate	28/38 (74%)	11/11 (100%)	2/2 (100%)	1/1 (100%)
First incidence (days)	452	462	363	315
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.012	P=0.002	P=0.171	P=0.001
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.045	P<0.001	P=0.007

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for 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 control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

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

Study	Incidence in Controls				
	Hemangioma	Hemangiosarcoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories					
1,3-Butadiene	0/50	0/50	13/50	11/50	21/50
Acetonitrile	0/50	1/50	13/50	7/50	19/50
Allyl Glycidyl Ether	0/49	0/49	15/49	10/49	23/49
α-Chloroacetophenone	0/50	0/50	5/50	11/50	16/50
Epinephrine Hydrochloride	0/50	1/50	10/50	12/50	20/50
Ethyl Chloride	0/50	0/50	6/50	9/50	15/50
Hexachlorocyclopentadiene	0/50	0/50	19/50	7/50	24/50
o-Chlorobenzalmalononitrile (CS-2)	1/49	0/49	4/49	14/49	18/49
Ozone	0/50	0/50	23/50	12/50	30/50
Total	1/448 (0.2%)	2/448 (0.5%)	108/448 (24.1%)	93/448 (20.8%)	186/448 (41.5%)
Standard deviation	0.7%	0.9%	13.0%	4.9%	9.2%
Range	0%-2%	0%-2%	8%-46%	14%-29%	30%-60%
Overall Historical Incidence					
Total	2/947 (0.2%)	12/947 (1.3%)	200/947 (21.1%)	184/947 (19.4%)	358/947 (37.8%)
Standard deviation	0.7%	1.7%	11.6%	5.8%	12.5%
Range	0%-2%	0%-6%	4%-46%	9%-29%	11%-60%

[a] Data as of 12 May 1995

TABLE C4b
Historical Incidence of Histiocytic Sarcoma in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	0/50
Acetonitrile	0/50
Allyl Glycidyl Ether	0/50
α-Chloroacetophenone	0/50
Epinephrine Hydrochloride	1/50
Ethyl Chloride	0/50
Hexachlorocyclopentadiene	0/50
o-Chlorobenzalmalononitrile (CS-2)	1/50
Ozone	0/50
Total	2/450 (0.4%)
Standard deviation	0.9%
Range	0%-2%
Overall Historical Incidence	
Total	6/950 (0.6%)
Standard deviation	1.2%
Range	0%-4%

[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 Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	58	58	58	58
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	6	24	26	27
Natural deaths	4	13	20	20
Survivors				
Terminal sacrifice	38	11	2	1
Animals examined microscopically	58	58	58	58
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(9)	(10)	(10)
Diverticulum	1 (10%)			
Inflammation, chronic	1 (10%)			
Liver	(10)	(10)	(10)	(10)
Angiectasis		1 (10%)	5 (50%)	2 (20%)
Basophilic focus			1 (10%)	1 (10%)
Clear cell focus			2 (20%)	1 (10%)
Eosinophilic focus			3 (30%)	
Fatty change	4 (40%)	1 (10%)	1 (10%)	1 (10%)
Granuloma				1 (10%)
Hematopoietic cell proliferation			1 (10%)	
Infarct				1 (10%)
Infiltration cellular, mixed cell			1 (10%)	2 (20%)
Mixed cell focus	1 (10%)	1 (10%)	3 (30%)	3 (30%)
Necrosis, coagulative, multifocal	1 (10%)	1 (10%)		1 (10%)
Salivary glands	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell	4 (40%)	2 (20%)	1 (10%)	3 (30%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Epithelium, hyperplasia				1 (10%)
Tooth				(1)
Inflammation, suppurative				1 (100%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Capsule, hyperplasia	6 (60%)	4 (40%)	7 (70%)	2 (20%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia			1 (10%)	1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst			1 (10%)	
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Ectasia		4 (40%)	1 (10%)	1 (10%)
Infiltration cellular, mononuclear cell	1 (10%)	2 (20%)	1 (10%)	
Inflammation, suppurative			3 (30%)	

[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 Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hyperplasia, neutrophil		1 (10%)	2 (20%)	1 (10%)
Lymph node, mandibular	(8)	(3)	(6)	(8)
Hyperplasia, plasma cell				1 (13%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	2 (20%)	4 (40%)	5 (50%)	3 (30%)
Infiltration cellular, polymorphonuclear			1 (10%)	
Integumentary System				
Skin	(10)	(9)	(10)	(10)
Inflammation, chronic		1 (11%)		
Musculoskeletal System				
Bone	(10)	(10)	(10)	(10)
Sternum, fracture healed			1 (10%)	
Nervous System				
Brain	(10)	(10)	(10)	(10)
Mineralization	5 (50%)		2 (20%)	6 (60%)
Respiratory System				
Larynx	(10)	(10)	(10)	(10)
Exudate, mucopurulent				1 (10%)
Lung	(10)	(10)	(10)	(10)
Alveolus, hemorrhage, multifocal	1 (10%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell	1 (10%)			
Inflammation, chronic active			1 (10%)	
Nephropathy	3 (30%)	3 (30%)		3 (30%)
Bilateral, pelvis, dilatation		1 (10%)	1 (10%)	
Renal tubule, dilatation			6 (60%)	10 (100%)
Renal tubule, karyomegaly			4 (40%)	10 (100%)
Urinary bladder	(10)	(10)	(10)	(10)
Inflammation, chronic active			1 (10%)	
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Special Senses System				

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study				
Alimentary System				
Gallbladder	(42)	(35)	(31)	(27)
Inflammation, chronic active				1 (4%)
Intestine small, jejunum	(46)	(40)	(34)	(34)
Peyer's patch, hyperplasia, lymphoid	1 (2%)	1 (3%)		
Intestine small, ileum	(46)	(39)	(35)	(36)
Peyer's patch, inflammation, chronic active	1 (2%)			
Liver	(48)	(48)	(48)	(48)
Angiectasis		6 (13%)	10 (21%)	13 (27%)
Basophilic focus	1 (2%)	1 (2%)	4 (8%)	3 (6%)
Clear cell focus	1 (2%)			
Eosinophilic focus	1 (2%)	6 (13%)	7 (15%)	7 (15%)
Fatty change	2 (4%)			
Hematopoietic cell proliferation	1 (2%)	2 (4%)	4 (8%)	
Hemorrhage		1 (2%)		1 (2%)
Infarct	1 (2%)	6 (13%)	2 (4%)	4 (8%)
Infiltration cellular, mixed cell	1 (2%)	5 (10%)	3 (6%)	3 (6%)
Mixed cell focus	2 (4%)	2 (4%)	3 (6%)	
Necrosis, coagulative, multifocal	4 (8%)	3 (6%)	13 (27%)	11 (23%)
Thrombosis		1 (2%)	3 (6%)	
Bile duct, hyperplasia		1 (2%)		
Centrilobular, necrosis			1 (2%)	1 (2%)
Hepatocyte, regeneration				1 (2%)
Mesentery	(2)	(3)	(2)	(7)
Angiectasis				1 (14%)
Fat, hemorrhage				2 (29%)
Fat, necrosis	1 (50%)	2 (67%)	1 (50%)	3 (43%)
Pancreas	(48)	(48)	(46)	(45)
Granuloma	1 (2%)			
Duct, ectasia			1 (2%)	
Salivary glands	(48)	(48)	(48)	(48)
Infiltration cellular, mononuclear cell	7 (15%)	7 (15%)		3 (6%)
Stomach, forestomach	(48)	(48)	(46)	(46)
Foreign body	1 (2%)			
Granuloma	1 (2%)		1 (2%)	
Hemorrhage	1 (2%)			
Hyperplasia, squamous			1 (2%)	
Inflammation, focal	1 (2%)			
Ulcer		1 (2%)		1 (2%)
Epithelium, hyperplasia	2 (4%)	3 (6%)	2 (4%)	3 (7%)
Serosa, inflammation	1 (2%)			
Stomach, glandular	(48)	(48)	(46)	(45)
Foreign body				1 (2%)
Necrosis				2 (4%)
Tooth	(2)	(2)	(4)	(7)
Dysplasia	1 (50%)	1 (50%)		3 (43%)
Inflammation, suppurative	1 (50%)		4 (100%)	4 (57%)
Peridontal tissue, proliferation connective tissue		1 (50%)		

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(48)	(48)	(48)	(48)
Cardiomyopathy	2 (4%)		2 (4%)	
Fibrosis				1 (2%)
Infiltration cellular, mixed cell			1 (2%)	
Atrium, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(48)	(48)	(47)	(48)
Accessory adrenal cortical nodule	1 (2%)			
Cyst		1 (2%)		
Hyperplasia	1 (2%)	3 (6%)		
Capsule, hyperplasia	29 (60%)	26 (54%)	24 (51%)	20 (42%)
Islets, pancreatic	(48)	(48)	(46)	(45)
Hyperplasia	2 (4%)	1 (2%)	7 (15%)	2 (4%)
Pituitary gland	(47)	(44)	(44)	(44)
Pars distalis, cyst	1 (2%)	1 (2%)	1 (2%)	
Pars distalis, hyperplasia		1 (2%)		
Pars intermedia, hemorrhage		1 (2%)		
Thyroid gland	(48)	(48)	(47)	(47)
Ultimobranchial cyst		1 (2%)	1 (2%)	
Follicle, cyst	1 (2%)	1 (2%)	1 (2%)	
Follicular cell, hyperplasia		1 (2%)	1 (2%)	
General Body System				
Tissue NOS	(1)	(2)	(2)	
Infiltration cellular, mononuclear cell			1 (50%)	
Necrosis			1 (50%)	
Genital System				
Epididymis	(48)	(48)	(48)	(48)
Granuloma sperm				1 (2%)
Hemorrhage				1 (2%)
Preputial gland	(48)	(48)	(46)	(48)
Atrophy			1 (2%)	
Ectasia	2 (4%)	2 (4%)	1 (2%)	
Infiltration cellular, mononuclear cell	6 (13%)	5 (10%)	7 (15%)	3 (6%)
Inflammation, chronic	5 (10%)	5 (10%)	4 (9%)	1 (2%)
Inflammation, suppurative	1 (2%)	4 (8%)	7 (15%)	3 (6%)
Prostate	(46)	(46)	(44)	(44)
Hyperplasia		1 (2%)		
Inflammation, chronic			1 (2%)	
Inflammation, suppurative	1 (2%)		1 (2%)	
Seminal vesicle	(48)	(47)	(47)	(44)
Dilatation	4 (8%)	1 (2%)	2 (4%)	
Hyperplasia	1 (2%)			
Inflammation, chronic	2 (4%)		2 (4%)	
Inflammation, suppurative	1 (2%)	1 (2%)		
Testes	(48)	(48)	(48)	(48)
Atrophy, focal			1 (2%)	

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(48)	(48)	(47)	(47)
Hyperplasia, neutrophil	2 (4%)		1 (2%)	1 (2%)
Lymph node	(3)	(1)	(2)	
Iliac, hemorrhage			1 (50%)	
Iliac, hyperplasia, lymphoid	1 (33%)			
Iliac, hyperplasia, plasma cell			2 (100%)	
Iliac, pigmentation, hemosiderin			1 (50%)	
Renal, hyperplasia, lymphoid	1 (33%)			
Lymph node, bronchial	(36)	(36)	(35)	(26)
Hemorrhage		2 (6%)		
Hyperplasia, lymphoid		2 (6%)	1 (3%)	
Pigmentation, hemosiderin		1 (3%)		
Lymph node, mandibular	(36)	(34)	(32)	(34)
Congestion		1 (3%)		
Hemorrhage	1 (3%)			
Hyperplasia, histiocytic		1 (3%)	2 (6%)	
Hyperplasia, lymphoid		1 (3%)	1 (3%)	
Pigmentation, hemosiderin		2 (6%)	1 (3%)	
Lymph node, mesenteric	(47)	(42)	(41)	(40)
Hematopoietic cell proliferation			1 (2%)	1 (3%)
Hemorrhage	1 (2%)	2 (5%)	2 (5%)	
Hyperplasia, histiocytic	2 (4%)	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	2 (5%)	
Inflammation, chronic active		1 (2%)	1 (2%)	1 (3%)
Lymph node, mediastinal	(30)	(34)	(32)	(29)
Congestion		1 (3%)		
Hematopoietic cell proliferation			1 (3%)	
Hemorrhage			3 (9%)	2 (7%)
Hyperplasia, histiocytic			1 (3%)	2 (7%)
Hyperplasia, lymphoid	1 (3%)		1 (3%)	
Spleen	(48)	(48)	(46)	(46)
Atrophy		1 (2%)		
Hematopoietic cell proliferation	14 (29%)	32 (67%)	41 (89%)	42 (91%)
Hyperplasia, lymphoid		1 (2%)		
Pigmentation, melanin		2 (4%)		
Thymus	(43)	(40)	(34)	(37)
Mineralization			1 (3%)	
Integumentary System				
Skin	(48)	(48)	(48)	(48)
Acanthosis	1 (2%)			
Atrophy			1 (2%)	
Inflammation, chronic	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Inflammation, suppurative				1 (2%)
Ulcer	2 (4%)	4 (8%)		5 (10%)
Prepuce, acanthosis	1 (2%)	2 (4%)		
Prepuce, inflammation, chronic		2 (4%)		
Prepuce, inflammation, suppurative				1 (2%)
Prepuce, pigmentation, melanin		1 (2%)		
Prepuce, ulcer		1 (2%)	1 (2%)	
Subcutaneous tissue, congestion				1 (2%)
Subcutaneous tissue, hemorrhage			1 (2%)	

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(48)	(48)	(48)	(48)
Fracture				1 (2%)
Sternum, developmental malformation				2 (4%)
Nervous System				
Brain	(48)	(48)	(48)	(48)
Hemorrhage	1 (2%)	1 (2%)		
Mineralization	23 (48%)	19 (40%)	13 (27%)	24 (50%)
Necrosis, liquifactive	2 (4%)			
Respiratory System				
Larynx	(47)	(48)	(46)	(46)
Cytoplasmic alteration	1 (2%)			
Exudate, mucopurulent			2 (4%)	1 (2%)
Hemorrhage				1 (2%)
Metaplasia, squamous				2 (4%)
Lung	(48)	(48)	(48)	(48)
Congestion		2 (4%)	5 (10%)	1 (2%)
Crystals		1 (2%)		
Hemorrhage	6 (13%)	4 (8%)	2 (4%)	1 (2%)
Infarct				1 (2%)
Pigmentation, hemosiderin			1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Alveolus, infiltration cellular, histiocyte	4 (8%)	5 (10%)	1 (2%)	1 (2%)
Interstitium, infiltration cellular, mixed cell	1 (2%)			
Nose	(48)	(47)	(46)	(47)
Inflammation, suppurative	1 (2%)		3 (7%)	1 (2%)
Proliferation connective tissue, multifocal		1 (2%)		
Nasolacrimal duct, inflammation, suppurative				1 (2%)
Respiratory epithelium, cytoplasmic alteration	1 (2%)			
Respiratory epithelium, degeneration				1 (2%)
Vomeronasal organ, hypertrophy			1 (2%)	
Trachea	(47)	(47)	(46)	(46)
Cytoplasmic alteration	1 (2%)			
Special Senses System				
Eye		(1)	(2)	
Degeneration, diffuse			1 (50%)	
Phthisis bulbi			1 (50%)	
Retinal detachment			1 (50%)	
Cornea, inflammation, chronic			1 (50%)	
Harderian gland	(6)	(8)	(5)	(6)
Hyperplasia			1 (20%)	1 (17%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(48)	(48)	(48)	(48)
Cyst	2 (4%)		1 (2%)	1 (2%)
Hemorrhage	1 (2%)			
Infiltration cellular, mononuclear cell	2 (4%)	1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Inflammation, suppurative	2 (4%)			
Nephropathy	32 (67%)	12 (25%)	10 (21%)	16 (33%)
Renal tubule, dilatation		4 (8%)	16 (33%)	36 (75%)
Renal tubule, karyomegaly	1 (2%)	2 (4%)	10 (21%)	28 (58%)
Urinary bladder	(48)	(43)	(43)	(42)
Infiltration cellular, mononuclear cell	1 (2%)			
Inflammation, chronic active	2 (4%)		1 (2%)	1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)		

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

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	58	58	58	58
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death			1	
Moribund	8	28	26	27
Natural deaths	4	16	15	17
Survivors				
Terminal sacrifice	36	4	6	4
Animals examined microscopically	58	58	57	58
15-Month Interim Evaluation				
Alimentary System				
Intestine small, jejunum	(10)	(10)	(10)	(10)
Liver	(10)	(10)	(10)	(10)
Hemangiosarcoma		1 (10%)		
Hepatocellular carcinoma		3 (30%)	1 (10%)	3 (30%)
Hepatocellular adenoma		2 (20%)	3 (30%)	1 (10%)
Hepatocellular adenoma, multiple				1 (10%)
Endocrine System				
Adrenal medulla	(10)	(10)	(10)	(10)
Pheochromocytoma benign	1 (10%)			
Thyroid gland	(10)	(10)	(10)	(10)
Follicular cell, adenoma	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma			1 (10%)	
Alveolar/bronchiolar adenoma, multiple		1 (10%)		
Hepatocellular carcinoma, metastatic, liver				1 (10%)
Special Senses System				
Harderian gland	(1)			(2)
Adenoma	1 (100%)			1 (50%)
Bilateral, adenoma				1 (50%)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Lymphoma malignant mixed				1 (10%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(47)	(45)	(42)	(40)
Sarcoma		1 (2%)		
Intestine large, cecum	(47)	(42)	(40)	(36)
Leiomyosarcoma	1 (2%)			
Sarcoma		1 (2%)		
Intestine small, duodenum	(45)	(39)	(39)	(35)
Sarcoma		1 (3%)		
Intestine small, jejunum	(46)	(37)	(39)	(35)
Intestine small, ileum	(46)	(39)	(40)	(35)
Leiomyosarcoma, metastatic, uterus		1 (3%)		
Sarcoma		1 (3%)		
Liver	(48)	(48)	(47)	(47)
Hemangioma		4 (8%)	1 (2%)	1 (2%)
Hemangioma, multiple		1 (2%)	1 (2%)	
Hemangiosarcoma		19 (40%)	15 (32%)	19 (40%)
Hemangiosarcoma, multiple		8 (17%)	12 (26%)	15 (32%)
Hepatocellular carcinoma	4 (8%)	23 (48%)	15 (32%)	13 (28%)
Hepatocellular carcinoma, multiple		5 (10%)	7 (15%)	7 (15%)
Hepatocellular adenoma	14 (29%)	10 (21%)	11 (23%)	8 (17%)
Hepatocellular adenoma, multiple	1 (2%)	7 (15%)	9 (19%)	7 (15%)
Histiocytic sarcoma	1 (2%)	21 (44%)	19 (40%)	18 (38%)
Sarcoma		1 (2%)		
Mesentery	(9)	(13)	(7)	(6)
Hemangiosarcoma		2 (15%)		
Histiocytic sarcoma	1 (11%)	1 (8%)		
Leiomyosarcoma, metastatic, uterus		1 (8%)		
Sarcoma		1 (8%)		1 (17%)
Pancreas	(48)	(47)	(44)	(47)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		2 (4%)	1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, uterus		1 (2%)		
Sarcoma		1 (2%)		
Stomach, forestomach	(48)	(48)	(47)	(47)
Leiomyosarcoma, metastatic, uterus		1 (2%)		
Squamous cell papilloma		1 (2%)	1 (2%)	
Stomach, glandular	(48)	(48)	(45)	(45)
Leiomyosarcoma, metastatic, uterus		1 (2%)		
Sarcoma		1 (2%)		

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(48)	(48)	(47)	(48)
Histiocytic sarcoma			1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(48)	(47)	(47)	(47)
Adenoma		1 (2%)		
Histiocytic sarcoma	1 (2%)	3 (6%)		1 (2%)
Capsule, adenoma	1 (2%)			
Capsule, carcinoma	1 (2%)			
Islets, pancreatic	(48)	(45)	(44)	(47)
Adenoma	1 (2%)	1 (2%)		
Pituitary gland	(46)	(45)	(44)	(46)
Histiocytic sarcoma	1 (2%)			
Pars distalis, adenoma	4 (9%)	5 (11%)	2 (5%)	6 (13%)
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(48)	(48)	(46)	(46)
Follicular cell, adenoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
General Body System				
Tissue NOS		(1)		
Sarcoma		1 (100%)		
Genital System				
Ovary	(47)	(47)	(45)	(46)
Cystadenoma	2 (4%)			2 (4%)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma	1 (2%)	5 (11%)	4 (9%)	3 (7%)
Luteoma	2 (4%)			
Sarcoma		1 (2%)		
Periovarian tissue, histiocytic sarcoma			1 (2%)	
Uterus	(48)	(48)	(45)	(47)
Histiocytic sarcoma	1 (2%)			
Leiomyosarcoma		1 (2%)		
Polyp stromal	1 (2%)			1 (2%)
Cervix, granular cell tumor NOS	1 (2%)			
Hematopoietic System				
Bone marrow	(48)	(48)	(46)	(47)
Histiocytic sarcoma		6 (13%)	5 (11%)	4 (9%)
Lymph node	(5)	(6)	(4)	(6)
Axillary, histiocytic sarcoma	1 (20%)			
Iliac, histiocytic sarcoma	1 (20%)	1 (17%)	1 (25%)	1 (17%)
Pancreatic, histiocytic sarcoma			1 (25%)	1 (17%)
Renal, histiocytic sarcoma		1 (17%)	2 (50%)	2 (33%)
Lymph node, bronchial	(40)	(36)	(40)	(38)
Histiocytic sarcoma		4 (11%)	6 (15%)	4 (11%)
Sarcoma		1 (3%)		

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(39)	(35)	(34)	(32)
Histiocytic sarcoma	1 (3%)	3 (9%)	2 (6%)	2 (6%)
Lymph node, mesenteric	(43)	(40)	(41)	(43)
Hemangioma			1 (2%)	
Histiocytic sarcoma	1 (2%)	6 (15%)	7 (17%)	6 (14%)
Lymph node, mediastinal	(28)	(35)	(35)	(33)
Histiocytic sarcoma	1 (4%)	9 (26%)	9 (26%)	4 (12%)
Spleen	(48)	(48)	(46)	(47)
Histiocytic sarcoma	1 (2%)	7 (15%)	8 (17%)	9 (19%)
Sarcoma		1 (2%)		
Thymus	(46)	(42)	(39)	(38)
Histiocytic sarcoma		2 (5%)	2 (5%)	2 (5%)
Integumentary System				
Mammary gland	(48)	(46)	(45)	(46)
Carcinoma	1 (2%)			
Skin	(47)	(48)	(47)	(48)
Hemangioma			1 (2%)	
Squamous cell papilloma				1 (2%)
Subcutaneous tissue, sarcoma				2 (4%)
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Osteosarcoma	1 (2%)			
Rib, leiomyosarcoma, metastatic, uterus		1 (2%)		
Skeletal muscle		(1)		
Leiomyosarcoma, metastatic, uterus		1 (100%)		
Nervous System				
Brain	(48)	(48)	(47)	(48)
Astrocytoma NOS	1 (2%)			
Histiocytic sarcoma		1 (2%)		1 (2%)
Respiratory System				
Lung	(48)	(48)	(47)	(47)
Alveolar/bronchiolar adenoma	5 (10%)		5 (11%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		1 (2%)	
Alveolar/bronchiolar carcinoma			2 (4%)	1 (2%)
Carcinoma		1 (2%)		
Carcinoma, metastatic, mammary gland	1 (2%)			
Hemangiosarcoma, metastatic, liver				3 (6%)
Hemangiosarcoma, metastatic, pancreas				1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	8 (17%)	6 (13%)	4 (9%)
Histiocytic sarcoma	1 (2%)	16 (33%)	13 (28%)	13 (28%)
Osteosarcoma, metastatic, bone	1 (2%)			
Sarcoma		1 (2%)		
Sarcoma, metastatic, skin				1 (2%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Special Senses System				
Harderian gland	(3)	(6)	(4)	(6)
Adenoma	2 (67%)	3 (50%)		6 (100%)
Urinary System				
Kidney	(48)	(48)	(47)	(47)
Histiocytic sarcoma	1 (2%)	7 (15%)	4 (9%)	3 (6%)
Osteosarcoma, metastatic, bone	1 (2%)			
Urinary bladder	(46)	(43)	(43)	(37)
Leiomyosarcoma, metastatic, uterus		1 (2%)		
Sarcoma		1 (2%)		
Systemic Lesions				
Multiple organs	(48)	(48)	(47)	(48)
Histiocytic sarcoma	1 (2%)	21 (44%)	19 (40%)	18 (38%)
Lymphoma malignant lymphocytic		1 (2%)		
Lymphoma malignant mixed	5 (10%)	2 (4%)		2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2	6	5	6
2-Year study	34	47	45	46
Total Primary Neoplasms				
15-Month interim evaluation	3	7	5	8
2-Year study	53	132	104	115
Total animals with benign neoplasms				
15-Month interim evaluation	2	3	4	4
2-Year study	27	24	26	29
Total benign neoplasms				
15-Month interim evaluation	3	3	4	4
2-Year study	37	34	34	36
Total animals with malignant neoplasms				
15-Month interim evaluation		3	1	4
2-Year study	14	46	45	46
Total malignant neoplasms				
15-Month interim evaluation		4	1	4
2-Year study	14	98	70	79
Total animals with metastatic neoplasms				
15-Month interim evaluation				1
2-Year study	3	9	6	9
Total metastatic neoplasms				
15-Month interim evaluation				1
2-Year study	4	16	6	9
Total animals with uncertain neoplasms-benign or malignant				
2-Year study	2			
Total uncertain neoplasms				
2-Year study	2			

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 0 ppm

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

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

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

Number of Days on Study	6 6 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	
Carcass ID Number	0 7 8	0 8 1	0 8 4	0 8 5	0 8 6	0 8 7	0 9 1	0 9 3	0 9 5	0 9 6	0 9 7	0 9 8	0 9 9	1 0 1	1 0 2	1 0 6	1 0 7	1 0 9	1 1 1	1 1 2	1 1 3	1 1 5	1 1 6	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyosarcoma																								1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma			X												X									4
Hepatocellular adenoma	X									X					X					X				14
Hepatocellular adenoma, multiple														X										1
Histiocytic sarcoma																								1
Mesentery															+									9
Histiocytic sarcoma																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																		+						2
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1
Capsule, adenoma																								1
Capsule, carcinoma						X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																							X	1
Parathyroid gland	+	+	M	M	M	+	M	M	+	M	M	M	+	M	M	M	M	+	+	+	M	+	+	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																								1
Pars distalis, adenoma										X							X			X				4
Pars intermedia, adenoma																					X			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma								X						X										2
General Body System																								
None																								

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

Number of Days on Study	4 0 0	4 0 8	5 3 1	5 4 1	5 7 3	5 9 5	5 9 7	6 0 3	6 1 7	6 2 1	6 2 6	6 6 0	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7
Carcass ID Number	1 1 0	0 8 9	1 0 3	0 8 2	0 7 4	1 1 4	1 0 5	0 9 4	0 7 7	1 0 0	0 6 0	0 6 4	0 5 9	0 6 1	0 6 2	0 6 3	0 6 5	0 6 6	0 6 7	0 6 9	0 7 0	0 7 1	0 7 2	0 7 3	0 7 5
Genital System																									
Clitoral gland	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma								X						X											
Histiocytic sarcoma	X																								
Luteoma													X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Polyp stromal																									
Cervix, granular cell tumor NOS																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+						+			+															
Axillary, histiocytic sarcoma	X																								
Iliac, histiocytic sarcoma	X																								
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma	X																								
Lymph node, mesenteric	+	+	I	+	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	M	M	+	M	M	M	+
Histiocytic sarcoma	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Thymus	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS								X																	

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

Number of Days on Study	6 6 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	
Carcass ID Number	0 7 8	0 8 1	0 8 4	0 8 5	0 8 6	0 8 7	0 9 1	0 9 3	0 9 5	0 9 6	0 9 7	0 9 8	0 9 9	1 0 1	1 0 2	1 0 6	1 0 7	1 0 9	1 1 1	1 1 2	1 1 3	1 1 5	1 1 6	Total Tissues/ Tumors
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma																								2
Histiocytic sarcoma																								1
Luteoma				X																				2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1
Polyp stromal																				X				1
Cervix, granular cell tumor NOS												X												1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node		+																					+	5
Axillary, histiocytic sarcoma																								1
Iliac, histiocytic sarcoma																								1
Lymph node, bronchial	M	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	I	+	M	+	+	40
Lymph node, mandibular	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	39
Histiocytic sarcoma																								1
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	43
Histiocytic sarcoma																								1
Lymph node, mediastinal	+	+	+	M	+	+	M	+	+	M	+	M	M	M	M	I	M	M	M	+	M	+	+	28
Histiocytic sarcoma																								1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																								1
Skin	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Osteosarcoma																								1
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Astrocytoma NOS																								1

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

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

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

Number of Days on Study	6 6 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	6 7 7	
Carcass ID Number	0 7 8	0 8 1	0 8 4	0 8 5	0 8 6	0 8 7	0 9 1	0 9 3	0 9 5	0 9 6	0 9 7	0 9 8	0 9 9	0 1 1	1 0 2	1 0 6	1 0 7	1 0 9	1 1 1	1 1 2	1 1 3	1 1 5	1 1 6	Total Tissues/ Tumors
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma	X															X				X				5
Alveolar/bronchiolar adenoma, multiple						X																		1
Carcinoma, metastatic, mammary gland																								1
Hepatocellular carcinoma, metastatic, liver																								1
Histiocytic sarcoma																								1
Osteosarcoma, metastatic, bone																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																								
Ear																								1
Harderian gland									+															3
Adenoma									X															2
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1
Osteosarcoma, metastatic, bone																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1
Lymphoma malignant mixed		X			X																		X	5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm

Number of Days on Study	4 2 9	4 2 9	4 5 4	4 5 5	4 9 3	5 3 0	5 3 0	5 3 9	5 4 1	5 4 1	5 4 1	5 4 1	5 6 6	5 8 5	5 8 8	5 9 6	6 0 0	6 0 0	6 0 3	6 0 7	6 0 9	6 1 4	6 1 4	6 1 4	6 1 4
Carcass ID Number	1 9 2	2 1 2	1 8 0	2 0 5	1 9 6	1 7 6	2 1 6	1 8 7	1 7 7	1 9 4	2 1 9	2 2 3	2 0 3	2 3 1	2 0 7	2 1 3	1 7 9	1 8 2	1 8 8	2 0 6	2 0 0	7 5	1 9 7	1 1 1	2 2 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	A	A	+	+	A	+	+	+	+	+	A	+	M	A	+	+	+	A	A	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Sarcoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Sarcoma																									
Intestine small, duodenum	+	+	A	A	A	+	+	A	+	+	+	+	I	+	+	A	A	+	+	+	+	M	+	+	+
Sarcoma																									
Intestine small, jejunum	+	+	A	A	A	A	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	A	A	+	+	A	+	+	+	+	+	+	A	A	A	+	+	+	+	A	+	+	+
Leiomyosarcoma, metastatic, uterus			X																						
Sarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma									X																
Hemangioma, multiple																						X			
Hemangiosarcoma						X					X			X	X				X				X		X
Hemangiosarcoma, multiple																X				X	X				
Hepatocellular carcinoma						X			X	X	X		X		X	X			X		X				X
Hepatocellular carcinoma, multiple																	X	X							
Hepatocellular adenoma						X					X						X		X	X					X
Hepatocellular adenoma, multiple															X							X			
Histiocytic sarcoma	X	X			X			X				X	X										X	X	
Sarcoma																									
Mesentery			+								+			+				+			+				
Hemangiosarcoma											X														
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, uterus			X																						
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X												X												
Leiomyosarcoma, metastatic, uterus			X																						
Sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus			X																						
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus			X																						
Sarcoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Histiocytic sarcoma	X																								
Adrenal medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	6 1 4	6 1 5	6 1 8	6 3 1	6 3 6	6 3 6	6 3 8	6 3 9	6 3 9	6 4 3	6 4 4	6 4 5	6 4 6	6 4 6	6 4 6	6 4 9	6 5 1	6 5 7	6 5 9	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	2 2 9	1 9 8	2 3 0	2 0 0	1 7 8	2 3 2	2 2 4	1 8 3	2 0 4	1 8 6	2 1 4	2 2 7	2 1 0	2 1 8	2 2 6	2 1 5	2 2 2	1 8 5	1 9 3	1 8 1	1 8 9	2 0 1	2 1 7	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	M	A	+	+	+	A	+	+	+	+	+	+	+	+	36
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Sarcoma								X																1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	42
Sarcoma								X																1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	39
Sarcoma								X																1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	37
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	39
Leiomyosarcoma, metastatic, uterus																								1
Sarcoma								X																1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma								X									X	X						4
Hemangioma, multiple																								1
Hemangiosarcoma	X	X		X					X	X		X				X		X		X	X	X	X	19
Hemangiosarcoma, multiple			X		X	X							X						X					8
Hepatocellular carcinoma		X		X			X	X	X	X	X		X				X		X		X	X	X	23
Hepatocellular carcinoma, multiple												X		X		X								5
Hepatocellular adenoma										X			X	X							X			10
Hepatocellular adenoma, multiple					X			X										X		X			X	7
Histiocytic sarcoma	X	X		X		X	X		X		X	X	X	X	X			X			X			21
Sarcoma								X																1
Mesentery					+			+			+	+		+		+				+	+			13
Hemangiosarcoma					X																			2
Histiocytic sarcoma												X												1
Leiomyosarcoma, metastatic, uterus																								1
Sarcoma								X																1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																								2
Leiomyosarcoma, metastatic, uterus																								1
Sarcoma								X																1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma, metastatic, uterus																								1
Squamous cell papilloma								X																1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma, metastatic, uterus																								1
Sarcoma								X																1
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																								1
Histiocytic sarcoma											X	X												3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma										X														1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	4 2 9	4 2 9	4 5 4	4 5 5	4 9 3	5 3 0	5 3 0	5 3 9	5 4 1	5 4 1	5 4 1	5 4 1	5 6 6	5 8 5	5 8 8	5 9 6	6 0 0	6 0 0	6 0 3	6 0 7	6 0 9	6 1 4	6 1 4	6 1 4	6 1 4
Carcass ID Number	1 9 2	2 1 2	1 8 0	2 0 5	1 9 6	1 7 6	2 1 6	1 8 7	1 7 7	1 9 4	2 1 9	2 2 3	2 0 3	2 3 1	2 3 7	2 1 3	1 7 9	1 8 2	1 8 8	2 0 6	2 2 0	1 7 5	1 9 7	2 1 1	2 2 5
Endocrine System (continued)																									
Parathyroid gland	M	+	+	M	+	M	+	+	+	M	M	+	M	+	+	M	M	M	+	M	M	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X						X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Sarcoma																									
Genital System																									
Clitoral gland	+	+	M	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	M
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Histiocytic sarcoma	X	X			X			X																	
Sarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma			X																						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X	X						X					X											X	
Lymph node							+																	+	
Iliac, histiocytic sarcoma																									
Renal, histiocytic sarcoma																								X	
Lymph node, bronchial	+	+	M	M	+	+	+	M	I	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M
Histiocytic sarcoma	X				X																			X	
Sarcoma																									
Lymph node, mandibular	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	+	+	+
Histiocytic sarcoma	X							X																X	
Lymph node, mesenteric	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma	X							X					X											X	
Lymph node, mediastinal	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	I	M	+	+	I	M	M	+	+
Histiocytic sarcoma	X	X			X			X																X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X	X						X					X										X	X	
Sarcoma																									
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	I	M	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X					X												
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	I
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, leiomyosarcoma, metastatic, uterus			X																						
Skeletal muscle			+																						
Leiomyosarcoma, metastatic, uterus			X																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	6 1 4	6 1 5	6 1 8	6 3 1	6 3 6	6 3 6	6 3 8	6 3 9	6 3 9	6 4 3	6 4 4	6 4 5	6 4 6	6 4 6	6 4 6	6 4 9	6 5 1	6 5 7	6 5 9	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	2 2 9	1 9 8	2 3 0	2 0 0	1 7 8	2 3 2	2 2 4	1 8 3	2 0 4	1 8 6	2 1 4	2 2 7	2 1 0	2 1 8	2 2 6	1 5	2 2	1 8 5	1 9 3	1 8 1	1 8 9	2 0 1	2 1 7	Total Tissues/ Tumors
Endocrine System (continued)																								
Parathyroid gland	+	M	+	+	+	+	+	M	M	M	+	M	+	M	M	+	+	M	+	+	+	M	M	25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	45
Pars distalis, adenoma			X																		X		X	5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma	X																							1
General Body System																								
Tissue NOS								+																1
Sarcoma								X																1
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																								1
Histiocytic sarcoma												X												5
Sarcoma								X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma																								1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma												X												6
Lymph node			+			+						+	+											6
Iliac, histiocytic sarcoma												X												1
Renal, histiocytic sarcoma																								1
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	36
Histiocytic sarcoma															X									4
Sarcoma								X																1
Lymph node, mandibular	+	+	+	M	I	+	+	+	+	+	+	+	+	M	M	I	+	+	M	+	+	M	+	35
Histiocytic sarcoma																								3
Lymph node, mesenteric	+	M	+	+	+	+	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	40
Histiocytic sarcoma	X												X											6
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	I	+	M	+	+	M	+	+	35
Histiocytic sarcoma	X					X	X					X												9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma												X												7
Sarcoma								X																1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Histiocytic sarcoma																								2
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Rib, leiomyosarcoma, metastatic, uterus																								1
Skeletal muscle																								1
Leiomyosarcoma, metastatic, uterus																								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	4 2 9	4 2 9	4 5 4	4 5 5	4 9 3	5 3 0	5 3 0	5 3 9	5 4 1	5 4 1	5 4 1	5 4 1	5 6 6	5 8 5	5 8 8	5 9 6	6 0 0	6 0 0	6 0 3	6 0 7	6 0 9	6 1 4	6 1 4	6 1 4	6 1 4
Carcass ID Number	1 9 2	2 1 2	1 8 0	2 0 5	1 9 6	1 7 6	2 1 6	1 8 7	1 7 7	1 9 4	2 1 9	2 2 3	2 0 3	2 3 1	2 0 7	2 1 3	1 7 9	1 8 2	1 8 8	2 0 6	2 2 0	1 7 5	1 9 7	2 1 1	2 2 5
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Respiratory System																									
Larynx	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Hepatocellular carcinoma, metastatic, liver									X	X	X				X		X								
Histiocytic sarcoma	X	X			X			X					X										X	X	
Sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear					+																				
Harderian gland			+															+						
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X												X										X		
Urinary bladder	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Leiomyosarcoma, metastatic, uterus			X																						
Sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X	X			X			X				X	X										X	X	
Lymphoma malignant lymphocytic							X																		
Lymphoma malignant mixed																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 312 ppm
(continued)

Number of Days on Study	6 1 4	6 1 5	6 1 8	6 3 1	6 3 6	6 3 6	6 3 8	6 3 9	6 3 9	6 4 3	6 4 4	6 4 5	6 4 6	6 4 6	6 4 6	6 4 9	6 5 1	6 5 7	6 5 9	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	2 2 9	1 9 8	2 3 0	2 0 0	1 7 8	2 3 2	2 2 4	1 8 3	2 0 4	1 8 6	2 1 4	2 2 7	2 1 0	2 1 8	2 2 6	2 1 5	2 2 2	1 8 5	1 9 3	1 8 1	1 8 9	2 0 1	2 1 7	Total Tissues/ Tumors
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																								1
Hepatocellular carcinoma, metastatic, liver		X							X										X					8
Histiocytic sarcoma	X			X		X	X		X			X	X	X	X									16
Sarcoma								X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																								
Ear																								1
Harderian gland					+				+								+					+		6
Adenoma									X								X					X		3
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma						X	X					X			X									7
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leiomyosarcoma, metastatic, uterus																								1
Sarcoma								X																1
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma	X	X		X		X	X		X		X	X	X	X	X			X			X			21
Lymphoma malignant lymphocytic																								1
Lymphoma malignant mixed											X			X										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm
(continued)

Number of Days on Study	5 9 7	6 0 8	6 1 4	6 1 5	6 1 9	6 2 9	6 3 0	6 3 0	6 3 1	6 3 6	6 4 2	6 5 0	6 5 2	6 5 3	6 5 3	6 5 3	6 6 1	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	3 1 9	3 1 4	3 2 7	2 9 6	2 9 3	3 1 5	3 0 6	3 1 3	2 9 9	3 3 3	3 4 2	3 3 2	3 3 0	3 3 5	3 3 6	3 4 7	4 4 0	0 3 3	1 1 0	2 1	2 8	3 1	3 4 6	Total Tissues/ Tumors
Alimentary System																							
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	34
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	39
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma															X								1
Hemangioma, multiple																							1
Hemangiosarcoma					X	X	X	X	X		X		X						X	X	X	X		15
Hemangiosarcoma, multiple	X	X	X							X		X		X			X						X	12
Hepatocellular carcinoma	X	X	X		X			X									X		X			X		15
Hepatocellular carcinoma, multiple												X		X	X			X		X				7
Hepatocellular adenoma	X			X	X								X					X					X	11
Hepatocellular adenoma, multiple											X	X			X		X		X	X		X		9
Histiocytic sarcoma		X					X		X					X										19
Mesentery				+																		+		7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Histiocytic sarcoma														X										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma										X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Tooth																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																								1
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Parathyroid gland	M	M	+	M	M	+	M	+	M	+	+	+	+	M	+	M	M	M	+	+	+	M	+	27
Pituitary gland	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pars distalis, adenoma													X	X										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell, adenoma				X																				1
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	38
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma																								4
Periovarian tissue, histiocytic sarcoma																								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm
(continued)

Number of Days on Study	4 5 7	4 7 6	4 7 8	4 8 1	4 8 4	4 8 9	4 9 2	5 1 0	5 3 5	5 4 1	5 4 1	5 4 1	5 4 1	5 5 2	5 5 5	5 5 6	5 6 6	5 6 9	5 6 9	5 6 9	5 6 9	5 8 0	5 8 9	5 9 5
Carcass ID Number	3 1 8	3 3 4	3 0 4	3 0 0	3 3 7	3 2 3	3 0 2	3 1 7	3 1 6	3 0 1	3 0 8	3 2 6	3 4 3	3 3 9	2 9 5	3 4 8	3 0 7	2 9 2	2 9 8	3 2 4	3 4 5	2 9 1	3 2 5	3 1 1
Hematopoietic System																								
Blood					+																			
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X	X		X										X										X
Lymph node				+	+															+		+		
Iliac, histiocytic sarcoma					X																			
Pancreatic, histiocytic sarcoma				X																				
Renal, histiocytic sarcoma				X	X																			
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+
Histiocytic sarcoma	X	X			X				X					X										
Lymph node, mandibular	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+		+	+	+	M	M	M	+
Histiocytic sarcoma					X																			X
Lymph node, mesenteric	+	+	+	+	+	+	+	A	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Histiocytic sarcoma	X			X	X												X						X	X
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	M	M	M	+	M	+	M	+	+	M	+	+
Histiocytic sarcoma	X	X		X	X	X			X															X
Spleen	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X	X			X	X								X										X
Thymus	M	+	+	+	M	+	+	+	M	I	+	+	+	I	+	+	+	M	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Integumentary System																								
Mammary gland	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	A	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X	X						X									
Alveolar/bronchiolar adenoma, multiple																			X					
Alveolar/bronchiolar carcinoma																								
Hepatocellular carcinoma, metastatic, liver			X							X		X							X		X			
Histiocytic sarcoma	X	X		X	X	X			X	X				X	X			X						X
Nose	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm
(continued)

Number of Days on Study	5 9 7	6 0 8	6 1 4	6 1 5	6 1 9	6 2 9	6 3 0	6 3 0	6 3 1	6 3 6	6 4 2	6 5 0	6 5 2	6 5 3	6 5 3	6 5 3	6 6 1	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	3 1 9	3 1 4	3 2 7	2 9 6	2 9 3	3 1 5	3 0 6	3 1 3	2 9 9	3 3 3	3 4 2	3 3 2	3 3 0	3 3 5	3 3 6	4 4 7	4 4 0	0 1 3	1 1 0	2 2 1	2 2 8	3 3 1	3 4 6	Total Tissues/ Tumors
Hematopoietic System																							
Blood																							1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																							5
Lymph node																							4
Iliac, histiocytic sarcoma																							1
Pancreatic, histiocytic sarcoma																							1
Renal, histiocytic sarcoma																							2
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	M	+	40
Histiocytic sarcoma														X									6
Lymph node, mandibular	+	+	+	I	M	+	+	+	+	+	M	+	+	I	M	+	+	+	+	M	+	+	34
Histiocytic sarcoma																							2
Lymph node, mesenteric	+	M	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	41
Hemangioma												X											1
Histiocytic sarcoma									X														7
Lymph node, mediastinal	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	35
Histiocytic sarcoma							X		X														9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma							X		X														8
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	39
Histiocytic sarcoma									X														2
Integumentary System																							
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma																						X	1
Musculoskeletal System																							
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nervous System																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Respiratory System																							
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma																			X		X		5
Alveolar/bronchiolar adenoma, multiple																							1
Alveolar/bronchiolar carcinoma				X											X								2
Hepatocellular carcinoma, metastatic, liver															X								6
Histiocytic sarcoma									X					X									13
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 625 ppm
(continued)

Number of Days on Study	5 9 7	6 0 8	6 1 4	6 1 5	6 1 9	6 2 9	6 3 0	6 3 0	6 3 1	6 3 6	6 4 2	6 5 0	6 5 2	6 5 3	6 5 3	6 5 3	6 6 1	6 6 7	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	3 1 9	3 1 4	3 2 7	2 9 6	2 9 3	3 1 5	3 0 6	3 1 3	2 9 9	3 3 3	3 4 2	3 3 2	3 3 0	3 3 5	3 3 6	3 4 7	4 4 0	0 3 3	1 1 0	2 2 1	2 2 8	3 3 1	3 4 6	Total Tissues/ Tumors
Special Senses System																							
Harderian gland				+	+																		4
Urinary System																							
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																							4
Urinary bladder	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	43
Systemic Lesions																							
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma		X					X		X					X									19

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

Number of Days on Study	5 8 7	5 8 8	5 8 8	5 8 9	5 9 7	5 9 7	6 0 0	6 0 6	6 0 8	6 0 8	6 0 8	6 1 9	6 2 3	6 2 6	6 2 9	6 3 9	6 4 2	6 4 6	6 4 6	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	4 5 7	4 1 8	4 5 9	4 3 2	4 5 2	4 5 6	4 5 8	4 4 9	4 2 0	4 3 7	4 4 4	4 6 4	4 6 0	4 4 8	4 2 3	4 3 8	4 2 4	4 3 0	4 4 3	4 3 4	4 3 6	4 4 0	4 4 7	Total Tissues/ Tumors
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	M	+	+	+	+	A	M	A	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	34
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	40
Intestine large, rectum	+	+	+	+	+	A	+	+	M	+	+	+	A	A	+	+	+	+	+	+	+	+	+	41
Intestine large, cecum	+	+	+	+	+	A	A	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	36
Intestine small, duodenum	A	+	+	+	+	A	+	A	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	35
Intestine small, jejunum	A	+	+	+	+	A	+	A	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	35
Intestine small, ileum	A	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	35
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma																							X	1
Hemangiosarcoma	X	X	X	X					X			X	X	X	X		X		X	X				19
Hemangiosarcoma, multiple							X	X			X					X		X				X		15
Hepatocellular carcinoma						X	X		X					X									X	13
Hepatocellular carcinoma, multiple				X	X					X		X					X							7
Hepatocellular adenoma	X		X					X			X									X				8
Hepatocellular adenoma, multiple							X							X					X				X	7
Histiocytic sarcoma	X	X			X						X			X	X		X	X	X	X				18
Mesentery									+							+						+		6
Sarcoma																						X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																								1
Histiocytic sarcoma																								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Tooth																					+			3
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	M	+	M	+	M	M	M	M	+	+	M	M	M	+	+	M	+	+	M	+	+	+	+	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X	X													X	X			X			6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell, adenoma					X																			1
General Body System																								
None																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

Number of Days on Study	1 3 5	1 4 4	3 6 6	4 6 8	4 8 4	4 8 4	5 0 7	5 0 9	5 1 3	5 1 8	5 3 6	5 4 1	5 4 1	5 4 8	5 5 2	5 5 2	5 5 5	5 6 3	5 6 5	5 6 9	5 8 0	5 8 5	5 8 6	5 8 6	5 8 6
Carcass ID Number	4 2 1	4 0 7	4 5 3	4 2 6	4 5 4	4 6 3	4 1 5	4 6 1	4 5 1	4 1 4	4 2 2	4 0 8	4 4 5	4 1 6	4 1 9	4 2 5	4 1 2	4 2 7	4 1 1	4 4 2	4 3 1	4 3 9	4 1 3	4 1 7	4 2 9
Genital System																									
Clitoral gland	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Ovary	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Histiocytic sarcoma																X					X				X
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																					X				
Hematopoietic System																									
Blood																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X						X				X
Lymph node					+											+									
Iliac, histiocytic sarcoma																									
Pancreatic, histiocytic sarcoma																									
Renal, histiocytic sarcoma					X											X									
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma															X						X				X
Lymph node, mandibular	A	+	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+	M	+	M	+	M		+	+
Histiocytic sarcoma																					X				X
Lymph node, mesenteric	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+
Histiocytic sarcoma																X					X				X
Lymph node, mediastinal	M	M	+	+	+	+	M	M	M	M	+	M	M	+	+	M	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X										X						X				
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X										X	X	X				X				X
Thymus	+	I	+	+	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X					X				
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, sarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

Number of Days on Study	5 8 7	5 8 8	5 8 8	5 8 9	5 9 7	5 9 7	6 0 0	6 0 6	6 0 8	6 0 8	6 0 8	6 1 9	6 2 3	6 2 6	6 2 9	6 3 9	6 4 2	6 4 6	6 4 6	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	4 5 7	4 1 8	4 5 9	4 3 2	4 5 2	4 5 6	4 5 8	4 4 9	4 2 0	4 3 7	4 4 4	4 6 4	4 6 0	4 4 8	4 2 3	4 3 8	4 2 4	4 3 0	4 4 3	4 3 4	4 3 6	4 4 0	4 4 4	Total Tissues/ Tumors
Genital System																								
Clitoral gland	+	+	+	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	39
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cystadenoma	X											X												2
Histiocytic sarcoma																								3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp stromal																								1
Hematopoietic System																								
Blood																	+							1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma														X										4
Lymph node	+												+					+	+					6
Iliac, histiocytic sarcoma	X																							1
Pancreatic, histiocytic sarcoma																		X						1
Renal, histiocytic sarcoma																								2
Lymph node, bronchial	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	38
Histiocytic sarcoma		X																						4
Lymph node, mandibular	M	+	+	+	+	+	+	M	M	M	+	M	+	M	M	+	+	+	+	+	+	+	+	32
Histiocytic sarcoma																								2
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Histiocytic sarcoma	X	X												X										6
Lymph node, mediastinal	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	33
Histiocytic sarcoma	X																							4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma														X	X		X							9
Thymus	M	+	+	+	+	+	+	+	+	M	+	M	+	+	M	M	+	+	M	+	M	+	+	38
Histiocytic sarcoma																								2
Integumentary System																								
Mammary gland	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																						X		1
Subcutaneous tissue, sarcoma										X														2
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Tetrafluoroethylene: 1,250 ppm
(continued)

Number of Days on Study	5 8 7	5 8 8	5 8 8	5 8 9	5 9 7	5 9 7	6 0 0	6 0 6	6 0 8	6 0 8	6 0 8	6 1 9	6 2 3	6 2 6	6 2 9	6 3 9	6 4 2	6 4 6	6 4 6	6 6 7	6 6 7	6 6 7	6 6 7	
Carcass ID Number	4 5 7	4 1 8	4 5 9	4 3 2	4 5 2	4 5 6	4 5 8	4 4 9	4 2 0	4 3 7	4 4 4	4 6 4	4 6 0	4 4 8	4 2 3	4 3 8	4 2 4	4 3 0	4 4 3	4 3 4	4 3 6	4 4 0	4 4 7	Total Tissues/ Tumors
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma			X																			X		3
Alveolar/bronchiolar carcinoma						X																		1
Hemangiosarcoma, metastatic, liver															X	X								3
Hemangiosarcoma, metastatic, pancreas																								1
Hepatocellular carcinoma, metastatic, liver												X												4
Histiocytic sarcoma	X	X									X				X		X	X						13
Sarcoma, metastatic, skin																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																								
Harderian gland									+							+				+			+	6
Adenoma									X							X				X			X	6
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																								3
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	I	M	A	+	+	+	+	+	I	+	+	+	37
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma	X	X			X						X			X	X		X	X	X	X				18
Lymphoma malignant mixed									X												X			2

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	2/48 (4%)	3/48 (6%)	0/47 (0%)	6/48 (13%)
Adjusted rate[b]	5.6%	39.7%	0.0%	61.6%
Terminal rate[c]	2/36 (6%)	1/4 (25%)	0/6 (0%)	2/4 (50%)
First incidence (days)	667 (T)	639	—[e]	484
Life table test[d]	P<0.001	P=0.012	P=0.669N	P<0.001
Logistic regression test[d]	P=0.009	P=0.109	P=0.669N	P=0.040
Cochran-Armitage test[d]	P=0.078			
Fisher exact test[d]		P=0.500	P=0.253N	P=0.134
Liver: Hemangioma				
Overall rate	0/48 (0%)	5/48 (10%)	2/47 (4%)	1/47 (2%)
Adjusted rate	0.0%	37.1%	13.0%	25.0%
Terminal rate	0/36 (0%)	0/4 (0%)	0/6 (0%)	1/4 (25%)
First incidence (days)	—	541	569	667 (T)
Life table test	P=0.145	P<0.001	P=0.084	P=0.091
Logistic regression test	P=0.523	P=0.024	P=0.224	P=0.091
Cochran-Armitage test	P=0.510N			
Fisher exact test		P=0.028	P=0.242	P=0.495
Liver: Hemangiosarcoma				
Overall rate	0/48 (0%)	27/48 (56%)	27/47 (57%)	34/47 (72%)
Adjusted rate	0.0%	100.0%	95.5%	93.5%
Terminal rate	0/36 (0%)	4/4 (100%)	5/6 (83%)	2/4 (50%)
First incidence (days)	—	530	481	468
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hemangioma or Hemangiosarcoma				
Overall rate	0/48 (0%)	31/48 (65%)	28/47 (60%)	35/48 (73%)
Adjusted rate	0.0%	100.0%	96.0%	96.7%
Terminal rate	0/36 (0%)	4/4 (100%)	5/6 (83%)	3/4 (75%)
First incidence (days)	—	530	481	468
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma				
Overall rate	15/48 (31%)	17/48 (35%)	20/47 (43%)	15/47 (32%)
Adjusted rate	37.2%	89.1%	93.2%	76.8%
Terminal rate	11/36 (31%)	3/4 (75%)	5/6 (83%)	2/4 (50%)
First incidence (days)	595	530	541	536
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.090	P=0.138	P=0.016	P=0.198
Cochran-Armitage test	P=0.515			
Fisher exact test		P=0.414	P=0.176	P=0.560

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	4/48 (8%)	28/48 (58%)	22/47 (47%)	20/47 (43%)
Adjusted rate	10.8%	95.0%	87.7%	72.5%
Terminal rate	3/36 (8%)	3/4 (75%)	4/6 (67%)	1/4 (25%)
First incidence (days)	660	530	478	484
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.042	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P=0.012			
Fisher exact test		P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	17/48 (35%)	33/48 (69%)	29/47 (62%)	28/47 (60%)
Adjusted rate	42.2%	100.0%	95.6%	88.6%
Terminal rate	13/36 (36%)	4/4 (100%)	5/6 (83%)	2/4 (50%)
First incidence (days)	595	530	478	484
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.045	P<0.001	P<0.001	P=0.005
Cochran-Armitage test	P=0.055			
Fisher exact test		P=0.001	P=0.009	P=0.015
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/48 (13%)	0/48 (0%)	6/47 (13%)	3/47 (6%)
Adjusted rate	16.7%	0.0%	40.6%	30.2%
Terminal rate	6/36 (17%)	0/4 (0%)	2/6 (33%)	1/4 (25%)
First incidence (days)	667 (T)	—	510	509
Life table test	P=0.056	P=0.442N	P=0.026	P=0.162
Logistic regression test	P=0.563	P=0.442N	P=0.505	P=0.636N
Cochran-Armitage test	P=0.424N			
Fisher exact test		P=0.013N	P=0.605	P=0.254N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/48 (13%)	1/48 (2%)	8/47 (17%)	4/47 (9%)
Adjusted rate	16.7%	2.5%	49.2%	33.8%
Terminal rate	6/36 (17%)	0/4 (0%)	2/6 (33%)	1/4 (25%)
First incidence (days)	667 (T)	541	510	509
Life table test	P=0.017	P=0.694N	P=0.003	P=0.064
Logistic regression test	P=0.413	P=0.148N	P=0.232	P=0.575
Cochran-Armitage test	P=0.565			
Fisher exact test		P=0.056N	P=0.370	P=0.384N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/46 (9%)	5/45 (11%)	2/44 (5%)	6/46 (13%)
Adjusted rate	10.6%	55.3%	18.2%	53.0%
Terminal rate	3/36 (8%)	2/4 (50%)	0/6 (0%)	1/4 (25%)
First incidence (days)	617	585	652	565
Life table test	P=0.002	P=0.018	P=0.374	P=0.002
Logistic regression test	P=0.071	P=0.282	P=0.665	P=0.123
Cochran-Armitage test	P=0.352			
Fisher exact test		P=0.486	P=0.360N	P=0.370

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Hemangioma				
Overall rate	0/48 (0%)	5/48 (10%)	4/47 (9%)	1/48 (2%)
Adjusted rate	0.0%	37.1%	33.5%	25.0%
Terminal rate	0/36 (0%)	0/4 (0%)	1/6 (17%)	1/4 (25%)
First incidence (days)	—	541	569	667 (T)
Life table test	P=0.054	P<0.001	P=0.002	P=0.091
Logistic regression test	P=0.353	P=0.024	P=0.018	P=0.091
Cochran-Armitage test	P=0.544N			
Fisher exact test		P=0.028	P=0.056	P=0.500
All Organs: Hemangiosarcoma				
Overall rate	0/48 (0%)	27/48 (56%)	27/47 (57%)	34/48 (71%)
Adjusted rate	0.0%	100.0%	95.5%	93.5%
Terminal rate	0/36 (0%)	4/4 (100%)	5/6 (83%)	2/4 (50%)
First incidence (days)	—	530	481	468
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	0/48 (0%)	31/48 (65%)	28/47 (60%)	35/48 (73%)
Adjusted rate	0.0%	100.0%	96.0%	96.7%
Terminal rate	0/36 (0%)	4/4 (100%)	5/6 (83%)	3/4 (75%)
First incidence (days)	—	530	481	468
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Histiocytic Sarcoma				
Overall rate	1/48 (2%)	21/48 (44%)	19/47 (40%)	18/48 (38%)
Adjusted rate	2.1%	77.6%	51.3%	78.2%
Terminal rate	0/36 (0%)	1/4 (25%)	0/6 (0%)	1/4 (25%)
First incidence (days)	400	429	457	484
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.015	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P=0.002			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Lymphocytic or Mixed Malignant Lymphoma				
Overall rate	5/48 (10%)	3/48 (6%)	0/47 (0%)	2/48 (4%)
Adjusted rate	12.8%	18.0%	0.0%	30.0%
Terminal rate	3/36 (8%)	0/4 (0%)	0/6 (0%)	1/4 (25%)
First incidence (days)	595	530	—	608
Life table test	P=0.471	P=0.348	P=0.250N	P=0.377
Logistic regression test	P=0.276N	P=0.419N	P=0.068N	P=0.551N
Cochran-Armitage test	P=0.115N			
Fisher exact test		P=0.357N	P=0.030N	P=0.218N

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign Neoplasms				
Overall rate	27/48 (56%)	24/48 (50%)	26/47 (55%)	29/48 (60%)
Adjusted rate	64.2%	100.0%	95.0%	100.0%
Terminal rate	21/36 (58%)	4/4 (100%)	5/6 (83%)	4/4 (100%)
First incidence (days)	595	530	510	484
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P=0.005	P=0.319	P=0.133	P=0.016
Cochran-Armitage test	P=0.290			
Fisher exact test		P=0.341N	P=0.546N	P=0.418
All Organs: Malignant Neoplasms				
Overall rate	14/48 (29%)	46/48 (96%)	45/47 (96%)	46/48 (96%)
Adjusted rate	32.3%	100.0%	100.0%	100.0%
Terminal rate	7/36 (19%)	4/4 (100%)	6/6 (100%)	4/4 (100%)
First incidence (days)	400	429	457	366
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	34/48 (71%)	47/48 (98%)	45/47 (96%)	46/48 (96%)
Adjusted rate	77.2%	100.0%	100.0%	100.0%
Terminal rate	26/36 (72%)	4/4 (100%)	6/6 (100%)	4/4 (100%)
First incidence (days)	400	429	457	366
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P=0.001	P<0.001

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

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

Study	Incidence in Controls				
	Hemangioma	Hemangiosarcoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories					
1,3-Butadiene	0/49	1/49	11/49	4/49	15/49
Acetonitrile	0/49	0/49	4/49	7/49	9/49
Allyl Glycidyl Ether	0/50	0/50	1/50	5/50	6/50
α-Chloroacetophenone	0/50	0/50	4/50	8/50	12/50
Epinephrine Hydrochloride	0/50	1/50	2/50	1/50	3/50
Ethyl Chloride	0/49	0/49	0/49	3/49	3/49
Hexachlorocyclopentadiene	0/49	0/49	5/49	4/49	9/49
o-Chlorobenzalmalononitrile (CS-2)	0/50	0/50	4/50	7/50	11/50
Ozone	0/50	0/50	20/50	15/50	27/50
Total	0/446	2/446 (0.5%)	51/446 (11.4%)	54/446 (12.1%)	95/446 (21.3%)
Standard deviation		0.9%	12.5%	8.1%	14.8%
Range		0%-2%	0%-40%	2%-30%	6%-54%
Overall Historical Incidence					
Total	1/937 (0.1%)	5/937 (0.5%)	114/937 (12.2%)	103/937 (11.0%)	200/937 (21.3%)
Standard deviation	0.5%	1.0%	9.7%	6.7%	11.9%
Range	0%-2%	0%-3%	0%-40%	0%-30%	3%-54%

[a] Data as of 12 May 1995

TABLE D4b
Historical Incidence of Histiocytic Sarcoma in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	3/50
Acetonitrile	2/49
Allyl Glycidyl Ether	3/50
α-Chloroacetophenone	1/50
Epinephrine Hydrochloride	1/50
Ethyl Chloride	0/49
Hexachlorocyclopentadiene	4/49
o-Chlorobenzalmalononitrile (CS-2)	0/50
Ozone	0/50
Total	14/447 (3.1%)
Standard deviation	3.0%
Range	0%-8%
Overall Historical Incidence	
Total	26/941 (2.8%)
Standard deviation	3.1%
Range	0%-10%

[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 Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	58	58	58	58
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental death			1	
Moribund	8	28	26	27
Natural deaths	4	16	15	17
Survivors				
Terminal sacrifice	36	4	6	4
Animals examined microscopically	58	58	57	58
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)	(10)	(10)	(10)
Developmental malformation			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Angiectasis		4 (40%)	2 (20%)	1 (10%)
Basophilic focus				1 (10%)
Clear cell focus				1 (10%)
Eosinophilic focus		1 (10%)	4 (40%)	5 (50%)
Fatty change			1 (10%)	1 (10%)
Hematopoietic cell proliferation				1 (10%)
Infarct, chronic				1 (10%)
Infiltration cellular, mixed cell	1 (10%)	4 (40%)	3 (30%)	1 (10%)
Mixed cell focus		1 (10%)		1 (10%)
Necrosis, coagulative, multifocal		1 (10%)		
Thrombosis		1 (10%)		
Hepatocyte, karyomegaly				1 (10%)
Mesentery	(1)	(1)		(1)
Fat, necrosis	1 (100%)	1 (100%)		1 (100%)
Salivary glands	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell	4 (40%)	3 (30%)	4 (40%)	1 (10%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Capsule, hyperplasia	5 (50%)	10 (100%)	5 (50%)	9 (90%)
X-zone, vacuolization cytoplasmic	1 (10%)	2 (20%)	3 (30%)	1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst			1 (10%)	
Genital System				
Clitoral gland	(9)	(9)	(9)	(9)
Ectasia		1 (11%)		
Infiltration cellular, mononuclear cell	1 (11%)		1 (11%)	
Ovary	(10)	(10)	(10)	(10)
Abscess		1 (10%)		
Cyst	1 (10%)	1 (10%)		2 (20%)
Uterus	(10)	(10)	(10)	(10)
Endometrium, hyperplasia, cystic	4 (40%)	6 (60%)	4 (40%)	7 (70%)

[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 Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hyperplasia, neutrophil		1 (10%)	1 (10%)	1 (10%)
Lymph node			(1)	
Pancreatic, hyperplasia, lymphoid			1 (100%)	
Lymph node, mandibular	(7)	(4)	(9)	(6)
Hyperplasia, lymphoid		1 (25%)		
Lymph node, mediastinal	(7)	(7)	(8)	(3)
Hemorrhage			1 (13%)	
Hyperplasia, lymphoid			1 (13%)	
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	2 (20%)	4 (40%)	4 (40%)	3 (30%)
Hyperplasia, lymphoid			1 (10%)	
Infiltration cellular, polymorphonuclear				1 (10%)
Nervous System				
Brain	(10)	(10)	(9)	(10)
Mineralization	4 (40%)	1 (10%)	1 (11%)	4 (40%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Embolus, focal		1 (10%)		
Hemorrhage	1 (10%)		1 (10%)	
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell	2 (20%)	2 (20%)		1 (10%)
Pelvis, infiltration cellular, mononuclear cell			1 (10%)	
Renal tubule, dilatation	1 (10%)			
Renal tubule, karyomegaly			10 (100%)	10 (100%)
Urinary bladder	(9)	(10)	(10)	(9)
Hyperplasia, lymphoid	2 (22%)	1 (10%)		1 (11%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Special Senses System				

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study				
Alimentary System				
Gallbladder	(42)	(36)	(34)	(34)
Inflammation, chronic active	1 (2%)			
Intestine large, colon	(47)	(45)	(42)	(40)
Infarct	1 (2%)			
Mesothelium, inflammation, chronic active	2 (4%)			
Intestine large, rectum	(48)	(48)	(42)	(41)
Mesothelium, inflammation, chronic active	1 (2%)			
Intestine large, cecum	(47)	(42)	(40)	(36)
Lymphoid tissue, hyperplasia, lymphoid		1 (2%)		
Mesothelium, inflammation, chronic active	1 (2%)			
Intestine small, duodenum	(45)	(39)	(39)	(35)
Mesothelium, inflammation, chronic active	1 (2%)			
Peyer's patch, hyperplasia, lymphoid	1 (2%)		1 (3%)	
Intestine small, jejunum	(46)	(37)	(39)	(35)
Hemorrhage		1 (3%)		
Perforation	1 (2%)			
Mesothelium, inflammation, chronic active	1 (2%)			
Peyer's patch, hyperplasia, lymphoid			1 (3%)	
Intestine small, ileum	(46)	(39)	(40)	(35)
Mesothelium, inflammation, chronic active	2 (4%)			
Peyer's patch, hyperplasia, lymphoid		1 (3%)	1 (3%)	
Liver	(48)	(48)	(47)	(47)
Angiectasis	1 (2%)	9 (19%)	6 (13%)	4 (9%)
Basophilic focus			1 (2%)	2 (4%)
Clear cell focus	1 (2%)			
Eosinophilic focus	5 (10%)	13 (27%)	12 (26%)	7 (15%)
Fatty change		3 (6%)		
Hematopoietic cell proliferation	3 (6%)	19 (40%)	13 (28%)	15 (32%)
Hyperplasia, lymphoid			1 (2%)	
Infarct	2 (4%)			1 (2%)
Infiltration cellular, mixed cell	8 (17%)	8 (17%)	9 (19%)	3 (6%)
Inflammation, suppurative	1 (2%)			
Mixed cell focus	3 (6%)			1 (2%)
Necrosis, coagulative, multifocal	4 (8%)	11 (23%)	8 (17%)	8 (17%)
Thrombosis				1 (2%)
Centrilobular, necrosis		3 (6%)	1 (2%)	
Serosa, fibrosis	1 (2%)	1 (2%)		
Mesentery	(9)	(13)	(7)	(6)
Angiectasis	1 (11%)			
Cyst		1 (8%)		
Hyperplasia, lymphoid			1 (14%)	
Mineralization			1 (14%)	
Fat, hemorrhage		1 (8%)		
Fat, necrosis	7 (78%)	8 (62%)	6 (86%)	5 (83%)
Mesothelium, inflammation, chronic active	1 (11%)			
Pancreas	(48)	(47)	(44)	(47)
Fibrosis	1 (2%)		1 (2%)	
Infiltration cellular, lymphocyte	1 (2%)			
Inflammation, acute			1 (2%)	
Inflammation, chronic active	3 (6%)			
Acinus, atrophy	1 (2%)	1 (2%)	3 (7%)	
Acinus, vacuolization cytoplasmic				1 (2%)
Duct, ectasia			1 (2%)	

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Salivary glands	(48)	(48)	(47)	(48)
Infiltration cellular, mononuclear cell	19 (40%)	6 (13%)	9 (19%)	2 (4%)
Inflammation, focal, suppurative				1 (2%)
Stomach, forestomach	(48)	(48)	(47)	(47)
Hyperplasia, squamous		1 (2%)		
Ulcer	1 (2%)			
Epithelium, hyperplasia	4 (8%)			4 (9%)
Serosa, inflammation, chronic active	1 (2%)			
Stomach, glandular	(48)	(48)	(45)	(45)
Mineralization		1 (2%)		
Serosa, inflammation, chronic active	1 (2%)			
Tooth	(2)			(3)
Dysplasia	1 (50%)			2 (67%)
Peridontal tissue, inflammation, suppurative				1 (33%)
Cardiovascular System				
Heart	(48)	(48)	(47)	(48)
Cardiomyopathy	2 (4%)			
Polyarteritis			1 (2%)	
Endocrine System				
Adrenal cortex	(48)	(47)	(47)	(47)
Cyst		1 (2%)	1 (2%)	
Degeneration, fatty				1 (2%)
Hyperplasia	1 (2%)			1 (2%)
Capsule, hyperplasia	45 (94%)	45 (96%)	47 (100%)	41 (87%)
Capsule, mineralization		1 (2%)		
X-zone, vacuolization cytoplasmic	1 (2%)		1 (2%)	2 (4%)
Adrenal medulla	(48)	(47)	(47)	(46)
Angiectasis			1 (2%)	
Islets, pancreatic	(48)	(45)	(44)	(47)
Hyperplasia		1 (2%)		
Pituitary gland	(46)	(45)	(44)	(46)
Pars distalis, angiectasis				2 (4%)
Pars distalis, congestion	2 (4%)			2 (4%)
Pars distalis, cyst	3 (7%)			1 (2%)
Pars distalis, hyperplasia	6 (13%)	3 (7%)	2 (5%)	5 (11%)
Thyroid gland	(48)	(48)	(46)	(46)
Inflammation, focal	1 (2%)	1 (2%)		
Polyarteritis			1 (2%)	
Ultimobranchial cyst	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Follicle, cyst	2 (4%)	2 (4%)		
Follicular cell, hyperplasia	2 (4%)			

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
General Body System				
None				
Genital System				
Clitoral gland	(42)	(42)	(38)	(39)
Infiltration cellular, mononuclear cell	1 (2%)	1 (2%)		
Ovary	(47)	(47)	(45)	(46)
Atrophy	2 (4%)	4 (9%)	5 (11%)	2 (4%)
Congestion		1 (2%)	2 (4%)	1 (2%)
Cyst	13 (28%)	27 (57%)	16 (36%)	18 (39%)
Hemorrhage			1 (2%)	
Inflammation, chronic	1 (2%)			
Metaplasia, osseous	1 (2%)			
Pigmentation, hemosiderin			1 (2%)	
Pigmentation, hemosiderin, cholesterol	1 (2%)			
Pigmentation, lipofuscin		1 (2%)		
Polyarteritis	1 (2%)			
Uterus	(48)	(48)	(45)	(47)
Dilatation	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage				1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)		
Necrosis			1 (2%)	
Endometrium, hyperplasia, cystic	23 (48%)	21 (44%)	24 (53%)	24 (51%)
Hematopoietic System				
Bone marrow	(48)	(48)	(46)	(47)
Hyperplasia, erythrocyte		2 (4%)	2 (4%)	
Hyperplasia, neutrophil	2 (4%)			1 (2%)
Lymph node	(5)	(6)	(4)	(6)
Axillary, hyperplasia, lymphoid			1 (25%)	
Iliac, angiectasis		1 (17%)		
Iliac, hyperplasia, lymphoid		1 (17%)	1 (25%)	
Iliac, inflammation, chronic active		1 (17%)		
Lumbar, hyperplasia, lymphoid			1 (25%)	
Pancreatic, hyperplasia, histiocytic	1 (20%)			
Pancreatic, hyperplasia, lymphoid		1 (17%)		1 (17%)
Renal, hemorrhage		1 (17%)		2 (33%)
Renal, hyperplasia, lymphoid		1 (17%)		
Lymph node, bronchial	(40)	(36)	(40)	(38)
Congestion			1 (3%)	
Hemorrhage		1 (3%)	2 (5%)	3 (8%)
Hyperplasia, histiocytic		1 (3%)	1 (3%)	
Hyperplasia, lymphoid	1 (3%)	5 (14%)	3 (8%)	
Hyperplasia, plasma cell	1 (3%)		1 (3%)	
Inflammation	1 (3%)			
Pigmentation, hemosiderin	1 (3%)		1 (3%)	1 (3%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(39)	(35)	(34)	(32)
Hemorrhage		1 (3%)	1 (3%)	
Hyperplasia, histiocytic			1 (3%)	1 (3%)
Hyperplasia, lymphoid	2 (5%)	1 (3%)	2 (6%)	1 (3%)
Hyperplasia, plasma cell		1 (3%)		1 (3%)
Inflammation	1 (3%)			
Lymph node, mesenteric	(43)	(40)	(41)	(43)
Angiectasis				1 (2%)
Hemorrhage	2 (5%)	1 (3%)	3 (7%)	2 (5%)
Hyperplasia, histiocytic	1 (2%)	1 (3%)	3 (7%)	
Hyperplasia, lymphoid		5 (13%)	4 (10%)	2 (5%)
Hyperplasia, plasma cell	1 (2%)			
Inflammation, chronic active		2 (5%)		
Lymph node, mediastinal	(28)	(35)	(35)	(33)
Congestion			1 (3%)	2 (6%)
Hematopoietic cell proliferation				1 (3%)
Hemorrhage			3 (9%)	
Hyperplasia, histiocytic		2 (6%)		
Hyperplasia, lymphoid	2 (7%)	2 (6%)	4 (11%)	
Hyperplasia, plasma cell	1 (4%)			
Inflammation	1 (4%)			
Pigmentation, hemosiderin		1 (3%)	1 (3%)	
Spleen	(48)	(48)	(46)	(47)
Hematopoietic cell proliferation	18 (38%)	39 (81%)	41 (89%)	41 (87%)
Hyperplasia, lymphoid	2 (4%)		2 (4%)	1 (2%)
Pigmentation, melanin		1 (2%)		
Capsule, hematocyst			1 (2%)	
Thymus	(46)	(42)	(39)	(38)
Atrophy			1 (3%)	
Hyperplasia, lymphoid	1 (2%)			
Necrosis			4 (10%)	
Integumentary System				
Mammary gland	(48)	(46)	(45)	(46)
Hyperplasia		1 (2%)	2 (4%)	2 (4%)
Skin	(47)	(48)	(47)	(48)
Congestion		1 (2%)		
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Fracture healed		1 (2%)		
Nervous System				
Brain	(48)	(48)	(47)	(48)
Compression	1 (2%)	1 (2%)		1 (2%)
Hemorrhage		1 (2%)		
Mineralization	20 (42%)	9 (19%)	14 (30%)	21 (44%)
Ventricle, dilatation				1 (2%)

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(48)	(48)	(47)	(47)
Congestion	2 (4%)		1 (2%)	
Hemorrhage	2 (4%)	5 (10%)	5 (11%)	3 (6%)
Inflammation, chronic			2 (4%)	
Pigmentation, hemosiderin		2 (4%)		3 (6%)
Pigmentation, hemoglobin			1 (2%)	
Alveolar epithelium, hyperplasia		1 (2%)		2 (4%)
Alveolus, infiltration cellular, histiocyte	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Interstitium, infiltration cellular, mixed cell		3 (6%)	1 (2%)	
Nose	(47)	(48)	(45)	(45)
Inflammation, suppurative				1 (2%)
Nasolacrimal duct, inflammation, suppurative				1 (2%)
Respiratory epithelium, cytoplasmic alteration		1 (2%)		
Special Senses System				
Harderian gland	(3)	(6)	(4)	(6)
Hyperplasia		2 (33%)	3 (75%)	
Urinary System				
Kidney	(48)	(48)	(47)	(47)
Hemorrhage	1 (2%)			
Infarct, chronic		2 (4%)	1 (2%)	
Infiltration cellular, mononuclear cell	3 (6%)	1 (2%)	4 (9%)	
Inflammation, chronic active			1 (2%)	
Metaplasia, osseous			1 (2%)	1 (2%)
Nephropathy		1 (2%)	1 (2%)	
Pigmentation, hemosiderin		1 (2%)		1 (2%)
Polyarteritis			1 (2%)	
Renal tubule, karyomegaly				38 (81%)
Glomerulus, amyloid deposition				1 (2%)
Urinary bladder	(46)	(43)	(43)	(37)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	2 (5%)	
Infiltration cellular, mononuclear cell	1 (2%)			
Inflammation, chronic active			1 (2%)	
Metaplasia, squamous			1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al*. (1990). Peripheral blood samples were obtained from male and female B6C3F$_1$ mice at the end of the 13-week study. Smears were immediately prepared and fixed in absolute methanol and stained with Giemsa. Slides were scanned at 630× or 1,000× magnification using a semi-automated image analysis system to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in each of 10 animals per exposure group. The criteria of Schmid (1976) were used to define micronuclei; the minimum size limit was approximately 1/20 the diameter of the NCE.

Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each exposure group were compared with the concurrent solvent control by Student's *t*-test.

RESULTS

No increases in the frequency of micronucleated NCEs were observed in peripheral blood samples obtained from male and female mice at the end of the 13-week inhalation study of tetrafluoroethylene (Table E1).

TABLE E1
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with Tetrafluoroethylene by Inhalation for 13 Weeks [a]

Dose (ppm)	Micronucleated Normochromatic Cells/ 1,000 Normochromatic Cells
Male	
0	1.15 ± 0.10
1,250	1.31 ± 0.07
2,500	1.29 ± 0.07
5,000	1.29 ± 0.06
	P=0.1276[b]
Female	
0	1.05 ± 0.08
1,250	1.04 ± 0.07
2,500	1.07 ± 0.07
5,000	1.14 ± 0.04
	P=0.7150

[a] Study was performed at USDA Western Regional Center. Data are presented as mean ± standard error. 10,000 normochromatic erythrocytes were scored for each of 10 animals per exposure group.
[b] Trend test, linear contrasts from analysis of variance

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 16-Day Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
n	5	5	5	5	5	5
Male						
Necropsy body wt	153 ± 4	161 ± 4	160 ± 3	153 ± 1	148 ± 2	130 ± 3**
Brain						
Absolute	1.702 ± 0.013	1.752 ± 0.026	1.738 ± 0.025	1.724 ± 0.012	1.686 ± 0.021	1.648 ± 0.023
Relative	11.12 ± 0.21	10.93 ± 0.18	10.87 ± 0.31	11.27 ± 0.08	11.40 ± 0.24	12.72 ± 0.31**
Heart						
Absolute	0.522 ± 0.010	0.610 ± 0.015*	0.602 ± 0.024*	0.604 ± 0.023*	0.594 ± 0.025	0.524 ± 0.014
Relative	3.41 ± 0.08	3.80 ± 0.07	3.77 ± 0.18	3.95 ± 0.17**	4.01 ± 0.14**	4.04 ± 0.10**
L. and R. Kidneys						
Absolute	1.200 ± 0.042	1.396 ± 0.037**	1.402 ± 0.031**	1.418 ± 0.017**	1.512 ± 0.038**	1.624 ± 0.049**
Relative	7.82 ± 0.15	8.70 ± 0.08**	8.75 ± 0.15**	9.27 ± 0.15**	10.21 ± 0.17**	12.51 ± 0.27**
Liver						
Absolute	4.952 ± 0.289	6.094 ± 0.339	6.198 ± 0.411*	5.888 ± 0.274	6.622 ± 0.257**	5.282 ± 0.219
Relative	32.20 ± 1.24	38.02 ± 2.08*	38.57 ± 1.92*	38.50 ± 1.87*	44.72 ± 1.60**	40.71 ± 1.49**
Lung						
Absolute	0.886 ± 0.025	1.150 ± 0.103*	1.288 ± 0.086**	1.114 ± 0.033	0.978 ± 0.051	0.926 ± 0.016
Relative	5.79 ± 0.17	7.13 ± 0.51*	8.03 ± 0.45**	7.29 ± 0.24*	6.60 ± 0.32	7.15 ± 0.20*
R. Testis						
Absolute	1.940 ± 0.039	2.070 ± 0.027	2.055 ± 0.054	2.018 ± 0.027	2.006 ± 0.023	1.728 ± 0.063**
Relative	12.68 ± 0.43	12.93 ± 0.35	12.85 ± 0.44	13.19 ± 0.16	13.57 ± 0.32	13.33 ± 0.48
Thymus						
Absolute	0.312 ± 0.017	0.355 ± 0.013	0.342 ± 0.019	0.313 ± 0.022	0.341 ± 0.012	0.258 ± 0.019
Relative	2.04 ± 0.12	2.21 ± 0.06	2.13 ± 0.08	2.05 ± 0.15	2.30 ± 0.06	1.98 ± 0.12
Female						
Necropsy body wt	116 ± 2	121 ± 2	115 ± 3	120 ± 2	110 ± 3	101 ± 2**
Brain						
Absolute	1.656 ± 0.018	1.686 ± 0.036	1.648 ± 0.021	1.620 ± 0.030	1.620 ± 0.007	1.620 ± 0.039
Relative	14.34 ± 0.31	13.95 ± 0.21	14.32 ± 0.23	13.57 ± 0.41	14.84 ± 0.49	16.16 ± 0.59*
Heart						
Absolute	0.458 ± 0.008	0.498 ± 0.010*	0.458 ± 0.013	0.470 ± 0.014	0.464 ± 0.005	0.438 ± 0.006
Relative	3.97 ± 0.11	4.12 ± 0.07	3.98 ± 0.11	3.93 ± 0.09	4.25 ± 0.13	4.36 ± 0.08*
L. and R. Kidneys						
Absolute	1.008 ± 0.020	1.130 ± 0.021	1.082 ± 0.020	1.142 ± 0.040*	1.202 ± 0.045**	1.456 ± 0.061**
Relative	8.73 ± 0.25	9.35 ± 0.04	9.41 ± 0.27	9.54 ± 0.23	10.97 ± 0.26**	14.49 ± 0.51**
Liver						
Absolute	4.016 ± 0.204	4.438 ± 0.177	4.006 ± 0.093	4.200 ± 0.245	3.986 ± 0.189	4.064 ± 0.110
Relative	34.74 ± 1.75	36.67 ± 1.06	34.82 ± 1.05	35.08 ± 1.71	36.34 ± 1.04	40.51 ± 1.34*
Lung						
Absolute	0.876 ± 0.028	0.918 ± 0.038	0.898 ± 0.038	0.984 ± 0.048	0.886 ± 0.029	0.714 ± 0.012*
Relative	7.59 ± 0.29	7.59 ± 0.28	7.83 ± 0.51	8.23 ± 0.37	8.09 ± 0.19	7.11 ± 0.11
Thymus						
Absolute	0.275 ± 0.018	0.308 ± 0.019	0.271 ± 0.012	0.274 ± 0.026	0.249 ± 0.011	0.233 ± 0.027
Relative	2.38 ± 0.14	2.54 ± 0.11	2.36 ± 0.11	2.29 ± 0.20	2.27 ± 0.05	2.32 ± 0.26

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

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	329 ± 5	343 ± 5	345 ± 4	333 ± 4	331 ± 4	301 ± 5**
Brain						
Absolute	1.889 ± 0.011	1.913 ± 0.018	1.895 ± 0.018	1.884 ± 0.014	1.886 ± 0.016	1.866 ± 0.017
Relative	5.75 ± 0.07	5.59 ± 0.06	5.50 ± 0.06	5.66 ± 0.05	5.71 ± 0.07	6.21 ± 0.08**
Heart						
Absolute	0.875 ± 0.021	0.913 ± 0.010	0.913 ± 0.017	0.964 ± 0.027*	0.981 ± 0.035**	0.904 ± 0.019
Relative	2.66 ± 0.05	2.67 ± 0.02	2.65 ± 0.04	2.90 ± 0.08**	2.97 ± 0.10**	3.00 ± 0.03**
R. Kidney						
Absolute	2.218 ± 0.055	2.369 ± 0.044	2.372 ± 0.051	2.512 ± 0.055**	3.527 ± 0.087**	2.915 ± 0.048**
Relative	6.74 ± 0.14	6.91 ± 0.08	6.88 ± 0.11	7.54 ± 0.12**	10.66 ± 0.20**	9.68 ± 0.06**
Liver						
Absolute	11.587 ± 0.337	13.125 ± 0.407**	13.494 ± 0.296**	13.829 ± 0.354**	14.825 ± 0.265**	14.398 ± 0.402**
Relative	35.19 ± 0.74	38.29 ± 0.98*	39.16 ± 0.82**	41.48 ± 0.72**	44.92 ± 1.10**	47.81 ± 1.01**
Lung						
Absolute	2.008 ± 0.064	2.033 ± 0.040	2.039 ± 0.041	2.175 ± 0.106	1.895 ± 0.072	1.890 ± 0.100
Relative	6.10 ± 0.17	5.94 ± 0.14	5.92 ± 0.12	6.56 ± 0.37	5.74 ± 0.24	6.28 ± 0.32
R. Testis						
Absolute	1.384 ± 0.023	1.412 ± 0.029	1.343 ± 0.043	1.375 ± 0.031	1.472 ± 0.019	1.417 ± 0.020
Relative	4.21 ± 0.05	4.12 ± 0.08	3.90 ± 0.12	4.13 ± 0.10	4.45 ± 0.05*	4.71 ± 0.05**
Thymus						
Absolute	0.236 ± 0.007	0.247 ± 0.014	0.256 ± 0.006	0.248 ± 0.007	0.244 ± 0.007	0.222 ± 0.006
Relative	0.72 ± 0.02	0.72 ± 0.04	0.74 ± 0.02	0.75 ± 0.02	0.74 ± 0.02	0.74 ± 0.02
Female						
Necropsy body wt	189 ± 5	198 ± 3	197 ± 5	194 ± 4	177 ± 8	173 ± 4*
Brain						
Absolute	1.755 ± 0.017	1.795 ± 0.013	1.784 ± 0.021	1.763 ± 0.018	1.716 ± 0.035	1.704 ± 0.017
Relative	9.32 ± 0.16	9.07 ± 0.12	9.13 ± 0.25	9.08 ± 0.12	9.89 ± 0.57	9.87 ± 0.20
Heart						
Absolute	0.596 ± 0.021	0.636 ± 0.012	0.644 ± 0.011	0.633 ± 0.014	0.597 ± 0.025	0.620 ± 0.010
Relative	3.15 ± 0.05	3.21 ± 0.04	3.28 ± 0.05	3.26 ± 0.05	3.38 ± 0.05**	3.59 ± 0.06**
R. Kidney						
Absolute	1.326 ± 0.039	1.432 ± 0.028	1.485 ± 0.027*	1.583 ± 0.038**	1.710 ± 0.083**	1.877 ± 0.043**
Relative	7.01 ± 0.08	7.23 ± 0.13	7.57 ± 0.12**	8.14 ± 0.12**	9.66 ± 0.10**	10.83 ± 0.13**
Liver						
Absolute	6.618 ± 0.260	6.687 ± 0.122	6.812 ± 0.114	7.044 ± 0.294	6.816 ± 0.331	7.567 ± 0.249*
Relative	34.95 ± 0.84	33.75 ± 0.43	34.79 ± 0.80	36.17 ± 1.17	38.55 ± 0.78**	43.58 ± 0.63**
Lung						
Absolute	1.411 ± 0.061	1.472 ± 0.023	1.501 ± 0.046	1.399 ± 0.037	1.307 ± 0.034	1.231 ± 0.030**
Relative	7.47 ± 0.27	7.44 ± 0.12	7.64 ± 0.14	7.20 ± 0.15	7.49 ± 0.31	7.11 ± 0.11
Thymus						
Absolute	0.204 ± 0.007	0.227 ± 0.004	0.227 ± 0.005	0.217 ± 0.007	0.188 ± 0.017	0.181 ± 0.006
Relative	1.08 ± 0.03	1.15 ± 0.02	1.16 ± 0.02	1.11 ± 0.03	1.05 ± 0.07	1.05 ± 0.04

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

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	156 ppm	312 ppm	625 ppm
n	10	10	10	10
Male				
Necropsy body wt	490 ± 9	490 ± 10	485 ± 11	484 ± 11
R. Kidney				
Absolute	1.487 ± 0.025	1.527 ± 0.045	1.592 ± 0.042	2.076 ± 0.077**
Relative	3.04 ± 0.03	3.12 ± 0.07	3.28 ± 0.05*	4.28 ± 0.11**
Liver				
Absolute	15.921 ± 0.258	16.155 ± 0.558	16.323 ± 0.507	16.912 ± 0.616
Relative	32.56 ± 0.40	32.92 ± 0.70	33.61 ± 0.50	34.96 ± 1.13
Lung				
Absolute	2.283 ± 0.160	2.354 ± 0.074	2.178 ± 0.106	2.378 ± 0.154
Relative	4.63 ± 0.25	4.81 ± 0.14	4.49 ± 0.20	4.92 ± 0.31

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
Necropsy body wt	301 ± 8	299 ± 8	327 ± 4*	304 ± 8
R. Kidney				
Absolute	0.915 ± 0.020	0.933 ± 0.019	1.051 ± 0.026**	1.178 ± 0.058**
Relative	3.04 ± 0.05	3.13 ± 0.07	3.21 ± 0.07	3.88 ± 0.16**
Liver				
Absolute	8.759 ± 0.225	8.818 ± 0.239	9.922 ± 0.224**	9.785 ± 0.226**
Relative	29.08 ± 0.24	29.53 ± 0.43	30.32 ± 0.52	32.26 ± 0.52**
Lung				
Absolute	1.578 ± 0.058	1.468 ± 0.060	1.560 ± 0.064	1.487 ± 0.052
Relative	5.25 ± 0.17	4.91 ± 0.15	4.76 ± 0.17	4.90 ± 0.15

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
n	5	5	5	5	5	5
Male						
Necropsy body wt	21.2 ± 0.4	21.2 ± 0.6	20.5 ± 0.5	20.4 ± 1.1	22.0 ± 0.7	21.2 ± 0.9
Brain						
Absolute	0.440 ± 0.005	0.456 ± 0.007	0.466 ± 0.009	0.452 ± 0.005	0.454 ± 0.009	0.494 ± 0.042
Relative	20.78 ± 0.37	21.59 ± 0.79	22.73 ± 0.39	22.28 ± 0.82	20.64 ± 0.41	23.23 ± 1.55
Heart						
Absolute	0.140 ± 0.015	0.128 ± 0.014	0.138 ± 0.007	0.124 ± 0.011	0.128 ± 0.009	0.146 ± 0.008
Relative	6.60 ± 0.67	6.07 ± 0.72	6.74 ± 0.38	6.11 ± 0.61	5.82 ± 0.39	6.90 ± 0.38
L. and R. Kidneys						
Absolute	0.408 ± 0.007	0.420 ± 0.013	0.404 ± 0.009	0.400 ± 0.017	0.428 ± 0.026	0.446 ± 0.019
Relative	19.26 ± 0.34	19.83 ± 0.56	19.71 ± 0.50	19.63 ± 0.52	19.43 ± 1.06	21.02 ± 0.53
Liver						
Absolute	0.988 ± 0.031	1.002 ± 0.032	0.970 ± 0.044	0.986 ± 0.031	1.078 ± 0.052	1.032 ± 0.054
Relative	46.66 ± 1.65	47.34 ± 1.60	47.19 ± 1.25	48.48 ± 1.46	49.04 ± 2.51	48.53 ± 0.65
Lung						
Absolute	0.190 ± 0.006	0.192 ± 0.008	0.208 ± 0.004	0.184 ± 0.005	0.204 ± 0.007	0.192 ± 0.008
Relative	8.97 ± 0.26	9.10 ± 0.53	10.16 ± 0.31	9.07 ± 0.39	9.26 ± 0.21	9.07 ± 0.34
R. Testis						
Absolute	0.197 ± 0.012	0.202 ± 0.006	0.204 ± 0.009	0.202 ± 0.013	0.202 ± 0.007	0.199 ± 0.007
Relative	9.31 ± 0.54	9.52 ± 0.13	9.94 ± 0.37	9.85 ± 0.27	9.18 ± 0.17	9.38 ± 0.18
Thymus						
Absolute	0.044 ± 0.009	0.042 ± 0.006	0.044 ± 0.007	0.047 ± 0.009	0.045 ± 0.006	0.045 ± 0.003
Relative	2.07 ± 0.41	1.99 ± 0.26	2.12 ± 0.33	2.27 ± 0.36	2.06 ± 0.26	2.13 ± 0.13
Female						
Necropsy body wt	16.2 ± 0.4	16.7 ± 0.8	16.1 ± 0.2	16.8 ± 0.8	17.5 ± 0.6	17.5 ± 0.5
Brain						
Absolute	0.458 ± 0.007	0.458 ± 0.020	0.458 ± 0.007	0.450 ± 0.018	0.464 ± 0.010	0.456 ± 0.002
Relative	28.33 ± 0.84	27.46 ± 0.86	28.49 ± 0.47	27.06 ± 1.79	26.55 ± 0.72	26.18 ± 0.79
Heart						
Absolute	0.104 ± 0.004	0.120 ± 0.012	0.122 ± 0.006	0.104 ± 0.002	0.122 ± 0.007	0.128 ± 0.006
Relative	6.44 ± 0.31	7.13 ± 0.54	7.58 ± 0.34	6.24 ± 0.28	6.96 ± 0.33	7.33 ± 0.31
L. and R. Kidneys						
Absolute	0.270 ± 0.009	0.284 ± 0.015	0.276 ± 0.010	0.278 ± 0.011	0.306 ± 0.015	0.316 ± 0.009*
Relative	16.65 ± 0.24	16.97 ± 0.15	17.15 ± 0.53	16.59 ± 0.27	17.48 ± 0.72	18.10 ± 0.38
Liver						
Absolute	0.722 ± 0.025	0.786 ± 0.031	0.736 ± 0.030	0.800 ± 0.058	0.858 ± 0.045*	0.900 ± 0.047**
Relative	44.66 ± 1.87	47.12 ± 1.04	45.72 ± 1.47	47.53 ± 1.89	48.88 ± 1.28	51.36 ± 1.35**
Lung						
Absolute	0.176 ± 0.009	0.178 ± 0.015	0.190 ± 0.004	0.182 ± 0.012	0.198 ± 0.011	0.184 ± 0.010
Relative	10.90 ± 0.67	10.59 ± 0.59	11.82 ± 0.32	10.83 ± 0.48	11.34 ± 0.70	10.52 ± 0.45
Thymus						
Absolute	0.046 ± 0.003	0.054 ± 0.003	0.046 ± 0.002	0.056 ± 0.006	0.055 ± 0.004	0.063 ± 0.005*
Relative	2.83 ± 0.19	3.23 ± 0.15	2.86 ± 0.15	3.31 ± 0.21	3.15 ± 0.23	3.63 ± 0.25*

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

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 pm	5,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	36.2 ± 0.7	35.3 ± 0.5	35.9 ± 0.8	34.6 ± 0.5*	34.0 ± 0.3**	32.1 ± 0.5**
Brain						
Absolute	0.464 ± 0.004	0.464 ± 0.006	0.465 ± 0.005	0.469 ± 0.002	0.464 ± 0.004	0.469 ± 0.006
Relative	12.84 ± 0.25	13.18 ± 0.21	12.99 ± 0.27	13.58 ± 0.22*	13.64 ± 0.13*	14.64 ± 0.24**
Heart						
Absolute	0.159 ± 0.004	0.157 ± 0.004	0.156 ± 0.004	0.158 ± 0.006	0.151 ± 0.005	0.145 ± 0.004
Relative	4.39 ± 0.12	4.45 ± 0.10	4.35 ± 0.10	4.57 ± 0.15	4.43 ± 0.13	4.52 ± 0.09
R. Kidney						
Absolute	0.588 ± 0.009	0.606 ± 0.019	0.571 ± 0.017	0.573 ± 0.013	0.557 ± 0.012	0.550 ± 0.011
Relative	16.26 ± 0.30	17.18 ± 0.44	15.89 ± 0.31	16.56 ± 0.28	16.35 ± 0.27	17.15 ± 0.24
Liver						
Absolute	1.672 ± 0.040	1.705 ± 0.047	1.687 ± 0.051	1.721 ± 0.045	1.622 ± 0.056	1.600 ± 0.049
Relative	46.13 ± 0.61	48.31 ± 0.91	46.93 ± 0.87	49.70 ± 0.86	47.58 ± 1.32	49.86 ± 1.28*
Lung						
Absolute	0.247 ± 0.004	0.242 ± 0.004	0.239 ± 0.007	0.232 ± 0.004*	0.230 ± 0.003**	0.216 ± 0.003**
Relative	6.82 ± 0.08	6.87 ± 0.07	6.65 ± 0.13	6.71 ± 0.13	6.76 ± 0.09	6.75 ± 0.17
R. Testis						
Absolute	0.117 ± 0.003	0.117 ± 0.002	0.116 ± 0.001	0.118 ± 0.001	0.114 ± 0.002	0.112 ± 0.003
Relative	3.24 ± 0.07	3.31 ± 0.04	3.25 ± 0.06	3.41 ± 0.07	3.36 ± 0.06	3.50 ± 0.10*
Thymus						
Absolute	0.032 ± 0.001	0.033 ± 0.002	0.033 ± 0.002	0.031 ± 0.001	0.031 ± 0.002	0.029 ± 0.001
Relative	0.89 ± 0.03	0.94 ± 0.04	0.93 ± 0.06	0.90 ± 0.04	0.90 ± 0.05	0.90 ± 0.05
Female						
Necropsy body wt	31.5 ± 0.7	30.8 ± 0.8	30.9 ± 0.8	29.8 ± 0.6	30.7 ± 0.8	29.2 ± 0.5
Brain						
Absolute	0.473 ± 0.004	0.468 ± 0.003	0.471 ± 0.006	0.479 ± 0.004	0.469 ± 0.005	0.474 ± 0.003
Relative	15.07 ± 0.32	15.28 ± 0.41	15.34 ± 0.39	16.11 ± 0.25	15.36 ± 0.35	16.26 ± 0.28
Heart						
Absolute	0.131 ± 0.003	0.127 ± 0.002	0.126 ± 0.002	0.127 ± 0.002	0.127 ± 0.004	0.126 ± 0.002
Relative	4.17 ± 0.09	4.14 ± 0.09	4.10 ± 0.11	4.27 ± 0.06	4.15 ± 0.11	4.32 ± 0.11
R. Kidney						
Absolute	0.384 ± 0.005	0.382 ± 0.014	0.372 ± 0.006	0.382 ± 0.009	0.382 ± 0.011	0.379 ± 0.010
Relative	12.22 ± 0.24	12.41 ± 0.38	12.11 ± 0.28	12.82 ± 0.19	12.46 ± 0.27	12.98 ± 0.33
Liver						
Absolute	1.475 ± 0.043	1.460 ± 0.069	1.508 ± 0.026	1.506 ± 0.052	1.503 ± 0.063	1.498 ± 0.036
Relative	46.81 ± 0.97	47.30 ± 1.63	49.09 ± 1.28	50.44 ± 1.08	48.92 ± 1.44	51.32 ± 1.25*
Lung						
Absolute	0.238 ± 0.010	0.229 ± 0.006	0.249 ± 0.005	0.226 ± 0.004	0.236 ± 0.009	0.237 ± 0.011
Relative	7.53 ± 0.20	7.45 ± 0.17	8.10 ± 0.21	7.59 ± 0.13	7.69 ± 0.18	8.15 ± 0.44
Thymus						
Absolute	0.041 ± 0.001	0.039 ± 0.002	0.039 ± 0.002	0.039 ± 0.002[b]	0.040 ± 0.002[c]	0.035 ± 0.003
Relative	1.29 ± 0.03	1.26 ± 0.05	1.26 ± 0.05	1.30 ± 0.06[b]	1.30 ± 0.06[c]	1.18 ± 0.10

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

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
n	10	10	10	10
Male				
Necropsy body wt	50.2 ± 1.6	50.8 ± 0.9	50.5 ± 1.6	48.5 ± 1.1
R. Kidney				
Absolute	0.413 ± 0.010	0.406 ± 0.012	0.420 ± 0.013	0.413 ± 0.011
Relative	8.26 ± 0.13	8.00 ± 0.22	8.41 ± 0.40	8.52 ± 0.15
Liver				
Absolute	2.845 ± 0.356	2.683 ± 0.231	2.455 ± 0.147	2.493 ± 0.175
Relative	59.58 ± 10.80	53.33 ± 5.04	49.30 ± 3.64	51.70 ± 3.96
Lung				
Absolute	0.297 ± 0.013	0.316 ± 0.019	0.291 ± 0.013	0.308 ± 0.010
Relative	5.95 ± 0.24	6.22 ± 0.36	5.77 ± 0.15	6.36 ± 0.17
Female				
Necropsy body wt	48.5 ± 1.5	50.8 ± 1.5	53.3 ± 3.0	48.3 ± 2.5
R. Kidney				
Absolute	0.286 ± 0.011	0.270 ± 0.006	0.287 ± 0.009	0.278 ± 0.010
Relative	5.96 ± 0.31	5.33 ± 0.13	5.49 ± 0.26	5.83 ± 0.21
Liver				
Absolute	1.886 ± 0.094	2.135 ± 0.173	2.210 ± 0.174	2.423 ± 0.321
Relative	39.02 ± 1.94	42.75 ± 4.42	41.34 ± 1.80	50.96 ± 7.10
Lung				
Absolute	0.258 ± 0.006	0.283 ± 0.016	0.275 ± 0.008	0.278 ± 0.012
Relative	5.38 ± 0.24	5.59 ± 0.30	5.31 ± 0.34	5.90 ± 0.42

[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). Differences from the control group were not significant by Williams' or Dunnett's test.

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1
Hematology Data for Rats in the 16-Day Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
n	5	5	5	5	4	5
Hematocrit (%)	43.0 ± 0.3	42.4 ± 0.6	41.7 ± 0.2	42.1 ± 0.4	41.9 ± 0.3	42.6 ± 0.5
Hemoglobin (g/dL)	16.2 ± 0.2	16.0 ± 0.3	15.7 ± 0.1	15.9 ± 0.2	15.8 ± 0.2	16.0 ± 0.2
Erythrocytes (10^6/µL)	7.93 ± 0.05	7.70 ± 0.14	7.67 ± 0.12	7.68 ± 0.10	7.72 ± 0.05	7.77 ± 0.10
Reticulocytes (per 5 oil immersion fields)	53.00 ± 8.56	54.40 ± 4.07	66.80 ± 8.29	70.00 ± 5.52	68.75 ± 7.22	69.20 ± 5.44
Nucleated erythrocytes (10^3/µL)	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	54.2 ± 0.2	55.0 ± 0.3	54.6 ± 0.7	55.0 ± 0.6	54.3 ± 0.3	55.0 ± 0.6
Mean cell hemoglobin (pg)	20.5 ± 0.1	20.8 ± 0.2	20.5 ± 0.3	20.8 ± 0.2	20.4 ± 0.2	20.6 ± 0.2
Mean cell hemoglobin concentration (g/dL)	37.8 ± 0.1	37.7 ± 0.2	37.7 ± 0.1	37.8 ± 0.1	37.6 ± 0.1	37.5 ± 0.1
Platelets (10^3/µL)	641.4 ± 10.3	699.4 ± 22.4	603.0 ± 74.8	677.6 ± 15.2	745.3 ± 20.3*	641.8 ± 31.4
Leukocytes (10^3/µL)	3.66 ± 0.17	4.12 ± 0.09	4.26 ± 0.49	3.68 ± 0.35	4.20 ± 0.67	4.18 ± 0.32
Segmented neutrophils (10^3/µL)	0.70 ± 0.09	0.71 ± 0.09	0.82 ± 0.16	0.70 ± 0.14	0.60 ± 0.04	0.65 ± 0.06
Lymphocytes (10^3/µL)	2.92 ± 0.16	3.35 ± 0.03	3.38 ± 0.41	2.91 ± 0.20	3.54 ± 0.67	3.52 ± 0.34
Monocytes (10^3/µL)	0.02 ± 0.02	0.03 ± 0.02	0.06 ± 0.04	0.07 ± 0.03	0.03 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/µL)	0.01 ± 0.01	0.04 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.04 ± 0.02	0.00 ± 0.00
Female						
n	5	5	5	5	5	5
Hematocrit (%)	45.6 ± 0.3	45.7 ± 0.5	45.8 ± 0.1	46.9 ± 0.4	46.6 ± 0.3	46.2 ± 0.6
Hemoglobin (g/dL)	16.8 ± 0.1	16.8 ± 0.2	16.9 ± 0.1	17.3 ± 0.1	17.2 ± 0.2	17.1 ± 0.3
Erythrocytes (10^6/µL)	8.11 ± 0.18	8.16 ± 0.11	8.12 ± 0.12	8.28 ± 0.09	8.49 ± 0.14	8.34 ± 0.11
Reticulocytes (per 5 oil immersion fields)	46.00 ± 7.77	42.00 ± 5.65	32.20 ± 1.59	37.20 ± 3.09	35.00 ± 3.48	31.40 ± 1.33
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	56.4 ± 1.3	56.0 ± 0.6	56.6 ± 1.0	56.8 ± 0.4	55.0 ± 0.6	55.6 ± 0.4
Mean cell hemoglobin (pg)	20.8 ± 0.5	20.6 ± 0.1	20.8 ± 0.4	20.9 ± 0.1	20.3 ± 0.2	20.5 ± 0.2
Mean cell hemoglobin concentration (g/dL)	36.9 ± 0.1	36.7 ± 0.2	36.9 ± 0.2	37.0 ± 0.1	36.9 ± 0.1	36.9 ± 0.2
Platelets (10^3/µL)	626.8 ± 22.5	705.6 ± 17.5	626.2 ± 12.7	650.2 ± 49.6	552.2 ± 20.8	599.8 ± 14.1
Leukocytes (10^3/µL)	4.80 ± 0.10	4.16 ± 0.46	3.96 ± 0.27	4.72 ± 0.48	4.82 ± 0.77	4.18 ± 0.44
Segmented neutrophils (10^3/µL)	0.81 ± 0.10	0.70 ± 0.14	0.55 ± 0.15	0.70 ± 0.03	1.07 ± 0.22	1.08 ± 0.23
Lymphocytes (10^3/µL)	3.86 ± 0.16	3.37 ± 0.42	3.29 ± 0.30	3.86 ± 0.41	3.68 ± 0.60	2.88 ± 0.31
Monocytes (10^3/µL)	0.11 ± 0.02	0.08 ± 0.03	0.10 ± 0.04	0.11 ± 0.04	0.07 ± 0.02	0.18 ± 0.04
Eosinophils (10^3/µL)	0.02 ± 0.01	0.02 ± 0.02	0.02 ± 0.01	0.05 ± 0.02	0.01 ± 0.01	0.04 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE G2
Hematology and Urinalysis Data for Rats in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
Hematology						
n	10	9	9	10	9	10
Hematocrit (%)	47.3 ± 0.3	45.5 ± 0.3**	45.9 ± 0.4**	44.9 ± 0.6**	44.3 ± 0.3**	44.3 ± 0.3**
Hemoglobin (g/dL)	15.8 ± 0.1	15.2 ± 0.1**	15.3 ± 0.1**	14.8 ± 0.2**	14.6 ± 0.1**	14.5 ± 0.1**
Erythrocytes (10^6/µL)	9.45 ± 0.06	9.11 ± 0.07**	9.22 ± 0.09*	9.02 ± 0.12**	8.91 ± 0.08**	8.80 ± 0.07**
Reticulocytes (10^3/µL)	91.2 ± 47.5	118.8 ± 60.3	109.9 ± 41.7	84.2 ± 44.1	116.9 ± 82.7	87.0 ± 61.2
Mean cell volume (fL)	50.2 ± 0.3	49.9 ± 0.2	49.7 ± 0.2	49.9 ± 0.2	49.8 ± 0.2	50.3 ± 0.2
Mean cell hemoglobin (pg)	16.7 ± 0.1	16.7 ± 0.1	16.6 ± 0.1	16.5 ± 0.2*	16.4 ± 0.1**	16.5 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.1	33.3 ± 0.1	33.3 ± 0.1	33.0 ± 0.3*	33.0 ± 0.1*	32.8 ± 0.1**
Platelets (10^3/µL)	515.4 ± 8.6	530.1 ± 15.8	540.6 ± 23.8*	599.4 ± 21.8**	581.1 ± 10.6**	637.4 ± 12.4**
Leukocytes (10^3/µL)	6.38 ± 0.20	6.27 ± 0.20	6.43 ± 0.27	6.59 ± 0.31	6.02 ± 0.45	6.59 ± 0.27
Segmented neutrophils (10^3/µL)	1.06 ± 0.10	1.16 ± 0.11	0.89 ± 0.07	0.91 ± 0.10	0.86 ± 0.11	0.97 ± 0.08
Lymphocytes (10^3/µL)	5.07 ± 0.18	4.82 ± 0.26	5.33 ± 0.19	5.51 ± 0.29	4.95 ± 0.38	5.39 ± 0.21
Monocytes (10^3/µL)	0.22 ± 0.05	0.18 ± 0.04	0.16 ± 0.06	0.09 ± 0.03	0.17 ± 0.04	0.19 ± 0.05
Eosinophils (10^3/µL)	0.04 ± 0.02	0.10 ± 0.01*	0.05 ± 0.02	0.07 ± 0.02	0.04 ± 0.02	0.04 ± 0.01
Urinalysis						
n	10	10	10	10	10	10
Fluoride (µg/16 hr)	7.98 ± 0.37	35.68 ± 1.82**	45.87 ± 2.42**	69.91 ± 5.63**	122.41 ± 12.02**	205.45 ± 16.71**
Glucose (mg/16 hr)	0.09 ± 0.01[b]	0.02 ± 0.00**[b]	0.08 ± 0.02	0.04 ± 0.01	0.05 ± 0.02	2.81 ± 1.27[b]
Protein (mg/16 hr)	14 ± 1	17 ± 1**	19 ± 1**	23 ± 2**	23 ± 1**	35 ± 2**
Volume (mL/16 hr)	24.8 ± 2.4	21.5 ± 3.1	27.0 ± 2.1	24.0 ± 2.8	28.7 ± 2.0	38.6 ± 4.5
Volume (mL) (concentrated)	0.9 ± 0.2[b]	0.8 ± 0.1[b]	0.9 ± 0.2[b]	1.1 ± 0.2	1.2 ± 0.1	1.1 ± 0.2
Specific gravity	1.010 ± 0.001	1.014 ± 0.002	1.009 ± 0.001	1.012 ± 0.002	1.009 ± 0.001	1.009 ± 0.001
Specific gravity (concentrated)	1.037 ± 0.006[b]	1.064 ± 0.001**[b]	1.060 ± 0.002[b]	1.058 ± 0.003*	1.055 ± 0.002	1.060 ± 0.002*

TABLE G2
Hematology and Urinalysis Data for Rats in the 13-Week Inhalation Study of Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Female						
Hematology						
n	10	10	10	10	9	10
Hematocrit (%)	47.5 ± 0.4	47.3 ± 0.3	46.8 ± 0.5	47.2 ± 0.3	48.0 ± 0.7	45.3 ± 0.3**
Hemoglobin (g/dL)	15.7 ± 0.2	15.7 ± 0.2	15.6 ± 0.2	15.6 ± 0.1	15.9 ± 0.2	14.9 ± 0.1**
Erythrocytes (10^6/µL)	8.67 ± 0.08	8.67 ± 0.08	8.67 ± 0.09	8.66 ± 0.05	8.79 ± 0.08	8.34 ± 0.09*
Reticulocytes (10^3/µL)	82.8 ± 36.4	88.6 ± 22.1	71.5 ± 30.5	86.6 ± 33.0	67.2 ± 41.2	96.4 ± 33.3
Mean cell volume (fL)	54.9 ± 0.2	54.4 ± 0.2	54.1 ± 0.2*	54.5 ± 0.2	54.7 ± 0.3	54.5 ± 0.4
Mean cell hemoglobin (pg)	18.1 ± 0.1	18.1 ± 0.1	17.9 ± 0.1	18.0 ± 0.1	18.0 ± 0.1	17.9 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	33.2 ± 0.1	33.1 ± 0.2	33.3 ± 0.2	33.1 ± 0.1	33.1 ± 0.1	32.8 ± 0.1
Platelets (10^3/µL)	589.0 ± 31.3	584.7 ± 11.8	571.1 ± 17.2	585.5 ± 14.3	614.4 ± 25.8	665.5 ± 19.1
Leukocytes (10^3/µL)	6.19 ± 0.43	5.07 ± 0.15	5.55 ± 0.28	5.35 ± 0.23	5.74 ± 0.33	4.84 ± 0.26*
Segmented neutrophils (10^3/µL)	0.66 ± 0.05	0.65 ± 0.09	0.86 ± 0.07	0.67 ± 0.09	0.82 ± 0.12	0.76 ± 0.06
Lymphocytes (10^3/µL)	5.39 ± 0.43	4.26 ± 0.20	4.58 ± 0.29	4.51 ± 0.22	4.81 ± 0.33	3.95 ± 0.22*
Monocytes (10^3/µL)	0.11 ± 0.03	0.10 ± 0.03	0.08 ± 0.02	0.13 ± 0.04	0.10 ± 0.03	0.11 ± 0.03
Eosinophils (10^3/µL)	0.03 ± 0.02	0.05 ± 0.01	0.03 ± 0.02	0.04 ± 0.02	0.02 ± 0.01	0.02 ± 0.01
Urinalysis						
n	10	10	10	10	8	10
Fluoride (µg/16 hr)	4.33 ± 0.17	20.71 ± 1.12**	32.30 ± 1.22**	49.86 ± 4.38**[b]	73.80 ± 4.68**	118.76 ± 5.00**[c]
Glucose (mg/16 hr)	0.12 ± 0.06	0.10 ± 0.03	0.18 ± 0.07	0.09 ± 0.02	0.21 ± 0.04**	0.06 ± 0.01
Protein (mg/16 hr)	1 ± 0	1 ± 0	1 ± 0	1 ± 0	2 ± 0**	2 ± 0**
Volume (mL/16 hr)	11.9 ± 1.5	18.1 ± 2.1*	20.0 ± 3.1*	23.3 ± 1.9**	34.3 ± 3.7**	38.5 ± 3.1**
Volume (mL) (concentrated)	0.5 ± 0.2[b]	0.8 ± 0.2[c]	0.6 ± 0.2[b]	0.6 ± 0.2[d]	0.4 ± 0.2[e]	0.4 ± 0.1
Specific gravity	1.015 ± 0.002	1.009 ± 0.001*	1.010 ± 0.001	1.008 ± 0.001**	1.005 ± 0.001**	1.006 ± 0.000**
Specific gravity (concentrated)	1.049 ± 0.007[b]	1.053 ± 0.013[c]	1.064 ± 0.005[b]	1.062 ± 0.012[d]	1.079 ± 0.011[e]	1.057 ± 0.007

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

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	156 ppm	312 ppm	625 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (automated) (%)	44.0 ± 0.9	45.0 ± 0.7	45.0 ± 1.0	42.1 ± 0.9
Hematocrit (manual) (%)	43.0 ± 0.8	43.5 ± 0.8	43.7 ± 0.9	41.1 ± 0.8
Hemoglobin (g/dL)	14.1 ± 0.3	14.2 ± 0.2	14.5 ± 0.3	13.4 ± 0.3
Erythrocytes (10^6/µL)	8.37 ± 0.13	8.40 ± 0.15	8.54 ± 0.20	7.79 ± 0.26
Reticulocytes (10^6/µL)	0.30 ± 0.03	0.30 ± 0.02	0.30 ± 0.02	0.36 ± 0.08
Nucleated erythrocytes (10^3/µL)	0.12 ± 0.03	0.13 ± 0.02	0.09 ± 0.02	0.27 ± 0.14
Mean cell volume (fL)	52.7 ± 0.8	53.6 ± 0.3	52.8 ± 0.4	54.2 ± 0.9
Mean cell hemoglobin (pg)	16.9 ± 0.3	16.9 ± 0.1	17.0 ± 0.1	17.3 ± 0.3
Mean cell hemoglobin concentration (g/dL)	32.2 ± 0.1	31.6 ± 0.1*	32.2 ± 0.1	31.9 ± 0.1
Platelets (10^3/µL)	535.7 ± 21.9	531.8 ± 8.2	562.0 ± 16.4	520.8 ± 32.4
Leukocytes (10^3/µL)	3.45 ± 0.83	2.89 ± 0.56	2.19 ± 0.13	3.06 ± 0.41
Segmented neutrophils (10^3/µL)	1.76 ± 0.49	1.11 ± 0.21	0.96 ± 0.08	1.11 ± 0.12
Lymphocytes (10^3/µL)	1.66 ± 0.35	1.74 ± 0.36	1.21 ± 0.12	1.89 ± 0.36
Monocytes (10^3/µL)	0.01 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Eosinophils (10^3/µL)	0.02 ± 0.01	0.03 ± 0.02	0.01 ± 0.01	0.05 ± 0.01
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	18.4 ± 0.3	19.7 ± 0.7	19.3 ± 0.5	20.6 ± 0.7*
Creatinine (mg/dL)	0.63 ± 0.02	0.67 ± 0.03	0.59 ± 0.02	0.67 ± 0.02
Sodium (mEq/L)	152 ± 1	152 ± 1	151 ± 1	151 ± 1
Potassium (mEq/L)	5.2 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	5.3 ± 0.1
Chloride (mEq/L)	107 ± 1	106 ± 1	107 ± 0	106 ± 1
Calcium (mg/dL)	11.42 ± 0.15	11.48 ± 0.15	11.78 ± 0.12	11.48 ± 0.15
Phosphorus (mg/dL)	5.9 ± 0.3	6.0 ± 0.3	6.4 ± 0.2	6.4 ± 0.2
Urinalysis				
Glucose (mg/16 hr)	1.5 ± 0.1	1.4 ± 0.1	1.0 ± 0.1**	1.0 ± 0.0**
Protein (mg/16 hr)	19 ± 2	17 ± 2	14 ± 1	27 ± 4
Volume (mL/16 hr)				
Week 63	14.7 ± 2.8	9.0 ± 0.8	8.3 ± 0.6*	12.9 ± 0.8
Week 64	0.7 ± 0.2	0.8 ± 0.2	1.0 ± 0.3	1.4 ± 0.3
Specific gravity				
Week 63	1.022 ± 0.002	1.029 ± 0.001	1.026 ± 0.001	1.023 ± 0.001
Week 64	1.048 ± 0.006[b]	1.045 ± 0.007[b]	1.039 ± 0.008[c]	1.045 ± 0.006[d]

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (automated) (%)	44.4 ± 0.4	44.9 ± 0.5	44.0 ± 0.4	43.9 ± 0.5
Hematocrit (manual) (%)	42.9 ± 0.4	43.4 ± 0.4	42.6 ± 0.4	42.9 ± 0.5
Hemoglobin (g/dL)	14.3 ± 0.2	14.4 ± 0.2	14.1 ± 0.1	14.0 ± 0.2
Erythrocytes (10^6/µL)	7.82 ± 0.07	7.95 ± 0.07	7.81 ± 0.09	7.87 ± 0.08
Reticulocytes (10^6/µL)	0.23 ± 0.02	0.25 ± 0.01	0.25 ± 0.01	0.27 ± 0.01*
Nucleated erythrocytes (10^3/µL)	0.09 ± 0.02	0.07 ± 0.01	0.08 ± 0.01	0.06 ± 0.01
Mean cell volume (fL)	56.9 ± 0.2	56.4 ± 0.2	56.3 ± 0.3	55.8 ± 0.2**
Mean cell hemoglobin (pg)	18.3 ± 0.1	18.1 ± 0.1	18.1 ± 0.1	17.8 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.1 ± 0.2	32.0 ± 0.1	32.0 ± 0.1	32.0 ± 0.1
Platelets (10^3/µL)	463.3 ± 16.9	492.4 ± 11.8	479.8 ± 12.6	491.0 ± 9.8
Leukocytes (10^3/µL)	1.45 ± 0.18	1.51 ± 0.15	1.86 ± 0.28	1.89 ± 0.16*
Segmented neutrophils (10^3/µL)	0.43 ± 0.06	0.47 ± 0.05	0.65 ± 0.10*	0.70 ± 0.09**
Lymphocytes (10^3/µL)	1.00 ± 0.14	1.01 ± 0.11	1.19 ± 0.19	1.16 ± 0.12
Monocytes (10^3/µL)	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/µL)	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	17.6 ± 0.8	17.4 ± 0.6	17.6 ± 0.7	17.7 ± 0.5
Creatinine (mg/dL)	0.67 ± 0.03	0.64 ± 0.02	0.61 ± 0.02	0.62 ± 0.03
Sodium (mEq/L)	148 ± 0	148 ± 1	148 ± 1	147 ± 1
Potassium (mEq/L)	5.2 ± 0.1	5.1 ± 0.1	5.0 ± 0.1	5.2 ± 0.1
Chloride (mEq/L)	100 ± 1	102 ± 1	99 ± 0	100 ± 1
Calcium (mg/dL)	11.55 ± 0.09	11.44 ± 0.17	11.26 ± 0.12	11.18 ± 0.17
Phosphorus (mg/dL)	6.2 ± 0.3	5.9 ± 0.4	6.0 ± 0.3	6.5 ± 0.2
Urinalysis				
Glucose (mg/16 hr)	0.8 ± 0.1	0.8 ± 0.0	0.7 ± 0.1	0.8 ± 0.4
Protein (mg/16 hr)	4 ± 1	4 ± 1	5 ± 1	5 ± 1
Volume (mL/16 hr)				
Week 63	9.6 ± 2.2	6.1 ± 0.5	7.4 ± 0.8	10.1 ± 0.7
Week 64	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Specific gravity				
Week 63	1.019 ± 0.002	1.027 ± 0.002*	1.021 ± 0.002	1.019 ± 0.001
Week 64	1.038 ± 0.012[e]	1.046 ± 0.006[c]	1.060 ± 0.002[e]	1.061 ± 0.007[e]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=6
[c] n=5
[d] n=9
[e] n=3

TABLE G4
Hematology Data for Mice in the 16-Day Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
n	5	5	5	5	5	5
Hematocrit (%)	44.3 ± 0.4	45.2 ± 0.9	44.4 ± 0.4	43.6 ± 0.5	43.5 ± 0.5	43.8 ± 0.3
Hemoglobin (g/dL)	17.7 ± 0.2	18.0 ± 0.4	17.6 ± 0.1	17.0 ± 0.3	17.2 ± 0.3	17.3 ± 0.2
Erythrocytes (10^6/µL)	8.24 ± 0.09	8.46 ± 0.17	8.38 ± 0.06	8.14 ± 0.09	7.94 ± 0.07	8.18 ± 0.03
Reticulocytes (per 5 oil immersion fields)	29.80 ± 2.99	15.20 ± 4.53*	21.80 ± 5.03	21.40 ± 5.77	23.20 ± 4.31	24.00 ± 1.55
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	53.8 ± 0.4	53.6 ± 0.6	53.0 ± 0.3	53.6 ± 0.2	55.0 ± 0.0	53.6 ± 0.2
Mean cell hemoglobin (pg)	21.4 ± 0.2	21.3 ± 0.2	21.0 ± 0.1	20.9 ± 0.2	21.7 ± 0.2	21.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	39.8 ± 0.3	39.9 ± 0.2	39.6 ± 0.1	39.1 ± 0.5	39.6 ± 0.4	39.6 ± 0.3
Platelets (10^3/µL)	805.0 ± 39.9	782.2 ± 16.7	759.8 ± 4.1	778.0 ± 24.1	815.6 ± 70.7	799.4 ± 34.8
Leukocytes (10^3/µL)	1.62 ± 0.26	1.54 ± 0.41	1.92 ± 0.59	1.24 ± 0.38	1.10 ± 0.30	1.90 ± 0.23
Segmented neutrophils (10^3/µL)	0.48 ± 0.09	0.22 ± 0.04	0.72 ± 0.35	0.26 ± 0.08	0.17 ± 0.08	0.52 ± 0.08
Lymphocytes (10^3/µL)	1.10 ± 0.30	1.29 ± 0.35	1.16 ± 0.26	0.92 ± 0.33	0.90 ± 0.23	1.33 ± 0.20
Monocytes (10^3/µL)	0.04 ± 0.02	0.03 ± 0.02	0.05 ± 0.02	0.05 ± 0.03	0.03 ± 0.01	0.05 ± 0.03
Eosinophils (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Female						
n	4	5	5	5	5	5
Hematocrit (%)	44.6 ± 0.7	43.8 ± 0.8	43.5 ± 0.6	43.3 ± 0.6	44.3 ± 0.3	43.3 ± 0.4
Hemoglobin (g/dL)	17.5 ± 0.3	17.2 ± 0.3	17.0 ± 0.3	17.1 ± 0.2	17.4 ± 0.1	17.0 ± 0.1
Erythrocytes (10^6/µL)	8.24 ± 0.12	8.16 ± 0.15	7.95 ± 0.11	8.08 ± 0.14	8.22 ± 0.06	8.07 ± 0.07
Reticulocytes (per 5 oil immersion fields)	25.00 ± 1.91	29.00 ± 3.39	21.40 ± 3.16	15.00 ± 2.02	29.40 ± 3.72	20.20 ± 4.18
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	54.3 ± 0.3	53.6 ± 0.4	54.6 ± 0.2	53.6 ± 0.2	53.8 ± 0.2	53.8 ± 0.2
Mean cell hemoglobin (pg)	21.2 ± 0.1	21.1 ± 0.2	21.4 ± 0.2	21.2 ± 0.3	21.1 ± 0.1	21.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	39.1 ± 0.1	39.3 ± 0.1	39.2 ± 0.2	39.6 ± 0.4	39.2 ± 0.3	39.3 ± 0.1
Platelets (10^3/µL)	797.3 ± 26.7	764.4 ± 32.2	734.2 ± 25.6	775.0 ± 27.0	785.6 ± 30.2	797.6 ± 24.9
Leukocytes (10^3/µL)	0.85 ± 0.22	0.76 ± 0.08	0.64 ± 0.13	0.94 ± 0.18	0.98 ± 0.22	0.86 ± 0.16
Segmented neutrophils (10^3/µL)	0.30 ± 0.04	0.14 ± 0.03	0.24 ± 0.04	0.29 ± 0.13	0.38 ± 0.18	0.13 ± 0.02
Lymphocytes (10^3/µL)	0.55 ± 0.21	0.62 ± 0.07	0.39 ± 0.12	0.64 ± 0.12	0.59 ± 0.07	0.72 ± 0.15
Monocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE G5
Hematology and Urinalysis Data for Mice in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male						
Hematology						
n	10	10	10	10	10	10
Hematocrit (%)	50.6 ± 0.4	50.0 ± 0.5	50.2 ± 0.4	50.4 ± 0.7	47.9 ± 0.4**	46.3 ± 0.5**
Hemoglobin (g/dL)	17.0 ± 0.2	16.7 ± 0.1	16.7 ± 0.1	16.7 ± 0.1	16.0 ± 0.1**	15.4 ± 0.2**
Erythrocytes (10^6/µL)	10.51 ± 0.10	10.35 ± 0.09	10.42 ± 0.11	10.44 ± 0.13	10.03 ± 0.08**	9.65 ± 0.14**
Reticulocytes (10^3/µL)	70 ± 43	93 ± 45	108 ± 135	80 ± 24	75 ± 27	102 ± 115
Howell-Jolly bodies (% erythrocytes)	0.1 ± 0.0	0.0 ± 0.0	0.2 ± 0.0	0.1 ± 0.	0.1 ± 0.0	0.2 ± 0.0
Mean cell volume (fL)	48.0 ± 0.3	48.4 ± 0.2	48.1 ± 0.2	48.2 ± 0.4	47.9 ± 0.3	48.0 ± 0.4
Mean cell hemoglobin (pg)	16.1 ± 0.1	16.2 ± 0.1	16.0 ± 0.1	16.0 ± 0.1	15.9 ± 0.1	16.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.1	33.4 ± 0.2	33.3 ± 0.2	33.1 ± 0.2	33.4 ± 0.2	33.3 ± 0.1
Platelets (10^3/µL)	961.6 ± 16.8	932.9 ± 20.3	969.7 ± 25.4	993.5 ± 18.9	996.2 ± 18.3	1,017.3 ± 27.7
Leukocytes (10^3/µL)	4.15 ± 0.44	3.36 ± 0.29	3.16 ± 0.28	3.71 ± 0.31	2.89 ± 0.34	3.16 ± 0.39
Segmented neutrophils (10^3/µL)	0.54 ± 0.08	0.49 ± 0.08	0.51 ± 0.12	0.67 ± 0.12	0.65 ± 0.12	0.82 ± 0.13
Lymphocytes (10^3/µL)	3.52 ± 0.38	2.77 ± 0.25	2.57 ± 0.27	2.93 ± 0.26	2.14 ± 0.28**	2.25 ± 0.31**
Monocytes (10^3/µL)	0.07 ± 0.02	0.07 ± 0.02	0.04 ± 0.01	0.08 ± 0.01	0.07 ± 0.01	0.05 ± 0.01
Eosinophils (10^3/µL)	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.02
Urinalysis						
n	10	10	9	10	10	10
Fluoride (µg/16 hr)	1.35 ± 0.10[b]	19.68 ± 3.15**[c]	18.06 ± 4.66**[d]	25.94 ± 3.62**	56.48 ± 11.66**	66.20 ± 6.15**
Glucose (mg/16 hr)	0.16 ± 0.01	0.13 ± 0.02	0.09 ± 0.02	0.13 ± 0.01	0.12 ± 0.03	0.16 ± 0.02
Protein (mg/16 hr)	1 ± 0	1 ± 0	1 ± 0	1 ± 0	2 ± 0	2 ± 0
Volume (mL/16 hr)	2.4 ± 0.5	1.2 ± 0.3	0.8 ± 0.2	2.0 ± 0.4	5.9 ± 1.2	5.6 ± 0.8
Specific gravity	1.027 ± 0.002	1.038 ± 0.004[b]	1.039 ± 0.004	1.025 ± 0.002	1.013 ± 0.002**	1.015 ± 0.003**

TABLE G5
Hematology and Urinalysis Data for Mice in the 13-Week Inhalation Study of Tetrafluoroethylene (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	49.1 ± 0.5	48.8 ± 0.3	48.4 ± 0.3	49.5 ± 0.3	48.3 ± 0.5	47.1 ± 0.5**
Hemoglobin (g/dL)	16.4 ± 0.2	16.4 ± 0.1	16.3 ± 0.1	16.3 ± 0.1	16.2 ± 0.2	15.8 ± 0.1**
Erythrocytes (10^6/µL)	10.20 ± 0.09	10.27 ± 0.07	10.16 ± 0.07	10.29 ± 0.06	10.17 ± 0.10	9.93 ± 0.11
Reticulocytes (10^3/µL)	111 ± 40	113 ± 39	90 ± 42	108 ± 61	132 ± 51	117 ± 52
Howell-Jolly bodies (% erythrocytes)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Mean cell volume (fL)	48.1 ± 0.2	47.6 ± 0.3	47.7 ± 0.3	48.1 ± 0.3	47.6 ± 0.2	47.4 ± 0.3
Mean cell hemoglobin (pg)	16.1 ± 0.1	16.0 ± 0.1	16.0 ± 0.1	15.9 ± 0.1	15.9 ± 0.1	15.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.2	33.7 ± 0.1	33.6 ± 0.1	33.0 ± 0.2	33.5 ± 0.2	33.6 ± 0.1
Platelets (10^3/µL)	899.1 ± 24.7	893.5 ± 14.5	901.0 ± 17.2	868.1 ± 17.4	911.2 ± 20.2	945.1 ± 21.2
Leukocytes (10^3/µL)	3.80 ± 0.25	3.18 ± 0.14*	3.17 ± 0.23*	3.36 ± 0.26	2.62 ± 0.30**	2.97 ± 0.21**
Segmented neutrophils (10^3/µL)	0.59 ± 0.08	0.50 ± 0.06	0.30 ± 0.03*	0.44 ± 0.05	0.39 ± 0.09	0.42 ± 0.07
Lymphocytes (10^3/µL)	3.11 ± 0.22	2.62 ± 0.11	2.78 ± 0.24	2.76 ± 0.21	2.15 ± 0.21**	2.41 ± 0.19**
Monocytes (10^3/µL)	0.03 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.07 ± 0.02	0.06 ± 0.02	0.10 ± 0.03
Eosinophils (10^3/µL)	0.07 ± 0.02	0.03 ± 0.01	0.05 ± 0.02	0.08 ± 0.02	0.02 ± 0.01	0.04 ± 0.01
Urinalysis						
Fluoride (µg/16 hr)	1.01 ± 0.07[b]	7.79 ± 2.20**	12.05 ± 2.73**	8.74 ± 1.38**	19.34 ± 3.65**[b]	23.94 ± 1.72**
Glucose (mg/16 hr)	0.12 ± 0.02	0.13 ± 0.02	0.12 ± 0.02	0.13 ± 0.02	0.18 ± 0.03	0.22 ± 0.02*
Protein (mg/16 hr)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	1 ± 0
Volume (mL/16 hr)	1.1 ± 0.2	1.2 ± 0.3	1.0 ± 0.1	1.1 ± 0.2	3.9 ± 0.8*	6.4 ± 1.0**
Specific gravity	1.025 ± 0.003	1.025 ± 0.003	1.027 ± 0.003	1.022 ± 0.002	1.012 ± 0.002**	1.008 ± 0.001**

* Statistically different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error; statistical tests were performed on unrounded data.
[b] n=9
[c] n=7
[d] n=5

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	1,250 ppm	5,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	329 ± 5	343 ± 5	333 ± 4	301 ± 5**
R. cauda	0.170 ± 0.004	0.175 ± 0.004	0.161 ± 0.004	0.161 ± 0.005
R. epididymis	0.472 ± 0.008	0.479 ± 0.010	0.469 ± 0.010	0.477 ± 0.009
R. testis	1.384 ± 0.023	1.412 ± 0.029	1.375 ± 0.031	1.417 ± 0.020
Epididymal spermatozoal parameters				
Abnormal sperm (%)	0.680 ± 0.085	0.480 ± 0.080	0.640 ± 0.088	0.600 ± 0.107
Motility (%)	82.22 ± 1.29	80.60 ± 1.63	79.42 ± 1.96	80.21 ± 0.76
Concentration (10^6/g cauda epididymal tissue)	452 ± 25	445 ± 21	408 ± 34	426 ± 20

** Significantly different ($P \leq 0.01$) from the control group by Williams' test
[a] Data are presented as mean ± standard error. Differences from the control group were not significant by Dunnett's test (organ weights) or Dunn's test (epididymal spermatozoal parameters).

TABLE H2
Summary of Estrous Cycle Characterization for Female Rats in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	1,250 ppm	5,000 ppm
n	10	10	10	10
Necropsy body wt (g)	189 ± 5	198 ± 3	194 ± 4	173 ± 4*
Estrous cycle length (days)	4.70 ± 0.21	5.10 ± 0.18	5.00 ± 0.27[b]	5.43 ± 0.43[c]
Estrous stage (% of cycle)				
Diestrus	38.6	42.9	35.7	51.4
Proestrus 14.3	12.9	11.4	21.4	
Estrus	21.4	27.1	27.1	14.3
Metestrus 24.3	17.1	25.7	12.9	
Unclear diagnosis	1.4	0.0	0.0	0.0

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed groups do not differ significantly from the control group in the relative length of time spend in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.
[c] Estrous cycle was longer than 12 days or unclear in 3 of 10 animals.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	1,250 ppm	5,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	36.2 ± 0.7	35.3 ± 0.5	34.6 ± 0.5*	32.1 ± 0.5**
R. cauda	0.016 ± 0.001	0.017 ± 0.001	0.016 ± 0.000	0.014 ± 0.000*
R. epididymis	0.049 ± 0.002	0.048 ± 0.001	0.047 ± 0.001	0.045 ± 0.002
R. testis	0.117 ± 0.003	0.117 ± 0.002	0.118 ± 0.001	0.112 ± 0.003
Epididymal spermatozoal parameters				
Abnormal sperm (%)	1.100 ± 0.141[b]	0.920 ± 0.108	1.360 ± 0.168	0.860 ± 0.116
Motility (%)	75.36 ± 4.15	73.56 ± 2.02	70.08 ± 1.26*	69.89 ± 2.60
Concentration (10^6/g cauda epididymal tissue)	976 ± 134[b]	1,010 ± 62	921 ± 72	947 ± 101

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (body weights), Dunnett's test (organ weights), or Dunn's test (epididymal spermatozoal parameters)
** Significantly different ($P \leq 0.01$) from the control group by Williams' test
[a] Data are presented as mean ± standard error.
[b] n=8

TABLE H4
Summary of Estrous Cycle Characterization for Female Mice in the 13-Week Inhalation Study of Tetrafluoroethylene [a]

	0 ppm	312 ppm	1,250 ppm	5,000 ppm
n	10	10	10	10
Necropsy body wt (g)	31.5 ± 0.7	30.8 ± 0.8	29.8 ± 0.6	29.2 ± 0.5
Estrous cycle length (days)	4.33 ± 0.24[b]	4.88 ± 0.23[c]	4.56 ± 0.18[b]	5.22 ± 0.28[b]
Estrous stage (% of cycle)				
Diestrus	34.3	42.9	34.3	31.4
Proestrus 18.6	11.4	22.9	20.0	
Estrus	28.6	30.0	22.9	27.1
Metestrus 18.6	15.7	20.0	21.4	

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for body weights were not significant by Dunnett's test. Differences from the control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed groups do not differ significantly from the control group in the relative length of time spend in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.
[c] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF TETRAFLUOROETHYLENE

Tetrafluoroethylene was obtained from SCM Specialty Chemicals (Gainesville, FL) in one lot (10271), which was used for the identity and purity analyses conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Tetrafluoroethylene was also obtained from ICI Americas, Inc. (Bayonne, NJ), in five lots. The study laboratory assigned a lot number to each shipment of as many as 12 cylinders. Lot 12017-8 was used during the 16-day studies and during most of the 13-week studies; lot 12017-77 was used during the remainder of the 13-week studies; and lots 12438-6, 12438-79, and 12438-92 were used during the 2-year studies. Identity and purity analyses were also conducted by the study laboratory on each lot used during the studies. Reports on analyses performed in support of the tetrafluoroethylene studies are on file at the National Institute of Environmental Health Sciences.

Each lot of the chemical, a colorless gas, was identified as tetrafluoroethylene by the analytical chemistry or study laboratory using infrared spectroscopy. The infrared spectrum for each lot was consistent with that expected for the structure of tetrafluoroethylene (Figure I1).

The purity of lot 10271 was determined by the analytical chemistry laboratory using gas chromatography. The purity of lots 12017-8, 12017-77, 12438-6, 12438-79, and 12438-92 was determined by the study laboratory using gas chromatography. Gas chromatography of each lot was conducted using a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute, a 60/80 Carbopack B/1% glass column, and an oven temperature program of 35 ° C for 5 minutes, then 35° to 200° C at 10° C per minute.

Gas chromatography of lot 10271 indicated one major peak and one impurity with an area greater than or equal to 0.1% relative to the major peak. In addition, analysis for *d*-limonene, which is added to tetrafluoroethylene as a stabilizer, was conducted by the analytical chemistry laboratory using gas chromatography with the same system as that used for the purity analyses but with a 10% SP-2100 on 100/120 Supelcoport glass column and an oven temperature program of 50 ° C for 5 minutes, then 50° to 250° C at 10° C per minute. The sample contained 0.03% ± 0.00% *d*-limonene. Gas chromatography conducted by the study laboratory for each cylinder of lots 12017-8 and 12017-77 indicated that perfluorocyclobutane, the most abundant dimer produced during tetrafluoroethylene decomposition, was present at concentrations less than or equal to 462 ppm and 2,604 ppm for the 16-day and 13-week studies, respectively. For lots 12438-6, 12438-79, and 12438-92, gas chromatography indicated peaks for perfluorocyclobutane with areas less than or equal to 1.21% relative to the major peak. Gas chromatography conducted by the study laboratory for each cylinder of lots 12017-8 and 12017-77 indicated that *d*-limonene was present at concentrations less than or equal to 2,837 ppm for the 13-week studies. During the 2-year studies, gas chromatography of lots 12438-6, 12438-79, and 12438-92 indicated peaks for *d*-limonene with areas less than or equal to 0.56% relative to the major peak. The manufacturer indicated that trifluoroethylene, methylene fluoride, vinyl fluoride, and vinylidene fluoride were also present as impurities at concentrations less than or equal to 1.7 ppm. The overall purities of lots 12017-8, 12017-77, and 12438-92 were determined to be greater than 99%. The overall purities of lots 12438-6 and 12438-79 were determined to be greater than 98%.

The manufacturer indicated that tetrafluoroethylene would be stable for up to 1 year when stored in the original containers at room temperature. To ensure stability, the bulk chemical was stored in the original metal cylinders at 10 ° to 22° C. Stability was monitored during the 13-week and 2-year studies using the same gas chromatography system used for the purity analyses. The relative concentrations of perfluorocyclobutane were expected to increase due to the slow dimerization of tetrafluoroethylene, and therefore the gas cylinders were monitored for this dimer as well as for *d*-limonene during the 2-year studies. Two cylinders from lot 12438-6 contained higher concentrations of these compounds than canisters from the same lot that were analyzed earlier in the studies. One of these two cylinders, which contained 1.21% perfluorocyclobutane and 0.56% *d*-limonene, was replaced immediately after gas chromatographic analysis was performed; it is not known if the dimer formed in the canister due to degradation of tetrafluoroethylene or was present as an impurity at receipt. Stability was generally considered acceptable throughout the studies.

VAPOR GENERATION AND EXPOSURE SYSTEM

A diagram of the tetrafluoroethylene generation and delivery system is shown in Figure I2. Because tetrafluoroethylene is a gas at room temperature, the system incorporated gas distribution under regulated pressure with individual adjustment and monitoring of the chemical flow rate to each chamber. Tetrafluoroethylene was taken directly from the cylinder in which it was shipped. The output pressure from the cylinder was regulated to 20 psi with a two-stage regulator. The gas was passed through a main exposure pneumatic valve, a check valve, and a filter to a manifold of five (16-day and 13-week studies) or six (2-year studies) flow meters with integral metering valves. The gas was metered to each exposure chamber through these flow meters, which were monitored by a pressure gauge at the manifold. A three-way solenoid valve was located in the gas delivery line to each exposure chamber. This valve and a nitrogen inlet valve just downstream from the main exposure valve allowed the system to be purged with nitrogen at the end of each exposure period. A sample line was included downstream from each gas cylinder. All equipment that came in contact with the tetrafluoroethylene gas was stainless steel, polytetrafluoroethylene, Viton® (E.I. DuPont de Nemours, Wilmington, DE), or glass.

Stainless-steel chambers designed at Battelle Pacific Northwest Laboratories were used for all studies (Figure I3). The total volume of 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 aerosol or vapor concentrations could be maintained throughout the chamber when the catch pans were in position, provided the aerosol or vapor was uniformly mixed with dilution air before entering the chamber. A diagram of the 16-day and 13-week exposure suite is shown in Figure I4, and a diagram of the 2-year exposure suite is shown in Figure I5.

VAPOR CONCENTRATION MONITORING

A diagram of the tetrafluoroethylene concentration monitoring system used in all studies is shown in Figure I6. The concentrations of tetrafluoroethylene were monitored using an on-line gas chromatograph with a flame ionization detector, an 80/100 Porapack Q nickel column, and a nitrogen carrier gas at a flow rate of 22 mL/minute. Samples were drawn and analyzed from each exposure chamber, the control chamber, the exposure suite, and an on-line standard using an automatic 8-port (16-day and 13-week studies) or 12-port (2-year studies) sample valve. Certified standards of tetrafluoroethylene in nitrogen (Byrne Specialty Gases, Inc., Seattle, WA; MG Industries Scientific Gases, Los Angeles, CA; Phoenix Distributors, Inc., Los Angeles, CA) were used to perform the absolute calibration of the on-line gas chromatograph and to check instrument drift throughout the exposure periods. Summaries of the chamber concentrations during the studies are presented in Tables I1 through I3. The monthly mean exposure concentrations for the 2-year studies are presented in Figures I7 through I15.

CHAMBER ATMOSPHERE CHARACTERIZATION

The times for the exposure concentration 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. During the 16-day studies, T_{90} was approximately 12 minutes and T_{10} was approximately 9 minutes with and without animals in the chambers. During the 13-week studies, T_{90} was 11 minutes with animals in the chambers and ranged from 11 to 14 minutes without animals; T_{10} ranged from 9 to 11 minutes with and without animals in the chambers. During the 2-year studies, T_{90} ranged from 8 to 10 minutes without animals in the chambers and from 10 to 16 minutes with animals present; T_{10} ranged from 7 to 9 minutes without animals and from 9 to 12 minutes with animals. The T_{90} value used for all studies was 12 minutes.

Uniformity of tetrafluoroethylene concentration in the exposure chambers was measured prior to the start of all studies, once during the 16-day and 13-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 8-port (16-day and 13-week studies) or 12-port (2-year studies) sample valve disabled to allow continuous monitoring from a single input line. Uniformity of exposure concentrations in all chambers was acceptable.

The persistence of tetrafluoroethylene in the 1,250 ppm exposure chamber after shutting off the system was monitored without animals before the 2-year studies began and with animals present during the 2-year studies. The concentration of

tetrafluoroethylene in the exposure chamber fell rapidly to less than 1% of the beginning concentration within 20 minutes. Tetrafluoroethylene concentrations in the building exhaust and room air were also monitored during all studies.

Information supplied by the manufacturer indicated that all cylinders contained *d*-limonene as a stabilizer. *d*-Limonene and perfluorocyclobutane are less volatile than tetrafluoroethylene and concentrate in the cylinder as the tetrafluoroethylene is removed. Cylinder usage was regulated to minimize concentrations of these chemicals in the exposure chambers; a maximum of 80% of the tetrafluoroethylene in each cylinder was used. Gas chromatography of chamber samples did not indicate any impurities other than perfluorocyclobutane and *d*-limonene. Concurrent analysis of cylinder headspace and chamber samples for perfluorocyclobutane demonstrated that chamber concentrations of perfluorocyclobutane matched those in the cylinder headspace. The contents of selected used cylinders were analyzed for *d*-limonene and perfluorocyclobutane. The results indicated that tetrafluoroethylene was stable during generation and in the exposure chambers and that perfluorocyclobutane was not formed in significant quantities by the generation system. As expected, the headspace concentrations of *d*-limonene and perfluorocyclobutane in the cylinders increased as tetrafluoroethylene was removed.

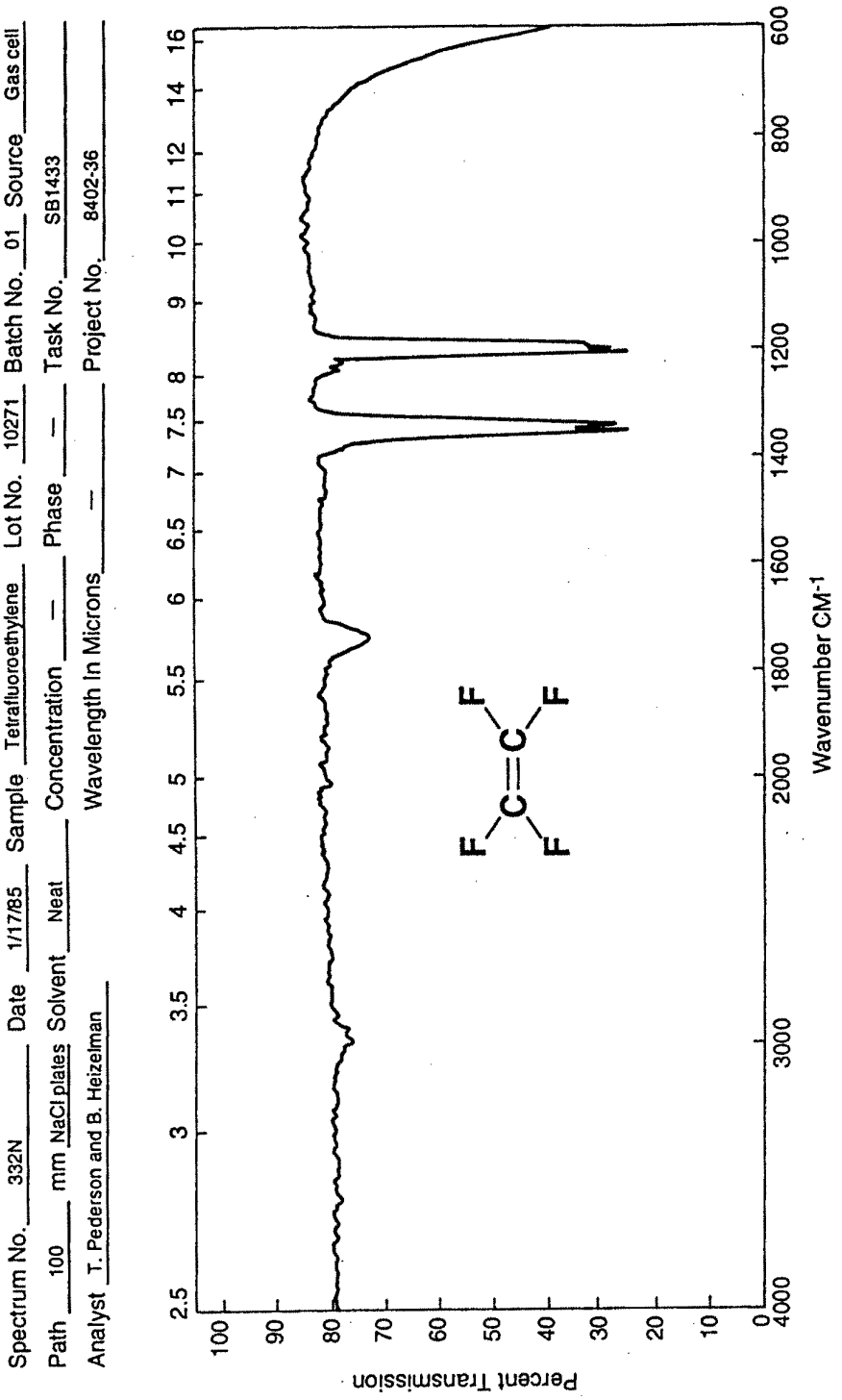

FIGURE I1
Infrared Absorption Spectrum of Tetrafluoroethylene

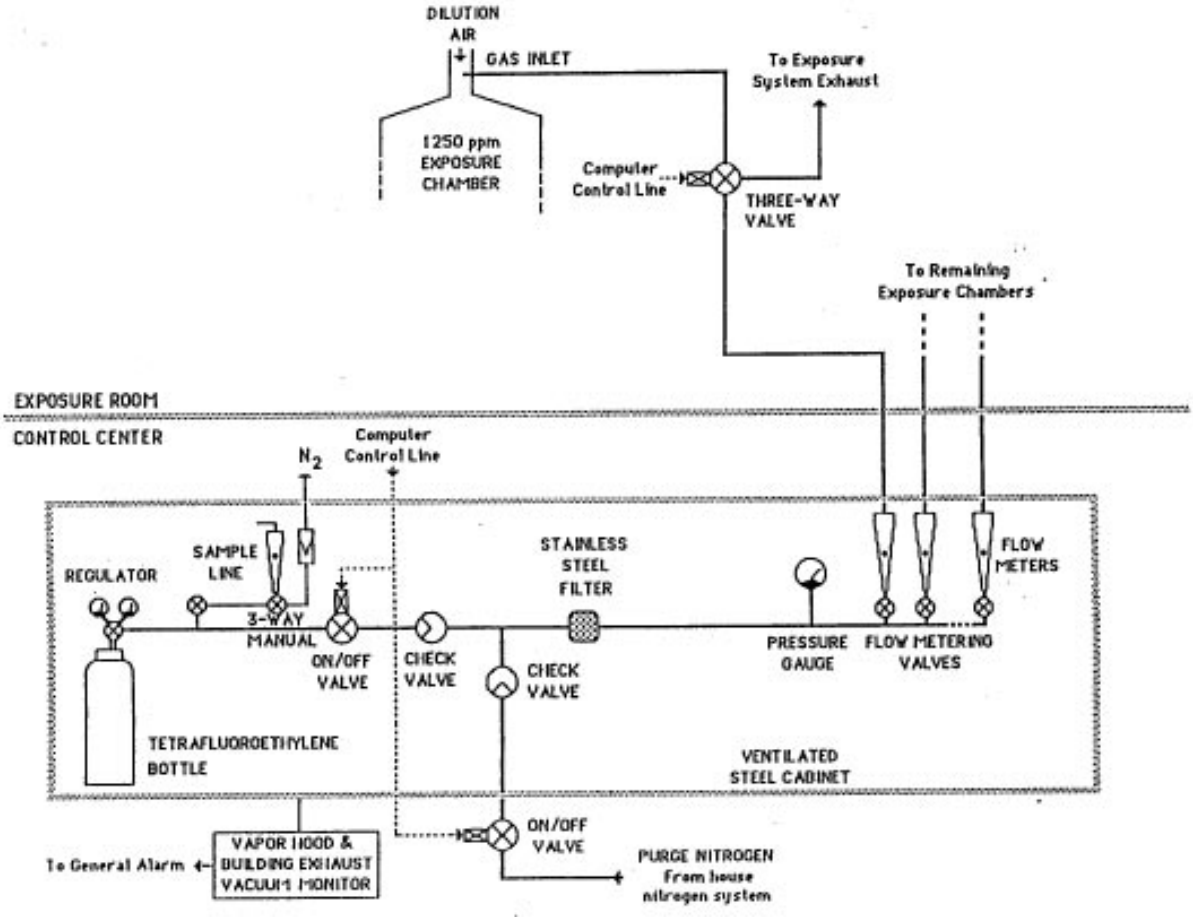

FIGURE I2
Schematic of the Generation and Delivery System

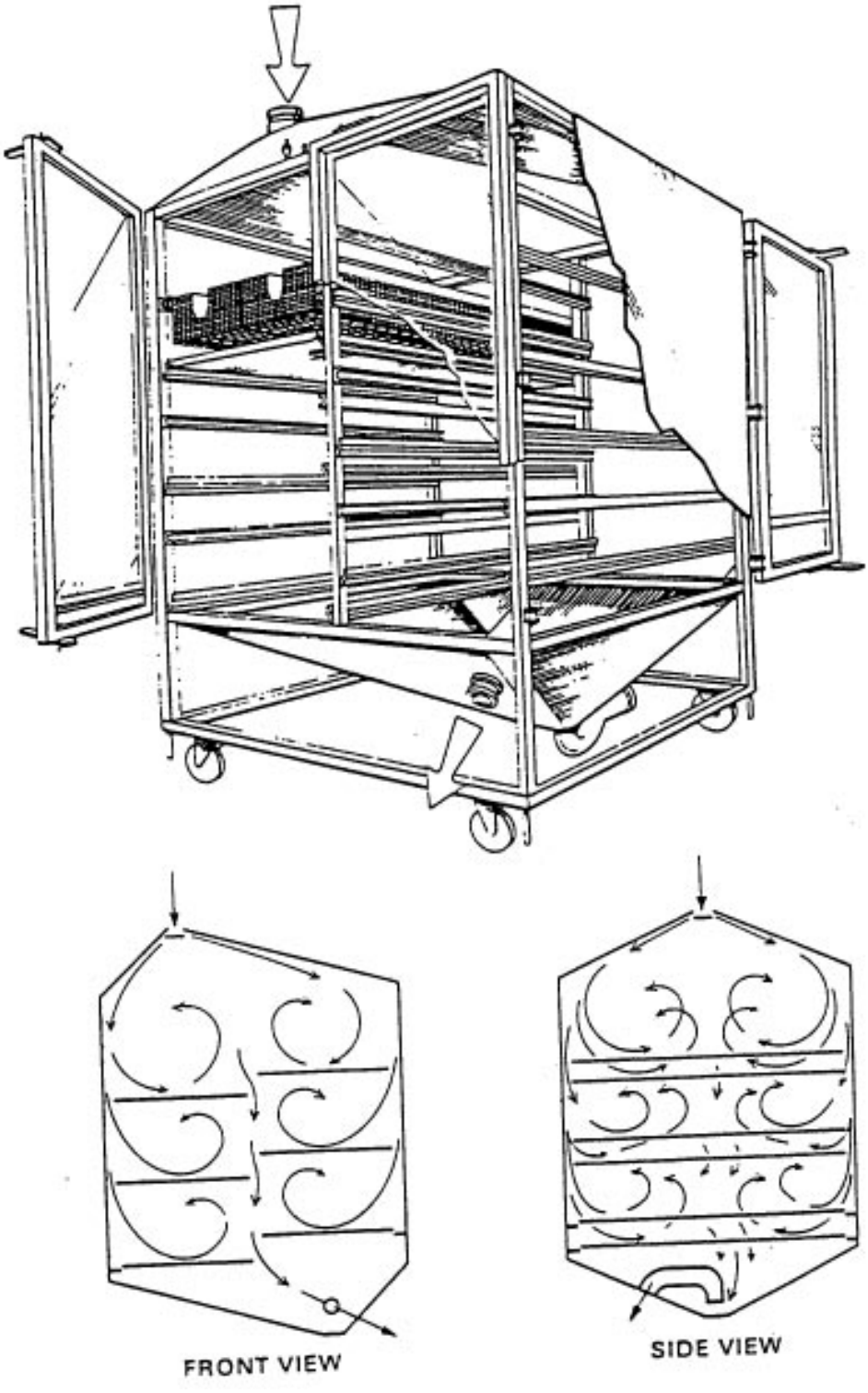

FIGURE I3
Schematic of the Exposure Chambers

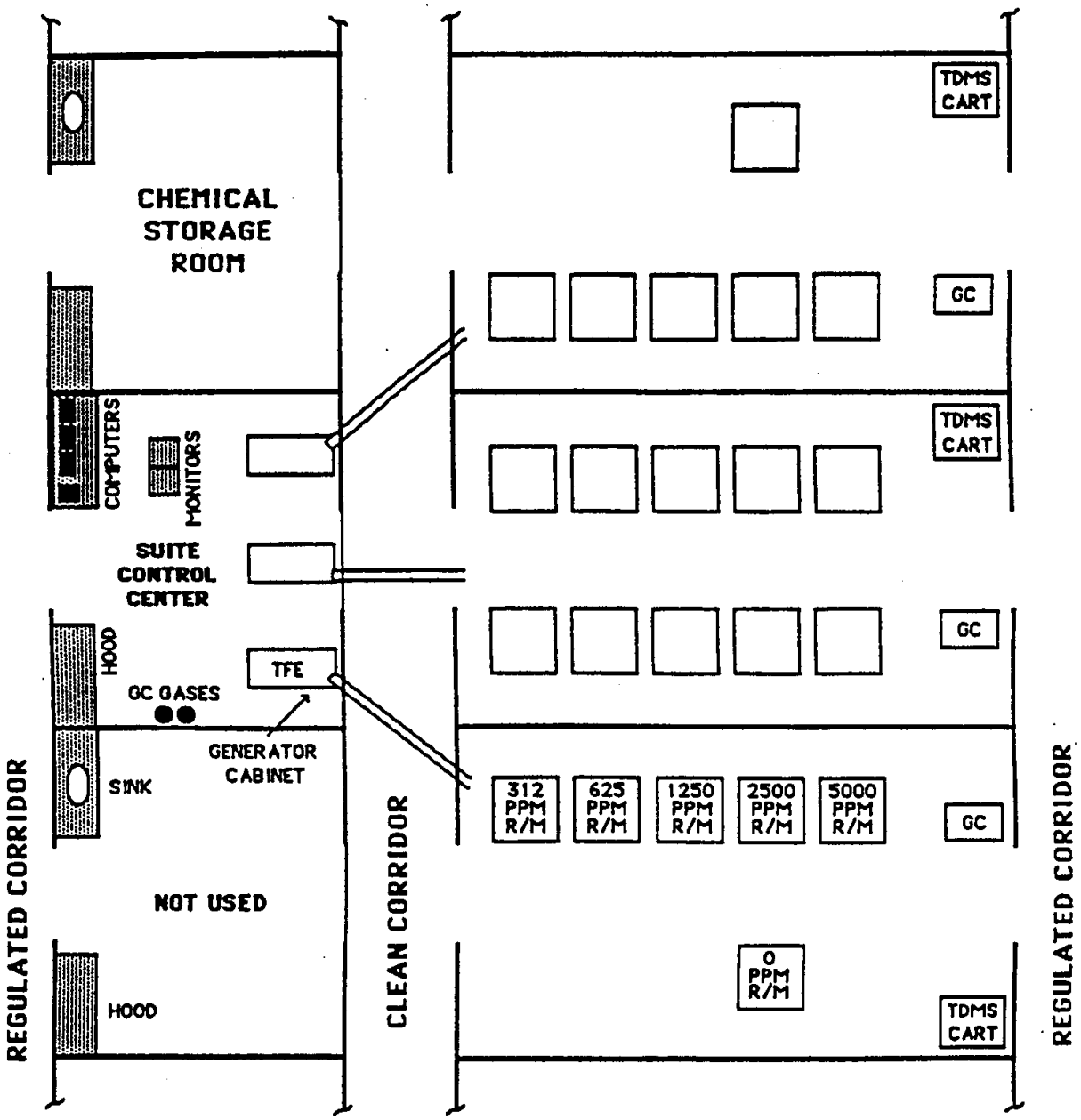

FIGURE I4
16-Day and 13-Week Inhalation Suite

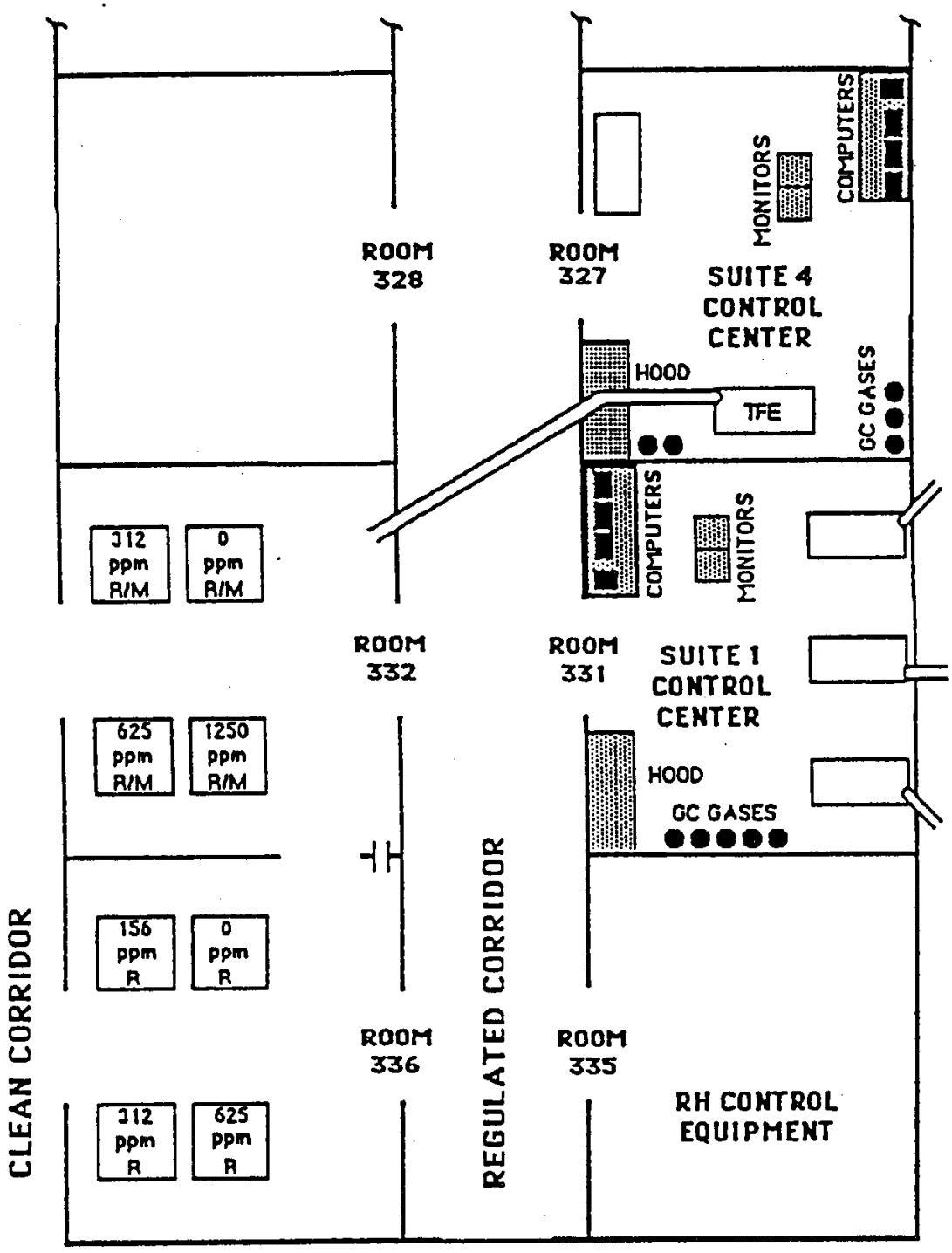

FIGURE I5
2-Year Inhalation Suite

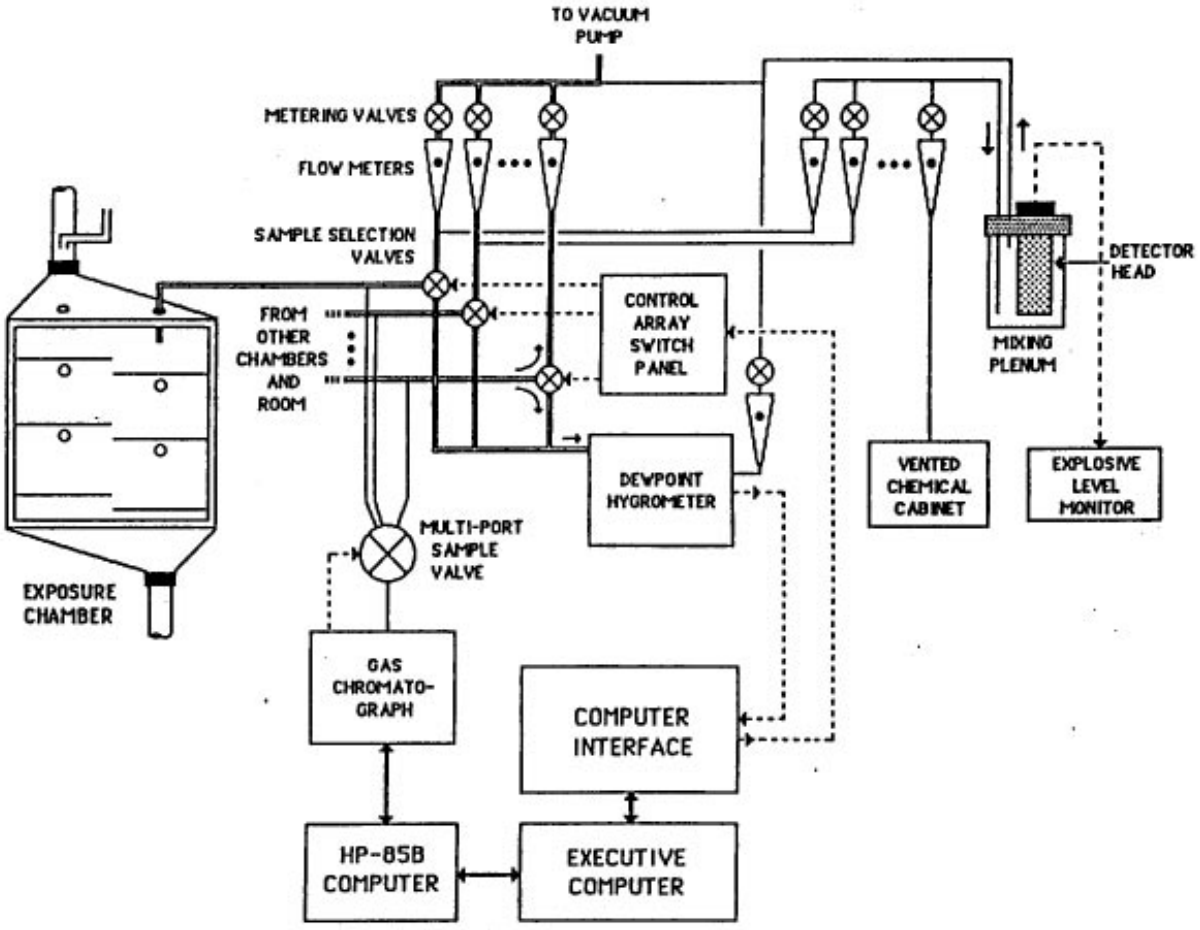

FIGURE I6
Schematic of the Concentration Monitoring System

TABLE I1
Summary of Chamber Concentrations in the 16-Day Inhalation Studies of Tetrafluoroethylene

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
312	250	312 ± 6.21
625	250	621 ± 9.66
1,250	252	1,250 ± 19.2
2,500	253	2,500 ± 33.9
5,000	255	4,990 ± 6.19
Mouse Chambers		
312	250	312 ± 5.60
625	249	622 ± 9.40
1,250	252	1,260 ± 19.2
2,500	253	2,500 ± 34.1
5,000	255	4,990 ± 59.4

[a] Mean ± standard deviation

TABLE I2
Summary of Chamber Concentrations in the 13-Week Inhalation Studies of Tetrafluoroethylene

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
312	1,107	314 ± 9.3
625	1,106	628 ± 16
1,250	1,146	1,260 ± 40
2,500	1,154	2,520 ± 77
5,000	1,149	5,050 ± 136
Mouse Chambers		
312	1,104	314 ± 9.4
625	1,103	627 ± 16
1,250	1,145	1,260 ± 35
2,500	1,153	2,520 ± 67
5,000	1,147	5,050 ± 128

[a] Mean ± standard deviation

TABLE I3
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Tetrafluoroethylene

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Male Rat Chambers		
156	6,470	155 ± 7
312	6,523	312 ± 12
625	6,533	623 ± 24
Female Rat Chambers		
312	6,106	312 ± 10
625	6,146	625 ± 20
1,250	6,154	1,250 ± 43
Mouse Chambers		
312	5,577	311 ± 10
625	5,619	625 ± 19
1,250	5,633	1,250 ± 42

[a] Mean ± standard deviation

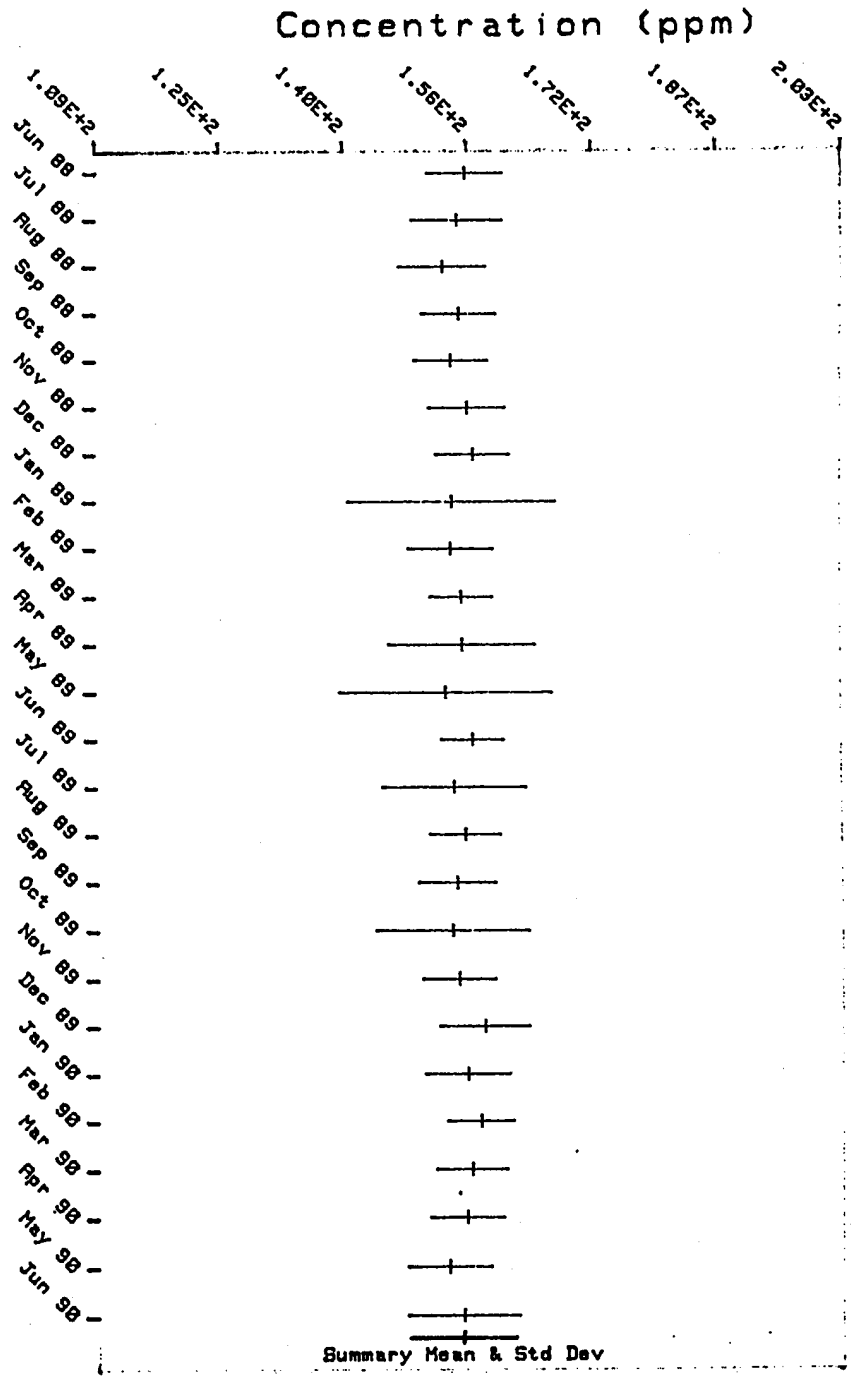

FIGURE I7
Monthly Mean Concentrations and Standard Deviations in the 156 ppm Tetrafluoroethylene Male Rat Exposure Chamber for the 2-Year Study

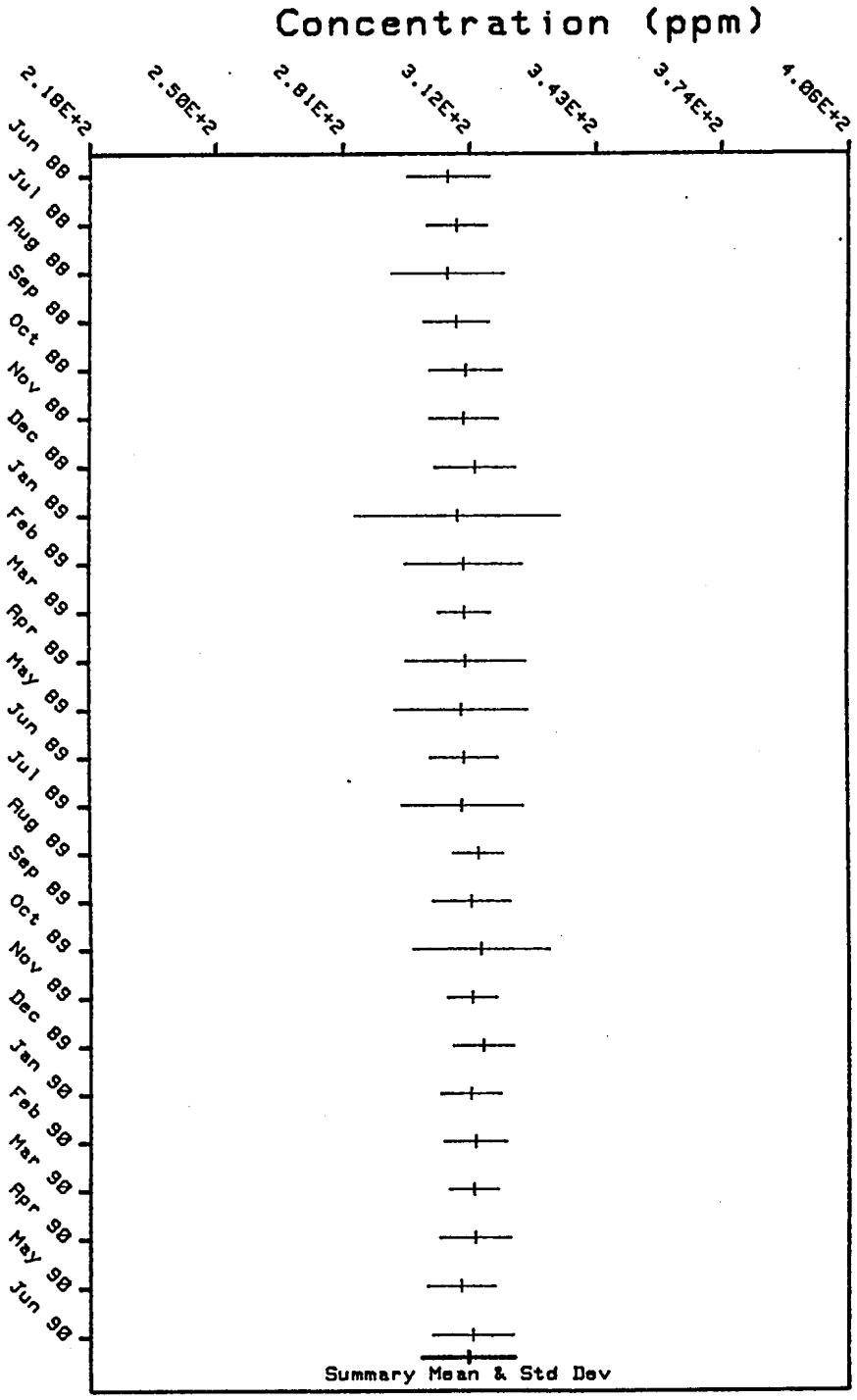

FIGURE I8
Monthly Mean Concentrations and Standard Deviations in the 312 ppm Tetrafluoroethylene Male Rat Exposure Chamber for the 2-Year Study

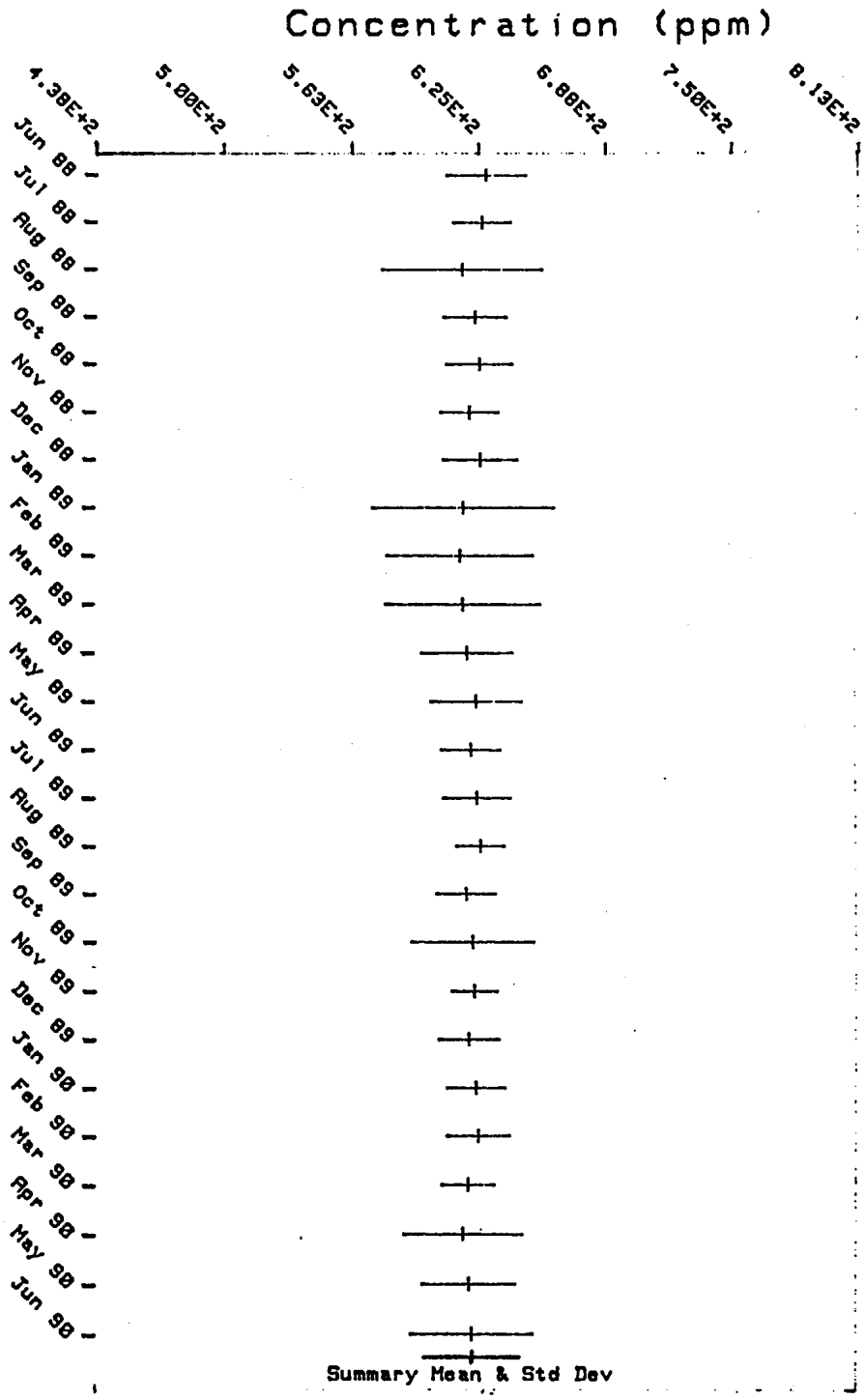

FIGURE I9
Monthly Mean Concentrations and Standard Deviations in the 625 ppm Tetrafluoroethylene Male Rat Exposure Chamber for the 2-Year Study

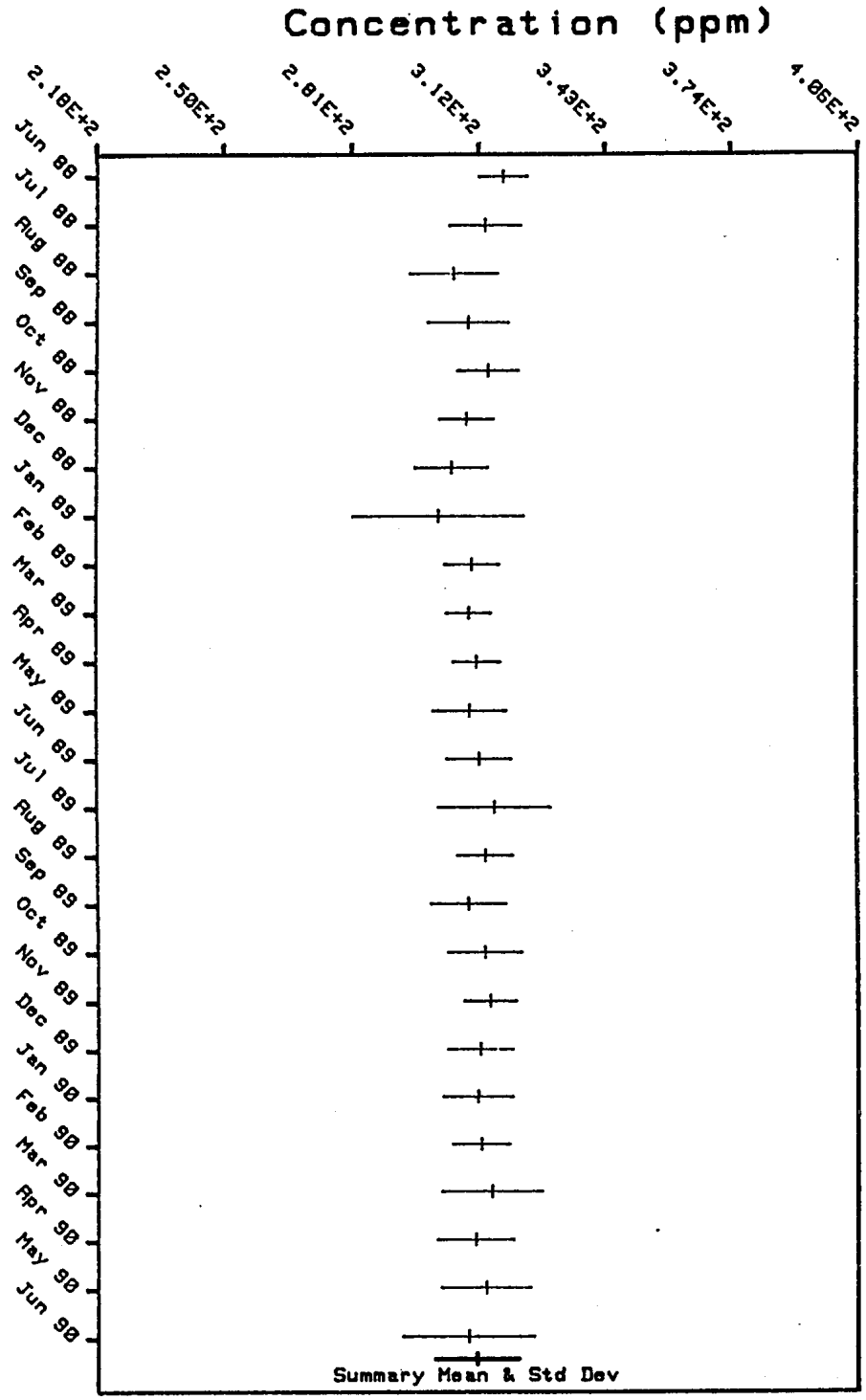

FIGURE I10
Monthly Mean Concentrations and Standard Deviations in the 312 ppm Tetrafluoroethylene Female Rat Exposure Chamber for the 2-Year Study

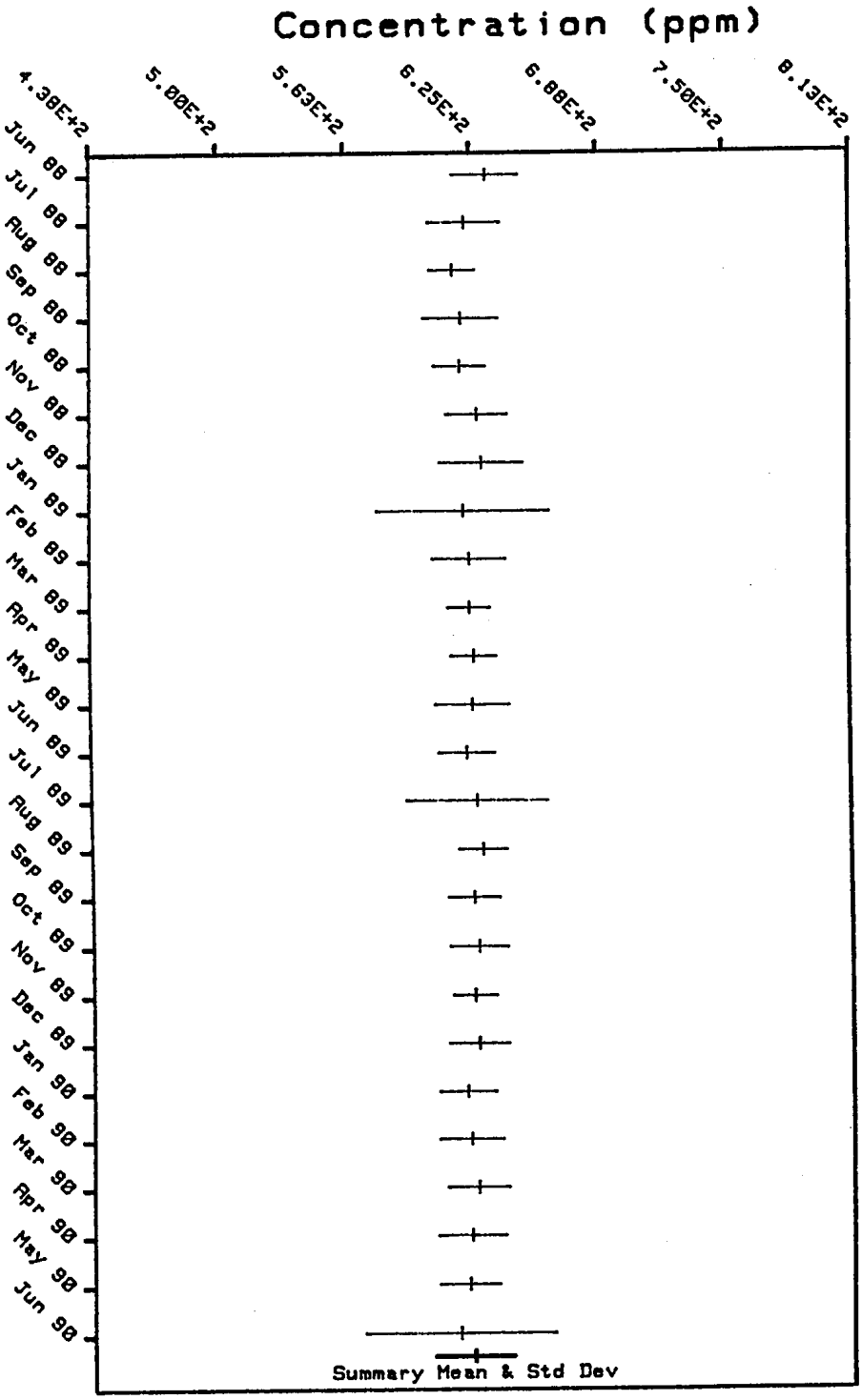

FIGURE I11
Monthly Mean Concentrations and Standard Deviations in the 625 ppm Tetrafluoroethylene Female Rat Exposure Chamber for the 2-Year Study

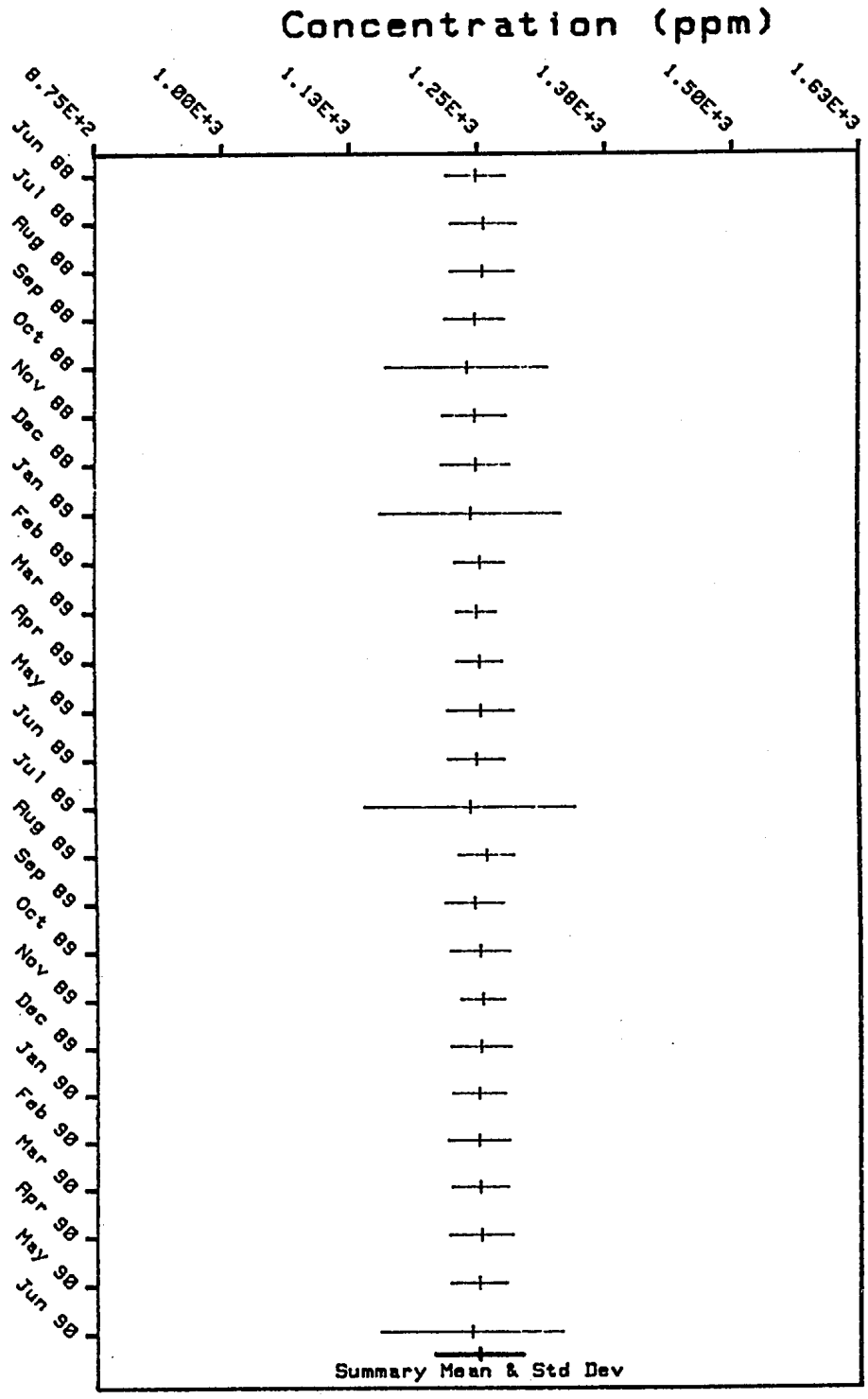

FIGURE I12
Monthly Mean Concentrations and Standard Deviations in the 1,250 ppm Tetrafluoroethylene Female Rat Exposure Chamber for the 2-Year Study

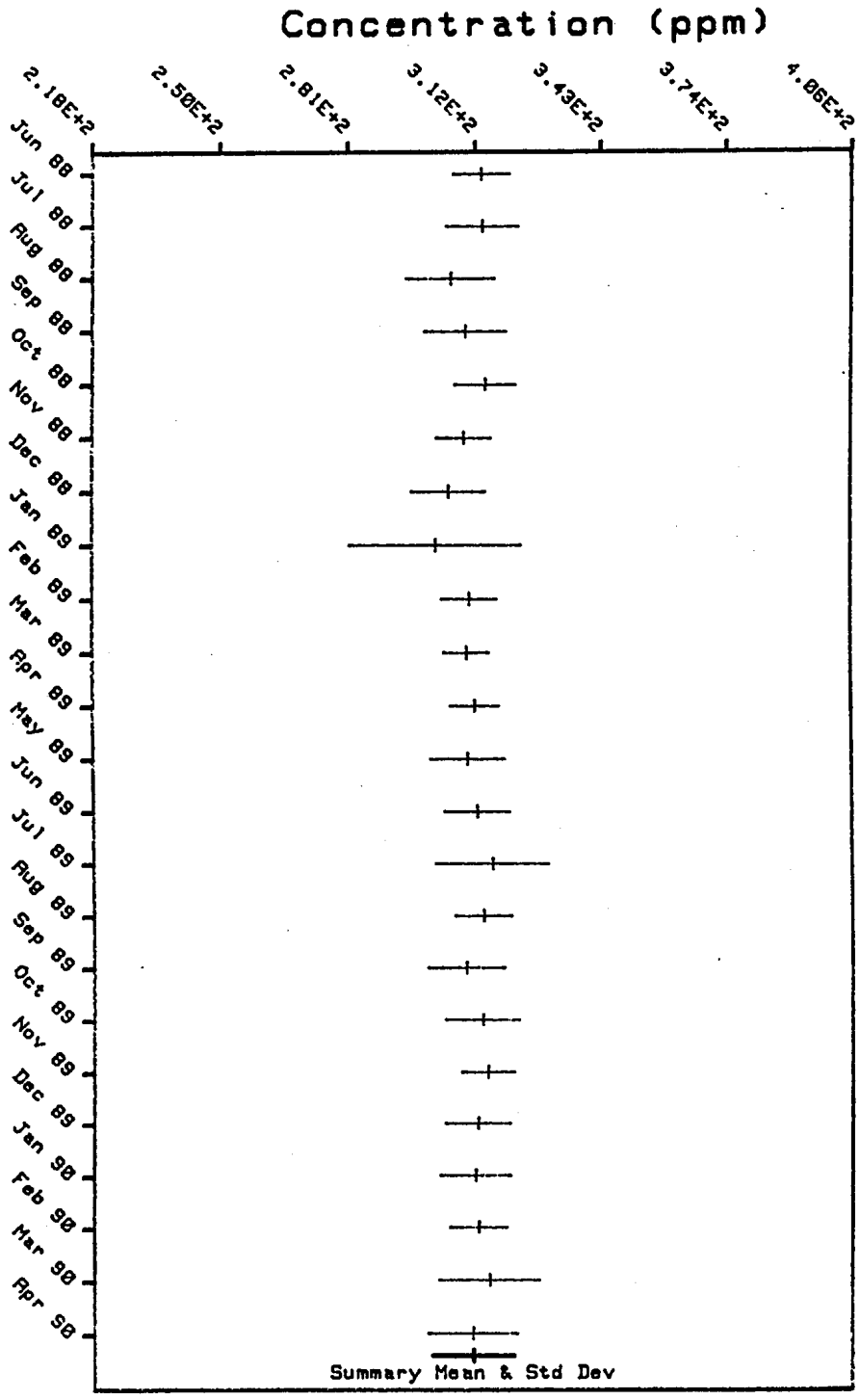

FIGURE I13
Monthly Mean Concentrations and Standard Deviations in the 312 ppm Tetrafluoroethylene Mouse Exposure Chamber for the 2-Year Study

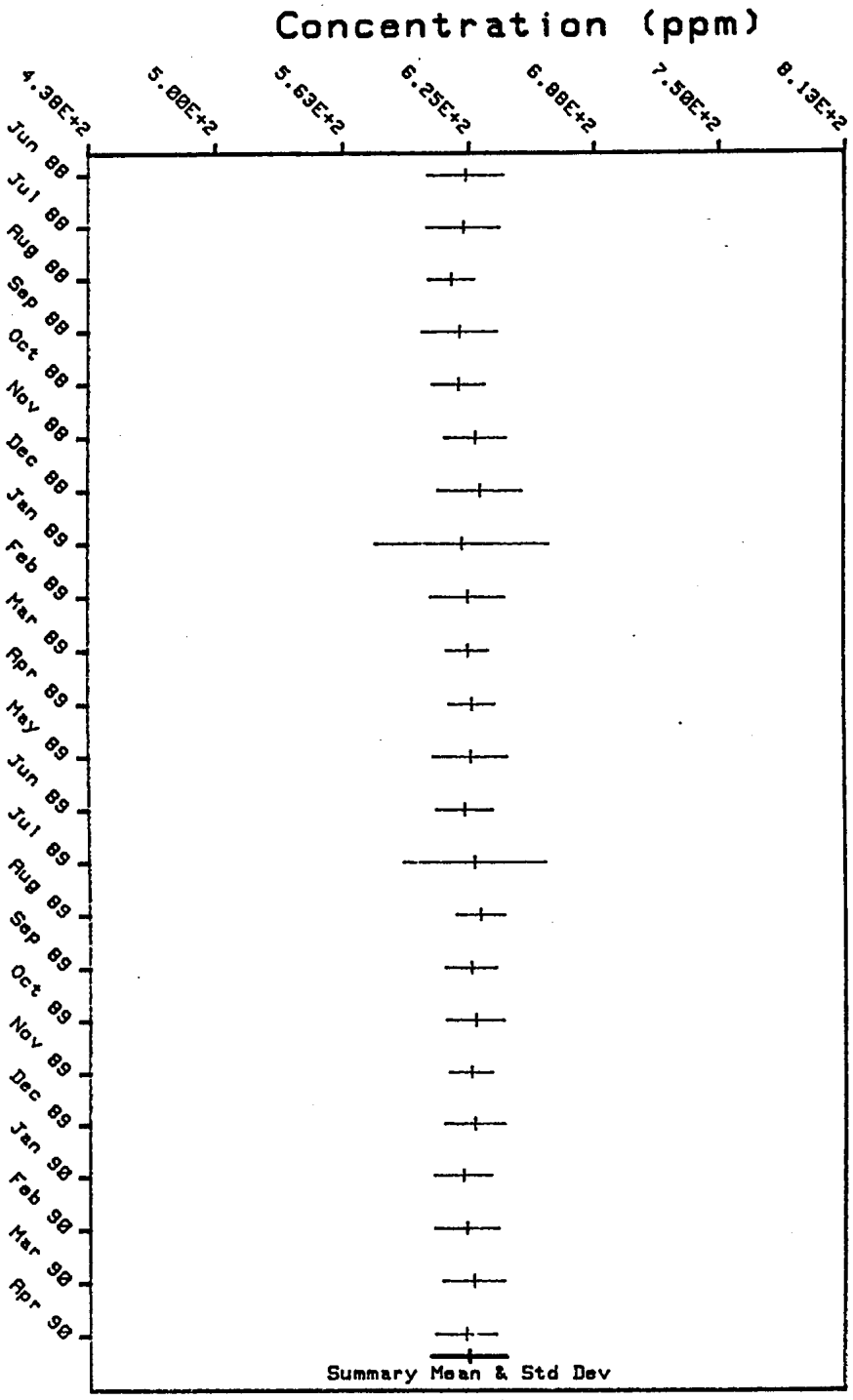

FIGURE I14
Monthly Mean Concentrations and Standard Deviations in the 625 ppm Tetrafluoroethylene Mouse Exposure Chamber for the 2-Year Study

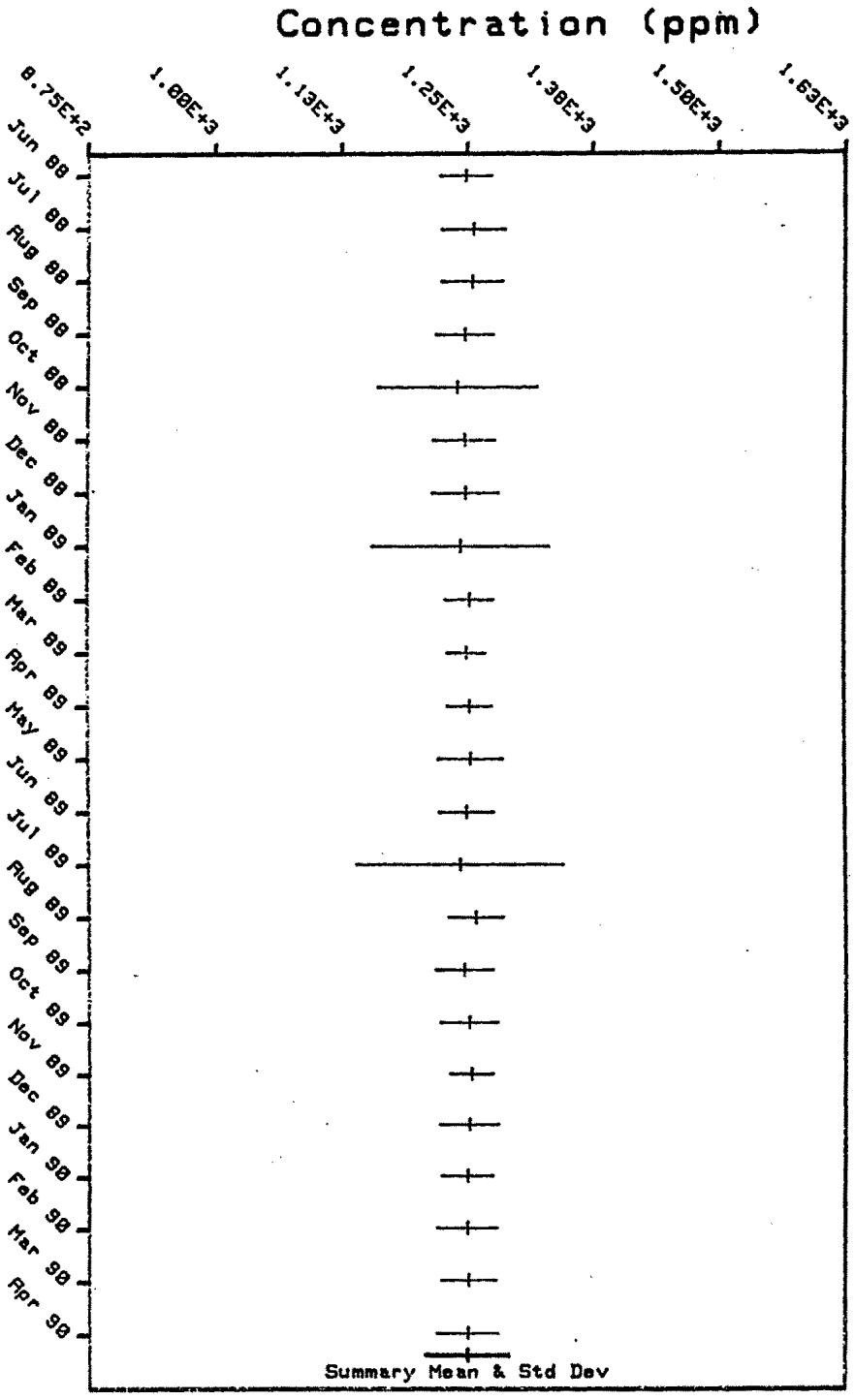

FIGURE I15
Monthly Mean Concentrations and Standard Deviations in the 1,250 ppm Tetrafluoroethylene Mouse Exposure Chamber for the 2-Year Study

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

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

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

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

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

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

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

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.97 ± 0.81	21.7) 24.2	24
Crude fat (% by weight)	5.37 ± 0.32	4.60) 5.90	24
Crude fiber (% by weight)	3.66 ± 0.39	2.80) 4.20	24
Ash (% by weight)	6.62 ± 0.31	6.11) 7.30	24
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)	6,771 ± 1,915	4,180) 12,140	24
Vitamin D (IU/kg)	4,450 ± 1,382	3,000) 6,300	4
α-Tocopherol (ppm)	36.12 ± 9.15	22.5) 48.9	10
Thiamine (ppm)	19.00 ± 2.36	16.0) 28.0	24
Riboflavin (ppm)	7.83 ± 0.92	6.10) 9.00	11
Niacin (ppm)	98.64 ± 25.51	65.0) 150.0	10
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	2,400) 3,430	10
Minerals			
Calcium (%)	1.25 ± 0.11	1.10) 1.54	24
Phosphorus (%)	0.95 ± 0.032	0.890) 1.00	24
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 J4
Contaminant Levels in NIH-07 Rat and Mouse Ration [a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.23 ± 0.17	0.05) 0.60	24
Cadmium (ppm)	0.09 ± 0.02	0.05) 0.10	24
Lead (ppm)	0.24 ± 0.18	0.10) 1.00	24
Mercury (ppm)	0.05 ± 0.02	0.02) 0.11	24
Selenium (ppm)	0.40 ± 0.20	0.16) 1.21	24
Aflatoxins (ppb)[c]	<5.0		23
Nitrate nitrogen (ppm)[d]	16.60 ± 4.13	8.60) 24.0	24
Nitrite nitrogen (ppm)[d]	0.20 ± 0.17	0.10) 0.60	24
BHA (ppm)[e]	1.54 ± 0.65	0.10) 3.00	24
BHT (ppm)[e]	1.30 ± 0.62	0.10) 3.00	24
Aerobic plate count (CFU/g)	46,404 ± 24,682	6,700) 120,000	24
Coliform (MPN/g)	50 ± 224	3) 1,100	24
Escherichia coli (MPN/g)	3 ± 0.2	3) 4	24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[f]	8.05 ± 3.23	3.60) 16.50	24
N-Nitrosodimethylamine (ppb)[f]	5.85 ± 2.71	2.60) 13.00	24
N-Nitrosopyrrolidine (ppb)[f]	2.20 ± 1.25	0.90) 5.20	24
Pesticides (ppm)			
α-BHC	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.10		24
Estimated PCBs	<0.20		24
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.24 ± 0.23	0.05) 1.00	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

[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] No aflatoxin measurement was recorded for the lot milled on 2 October 1989.
[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 K
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

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

Method and Test	Time of Analysis
RATS	
13-Week Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
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	
M. arthritidis	22 and 24 months
M. pulmonis	22 and 24 months
PVM	6, 12, 18, 22, and 24 months
RCV/SDA	6, 12, 18, 22, and 24 months
Sendai	6, 12, 18, 22, and 24 months
Hemagglutination Inhibition	
H-1	6, 12, 18, 22, and 24 months
KRV	6, 12, 18, 22, and 24 months

MICE

13-Week Study

Complement Fixation

LCM (lymphocytic choriomeningitis virus)	Study termination

ELISA

Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	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
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA

Ectromelia virus	6, 12, 18, and 22 months
EDIM	22 months
GDVII	6, 12, 18, and 22 months
LCM	18 and 22 months
MVM	6 and 12 months
Mouse adenoma virus	6, 12, 18, and 22 months
MHV	6, 12, 18, and 22 months
M. arthritidis	22 months
M. pulmonis	22 months
PVM	6, 12, 18, and 22 months
Reovirus 3	6, 12, 18, and 22 months
Sendai	6, 12, 18, and 22 months

Immunofluorescence Assay

EDIM	6, 12, 18, and 22 months
LCM	6 and 12 months
Reovirus 3	12 months
MVM	18 and 22 months
Mouse adenoma virus	22 months

Hemagglutination Inhibition

K	6, 12, 18, and 22 months
MVM	18 months
Polyoma virus	6, 12, 18, and 22 months

Results of serology tests are presented in Table K1.

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

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-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	0/11	None positive
22 Months	0/2	None positive
24 Months	2/10	*M. arthritidis*[a]
Mice		
6 Months	0/16	None positive
12 Months	1/16	Reovirus 3[b]
18 Months	0/13	None positive
22 Months	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 be due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in mice with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.
[b] Negative for Reovirus 3 by Western blot; false positive

APPENDIX L
H-*RAS* CODON 61 MUTATION SPECTRA IN HEPATOCELLULAR NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO TETRAFLUOROETHYLENE FOR 2 YEARS

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H-*RAS* CODON 61 MUTATION SPECTRA IN HEPATOCELLULAR NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO TETRAFLUOROETHYLENE FOR 2 YEARS

INTRODUCTION

Liver neoplasms are commonly seen in B6C3F$_1$ mice in 2-year inhalation studies, occurring with a typical incidence of 40% in control males and 20% in control females. Chemical-induced neoplasms in mice have a high frequency of proto-oncogene activation, particularly by point mutations in codon 61 of H-*ras* genes (Maronpot *et al.*, 1995). The frequency of *ras* activation in these neoplasms is often greater than detected in neoplasms occurring in control animals (Reynolds *et al.*, 1987), and there is evidence for chemical specificity in the pattern of oncogene activation (Wiseman *et al.*, 1986; Maronpot *et al.*, 1995). The specific types of oncogene-activating mutations induced by a chemical carcinogen often agree with what is expected based on the DNA adducts formed by the agent (Wiseman *et al.*, 1986). Even for "nongenotoxic carcinogens," the patterns of *ras* gene mutations in neoplasms can give clues about the mechanism of tumorigenesis (Devereux *et al.*, 1993; Maronpot *et al.*, 1995).

MATERIALS AND METHODS

Liver neoplasms: Male and female B6C3F$_1$ mice were exposed to 0, 312, 625, or 1,250 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week for 2 years. At necropsy, liver neoplasms were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, sectioned to a thickness of 5 µm, and stained with hematoxylin and eosin (H&E). Subsequently, six unstained serial sections (10 µm thick) were prepared from paraffin blocks containing hepatocellular adenomas or carcinomas for isolation of DNA for polymerase chain reaction (PCR)-based assays. In order to isolate adequate amounts of DNA, liver neoplasms greater than 1 mm in diameter were identified for analysis. Based on the size criterion, a total of 66 paraffin-embedded neoplasms were examined for genetic alterations in the H-*ras* gene. These included 53 neoplasms from tetrafluoroethylene-exposed mice and 13 neoplasms from control mice. Also, 13 frozen liver neoplasms were evaluated for H-*ras* and K-*ras* mutations. For the liver neoplasms from which frozen and paraffin-embedded tissue were available, both were examined to confirm the results.

DNA isolation: The DNA isolation procedure is described in Marmur (1961) and in Sills *et al.* (1995). The paraffin-embedded tissue was deparaffinized and rehydrated before digesting with proteinase K (Wright and Manos, 1990). The frozen tumor tissue was digested with 10 mg/mL pronase in 1% sodium dodecyl sulfate in TNE buffer (10 mM TRIS; 150 mM NaCl; and 2 mM EDTA disodium salt, pH 7.5). DNA was extracted with phenol and chloroform and precipitated with ethanol. DNA was quantified by optical density at 260 nm and 200 ng/µL was used for amplification.

DNA amplification: DNA was amplified by the polymerase chain reaction (Saiki *et al.*, 1988; Sills *et al.*, 1995); details of the use of nested primers are described in Devereux *et al.* (1991, 1993).

Restriction fragment length polymorphic identification: A "cold" method was employed to identify mutation in the H-*ras* gene at codon 61 from liver neoplasms. This was based on restriction fragment length polymorphism in the DNA containing a CAA to AAA, CTA, or CGA mutation in codon 61 of exon 2 (Sukumuar and Barbacid, 1990). The sense primer used for amplification of exon 2 was 5′-GACATCTTAGACACAGCAGTT-3′. A restriction site for MSEI, XbaI, or TaqI enzyme (New England Biolaboratory, Beverly, MA) is created by the presence of a C to A, A to T, or A to G mutation in the first or second base of codon 61, respectively. By using this technique, we detected codon 61 AAA, CTA, and CGA mutations by MSEI, XbaI, and TaqI digestion, respectively; the normal sequence (CAA) of codon 61 is not cut by these enzymes. The reaction was incubated at 37° C (for MSEI or XbaI) or 60° C (for TaqI) for 2 hours. Fifteen µL of the mixture with bromophenol blue dye was loaded onto the 6% acrylamide TBE gel (8 × 8 cm × 1 mm; 15 wells) (Novex, San Diego, CA). The gel was run at 100 volts for 1 hour on the Novex gel electrophoresis unit. Gels were stained with a 5 µg/mL solution of ethidium bromide for

20 minutes and then destained in distilled water. Ethidium bromide-stained bands were visualized using a 312 nm ultraviolet viewing box and were photographed.

Single-strand conformational analysis: Single-strand conformation analysis (Orita *et al.*, 1989) was performed with PCR products into which [α-^{33}P]dATP was incorporated during the inner amplification. For the first exon of K-*ras*, 10% acrylamide gel containing 10% glycerol and 1X TRIS-borate-EDTA buffer was electrophoresed at room temperature with constant power at 8 watts for 16 hours on a Model S2 sequencing gel electrophoresis apparatus (Bethesda Research Labs, Gaithersburg, MD). For the second exon of H-*ras*, 12% acrylamide gel with 5% glycerol in 1X TRIS-borate-EDTA buffer was used at 35 watts in a 4 $^{\circ}$ C cold room for 5 hours.

RESULTS

In order to determine if the tetrafluoroethylene-induced neoplasms contained an H-*ras* mutation profile similar to that observed with ``spontaneous" neoplasms, sample groups of 29 neoplasms consisting of adenomas and carcinomas from the two highest exposure groups, four neoplasms from the low exposure group, and 17 neoplasms from the chamber controls were evaluated by polymerase chain reaction amplification of H-*ras* exon 2 followed by restriction fragment length polymorphism analysis for the three common codon 61 mutations in the B6C3F$_1$ mouse (Table L1). Single-stranded conformation polymorphism was used as an alternative screening method for detection of H- and K-*ras* mutations in DNA from 19 neoplasms following tetrafluoroethylene exposure and from four chamber controls (Table L2). A low frequency (9/62, 15%) of H-*ras* mutations was detected in hepatocellular neoplasms when compared to the high frequency (10/17 or 59% in controls from the present study and 183/333 or 56% in historical controls) detected in spontaneous liver neoplasms from B6C3F$_1$ mice (Table L1). In addition, the proportion of H-*ras* mutations in hepatocellular neoplasms was 1:1:1 for codon 61 AAA, CGA, and CTA mutations, respectively, when compared to 3:6:1 for controls from the present study or 5:2:1 for spontaneous hepatocellular neoplasms in historical controls. There were generally no differences in the mutation frequency and spectrum between exposure groups and between benign and malignant hepatocellular neoplasms (Tables L1 and L3). K-*ras* mutations were not detected in hepatocellular neoplasms following tetrafluoroethylene exposure.

DISCUSSION

The low frequency (9/62, 15%) of H-*ras* mutations detected in hepatocellular neoplasms following tetrafluoroethylene exposure is similar to that reported with other nongenotoxic agents such as phenobarbital (7%), chloroform (21%), and ciprofibrate (31%) when compared to the generally higher frequency (183/333, 56%) observed in spontaneous liver neoplasms from B6C3F$_1$ mice (Fox *et al.*, 1990; Maronpot *et al.*, 1995). Other nongenotoxic hepatocellular carcinogens associated with low frequencies of H-*ras* include hexachlorobenzene (Rumsby *et al.*, 1992), dieldrin, (Bauer-Hofmann *et al.*, 1992), methylclofenapate (Stanley *et al.*, 1994), and oxazepam (NTP, 1993). Nongenotoxic agents, by definition, are not positive in *in vitro* mutation assays, and therefore the parent chemical or metabolites do not react with the DNA directly to cause mutations. Our findings of a decreased frequency of *ras* mutations at codon 61 are consistent with the lack of mutagenicity in the *Salmonella typhimurium* assay and suggest that tetrafluoroethylene may be acting in the liver as a nongenotoxic carcinogen. In addition, the finding of no increases in the frequency of micronucleated erythrocytes in peripheral blood samples supports this theory.

The decreased frequency of H-*ras* mutations in tetrafluoroethylene-induced hepatocellular neoplasms is similar to that detected in B6C3F$_1$ mice exposed to the structurally similar tetrachloroethylene (24%) (Anna *et al.*, 1994). Unlike the lack of K-*ras* mutations in the tetrafluoroethylene study, a few K-*ras* mutations were detected in the tetrachloroethylene study. Data from the present study support the hypothesis that the liver tumors induced by these two structurally similar hepatocellular carcinogens may be acting via a *ras*-independent pathway. Recently, chlordane-induced hepatocarcinogenesis in B6C3F$_1$ mice was shown to be independent of *ras* activation (Malarkey *et al.*, 1995). Alternate pathways such as cytotoxicity followed by enhanced cell proliferation may also not be playing a major role in the development of hepatocellular neoplasms with tetrafluoroethylene since at 16 days or 13 weeks, there was no evidence of hepatocellular toxicity. Furthermore, since the mutation spectrum at H-*ras* codon 61 was not similar to that of spontaneous hepatocellular neoplasms, the data also argue against the theory that tetrafluoroethylene-induced tumors may be acting by a simple promotional mechanism involving *ras*-mutated cells. If this was

the case, one would expect that a number of the hepatocellular neoplasms would have had similar mutation profiles to those of the controls, due to the clonal expansion of spontaneously initiated cells with *ras* mutations.

The low frequency of H-*ras* mutations in the liver is consistent with the findings with various nongenotoxic carcinogens; however, the variety of different types of neoplasms in the liver of B6C3F$_1$ mice supports the hypothesis that a potential *in vivo* genotoxic event(s) may be associated with the carcinogenesis process. The multiplicity of hepatocellular neoplasms and the development of liver hemangiosarcomas, and the significant increase in histiocytic sarcomas in the liver suggest that metabolizing enzymes in the liver may have produced unique tetrafluoroethylene metabolites which may have played a role, perhaps through as yet undetected genotoxic events, in the development of the marked increase in tumors in the liver. Similar to tetrafluoroethylene, 1,3-butadiene (Melnick *et al.*, 1990) and vinyl chloride (Froment *et al.*, 1994) induced hepatic hemangiosarcomas and hepatocellular neoplasms and were both genotoxic carcinogens.

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TABLE L1
H-*ras* Mutations at Codon 61 in Spontaneously Occurring and Tetrafluoroethylene-Induced Liver Neoplasms from B6C3F$_1$ Mice

Treatment	Activated H-*ras* (%)	H-*ras* Codon 61		
		AAA	CGA	CTA
Control, Historical[a]	183/333 (56%)	106/177 (60%)	50/177 (28%)	21/177 (12%)
Control	10/17 (59%)	3/10 (30%)	6/10 (60%)	1/10 (10%)
Tetrafluoroethylene (312 ppm)	0/3 (0%)	—	—	—
Tetrafluoroethylene (625 ppm)	6/29 (21%)	2/6 (33%)	2/6 (33%)	2/6 (33%)
Tetrafluoroethylene (1,250 ppm)	3/27 (10%)	1/3 (33%)	1/3 (33%)	1/3 (33%)
Tetrafluoroethylene (Total)	9/59 (15%)	3/9 (33%)	3/9 (33%)	3/9 (33%)

[a] Data are presented in Maronpot *et al.* (1995).

TABLE L2
Frequency of K-*ras* Proto-oncogene Activation in Spontaneously Occurring and Tetrafluoroethylene-Induced Liver Neoplasms from B6C3F$_1$ Mice

Treatment	K-*ras* Mutations (%)
Control, Historical[a]	3/167 (1.8%)
Control[b]	0/4 (0%)
Tetrafluoroethylene[b]	0/19 (0%)

[a] Data are presented in Maronpot *et al.* (1995).
[b] Determined only for first exon of K-*ras* at codons 12 and 13.

TABLE L3
H-*ras* Mutations at Codon 61 Detected in Hepatocellular Adenomas and Carcinomas from B6C3F$_1$ Mice

Treatment	Activated H-*ras* (%)	H-*ras* Codon 61		
		AAA	CGA	CTA
Controls				
Hepatocellular Adenoma	5/11 (46%)	1	3	1
Hepatocellular Carcinoma	5/6 (83%)	2	3	0
Tetrafluoroethylene				
Hepatocellular Adenoma	4/20 (20%)	1	2	1
Hepatocellular Carcinoma	5/39 (13%)	2	1	2