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CARCINOGENESIS BIOASSAY OF TRICHLOROETHYLENE

CAS No. 79-01-6

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NCI-CG-TR-2

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These studies were conducted by Hazleton Laboratories, Inc., initially under direct contract to the National Cancer Institute and subsequently under subcontract with Tracor Jitco, Inc., Prime Contractor for the Carcinogenesis Bioassay Program, National Cancer Institute.

CARCINOGEN BIOASSAY AND PROGRAM RESOURCES BRANCH
CARCINOGENESIS PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE
BETHESDA, MARYLAND

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FOREWORD

One of the major goals of the National Cancer Institute is to determine the causative factors responsible for human cancer as a basis for preventive measures, both at the environmental and at the host levels. The identification of chemical and physical agents which represent carcinogenic hazards has been recognized as an essential task. The Carcinogenesis Program of the Division of Cancer Cause and Prevention includes among its responsibilities that of testing chemicals for carcinogenic activity.

Methods for carcinogenesis bioassay have continued to evolve in the last few decades. While progress was initially slow, and bioassay methods were crude, methodology has greatly improved within the past decade. With better bioassay testing procedures and more extensive efforts in this direction, more chemicals capable of causing cancer in humans will be detected first through experimental tests rather than exclusively through epidemiological studies. More than ever the experimentalists and epidemiologists can now interact to provide direction and leads to the enormous task of exploring the complex problems associated with chemicals and cancer in our society.

Technological developments of the last few decades have resulted in thousands of chemicals being introduced into the environment. A number of these chemicals can be expected to be found carcinogenic. The number of chemicals which have been shown to have carcinogenic activity has continued to increase.

Two of the major goals of the Carcinogenesis Program are to identify carcinogenic chemicals and to develop improved methodology for testing. The most reliable test method available at this time is the long term bioassay study using laboratory rodents. This is the primary procedure used currently by the bioassay program in its systematic testing for carcinogenicity.

Due to the lack of in-house facilities adequate for conducting carcinogenesis bioassay studies, the NCI Carcinogenesis Program has implemented this activity through collaborative research contracts.

Several hundred chemicals have been selected for bioassay in recent years. Included among these is a series of chlorinated organic compounds. The bioassay of trichloroethylene, the

subject of the present report, is one of the first of this series to have been completed.

The selection of this test dates back to decisions made in the early phases of implementation of the Carcinogenesis Program during the development of research on screening methods for carcinogenicity testing. Trichloroethylene was one of 18 chemicals tested under a contract awarded to Hazleton Laboratories, Incorporated. Vienna, Virginia, on May 1, 1971, as a result of a Request for Proposals advertised in the Commerce Business Daily on March 15, 1969.

This bioassay was initiated in 1972 according to the methods used and widely accepted at that time; it represents a valid carcinogenesis test. The design of carcinogenesis bioassays has evolved since then in some respects and several improvements have been developed. The currently recommended procedures are described in detail in the first volume of this series (NCI-CG-TR-1) entitled "Guideline for Carcinogenesis Testing in Small Rodents" (1976). The most notable changes pertain to preliminary toxicity studies, number of controls used, and extent of pathological examination.

The present report, the first of its kind, provides a detailed documentation of all the aspects of the bioassay, including all the individual animal data and diagnoses.

The publication of such detailed reports fulfills a commitment made in 1968 when NCI developed its "Plan for Chemical Carcinogenesis and the Prevention of Cancers". Methods and capabilities for a fully detailed documentation and publication of well defined and relatively large bioassay studies had to be developed by the Program. They include the development of the Carcinogenesis Bioassay Data System, guidelines for bioassay protocols and procedures, and a network of bioassay resources for chemicals, animals, testing facilities, experimental design, pathology, data processing, and statistical analysis. Methods and criteria for pathological diagnosis and classification were developed.

This type of publication also fulfills a recommendation made by the International Union Against Cancer (UICC) in 1969 (Berenblum, 1969). In fact, the definition and exhaustive documentation of carcinogenesis bioassays was recommended by the UICC international expert panels. Those recommendations served as an essential basis for the development of the present reporting and publication system. A workshop on "Data Dissemination in Carcinogenesis" held by the NCI Carcinogenesis Program in January 1974 endorsed the Technical Report series as a means for disseminating carcinogenesis test results.

The present bioassay is clearly the result of team effort. Many people contributed to the selection of the test, the

development and design of the protocols and the diagnostic and analytical procedures, the establishment and monitoring of facilities, the conduct of the animal tests, and the analysis of results. All of them share in the authorship of this study. Their names and credit for their contribution to the study are given under the heading of "Contributors".

The interpretation of carcinogenesis bioassay results, in relation to the complex task of assessing human hazards, is beyond the scope of the present study. This report is designed to provide a factual basis for the interpretative efforts by giving a full, open, and detailed account of the observations made during this bioassay.

Norbert P. Page, D.V.M
Chief, Carcinogen Bioassay
and Program Resources Branch
Carcinogenesis Program
Division of Cancer Cause
and Prevention
National Cancer Institute

Umberto Saffiotti, M.D.
Associate Director,
Carcinogenesis Program
Division of Cancer Cause
and Prevention
National Cancer Institute

CONTRIBUTORS

Many individuals and institutions have participated in the planning and conduct of this study. The selection of the chemical and test animals, design of the experiments, and much of the monitoring of progress was the responsibility of Dr. John Weisburger, previously of the National Cancer Institute, now with the American Health Foundation, and Dr. Elizabeth Weisburger, National Cancer Institute (NCI). Dr. John Weisburger served as project officer from inception of the contract until the fall of 1972. Drs. Elizabeth Weisburger and Norbert Page served in that capacity from that time until the present.

The actual animal experiments were conducted under contract to the Hazleton Laboratories, Incorporated (HLI), Vienna, Virginia. Principal Investigators for HLI were Drs. Willard Weatherholtz, William Olson, Marcelina Powers, and Richard Voelker. Dr. Robert Habermann conducted the microscopic examination of the tissues. Ms. Klara Petrovics was responsible for much of the routine technical aspects of the study. Tracor Jitco, Incorporated, Rockville, Maryland, as Prime Contractor for Bioassay Operations, with the assistance of the Hazleton Laboratories, Incorporated and National Cancer Institute staffs, has prepared this report. Dr. Jane Robens was responsible for the coordination and major effort required in its preparation. Dr. Charlie Barron conducted a review and confirmation of the histopathologic diagnoses as submitted by Hazleton Laboratories. Dr. Miles Davis conducted the statistical analysis, Dr. Stephen Olin prepared the chemical sections of this report, and Ms. Nancy Palmer functioned as Technical Editor.

The Biomedical Information Sciences Department, EG&G/Mason Research Institute, Bethesda, Maryland, operations contractor for the Carcinogenesis Bioassay Data System (CBDS), under the direction of Mr. Dalton Tidwell, was responsible for the compilation of the individual animal pathology tables and some of the summary tables. Drs. Norbert Page, Cipriano Cueto, and Umberto Saffiotti of the National Cancer Institute outlined the format of this report, worked closely with the Tracor Jitco and Hazleton Laboratories staffs in preparing it, reviewed its content, and contributed to the discussion and interpretation of the findings. Dr. John Gart, Head, Mathematics and Statistics Section, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, NCI, and his staff were responsible for verifying the accuracy of the data, tables, and the statistical analysis of the data.

Advisory Groups to the Carcinogenesis Program have provided guidance in the further development of the carcinogenesis bioassay methodology and the review of the Carcinogenesis Bioassay Program and its contracts. Members include Dr. Richard Adamson, NCI; Dr. Clyde Dawe, NCI; Dr. William Deichmann, University of Miami; Dr. Leo Friedman (deceased), Food and Drug Administration; Dr. John Gilbert, Harvard Computing Center; Dr. Harold Grice, Canadian Food and Drug Directorate; Dr. Paul Harris, Indianapolis, Indiana; Dr. Charles Irving, Memphis Veterans' Administration Hospital; Dr. Gerhard Krueger, NCI; Dr. Bernard McNamara, Edgewood Arsenal; Dr. Paul Newberne, Massachusetts Institute of Technology; Dr. Norbert Page, NCI; Dr. Lionel Poirier, NCI; Dr. William Priester, NCI; Dr. James Sontag, NCI; Dr. Robert Squire, NCI; Dr. Elizabeth Weisburger, NCI; Dr. John Weisburger, American Health Foundation; Dr. Harry Wood, NCI; and Mr. Samuel Poiley, NCI.

We are especially grateful for the contributions and valuable constructive criticism provided by the reviewers of this report. NCI staff reviewers were Drs. Thomas Cameron, John Cooper, Kenneth Chu, Cipriano Cueto, Herman Kraybill, Umberto Saffiotti, Sidney Siegel, James Sontag, Robert Squire, and Elizabeth Weisburger. Consultants who reviewed the report and provided valuable advice were Dr. Norman Breslow, University of Washington; Dr. Herbert Blumenthal, Food and Drug Administration; Dr. William D'Aguanno, Food and Drug Administration; Dr. Harold Grice, Canadian Food and Drug Directorate; Dr. Elton Homan, U.S. Environmental Protection Agency; Dr. Philip Issenberg, University of Nebraska Medical Center; Dr. William Lloyd, National Institute for Occupational Safety and Health; Dr. Roscoe Moore, National Institute for Occupational Safety and Health; Dr. Verald Rowe, Dow Chemical Company; Mr. Sheldon Samuels, American Federation of Labor/Congress of Industrial Organizations; Dr. Raymond Shapiro, Food and Drug Administration; Dr. Zeb Bell, Jr., PPG Industries, Inc.; Mr. Larry Sargert, PPG Industries, Inc.; Dr. John Weisburger, American Health Foundation; Dr. Jerome Wesolowski, California Department of Health.

In addition to those mentioned, appreciation is given to the numerous other staff personnel of Tracor Jitco, Inc., the National Cancer Institute's contractors, and the NCI Carcinogenesis Program for their contributions to these studies.

While this Technical Report documents in detail the design, conduct, and results of the study, any further inquiries regarding the study should be directed to the Carcinogenesis Program of the National Cancer Institute.

SUMMARY

Trichloroethylene (TCE), a halogenated chemical, has been tested for carcinogenicity in the National Cancer Institute's Carcinogenesis Bioassay Program. Trichloroethylene has been used primarily as a solvent in industrial degreasing operations. Other uses have been as a solvent in dry cleaning and food processing, as an ingredient in printing inks, paints, etc., and as a general anesthetic or analgesic.

Industrial grade (>99% pure) trichloroethylene was tested using 50 animals per group at 2 doses and with both sexes of Osborne-Mendel rats and B6C3F1 mice. Twenty of each sex and species were maintained as matched controls, in addition to colony and positive carcinogen controls. Animals were exposed to the compound by oral gavage 5 times per week for 78 weeks. At the end of treatment, animals were observed until terminal sacrifice at 110 weeks for rats and 90 weeks for mice. A complete necropsy and microscopic evaluation of all animals (except 7 of the original 480) was conducted.

Two doses were used with animals started on test at approximately 6 weeks of age. The initial doses used in this test were the estimated maximum tolerated dose (MTD) and 1/2 MTD, as predicted from data obtained in a 6-week toxicity study. For rats, the initial doses were 1300 and 650 mg/kg body weight. These were changed, based upon survival and body weight data, so that the "time-weighted average" doses were 549 and 1097 mg/kg for both male and female rats. For mice, the initial doses were 1000 and 2000 mg/kg for males and 700 and 1400 mg/kg for females. The doses were increased so that the "time-weighted average" doses were 1169 and 2339 mg/kg for male mice and 869 and 1739 mg/kg for female mice.

Clinical signs of toxicity, including reduction in weight, were evident in treated rats. These, along with an increased mortality rate, necessitated a reduction in doses during the test. In contrast, very little evidence of toxicity was seen in mice, so doses were increased slightly during the study. The increased mortality in treated male mice appears related to the presence of liver tumors.

A variety of neoplastic lesions were observed in rats with no significant difference between trichloroethylene-treated and control animals. The only lesion that might be attributed to

the treatment was a chronic nephropathy found in both sexes and at both dose levels.

With both male and female mice, primary malignant tumors of the liver, i.e., hepatocellular carcinoma, were observed in high numbers. For males, 26/50 low dose and 31/48 high dose animals had hepatocellular carcinomas as compared with 1/20 matched controls and 5/77 colony controls. The differences between treated and matched control males at both doses were highly significant ($P < 0.01$). For females, hepatocellular carcinomas were observed in 4/50 low dose and 11/47 high dose animals as compared with 0/20 matched controls and 1/80 colony controls. While the difference between the high dose female mice and matched controls was also highly significant ($P < 0.01$), the difference at the low dose was less ($P = 0.09$). For both male and female mice, age-adjusted tests for linear trend (dose response) were highly significant for hepatocellular carcinoma ($P < 0.001$ for males and $P = 0.002$ for females).

In male mice at the high doses, hepatocellular carcinomas were observed early in the study. The first was seen at 27 weeks; 9 others were found in male mice dying by the 78th week. The tumor was not observed so early in low dose male or female mice. The diagnosis of hepatocellular carcinoma was based on size, histologic appearance, and presence of metastasis, especially to the lung. No other lesion was significantly elevated ($P < 0.05$) in treated mice. The incidence of hepatocellular carcinomas in the trichloroethylene-matched controls was typical of that observed in colony controls.

Carbon tetrachloride (CCl_4) was used as a positive control for the series of chlorinated chemicals which included trichloroethylene. While virtually all male and female mice developed hepatocellular carcinomas following carbon tetrachloride treatment, the response in the Osborne-Mendel rat was considerably less. Only about 5% developed hepatocellular carcinomas. Thus, there appears to be a marked difference in sensitivity to induction of carcinomas by chlorinated compounds between the B6C3F1 mouse and the Osborne-Mendel rat.

The results of this carcinogenesis test of trichloroethylene clearly indicate that trichloroethylene induced a hepatocellular carcinoma response in mice. While the absence of a similar effect in rats appears most likely attributable to a difference in sensitivity between the Osborne-Mendel rat and the B6C3F1 mouse, the early mortality of rats due to toxicity must also be considered.

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1.0 INTRODUCTION

In the late 1960s, scientists at the National Cancer Institute noted that a group of halogenated compounds extensively used as solvents in industrial processes had not been adequately tested for chronic toxicity. A related compound, carbon tetrachloride, however, had already been found carcinogenic in mice (Eschenbrenner and Miller, 1944, 1946), hamsters (Della Porta et al., 1961), and rats (Reuber and Glover, 1970). Thus, carcinogenesis bioassays of a group of these solvents were initiated.

Trichloroethylene was one of the chemicals selected to be tested and this report describes the conduct and results of its bioassay. Production of trichloroethylene was reported as 609, 514, and 427 million pounds in 1970, 1971, and 1972, respectively, in the Chemical Economics Handbook (1972). The primary use (about 90%) of trichloroethylene is in the vapor degreasing of metals and equipment. It has also been used as a solvent in dry cleaning, in the processing of certain medicines and foods, and in other processes, as an ingredient in printing inks, paints, lacquers, varnishes, and adhesives, as a chemical intermediate, and in a variety of other applications such as a grain fumigant (Wiseman, 1972; Frear, 1969).

A pharmaceutical grade of trichloroethylene has also been used as a general anesthetic in surgical and obstetrical procedures, administered by inhalation. It is a potent analgesic but will not produce appreciable skeletal muscle relaxation at the concentrations used. As an analgesic it has been used for minor procedures such as cleaning and debridement of burns, orthopedic manipulations, cystoscopy, incision of abscesses, surface biopsy, changing painful dressings, and treating trigeminal neuralgia (Price and Dripps, 1965).

Trichloroethylene has been identified in low concentrations in certain municipal water supplies as reported by the Environmental Protection Agency (Dowty et al., 1975). Residues may result from the use of trichloroethylene as a solvent in the processing of foods. Tolerances for trichloroethylene of 25 ppm in decaffeinated ground coffee, 10 ppm in decaffeinated soluble (instant) coffee extract, and 30 ppm in spice oleoresins have been established by the Food and Drug Administration (Code of Federal Regulations, Title 21). Thus, exposure may occur indirectly to the general population through residues in water and food.

The National Institute of Occupational Safety and Health (1973) has issued a comprehensive review of the uses, exposure, and known biological effects of trichloroethylene. Criteria for a recommended standard for occupational exposures are given in this document. It recommends that occupational exposure to trichloroethylene be controlled so that no worker shall be exposed to a peak concentration of trichloroethylene in excess of 150 ppm as measured over a maximum sampling time of 10 minutes, or to a concentration in excess of 100 ppm determined as a time-weighted average exposure for an 8-hour workday as measured over a minimum sampling time of 10 minutes. The Occupational Safety and Health Administration has recently proposed changes in their regulations to reflect these recommendations.

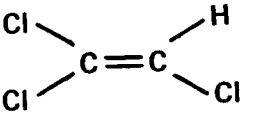
2.0 MATERIALS

2.1 Name and Synonyms

Chemical Abstracts and IUPAC Name: Trichloroethene
Synonyms and Common Name: Trichloroethylene
Acetylene trichloride
Ethinyl trichloride
1,1,2-Trichloroethylene
TCE
(Christensen and Luginbyhl, 1974; Deichmann and Gerarde, 1969)

2.2 Formula, Molecular Weight, Identifying Numbers, and Characteristics

Formula: C_2HCl_3



Molecular Weight: 131.40
Wiswesser Line Notation: GYGU1G
Chemical Abstracts Service Registration Number: 79-01-6
NCI Number: C04546

For chemical and physical characteristics, technical product and impurities, and manufacturing processes, see Appendix A.

2.3 Procurement

Four batches of trichloroethylene were procured from Aldrich Chemical Company as given in Table I:

Table I. Identification of Trichloroethylene Used in Study

Batch No.	Manufacturer's Lot No.	Received by Hazleton (date)	Analysis Report (date)	Use
1	050191	7/23/71	1/9/73	Prechronic study and first 2 weeks of chronic study.
2	061891	7/23/71		Weeks 3-15 in chronic study.
3	063017	5/5/72	2/16/74	Weeks 16-36 in chronic study.
4	063014	10/12/72	7/8/74	Weeks 37-78 in chronic study.

Each batch was received in one or more large amber bottles. Containers were stored in the dark at room temperature.

2.4 Chemical Analysis

The purity of the trichloroethylene used in the bioassay was determined by gas chromatography and infrared spectroscopy. Minor components subsequently were identified by gas chromatography-mass spectrometry and confirmed with reference standards.

Analyses of gas chromatographic total area data showed the major component to be at least 99% in each batch. Infrared spectra compare well with trichloroethylene reference spectra. The minor components comprise a mixture of stabilizers routinely added to commercial formulations of trichloroethylene. They include 1,2-epoxybutane (0.19%), ethyl acetate (0.04%), epichlorohydrin (0.09%), N-methylpyrrole (0.02%), and diisobutylene (0.03%). Percentages were determined by FID gas chromatography with standards after completion of the bioassay. No detectable quantities of 1,1,2,2-tetrachloroethane (<5 ppm) or 1,1,1,2-tetrachloroethane (<2 ppm) were indicated by gas chromatography, using reference standards. (For details of chemical analysis, see Appendix A.)

2.5 Preparations Used for All Bioassays

Fresh solutions of trichloroethylene in corn oil were prepared weekly in amounts sufficient to treat all animals for one week, sealed, and refrigerated until use. Concentrations for the chronic test are given in Table III. The corn oil (purchased from the distributor, C. F. Sauer Company, Richmond, VA) was not analyzed for impurities or reaction products during this study.

2.6 Safety Procedures

Laboratory personnel working with undiluted experimental compound were required to wear the following protective gear: safety goggles, latex gloves, disposable full-body protective suit with attached feet and open-face hood, half-face Welsh respirator fitted with a dust and mist filter over a chemical cartridge for organic vapors. All work with these materials was conducted in a negative-pressure room and under a hood. Personnel involved with compound administration, animal weighing, and feeding wore a disposable laboratory coat, head covering, the Welsh respirator, and disposable latex gloves. Personnel involved with animal care, i.e., cage changing and washing, wore heavy duty gloves, safety shoes, half-face surgical mask (3M), and head covering. Any person entering the animal rooms was required to wear a head covering and 3M mask. As an additional personnel safety measure and to minimize cross contamination within animal rooms, actual intubation procedures were performed within the confines of a fume hood. Test solutions were kept in an ice bath during the dosing procedures to minimize evaporation. In the rooms housing rats, hoods were located in the corner of the room and each rack was wheeled to the hood each time the animals were dosed. Mouse racks were transported through the hall to another room with a large hood and each cage was placed directly under the hood during the intubation process. The testing

laboratory's health and safety officer in conjunction with laboratory personnel made on-site inspections to insure compliance with the above safety precautions.

3.0 TEST ANIMALS AND ENVIRONMENT

Random-bred Osborne-Mendel rats (Battelle Memorial Institute, Columbus, OH) and B6C3F1 (C57BL/6 x C3H/He) hybrid mice (Charles River, Wilmington, MA) in the chronic study were obtained at 35 and 25 days of age, respectively, from suppliers under contract to NCI. Trichloroethylene-treated rats and their controls were born within 6 days of each other, with a median birth date of February 23, 1972. Trichloroethylene-treated mice and their controls were born within 6 days of each other, with a median birth date of July 17, 1972. Upon arrival at the laboratory, all animals were isolated for at least 10 days. They were observed at arrival and weighed immediately before being placed on study. Weight ranges of trichloroethylene-treated animals and their controls in the chronic study were: male rats, 168-229 g; female rats, 130-170 g; male mice, 11-22 g; female mice, 11-18 g. Animals were randomly[1] assigned to treatment groups, so that initially the average weight in each group was approximately the same.

The rats were individually housed in hanging galvanized steel cages, 25.4 x 17.8 x 17.8 cm (Wahmann) with wire mesh fronts and floors. There were 72 cages per rack placed to allow 2 racks per 100 square feet of floor space. Paper collection trays (National Paper Products) were placed under the cages and were changed twice weekly. The rats were transferred to freshly cleaned cages weekly. The soiled cages and racks were washed under pressure at 80°C in water containing Super Soilax detergent (Economics Laboratory, Inc.), rinsed at 80°C, and steamed in a Matawan 375 gallon automatic cycle industrial washer. The water bottles with stainless steel sipper tubes inserted in rubber stoppers were changed twice weekly; the dirty bottles and tubes were washed, rinsed, and steamed in a 220 gallon industrial washer similar to that used for cage washing. Feed was supplied in glass jars within each cage. Trichloroethylene-treated rats and their controls were maintained in a room housing other rats being treated with one of the following compounds: dibromochloropropane, ethylene dichloride, 1,1- dichloroethane, and carbon disulfide. Four groups of vehicle-treated controls were in the same room.

The mice in the chronic phase were housed in polypropylene cages (Lab Products), 47 x 24.1 x 15.2 cm, which contained 10 animals of one sex per cage. (In the prechronic phases mice were housed individually in hanging wire mesh steel cages, 17.8 x 12.7 x 10.2 cm.) Animal rooms contained 40 cages per rack to allow 1.5 racks per 100 square feet of floor space. The cover for each unit was welded stainless steel wire over which was placed a non-woven polyester fiber filter bonnet. Each cage contained a galvanized iron, compartmentalized "gang" feeder (Dixie Sheet Metal Co.) with a screen top. All mice were transferred to clean cages containing fresh bedding (Sanichips, a heat-treated hardwood product, Shurfire Products, Inc.) twice weekly. The soiled cages were washed and rinsed at 80°C and steamed. The steel wire bar covers of the cages were washed on a weekly basis and the racks on a monthly basis. The filter bonnets were washed and autoclaved weekly. The water bottles and stainless steel drinking tubes were changed

[1]Animals were not distributed according to a table of random numbers.

3 times a week and cleaned by washing, rinsing, and steaming as stated above.

Mice treated with trichloroethylene were maintained in a room housing other mice being treated with one of the following 17 compounds: 1,1,2,2-tetrachloroethane, chloroform, 3-chloropropene, chloropicrin, 1,2-dibromochloropropane, 1,2-dibromoethane, ethylene dichloride, 1,1-dichloroethane, 3-sulfolene, iodoform, methyl chloroform, 1,1,2-trichloroethane, tetrachloroethylene, hexachloroethane, carbon disulfide, trichlorofluoromethane, and carbon tetrachloride. Nine groups of vehicle controls and 9 groups of untreated controls were also housed in this room.

All feeders for both rats and mice were changed weekly for the first 10 weeks and every 4 weeks thereafter and were cleaned by the same process of washing, rinsing, and steaming.

Following changing, the clean cages for all animals were placed on the racks in the same manner as before; however, the racks were repositioned within the room on a daily basis for the first 78 weeks, and weekly thereafter. The floors of each room were cleaned daily using Mikro-Bac, a phenolic detergent-disinfectant (Economics Laboratory, Inc.).

The total air in each room was changed 10-15 times per hour with all incoming air filtered through 2-inch thick fiberglass disposable filters which were changed at least once weekly. The relative humidity of the room air was maintained between 45 and 55% and the temperature range was 20 to 24°C. Rooms were illuminated by fluorescent lighting 12 hours per day. There was no communication between rooms, i.e., there were no connecting doors, separate groups of technicians handled the rats and mice, each room had individual air ducts, and rooms were under negative pressure. Samples of ambient air were not tested for presence of volatile materials.

Wayne Lab-Blox meal was fed to the animals ad libitum. (Appendix A contains a feed ingredient list, analysis of protein, fat, and fiber by the manufacturer, and analyses for pesticide residues in selected feed batches.) Drinking water, from a local artesian well, was supplied ad libitum in glass bottles. (Appendix A presents a water analysis.)

Hazleton Laboratories, Inc., was certified as a research facility in August 1967 under the Animal Welfare Act by the USDA, Animal and Plant Health Inspection Service. The animal care facilities were fully accredited by the American Association for Accreditation of Laboratory Animal Care beginning June 4, 1971.

4.0 PRECHRONIC PHASES: METHODS AND RESULTS

4.1 Acute Study

Single-dose range-finding studies were conducted with male rats and female mice to determine the highest dose to be used in the 8-week subchronic study. Groups of 2 animals each were administered a single dose of trichloroethylene in corn oil by gavage by oral intubation and observed for 14 days. Ten dosages were used: 100, 178, 316, 562, 1000, 1420 (rats only), 1780 (mice only), 3160, 5620, 10,000, and 17,800 mg/kg. The lowest doses causing death, 5620 mg/kg for rats and 10,000 mg/kg for mice, were selected as the highest doses to be used in the 8-week subchronic study.

4.2 Eight-Week Subchronic Study

The objective of this study was to estimate the Maximum Tolerated Dose (MTD) for trichloroethylene to be used in rats and mice in the bioassay for carcinogenicity. In this context the MTD is defined as the highest dose that can be administered during the chronic study, which will not be expected to alter the animals' survival rate from effects other than carcinogenicity.

4.2.1 Methodology

Animals were placed into 6 groups each of 5 males and 5 females so that initially the average weight per animal in each treatment group was the same. Five groups received the test compound at varying dosages; one group served as the control and received only the vehicle (corn oil).

Trichloroethylene was dissolved in corn oil and animals were dosed by gavage under a hood for 5 consecutive days per week for 6 weeks on the basis of milligrams trichloroethylene per kilogram body weight. Doses ranged from 562 to 5620 mg/kg in rats and from 1000 to 10,000 mg/kg in mice (Table II).

Table II. Design and Survival Results - Trichloroethylene Subchronic Study

	Rats				Mice			
Group	Dose	Concn	Survival[c]		Dose	Concn	Survival[c]	
No.	(mg/kg)[a]	(mg/ml)[b]	Males	Females	(mg/kg)[a]	(mg/ml)[b]	Males	Females
1	0	0	5/5	5/5	0	0	5/5	5/5
2	562	562	5/5	5/5	1000	100	5/5	5/5
3	1000	1000	5/5	5/5	1780	178	5/5	5/5
4	1780	1780	5/5	5/5	3160	316	5/5	3/5
5	3160	3160	5/5	5/5	5260	562	1/5	1/5
6	5620	5620	0/5	0/5	10,000	1000	0/5	0/5

[a]mg Trichloroethylene/kg body weight.
[b]mg Trichloroethylene/ml corn oil.
[c]At 8 weeks.

Animals were weighed weekly and the most recent weight was used as a guide for the dosage. All animals of one sex within a treatment group received the same dosage, that is, the volume administered to all animals was based on the mean body weight for the group.

Dosing was stopped after 6 weeks and the animals were maintained for an additional 2 weeks under control conditions to detect delayed toxicity. Body weight was recorded on day 0 and weekly thereafter. Food consumption and observations of appearance, behavior, and signs of toxic effects were recorded weekly. Observations of mortality were made daily. Each animal that died and all animals killed at termination at 8 weeks were gross necropsied. No histopathology was performed. Mean body weights for each group, including standard deviations, and survival by week were determined (Tables XIIIa, XIIIb, XIVa, and XIVb, Appendix B).

4.2.2 Results - Rats

While body weight gains of all treated groups were below those of controls, the reduction exceeded 20% for doses above 1780 for females and 3160 mg/kg/day for males.

No abnormal clinical signs were evident for doses of 1780 mg/kg/day and below. Hunching, discoloration of the fur due to urine stains, alopecia, and labored respiration were observed at 3160 and 5620 mg/kg/day. Kidney lesions were observed in 2 males at 1780 mg/kg/day, one a dilated kidney pelvis and the other a dark red renal medulla. Incidental findings included large abscessed areas in all lobes of the lungs of 2 test animals. No other gross lesions were noted.

4.2.3 Results - Mice

Body weight gains in all surviving groups were not significantly affected in a dose-related manner. Except for death at the higher doses, there were no signs attributable to the compound. All survivors appeared normal at termination. No lesion was noted in any mouse at necropsy.

4.2.4 Selection of MTD

Based on body weight gains and survival rates, the initial high doses (estimated maximum tolerated dose) were selected as 1300 mg/kg for both male and female rats, 2000 mg/kg for male mice, and 1400 mg/kg for female mice.

5.0 CHRONIC TESTING: METHODOLOGY

5.1 Experimental Design

5.1.1 Experimental Groups

Trichloroethylene was administered at 2 doses to both sexes of Osborn-Mendel rats and B6C3F1 mice, in groups of 50 animals each. Therefore, a total of 400 treated animals divided into 8 groups was used. Groups of 20 matched[1] vehicle-treated controls were used for each sex of each species. Ninety-nine male and 98 female rats and 77 male and 80 female mice were used as vehicle-treated "colony controls", and 70 male and 76 female mice were used as untreated colony controls. They served as matched controls to trichloroethylene and to other compounds that were tested simultaneously. A group of positive control animals treated with carbon tetrachloride was also studied; see section 5.6. Treated and control animals came from the same source and were otherwise comparable. Animals were randomly[2] assigned to treatment and control groups, so that initially the average weight in each group was approximately the same.

5.1.2 Dates of Study

Rats receiving trichloroethylene and their controls were placed on study at 48 days of age on April 11, 1972 and killed after 110 weeks on May 23, 1974. Mice receiving trichloroethylene and their controls were placed on study at 35 days of age on August 21, 1972 and killed after 90 weeks on May 15, 1974.

5.1.3 Preparations and Doses

Trichloroethylene was dissolved in corn oil at concentrations of 60% w/v for rats and 10-24% w/v for mice and administered by gavage for 5 consecutive days per week. The amount of solution to be administered was calculated weekly on the basis of the animal body weight, using the following factor: dose (mg/kg)/concentration (mg/ml) = F (ml/kg). For instance, a group of mice scheduled to receive trichloroethylene at a dose of 1000 mg/kg/day and weighing an average of 20 g at the end of week 2 actually received 0.13 ml of a 15% solution during week 3 (1000/15 = F = 6.6 ml/kg; 6.6 x 20/1000 = 0.13 ml/20 g). Later in the study when weighing was done only once monthly, each newly calculated dose was administered for 4 weeks. All animals of one sex within a treatment group received the same dosage, that is, the volume of trichloroethylene solution administered to all animals was based on the mean body weight for the group. Controls received by gavage a dose of vehicle (corn oil) based on the factor calculated for the high dose group.

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[1]Vehicle-treated controls will be assumed to be matched, and will not be referred to as such in the remainder of this report.

[2]Animals were not distributed according to a table of random numbers.

5.1.4 Treatment Schedule

At the beginning of the chronic study, the high dose groups received the estimated maximum tolerated dose as determined in the 8-week subchronic study. The low dose was one-half of the high dose in all cases. In order to maintain the animals at the maximum doses that could be actually tolerated, body weight changes and survival were monitored, and, accordingly, doses were changed for the rats after 7 and 16 weeks of treatment, and for the mice after 12 weeks. To help assure survival until planned termination the dosing schedule was changed for rats to a cycle of 1 week of no treatment followed by 4 weeks of treatment. Seventy-eight weeks after the start of the test, dosing of rats and mice was stopped and observation of the animals continued until the test was terminated after 110 weeks for rats and 90 weeks for mice. This dosing schedule is outlined in Table III and Figures 1a and 1b.

5.2 Observations

Individual body weights and food consumption per cage were recorded weekly for the first 10 weeks and monthly thereafter (Tables XVa, XVb, XVIa, and XVIb, and Figures 13a, 13b, 14a, and 14b, Appendix B). Records of appearance, behavior, and signs of toxic effects were maintained at the same intervals as above. Animals were checked daily for mortality, and moribund animals were killed.

5.3 Necropsy

A gross necropsy was performed on each animal that died or was killed and on all survivors at termination. The weight of any discrete subcutaneous tissue mass was recorded. The dissection of rats and mice followed the same systematic technique whether the animals died or were killed. However, their blood smears for microscopic evaluation were prepared from the tail of each living animal immediately prior to injecting it with Diabutal^{R} intraperitoneally (0.3 to 0.5 ml for rats and 0.05 to 0.1 ml for mice). After induction of a state of anesthesia, the spinal cord and blood vessels at the back of the neck were severed with sharp-pointed scissors and the animal was exsanguinated and immediately necropsied.

The cervical lymph nodes, salivary glands, and thyroid with attached parathyroids, trachea, larynx, and esophagus (en bloc) were removed. The eyes, brain, pituitary, and nasal turbinates were removed, examined, and fixed. Thigh muscle and accompanying sciatic nerve and the femur were then excised, followed by abdominal skin (with mammary gland) and subcutaneous masses. The thoracic and abdominal cavities were then opened and the sternum was removed by cutting through the costochondral junctions. The thymus, heart (with small attached length of aorta), and lungs were removed. The lungs were fixed in their entirety. The thoracic spinal cord was removed. All lobes of the liver were taken including the free margin of each lobe. Any nodule or mass was represented in a block 10 x 5 x 3 mm cut from the liver and fixed in a marked capsule. The spleen was removed with a small piece of pancreas attached. The stomach was separated from the small intestines and esophagus and opened. Following removal of the stomach contents, its lining was examined. The mesenteric lymph nodes were

Table III. Dosage and Observation Schedule - Trichloroethylene Chronic Study

Dosage Group	Dose (mg TCE/kg Body Wt)	Percent of TCE in Corn Oil	Age at Dosing[a] (weeks)	Treatment Period (weeks)	Time-Weighted Av. Dose[b] (mg TCE/kg Body Wt)
Rats					
Low dose males and females	650	60.0	7	7[c]	
	750	60.0	14	9[c]	
	500	60.0	23	14[c]	
	500	60.0	37	48[d]	
	no treatment		85	32	549
High dose males and females	1300	60.0	7	7[c]	
	1500	60.0	14	9[c]	
	1000	60.0	23	14[c]	
	1000	60.0	37	48[d]	
	no treatment		85	32	1097
Mice					
Low dose males	1000	15.0	5	6[c]	
	1000	10.0	11	6[c]	
	1200	24.0	17	66[c]	
	no treatment		83	12	1169
High dose males	2000	15.0	5	6[c]	
	2000	20.0	11	6[c]	
	2400	24.0	17	66[c]	
	no treatment		83	12	2339
Low dose females	700	10.0	5	12[c]	
	900	18.0	17	66[c]	
	no treatment		83	12	869
High dose females	1400	10.0	5	6[c]	
	1400	20.0	11	6[c]	
	1800	18.0	17	66[c]	
	no treatment		83	12	1739

Matched controls received doses of corn oil by gavage calculated on the basis of the factor for the high dose animals (see section 5.1.3).

[a]Age at initial dose or dose change.

[b]Time-weighted average dose = Σ (dose in mg/kg x no. of days at that dose)/Σ (no. of days receiving any dose). In calculating the time-weighted average dose, only the days an animal received a dose are considered.

[c]Dosing 5 days per week each week.

[d]Dosing 5 days per week, cycle of 1 week of no treatment followed by 4 weeks of treatment. (Animals were treated for 38 weeks of the 48 week period.)

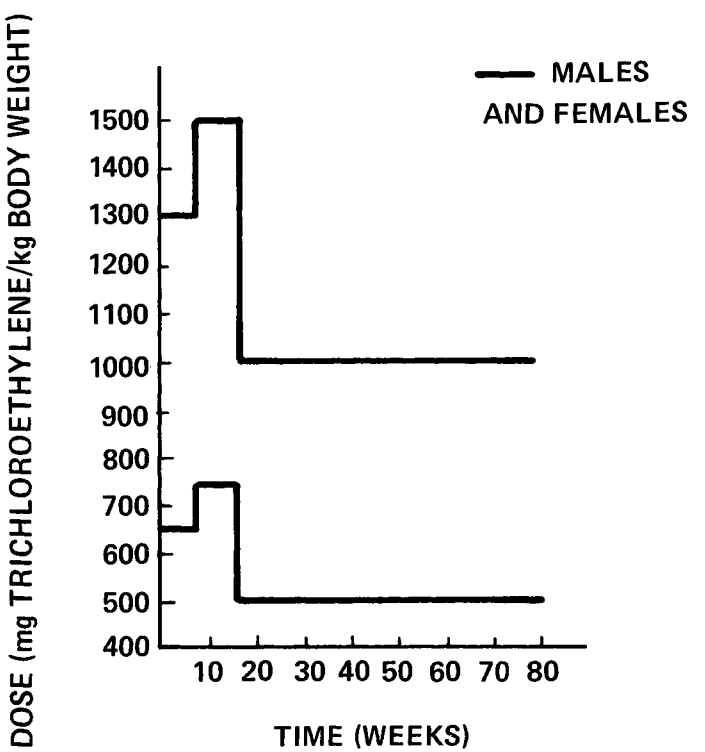

Figure 1a. Dosage Schedule - Chronic Study - Trichloroethylene-Treated Rats

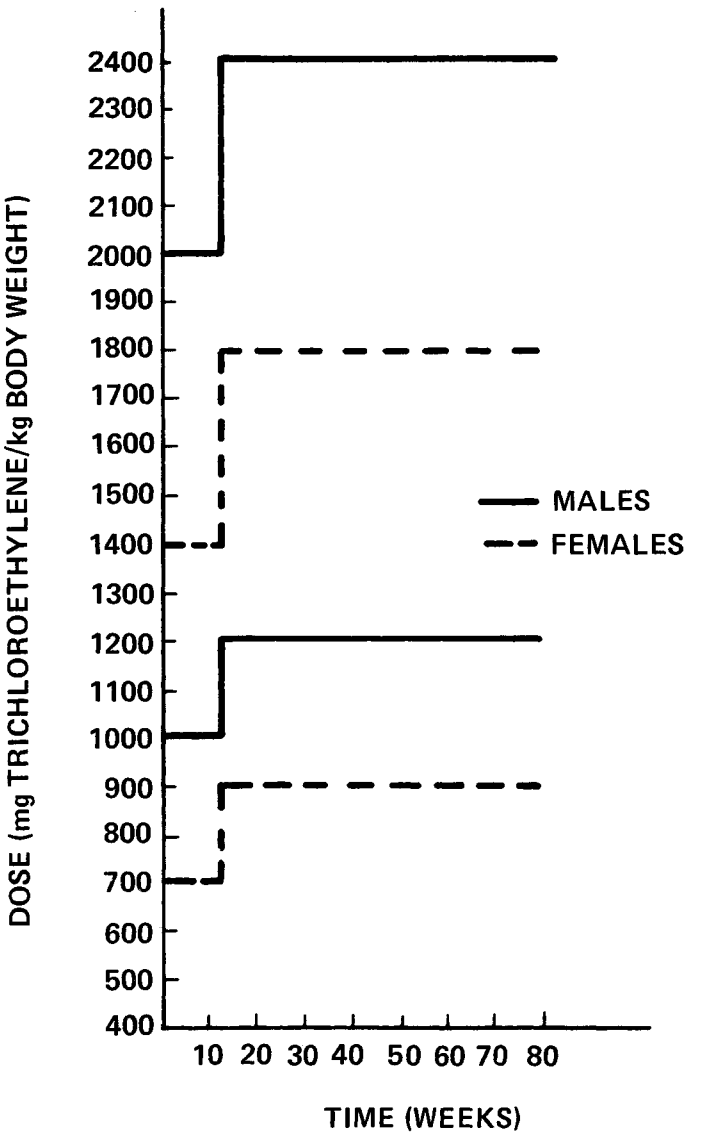

Figure 1b. Dosage Schedule - Chronic Study - Trichloroethylene-Treated Mice

excised along with a small amount of surrounding fatty tissue. The intestines were removed and straightened by cutting through their mesenteric attachment and were examined externally for abnormalities. Portions of duodenum, jejunum, ileum, and colon (about 1.5 cm long) were excised and placed in a capsule for fixation. If any gross lesion was noted from the serosal surface, the intestines were opened. After the selected portions were excised for separate preservation, the remaining portions of intestines and cecum were fixed in the container with the bulk of the tissues. The adrenals were removed with surrounding fatty tissue. After the kidneys were removed and their capsular surface freed of other tissues, they were bisected longitudinally and placed in tissue capsules. The urinary bladder was removed, a small amount of 10% formalin was injected if contracted, and it was opened slightly to examine the lining. The prostate and seminal vesicles were removed together. The testes with epididymides attached were fixed en bloc after the attached fat pad was removed. The ovaries, uterus, and vagina were removed and fixed en bloc. The posterior 2 cm of rectum was removed with surrounding connective tissue and fixed en mass.

Subcutaneous and other masses were removed and weighed. Location, size (dimensions or weight), color, consistency, and general appearance were recorded. Representative sections, 5 mm thick, were excised and fixed. If an animal had more than one mass or nodule, sections of each were placed in a marked capsule. If a mass involved the head, the entire skull was fixed after the cranial cavity had been opened.

The above protocol applied to animals necropsied after February 28, 1974, when the carcasses were no longer retained. Before that time, similar procedures were used, but fewer tissues were taken, and the carcasses were preserved.

5.4 Histological Preparation and Microscopic Examination

The necropsy was conducted by a dissector under the supervision of a pathologist. Each time a tissue was removed the presence of any gross lesion was recorded. All tissues were fixed in 10% buffered formalin (Appendix D, Tables XXVIIIa and XXVIIIb). The histologic technician trimmed the tissues under a fume hood to a thickness of 3-6 mm; any missing tissues or unusual lesions were brought to the attention of the pathologist. Tissues were dehydrated, cleared, and infiltrated on an Autotechnicon tissue processor, using a series of Technicon reagents (S-29 and UC-670) and Paraplast. Tissues were placed in a vacuum oven and subsequently embedded in Paraplast, using a Tissue Tek system. All blocks were sectioned at 5 microns; one slide was prepared from each block and stained with hematoxylin and eosin. Special staining procedures such as PAS, Trichrome, and PTAH were used occasionally as requested by the pathologist to diagnose a specific tumor cell type. All paraffin blocks were sealed with Paraplast and stored in plastic cabinets. Slides were boxed and delivered with all necropsy forms and work sheets to the pathologist at Hazleton Laboratories, Inc., for examination. Seven to 9 slides were prepared per mouse, and 7-10 per rat.

5.5 Data Processing and Confirmation

Summaries of the numbers of tissues examined for rats and mice are given in Tables XXVIIIa and XXVIIIb. The pathologist recorded his findings into a dictaphone for the typist to transcribe on a computer data form, the Individual Animal Data Record (IADR). Information was included on the death of the animal, details of the necropsy, including physical abnormalities and tumors. IADRs were transmitted to EG&G/Mason Research Institute, Bethesda, MD, NCI operations contractor for the computerized system for collection, maintenance, and analysis of bioassay data. This system is known as the Carcinogenesis Bioassay Data System (CBDS) (Linhart et al., 1974). Diagnoses of tumors and other animal abnormalities were coded using the coding system described in the "Systematized Nomenclature of Pathology" (SNOP), prepared by the Committee on Nomenclature and the Classification of Disease, College of American Pathologists, Chicago, 1965. The SNOP code has been modified for use in the Carcinogenesis Bioassay Data System. One code is entered for the topography or site of the lesion, and another for the diagnosis. Output from CBDS is in the form of the Individual Animal Pathology Report, which presents the complete pathology data for the animals within a group, including both tumor and non-tumor diagnoses. The initial output was reviewed and corrected by the pathologist at Hazleton. A further review of the findings was conducted by pathologists at Tracor Jitco, Inc., and the National Cancer Institute with special attention given to liver lesions. The differences in opinion were minor, and, in general, supported the diagnoses as presented. The final data are presented in the form as seen in Tables XXXIa, XXXIb, XXXIIa, and XXXIIb.

5.6 Positive Controls

In this bioassay carbon tetrachloride was administered as a positive control to both rats and mice, obtained from the same source and maintained under the same environmental conditions as the animals receiving trichloroethylene. Solutions were prepared and administered by gavage in the manner described for trichloroethylene. Dosing was 5 times per week thoughout the study according to the dosage schedule in Table IV:

Table IV. Dosage and Observation Schedule - Carbon Tetrachloride Study

Dosage Group	Dose (mg CCl_4/kg Body Wt)	Percent of CCl_4 in Corn Oil	Age at Dosing[a] (weeks)	Treatment Period (weeks)	Time-Weighted Av. Dose[b] (mg CCl_4/kg Body Wt)
		Rats			
Low dose males	25	2.5	6	10[c]	
	50	5.0	16	68[c]	
	no treatment		84	32	47
High dose males	50	2.5	6	10[c]	
	100	5.0	16	68[c]	
	no treatment		84	32	94
Low dose females	100	10.0	6	14[c]	
	75	7.5	20	64[c]	
	no treatment		84	32	80
High dose females	200	10.0	6	14[c]	
	150	7.5	20	64[c]	
	no treatment		84	32	159
		Mice			
Low dose males and females	1250	25.0	5	78[c]	
	no treatment		83	12	1250
High dose males and females	2500	25.0	5	78[c]	
	no treatment		83	12	2500

Matched controls received doses of corn oil by gavage calculated on the basis of the factor for the high dose animals (see section 5.1.3).

[a]Age at initial dose or dose change.

[b]Time-weighted average dose = Σ (dose in mg/kg x no. of days at that dose)/Σ (no. of days receiving any dose). In calculating the time-weighted average dose, only the days an animal received a dose are considered.

[c]Dosing 5 days per week each week.

6.0 CHRONIC TESTING: RESULTS - RATS

Sections 6.1 - 6.5 refer to trichloroethylene-treated rats and their vehicle-treated controls.

6.1 Body Weights

The range of the mean body weights for male rats was 193-194 g, and for female rats, 144-146 g, when placed on experiment (Tables XVa and XVb, Appendix B). Weights in male rats peaked at 622 g at 46 weeks in control, 575 g at 46 weeks in low dose, and 535 g at 38 weeks in high dose animals. At these times there were, respectively, 20 control, 43 low dose, and 39 high dose animals. The average weights of surviving males in all groups were much lower than this at the termination of the test at 110 weeks. At this time the surviving 2 controls averaged 382 g, the 8 low dose males, 383 g, and the 3 high dose males, 423 g.

Average group weights of female rats peaked at 404 g at 62 weeks in control, 322 at 70 weeks in low dose, and 326 g at 94 weeks in high dose animals. At these times there were, respectively, 17 control, 23 low dose, and 20 high dose animals. The average weights of female rats were also lower at termination at 110 weeks. At this time, 8 surviving controls averaged 326 g, and 13 low dose and 13 high dose females both averaged 311 g. These decreases in average weights may reflect weight losses in individual animals and/or a mortality pattern where larger animals died sooner.

6.2 Clinical Observations

During the first year of the study, the appearance and behavior of the treated rats were generally comparable with the controls except that occasionally hunched appearance and discoloration of the fur of the lower abdomen by urine stains were noted in a few test animals as early as week 2. Respiratory involvement characterized by labored breathing, wheezing, and/or reddish nasal discharge was noted in both treated and control groups, and increased as the animals aged.

Adverse clinical signs in all treatment groups were noted at a low or moderate incidence during the first year, and with gradually increasing frequency in the treated animals during the second year of the study. These signs included hunched appearance; roughening of the haircoat; eyes squinted or showing a reddish discharge; localized alopecia on extremities or body; sores, particularly on the tail; and stains on the haircoat.

6.3 Survival

Data for rats are given in the individual pathology tables in Appendix D. The methodology for statistical analysis is described in Appendix C. Data for statistical analysis are summarized in Tables XVIIIa and XVIIIb, Appendix C. Tables of results are also in Appendix C.

A high proportion of rats died during the experiment. For males, 17/20 control, 42/50 low dose, and 47/50 high dose animals died prior to

scheduled termination. For females, 12/20 control, 35/48 low dose, and 37/50 high dose animals died before scheduled termination. (Two low dose females were missing and were not counted in the denominator for that group.)

Survival probabilities were estimated by the product-limit procedure of Kaplan and Meier (1958) (Tables XXa and XXb and Figures 2a and 2b). The estimated probabilities (standard errors) of survival to 110 weeks were 0.100 (0.067) for male control, 0.140 (0.049) for male low dose, 0.060 (0.034) for male high dose, 0.400 (0.110) for female control, 0.252 (0.061) for female low dose, and 0.260 (0.062) for female high dose.

The survival times of vehicle control, low dose, and high dose groups of rats were compared (Table XXc). Among male rats, the age-adjusted test for linear trend (Tarone, 1975) is significant at P = 0.001, and the high dose vs. control test and the high dose vs. low dose test are significant at P = 0.001, indicating that high dose male rats died earlier than low dose and control male rats and that earlier death is associated with higher dose. Among female rats, the low dose group died earlier than the control group, as shown by a test with P = 0.028. The high dose female rats died earlier than control female rats (P = 0.049), but slightly, and not significantly, later than the low dose female rats. The dose-response test, therefore, shows only P = 0.117.

6.4 Pathology

A variety of neoplastic and non-neoplastic lesions were recorded among control, low dose, and high dose rats. Tumors in specific organ systems by site of origin and by anatomic site are summarized in Tables XXIXa (page 121) and XXIXb (page 124), and pathologic observations for individual animals are listed in Tables XXXIa (page 135) and XXXIb (page 147) in Appendix D.

There are no significant differences in the incidences of total tumors or of a specific tumor type between treated and control rats. As seen in Table V, there is no indication of a treatment-related effect. While the percentage of tumor-bearing animals is actually lower in treated animals, this is likely related to the decrease in their survival.

Table V. Tumor Incidence - Rats with Tumors

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Before 110 weeks	4/17	5/42	4/47	4/12	6/35	4/37
At 110 weeks	1/3	2/8	1/3	3/8	6/13	8/13
Total	5/20	7/50	5/50	7/20	2/48	12/50
Percent	20%	14%	10%	35%	25%	24%

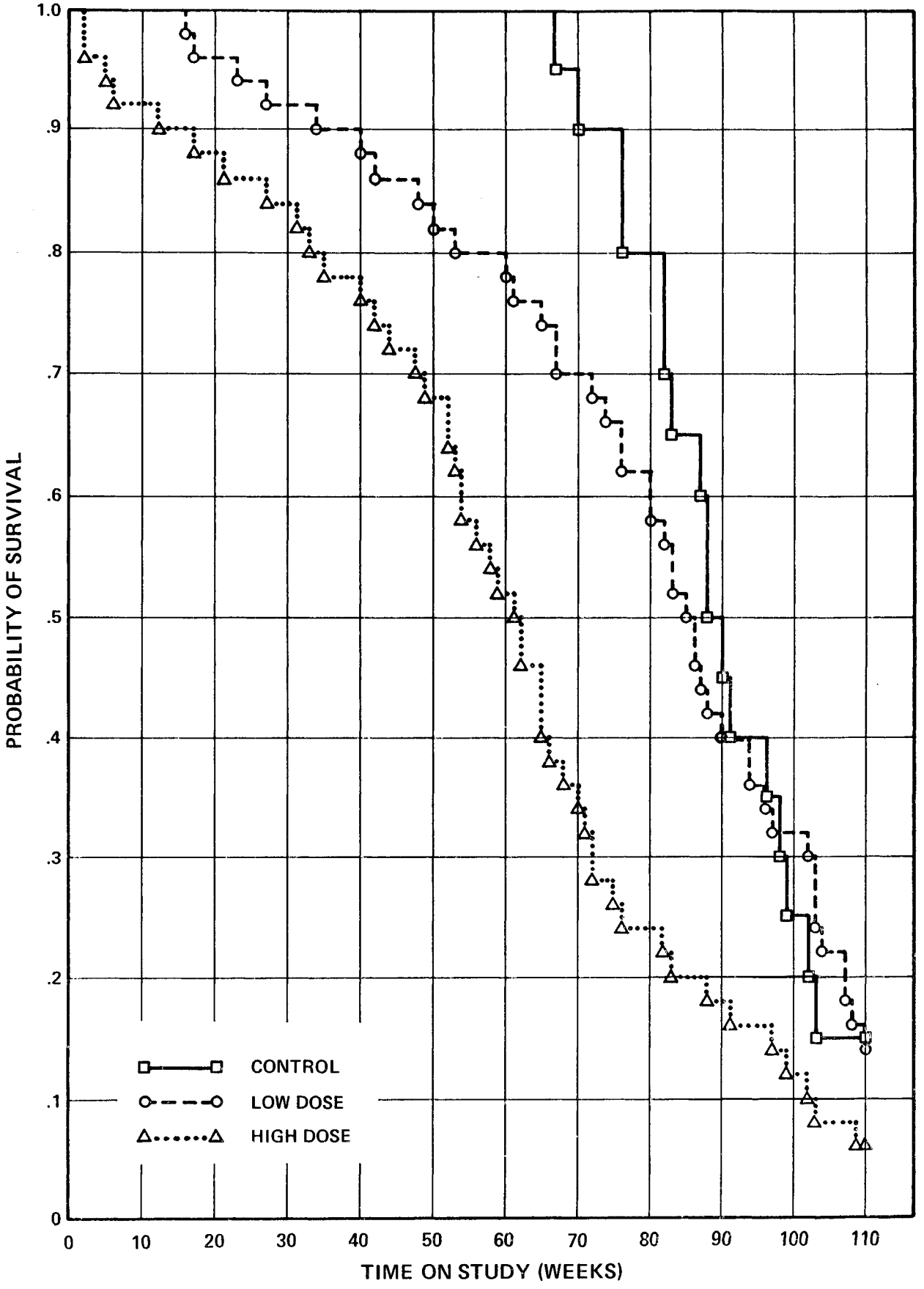

Figure 2a. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Male Rats

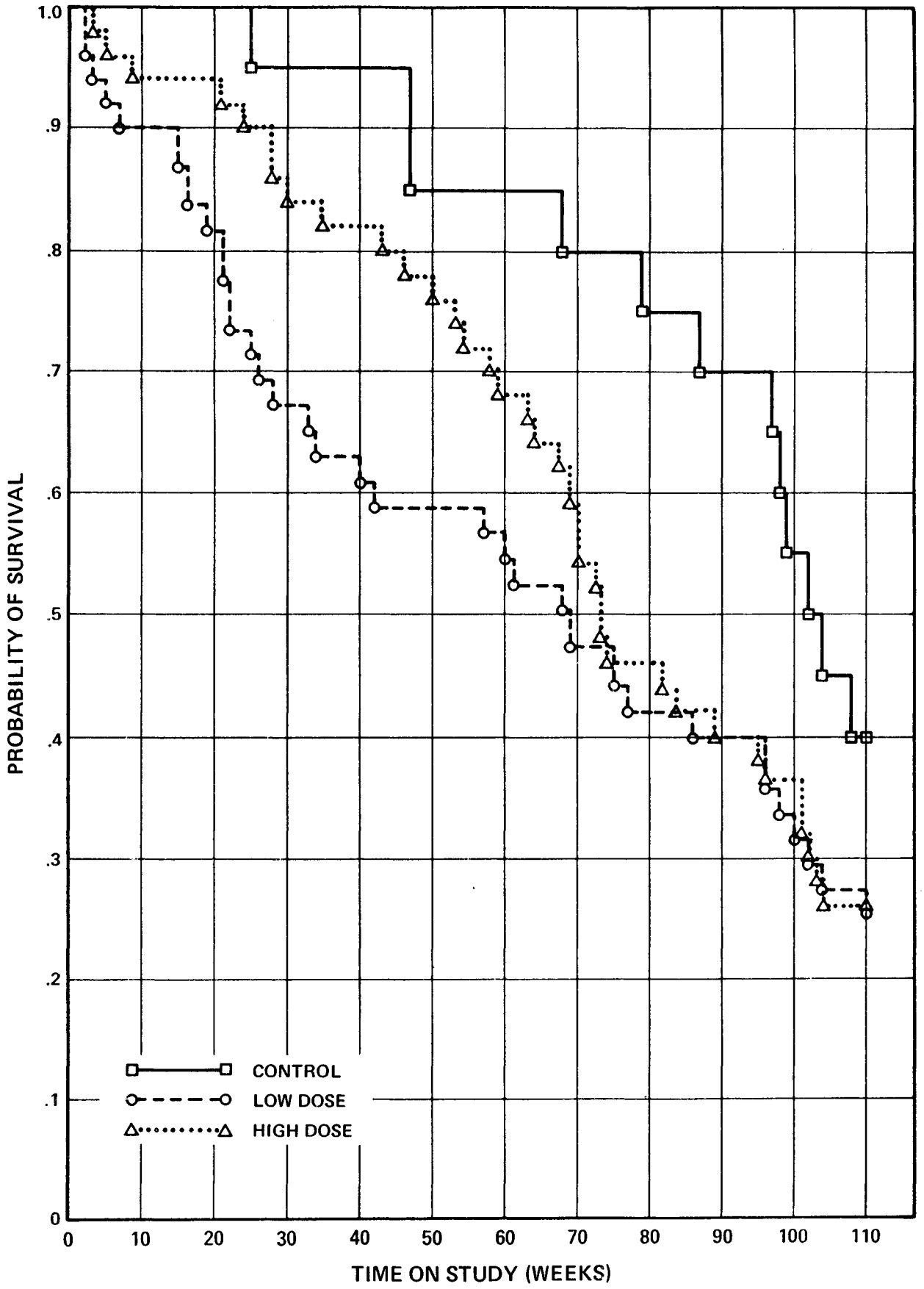

Figure 2b. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Female Rats

Incidences of the most common tumor types according to those dying before and at 110 weeks are presented in Table XXII (page 102) in Appendix C. The tumors observed are described in the following paragraphs.

Primary malignant renal tumors were observed in 4 rats, 2 of which were unilateral malignant mixed tumors of the kidney in male controls (010, 019). One of these (010) also had a hamartoma in the outer medulla of the opposite kidney. A similar hamartoma affected the outer renal medulla of one of the low dose males (002). The hamartomas contained an admixture of adipose tissue, spindle cells, and tubular structures with ciliated columnar epithelium. The malignant mixed tumors consisted primarily of proliferating fat cells and spindle cells mushrooming from the renal medulla through the cortex to form a large extrarenal protuberance. Mitoses were abundant and frequently abnormal. The proliferating tissues were invasive and contained as an integral component small tubular nests of proliferating epithelial tissue. Thus, the 2 renal hamartomas and the 2 malignant mixed tumors contained the same cellular elements. They appeared to arise in or near the renal medulla. The only other primary renal tumor was an adenocarcinoma arising from nephronic epithelium in a low dose male (015).

The relationship between the renal hamartomas (2 rats) and renal malignant mixed tumors (one of the same rats and another) remains to be clarified. The hamartomas clearly arose near the corticomedullary junction, the mixed tumors apparently so. The similarities of site of origin and tissue components suggest that they were developmentally related. The hamartoma was probably congenital and may have undergone malignant transformation to the malignant mixed tumor. The mixed tumor had structural similarities comparable to nephroblastoma, a well known tumor in many species including human beings, swine, and others. Because the mixed tumors in these older rats had both epithelial and nonepithelial components and were obviously highly aggressive, the term malignant mixed tumor is considered suitable.

Primary tumors of the thyroid were found in 5 animals. Of these, 2 were benign follicular-cell adenomas found in a control male and a low dose male. Three malignant follicular-cell adenocarcinomas were also found in a low dose male, a high dose male, and a high dose female.

No pituitary or mammary tumors were seen in the male rats. Among the females, however, chromophobe adenomas and a benign tumor of the pituitary were found in 4/20 controls, 2/47 low dose, and 6/49 high dose groups. Mammary fibroadenomas were found in 3/20 controls, 5/45 low dose, and 7/48 high dose female rats. Multiple mammary fibroadenomas were found in one low dose female (050), and 3 high dose females (023, 030, and 033). The only other primary mammary tumor was an adenocarcinoma in a control female (014). Three other tumors of the reproductive system were found, an ovarian granulosa-cell carcinoma in a control female (009) and 2 sarcomas of the endometrium in a low dose female (026) and a high dose female (037). The sarcomas were rather poorly differentiated and a more specific classification is not considered feasible.

There were several other miscellaneous malignant neoplastic entities of epithelial origin, each occurring in a different animal. One control male

(007) had a primary pulmonary carcinoma with both glandular and squamous differentiation; multiple metastases with similar biphasic differentiation were present in the lungs, cervical lymph node, and kidneys. This was a very aggressive tumor. A low dose male (011) had a squamous cell carcinoma in the axillary region. A high dose male (034) had a pilomatrixoma of the skin and another (014) had a massive aortic body tumor at the base of the heart. One low dose female (023) had an adrenal cortical carcinoma.

Two rats had fibromas of the subcutis, a low dose male (025) and a low dose female (013). Malignant tumors included a fibrosarcoma of the subcutis in a low dose male (004) and a malignant anaplastic giant-cell tumor in the abdomen of a control male (002). The latter is the only tumor of this type in any rat on the study. A low dose female (032) had a subcutaneous liposarcoma. Hemangiosarcomas were recognized in a control male, a low dose male, 2 high dose males, and a low dose female.

Tumors of hematopoietic type were limited to reticulum-cell sarcoma, a malignant tumor which affected 1 control female (004), 1 low dose female (016), and 1 high dose female (006).

No non-neoplastic lesions appeared to be related to treatment with the exception of renal changes. Slight to moderate degenerative and regenerative tubular alterations, primarily affecting proximal tubular epithelium, were common in treated rats but lacking in controls. However, chronic renal disease occurred frequently among aged treated and control rats. A high incidence of chronic respiratory disease was observed among the rats without any apparent difference in type, severity, or morbidity as to sex or group. No significant toxic hepatic changes were observed.

6.5 Tumor Probabilities

For the purpose of statistical analysis, letters, or marks, were assigned to sets of pathologic diagnoses (Table XVII). Frequencies of the more commonly observed marks are summarized in Table XXII, Appendix C.

The probabilities of observing histopathologic diagnoses among control, low dose, and high dose groups of rats were estimated. See Appendix C for a description of methods of estimation and statistical testing. Tests were performed for reticulum-cell sarcoma, lymphosarcoma, or malignant lymphoma (mark b), fibroadenoma of the mammary gland (mark g), hemangioma of any site (mark h), follicular adenocarcinoma of the thyroid (mark p), and chromophobe adenoma of the pituitary (mark t). Since neither hepatocellular carcinoma of the liver (mark a) nor adenoma and carcinoma of the lung (mark c and d) was observed in any rat, as they were in mice, tests comparing these marks were not performed. Test results are shown in Tables XXIIIa-e. None of the tests demonstrates increases in the probability of observing a tumor for dosed rats over control rats.

6.6 Controls

6.6.1 Survival

Table VI shows a comparison of the survival of the rats receiving carbon tetrachloride and trichloroethylene with pooled colony controls at 78 and 110 weeks:

Table VI. Comparison of Survival of Colony Controls and Trichloroethylene- and Carbon Tetrachloride-Treated Rats

			Trichloroethylene				Carbon Tetrachloride			
	Controls		Low Dose		High Dose		Low Dose		High Dose	
Interval	M	F	M	F	M	F	M	F	M	F
Initial	100	100	50	50	50	50	50	50	50	50
78 weeks	67	75	31	20	12	23	34	38	34	21
110 weeks	26	51	8	13	3	13	14	26	7	14

At both time periods a slightly greater number of rats survived which had received carbon tetrachloride than those which had received trichloroethylene. Survival among the controls was generally greater.

6.6.2 Tumors

The incidence of both hepatocellular carcinoma and neoplastic nodule in colony controls and in rats receiving carbon tetrachloride is given in Table VII:

Table VII. Incidence of Liver Tumors - Colony Control and Carbon Tetrachloride-Treated Rats

Animal Group		Hepatocellular Carcinoma	Neoplastic Nodule
Males	controls	1/99	0/99
	low dose	2/50	2/50
	high dose	2/50	1/50
Females	controls	0/98	2/98
	low dose	4/49	2/49
	high dose	1/49	3/49

A low incidence of both hepatocellular carcinoma and neoplastic nodule was found in both colony controls and carbon tetrachloride-treated rats. Neither of these lesions was found in any of the rats receiving trichloroethylene. Statistical tests show no difference between control and trichloroethylene-treated animals (Tables XXIVa and XXIVb). However, the comparison of observed hepatocellular carcinomas in carbon tetrachloride-treated low dose female rats compared with pooled vehicle-treated female controls is significant by a one-tailed Fisher exact test (P = 0.011) (see Table XXIVc). When observed hepatocellular carcinomas and neoplastic nodules are analyzed together by the same test, there are significantly

more lesions among both the carbon tetrachloride-treated male rats (P = 0.033) and female rats (P = 0.009) than among respective male and female pooled controls (see Table XXIVd). Individual animal data for carbon tetrachloride-treated rats are given in Tables XXXIIIa-d, Appendix D.

In the carbon tetrachloride-treated rats marked hepatotoxicity with resultant fibrosis, bile duct proliferation, and regeneration was observed. The majority of liver nodules observed were diagnosed as being regenerative rather than neoplastic. These regenerative nodules were composed of hepatocytes which were generally larger and paler staining than the adjacent hepatic parenchyma. These nodules were multiple and circumscribed by mature fibrous connective tissues.

The lesions diagnosed as neoplastic nodules contained hepatocytes which varied in appearance from large pale-staining cells to smaller, more basophilic cells with a disorganized pattern, poorly defined sinusoids, and essential absence of portal triads. The hepatocytes composing the neoplastic nodules were much more variable in appearance than those of the regenerative nodules.

The diagnosis of hepatocellular carcinoma was based on the presence of less organized architecture and more variability in the cells comprising the neoplasms. Often the neoplastic cells were arranged in thickened cell plates or occasionally in an acinar pattern. Several of the carcinomas had a prominent vascular supply as opposed to the neoplastic and regenerative nodules.

7.0 CHRONIC TESTING: RESULTS - MICE

Sections 7.1 - 7.6 refer to trichloroethylene-treated mice and their vehicle-treated controls.

7.1 Body Weights

Weights of male mice averaged 17 g, and female mice, 14 g, when placed on experiment (Tables XVIa and XVIb). Average weights in male mice peaked at 34 g at 34 weeks in all groups and average weights in female mice peaked at 27 g at 34 weeks. Survivors of both sexes maintained approximately these respective weights until termination of the experiment after 90 weeks.

7.2 Clinical Observations

During the first year of the study, the appearance and behavior of the treated and control mice were generally comparable. Alopecia (generalized and/or localized), sores on the tail and other parts of the body, and a hunched appearance were noted in an increasing number of mice, mostly males, in all groups beginning on week 14 and persisting during the study.

After 50 weeks of treatment, bloating or abdominal distention was the predominant observation in the high dose males. By week 74, approximately 50% of all treated males had a bloated appearance which persisted until they died or were killed after 90 weeks. A few treated females also showed abdominal distention prior to termination. Subsequent necropsy of the animals confirmed the presence of liver tumors.

7.3 Survival

Data for mice are given in the pathology tables in Appendix D. Data for statistical analysis are summarized in Tables XIXa and XIXb, Appendix C. Tables of results are also in Appendix C.

Some mice died before the end of the experiment at 90 weeks from other than accidental causes. For males, 12/20 controls, 14/50 low dose, and 28/50 high dose died before termination. For females, 0/20 controls, 8/50 low dose, and 8/47 high dose died. (Three high dose females were missing and were not counted in the denominator for that group.)

Survival probabilities were estimated by the product-limit procedure of Kaplan and Meier (1958) (Tables XXIa and XXIb, Figures 3a and 3b). The estimated probabilities (standard errors) of survival of mice to the end of the chronic test at 90 weeks were 0.400 (0.110) for male control, 0.715 (0.064) for male low dose, 0.409 (0.070) for male high dose, 1.000 (0.000) for female control, 0.835 (0.053) for female low dose, and 0.830 (0.055) for female high dose.

The survival of control, low dose, and high dose groups of mice was compared (Table XXIc). The age-adjusted test for linear trend (Tarone, 1975) among male mice is marginally significant ($P = 0.096$), but high dose is not significantly different from control. High dose male mice lived

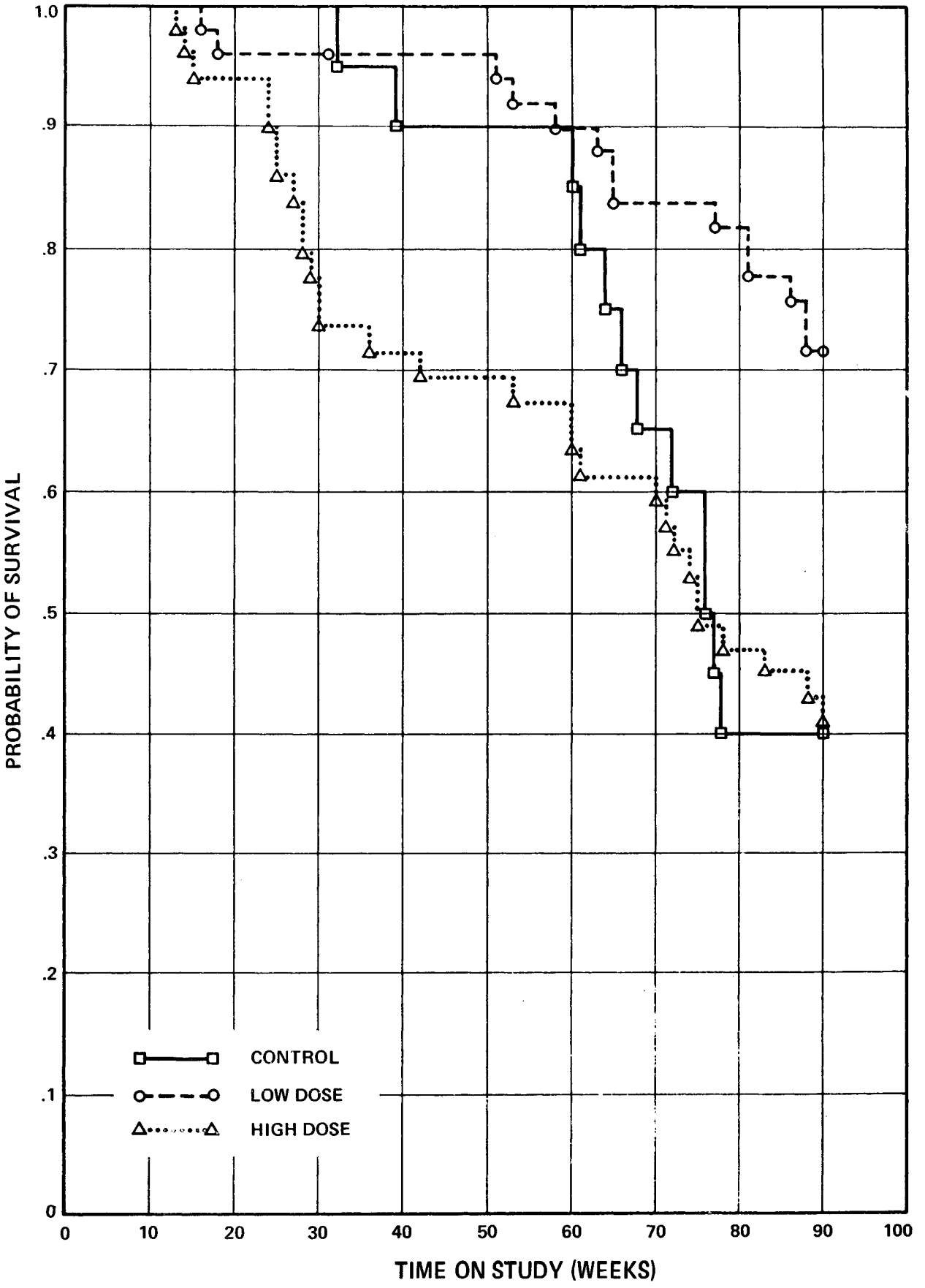

Figure 3a. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Male Mice

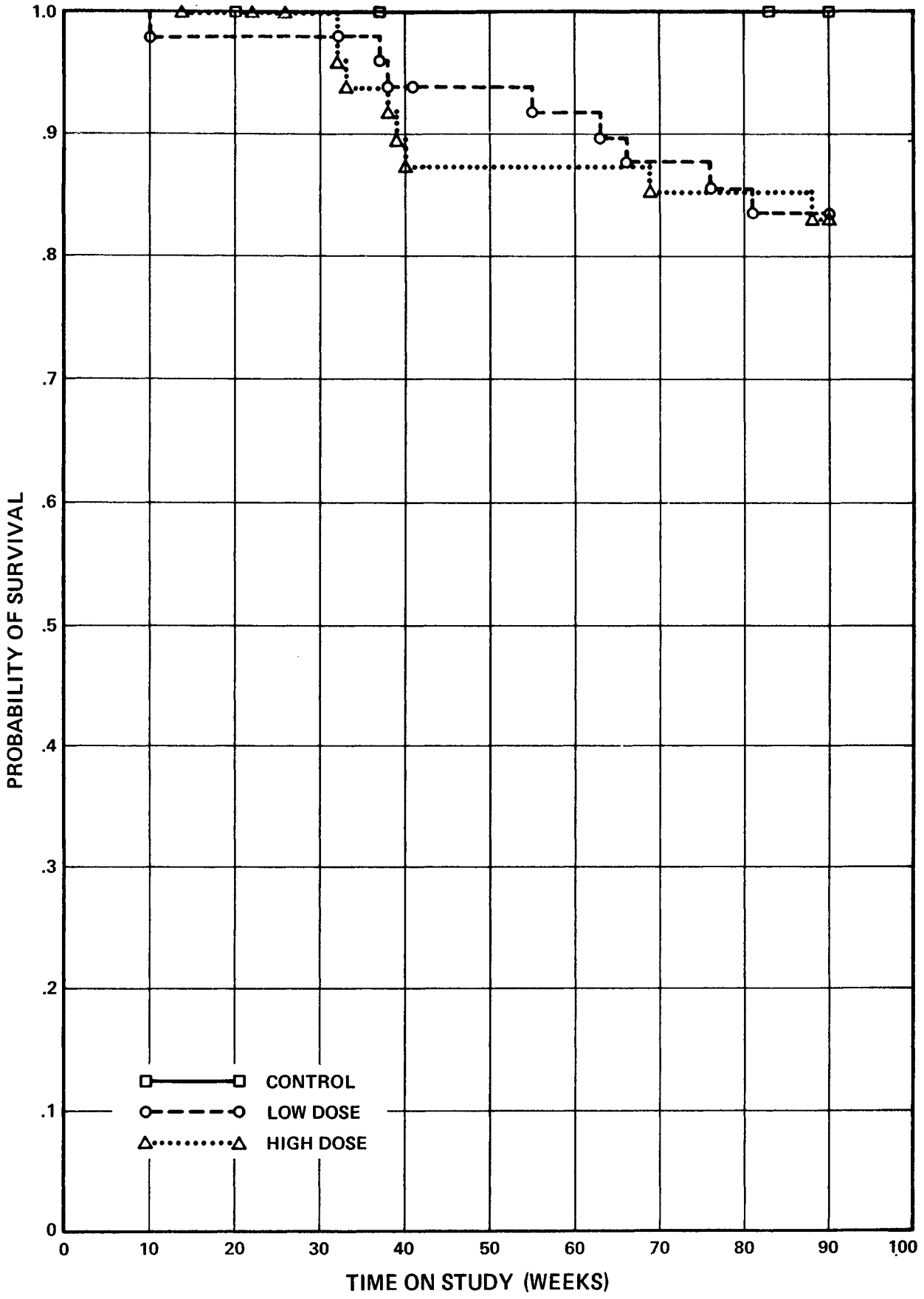

Figure 3b. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Female Mice

significantly shorter lives than low dose male mice (P = 0.001), but control male mice also had significantly shorter lives than low dose male mice (P = 0.004). Among female mice, low dose and high dose groups are not significantly different, but mice in both groups had significantly shorter lives than the control group (P = 0.035). The age-adjusted test for linear trend yields P = 0.068, only marginally significant.

7.4 Pathology

A variety of neoplastic and non-neoplastic lesions were observed among control and treated mice. Tumors in specific organ systems by site of origin and by anatomic site are summarized in Tables XXXa (page 127) and XXXb (page 130), and individual animal pathology is listed in Tables XXXIIa (page 158) and XXXIIb (page 168) in Appendix D.

As presented and discussed in section 7.5, highly significant differences in the incidences of primary malignant tumors of the liver, i.e., hepatocellular carcinomas, were found between treated and control groups. Hepatocellular carcinoma was observed in 1/20 control males, 26/50 low dose males, 31/48 high dose males, 0/20 control females, 4/50 low dose females, and 11/47 high dose females (Table XXV). Metastasis of the hepatocellular carcinoma to the lung, looked for on the basis of single sections, occurred in 4/50 low dose males, and in 3/48 high dose males. One control male (019) with hepatocellular carcinoma died during week 72 of the study. Among the low dose males the first hepatocellular carcinoma was observed in a mouse (029) that died during week 81 and the first metastasis was in one (007) that died during week 88. Among the high dose males the first hepatocellular carcinoma was observed in a mouse (046) that died during week 27; 10 mice that died on or before week 78 had hepatocellular carcinoma and the first metastasis was in a mouse (035) that died during week 83. Hepatocellular carcinoma was found only in females killed at termination at 90 weeks. Thus, the incidence of hepatocellular carcinoma was higher in dosed than in control mice of each sex and much higher in males than females. The major difference between low and high dose males is the earlier detection of these tumors in high dose mice.

The hepatocellular carcinoma varied in size and number among the affected mice. The diagnosis was based on size of neoplasm, histologic appearance, and the presence of metastasis. The tumors varied from those composed of well differentiated hepatocytes in a relatively uniform trabecular arrangement to rather anaplastic lesions in which mitotic figures occurred in cells which varied greatly in size and tinctorial characteristics. Many of the tumors were characterized by the formation of relatively discrete areas of highly anaplastic cells within the tumor proper which were, in turn, surrounded by relatively well differentiated neoplastic cells. In general, various arrangements of hepatocellular carcinoma occurred, as described in the literature, including those with an orderly cord-like arrangement of neoplastic cells, those with a pseudoglandular pattern resembling adenocarcinoma, and those composed of sheets of highly anaplastic cells with minimal cord or gland-like arrangement. Multiple metastatic lesions were observed in the lung, including several neoplasms which were differentiated and relatively benign in appearance. The morphology of these tumors is illustrated in Figures 4-10.

Figure 4. Primary hepatocellular carcinoma, mouse (high dose male #32). The rather well differentiated tumor of trabecular pattern has a recognizable boundary (->) with the pre-existent hepatic tissue. Rematoxylin and eosin, x75

Figure 5. Same as Figure 4, x300

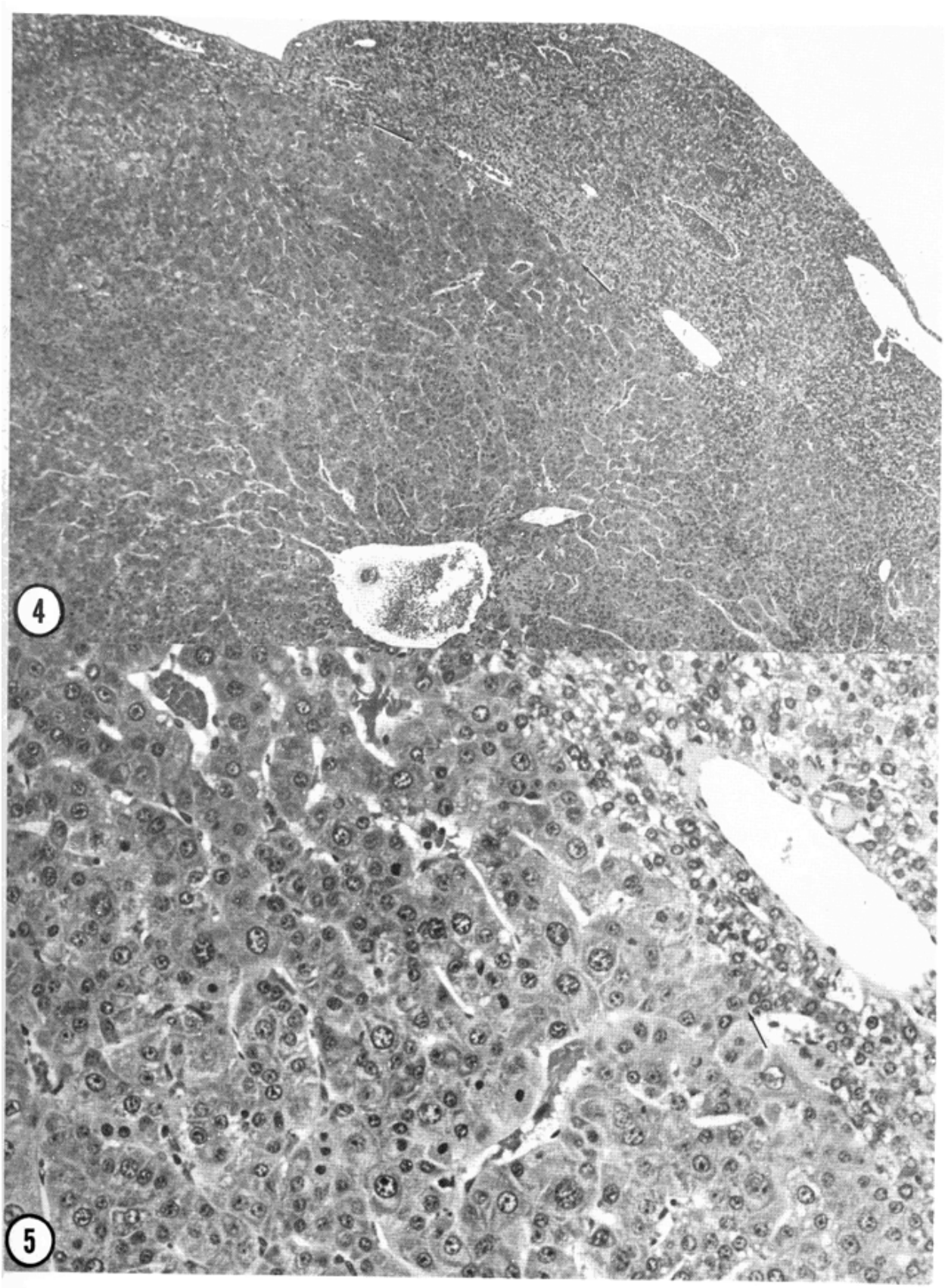
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Figure 6. Primary hepatocellular carcinoma, mouse (high dose male #26). The rather anaplastic solid tumor has a recognizable boundary (->) with the pre-existent hepatic parenchyma. Mitoses are abundant. Hematoxylin and eosin, x240

Figure 7. Primary hepatocellular carcinoma, mouse (high dose male #15) with both solid trabecular pattern and papillary pattern. Most cells are large and resemble normal hepatocytes. There are also smaller cells with less cytoplasm and smaller, more basophilic nuclei. These cells usually occur in clusters and are especially prominent in the larger papillary structures.

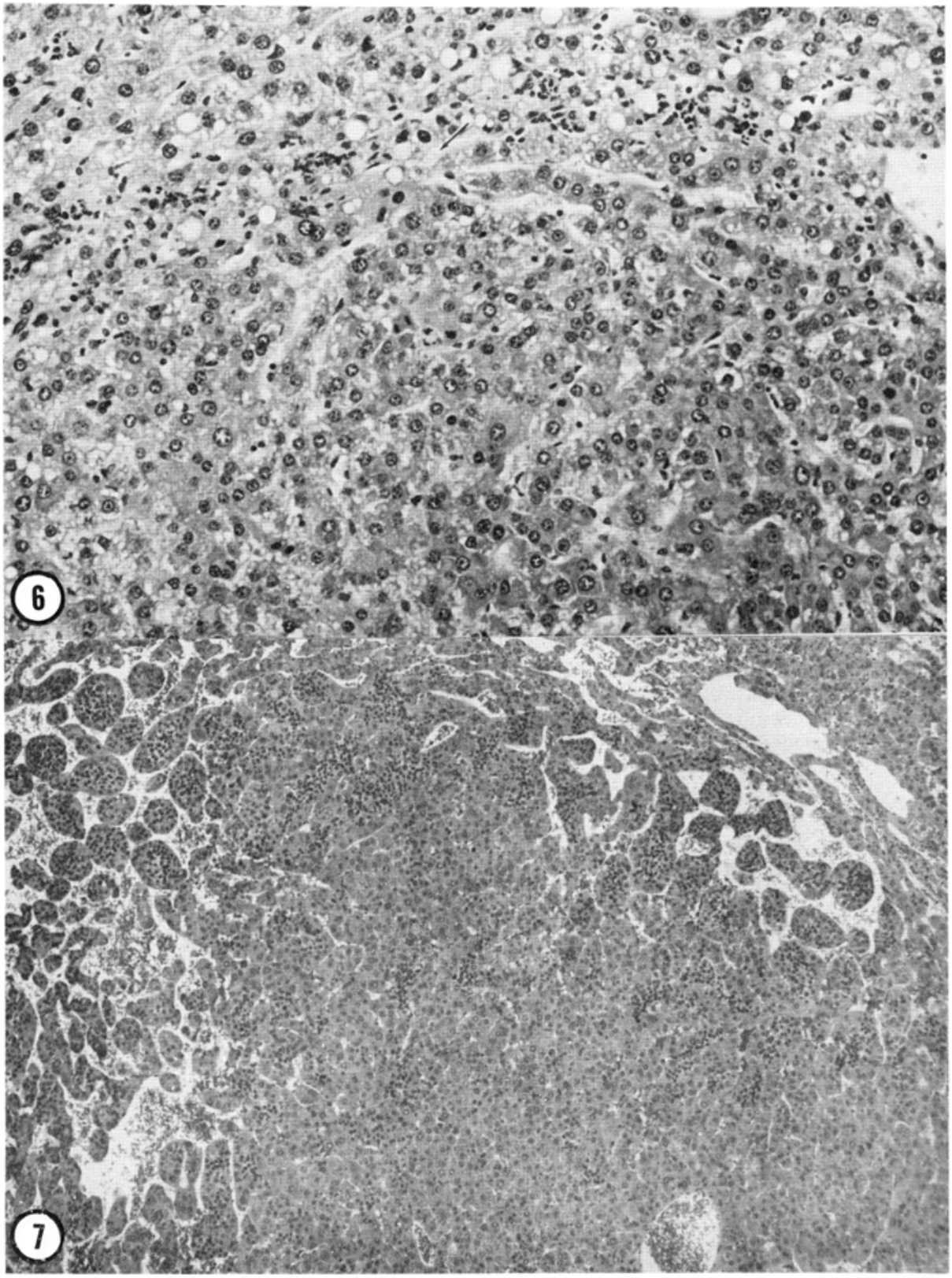
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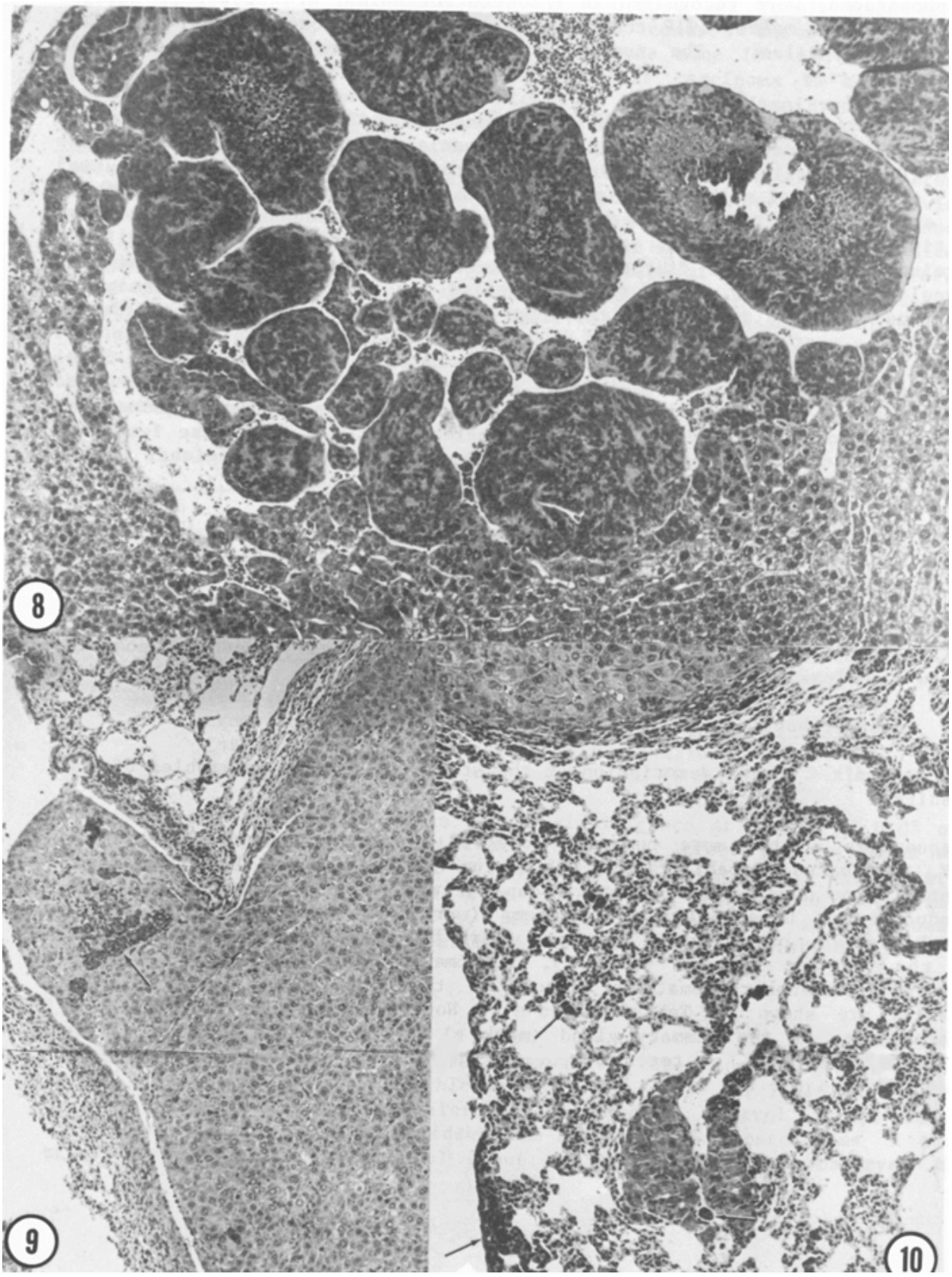
Figure 8. Primary hepatocellular carcinoma, mouse (high dose male #32). There is an area of highly anaplastic cells in a papillary pattern contiguous with an area of well differentiated cells in a trabecular pattern. Hematoxylin and eosin, x120

Figure 9. Secondary hepatocellular carcinoma, lung, mouse (high dose male #15). The metastatic hepatocellular carcinoma has invaded and extended into a bronchiole. The bulk of the tumor consists of rather well differentiated hepatocytes but there are scattered foci of smaller, more anaplastic, basophilic, neoplastic cells (->) also. Hematoxylin and eosin, x120

Figure 10. Metastatic hepatocellular carcinoma, lung, mouse (high dose male #15). Well differentiated hepatocytes comprise a large nodule (edge at upper left) and invade perivascularly at lower center. Numerous foci of smaller, more anaplastic, basophilic, neoplastic cells occur in vessels (->) and alveolar capillaries, and invade perivascularly. Hematoxylin and eosin, x96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In addition to hepatocellular carcinomas, malignant lymphoid tumors and pulmonary tumors appeared somewhat elevated although not significantly at the 0.05 level. Malignant lymphoid tumors (reticulum-cell sarcoma and lymphosarcoma) were recognized in 1/20 control males, 4/47 low dose males, 2/45 high dose males, 1/19 control females, 5/49 low dose females, and 6/47 high dose females. The number of tissues involved varied among the different cases.

Benign fibrous tumors consisted of fibroma of the subcutis in a low dose male (002) and neurofibroma in skeletal muscle of the back of a high dose male (044). Malignant tumors included fibrosarcoma of the skin or subcutis in 3 of 20 control males. A high dose male (034) that died after 90 weeks on study had a primary fibrosarcoma within the abdominal cavity with multiple metastases. Among the females, one low dose mouse (003) killed terminally had uterine fibrosarcoma. A control female (008) had a highly vascular osteosarcoma of the soft tissues of the back and a high dose male (043) had a hemangiosarcoma of the lung.

Of the respiratory tumors, benign pulmonary adenomas were diagnosed in 5/50 low dose males, 1/48 high dose males, 3/50 low dose females, and 5/47 high dose females. Alveolar adenocarcinoma, a malignant tumor, was diagnosed in 1/48 high dose males, 2/49 low dose females, and 2/47 high dose females. The one in the high dose male (035) had metastasized to regional lymph nodes, periaortic tissues, and the skin of the chest.

Other benign tumors included adenoma of the Harderian gland in 1 low dose male, 1 low dose female, and 2 high dose females. An adenoma of tubular origin was found in the kidney of a high dose male (013), and an ovarian cystadenoma in a low dose female (043). Other carcinomas included an endometrial adenocarcinoma in a control female (003), an ovarian granulosa-cell carcinoma in a low dose female (033), and a mammary adenocarcinoma in a low dose female (038).

7.5 Tumor Probabilities

See Appendix C for a description of the statistical tests and tables of the results.

Frequencies of the more commonly observed marks are summarized in Table XXV. Estimated probabilities of observing histopathologic diagnosis among control, low dose, and high dose groups of mice were compared. Tests were conducted for hepatocellular carcinoma (mark a), reticulum-cell sarcoma, lymphosarcoma, or malignant lymphoma (mark b), carcinoma or adenocarcinoma of the lung or alveoli (mark c), adenoma of the lung (mark d), and carcinoma, adenocarcinoma, or adenoma of the lung (mark c or d). Test results are shown in Tables XXVIa-e. No mouse was observed to have fibroadenoma of the mammary gland (mark g) or chromophobe adenoma of the pituitary (mark t), so tests comparing these marks were not performed as they had been for the rats.

The age-adjusted tests for linear trend (Tarone, 1975) were highly significant for hepatocellular carcinoma in male mice ($P < 0.001$) and female mice ($P = 0.002$). The tests of high dose vs. control are also highly significant in both male mice ($P < 0.001$) and female mice ($P = 0.008$). A similar test of low dose vs. control shows significant differences for male mice ($P = 0.004$) and female mice ($P = 0.090$). Estimated probabilities of observing hepatocellular carcinoma in male mice, depending on the week on study in which they died, are displayed in Table IX and are graphed in Figure 11. In male mice, the tumors were observed earlier in the high dose group than in the low dose group, which may result from earlier mortality among high dose male mice. At the end of the study at 90 weeks, the estimated probability (standard error) of observing hepatocellular carcinoma in male mice was 0.938 (0.043) for high dose, 0.683 (0.076) for low dose, and 0.077 (0.074) for control. In female mice, no tumors were observed before terminal sacrifice at 90 weeks; therefore, no graphic presentation is included. At 90 weeks the estimated probabilities (standard errors) of observing hepatocellular carcinoma in female mice were 0.282 (0.072) for the high dose, 0.100 (0.047) for the low dose, and 0.000 (0.000) for the controls. Figure 12 shows a comparison of the percentage of animals of either sex with observed hepatocellular carcinoma. These data are summarized in Table VIII:

Table VIII. Incidence of Hepatocellular Carcinoma - Trichloroethylene-Treated Mice

	Males	Females
Controls	1/20	0/20
Low dose	26/50 ($P = 0.004$)	4/50 ($P = 0.090$)
High dose	31/48 ($P < 0.001$)	11/47 ($P = 0.008$)

Test for significant difference of each group from controls. In addition, age-adjusted tests for linear trend were also highly significant for male mice ($P < 0.001$) and female mice ($P = 0.002$).

None of the tests of other marks showed significance at levels of 0.05 or less. However, the age-adjusted tests for linear trend for carcinoma or adenocarcinoma of the lung (mark c) may indicate a relationship with treatment at a level $P = 0.109$ for male mice and $P = 0.225$ for female mice. Similarly, the comparison of mark b, sarcoma, lymphosarcoma, and lymphoma, between high dose and control female mice may indicate a relationship ($P = 0.172$).

7.6 Colony Controls

The incidence of hepatocellular carcinomas for other control groups maintained in the same room as trichloroethylene is given in Table X. Groups A-D, which include the trichloroethylene-matched control group, were treated with corn oil. The incidence of hepatocellular carcinomas in the trichloroethylene-matched control group was typical of that observed in

Table IX. Estimated Probabilities of Observing Hepatocellular Carcinoma - Trichloroethylene-Treated Male Mice

Control				Low Dose				High Dose			
j	n	n′	P	j	n	n′	P	j	n	n′	P
0	20	20	.000	0	50	50	.000	0	48	48	.000
32	20	20	.000	16	50	50	.000	13	48	48	.000
39	19	19	.000	18	49	49	.000	14	47	47	.000
60	18	18	.000	31	48	48	.000	15	46	46	.000
61	17	17	.000	51	47	47	.000	24	44	44	.000
64	16	16	.000	53	46	46	.000	25	42	42	.000
66	15	15	.000	58	45	45	.000	27	40	39	.025
68	14	14	.000	63	44	44	.000	28	39	38	.050
72	13	12	.077	65	43	43	.000	29	37	37	.050
76	12	12	.077	77	41	41	.000	30	36	35	.076
77	10	10	.077	81	40	39	.025	36	34	33	.104
78	9	9	.077	86	38	37	.051	42	33	33	.104
90	8	8	.077	88	37	36	.076	53	32	31	.132
				90	35	12	.683	60	31	31	.132
								61	29	28	.162
								70	28	27	.191
								71	27	26	.221
								74	26	25	.251
								75	25	25	.251
								78	24	23	.283
								83	23	22	.314
								88	22	21	.345
								90	21	2	.938

j = Week on study

n = No. of animals alive at beginning of the week

n′ = No. of animals without observed tumor at the end of the week

P = Kaplan-Meier estimate of the probability of observed tumor

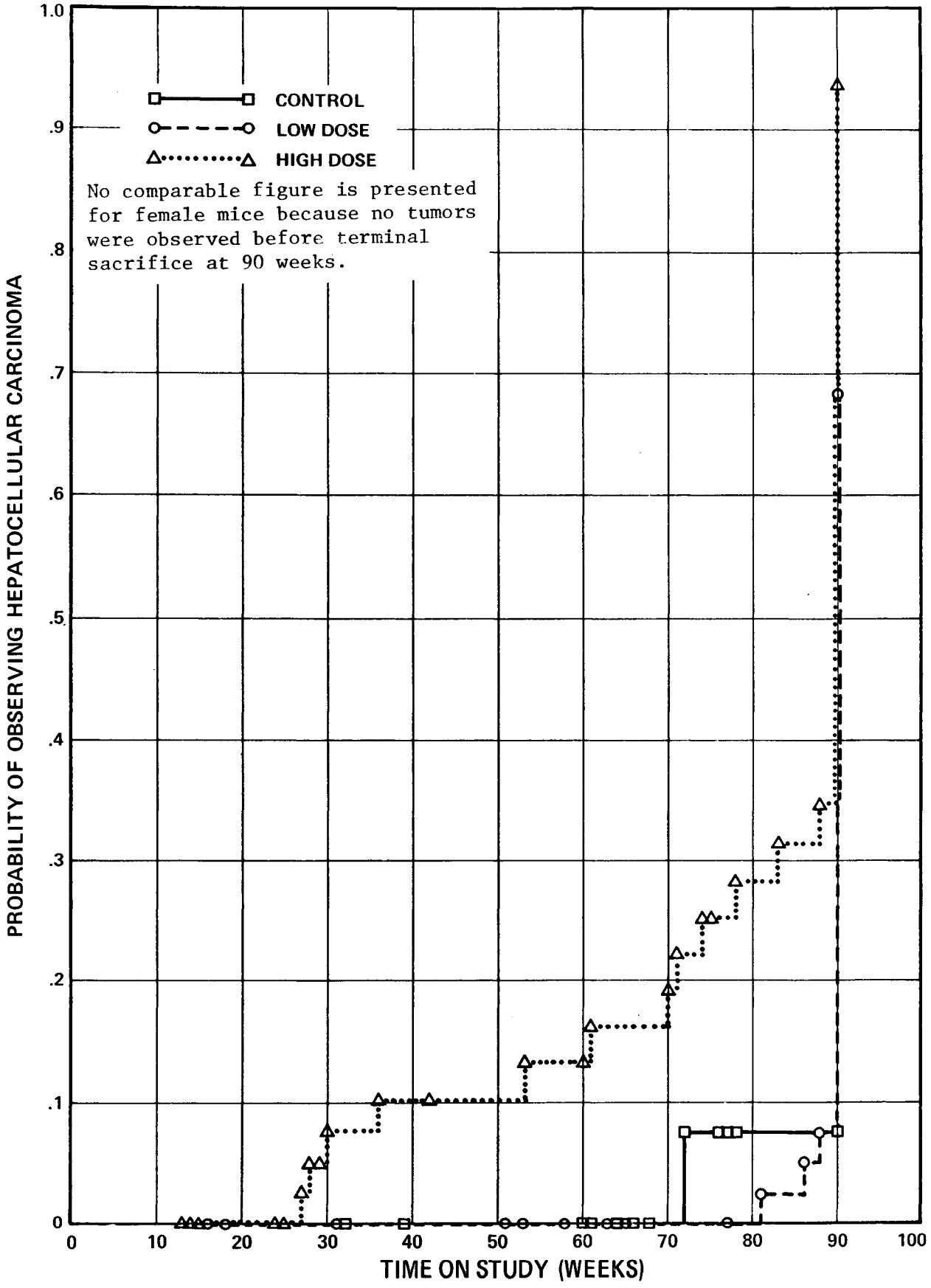

Figure 11. Product-Limit Estimates of Probability of Observing Hepatocellular Carcinoma - Trichloroethylene-Treated Male Mice

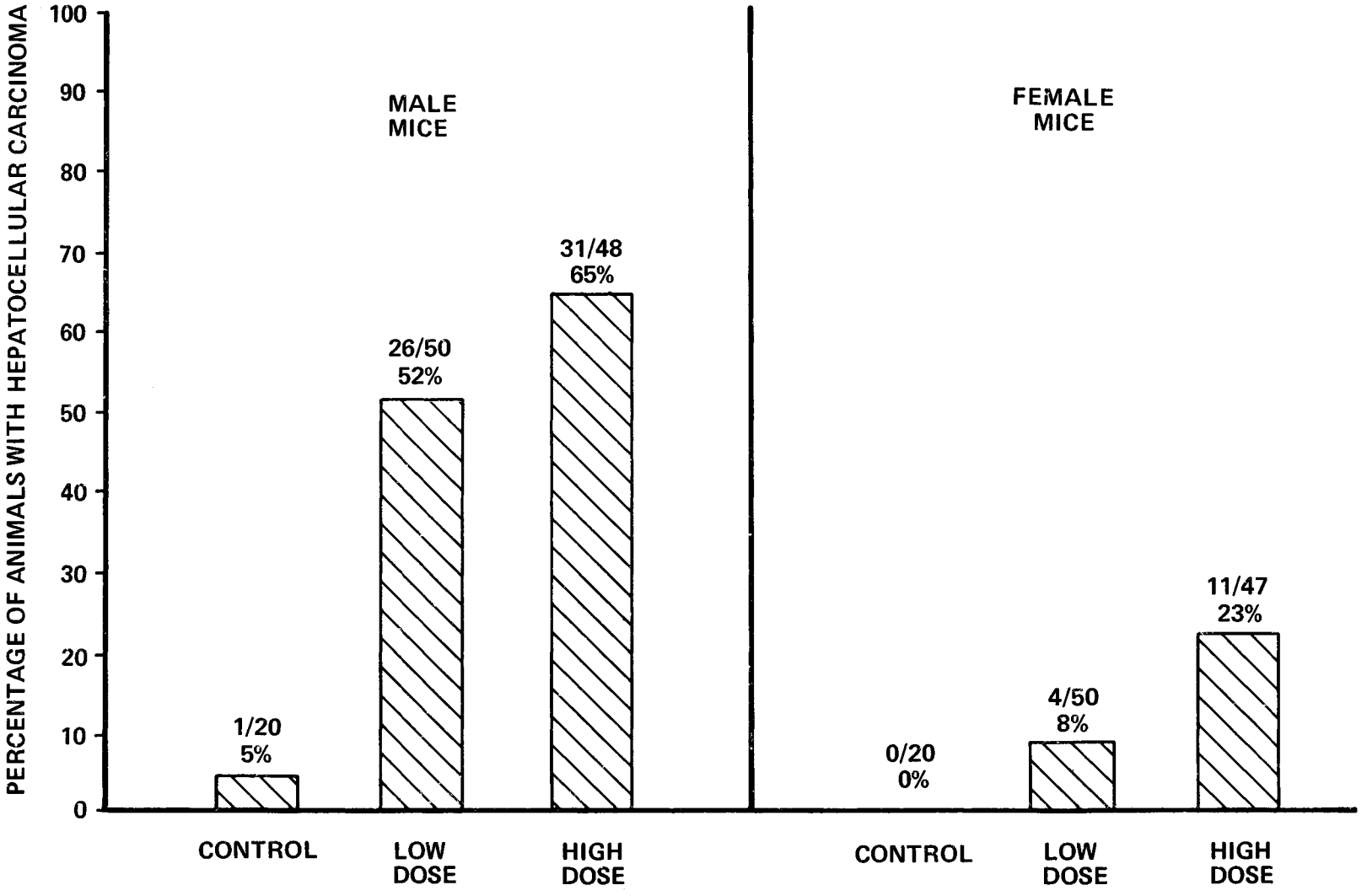

Figure 12. Comparison of Incidence of Hepatocellular Carcinoma in Trichloroethylene-Treated Male and Female Mice

other control groups, thus the significance of heptocellular carcinoma in trichloroethylene-treated mice remained similar when compared with the pooled colony controls.

Table X. Incidence of Hepatocellular Carcinoma - Colony Control Mice

Control Group	Median Birth Date	Males		Females	
		Vehicle	Untreated	Vehicle	Untreated
A[a]	7-17-72	1/20		0/20	
B	3-20-72	1/18		0/20	
C	5/31/72	1/19		1/20	
D	10/12/72	2/20		0/20	
E	3/27/72		1/19		0/19
F	6/15/72		2/18		0/19
G	10/27/72		2/18		2/20
H	10/04/72		0/15		0/18
	Total	5/77	5/70	1/80	2/76

[a]Matched controls for trichloroethylene.

7.7 Positive Controls

Few mice receiving carbon tetrachloride survived until the planned termination of the test, compared with a considerable number in each of the trichloroethylene-treated groups as shown in Table XI:

Table XI. Comparison of Survival in Colony Controls - Vehicle-Treated and Trichloroethylene- and Carbon Tetrachloride-Treated Mice

			Trichloroethylene				Carbon Tetrachloride			
	Controls		Low Dose		High Dose		Low Dose		High Dose	
Interval	M	F	M	F	M	F	M	F	M	F
Initial	77	80	50	50	48	47	50	50	50	50
78 weeks	53	71	40	41	23	21	11	10	2	4
90 weeks	38	65	35	40	40	39	0	0	0	1

Hepatocellular carcinomas were found in practically all mice receiving carbon tetrachloride, including those dying before termination of the test. The incidence of liver tumors was considerably greater in carbon tetrachloride-treated mice than in trichloroethylene-treated mice as shown in Table XIIa. Individual animal data for carbon tetrachloride-treated mice are given in Tables XXXIVa-d, Appendix D.

Table XIIa. Comparison of Hepatocellular Carcinoma Incidence in Colony Controls - Vehicle-Treated and Trichloroethylene- and Carbon Tetrachloride-Treated Mice

		Trichloroethylene		Carbon Tetrachloride	
Animals	Controls	Low Dose	High Dose	Low Dose	High Dose
Males	5/77	26/50	31/48	49/49	47/48
Females	1/80	4/50	11/47	40/40	43/45

These liver tumors in carbon tetrachloride-treated mice varied greatly in appearance from lesions which contained well differentiated hepatic cells that had a relatively uniform arrangement of the cords to very anaplastic liver cells having large hyperchromatic nuclei, often with inclusion bodies, and with vacuolated, pale cytoplasm. Arrangement of the neoplastic liver cells varied from short stubby cords to nests of hepatic cells and occasionally acinar arrangements. Mitotic figures were often present. Some of the tumors were characterized by discrete areas of highly anaplastic cells surrounded by relatively well differentiated tumor cells. The neoplasms occurring in the treated mice were similar in appearance to those noted in the trichloroethylene-treated mice.

The test week at which the first animal died in which a hepatocellular carcinoma was observed in each group is given in Table XIIb:

Table XIIb. Comparison of Time (weeks) to Liver Tumor Detection in Colony Controls - Vehicle-Treated and Trichloroethylene- and Carbon Tetrachloride-Treated Mice

		Trichloroethylene		Carbon Tetrachloride	
Animals	Controls	Low Dose	High Dose	Low Dose	High Dose
Males	72	81	27	48	26
Females	90	90	91	16	19

In addition to the higher incidence, hepatocellular carcinomas were observed much earlier in carbon tetrachloride-treated mice than in the trichloroethylene-treated mice. Tumors in control mice were observed much later.

8.0 DISCUSSION

Trichloroethylene is one among a series of halogenated chemicals tested in the National Cancer Institute carcinogenesis bioassay program. The results clearly indicate that exposure to trichloroethylene has resulted in hepatocarcinogenicity in both sexes of the B6C3F1 mouse. No evidence of such activity was apparent in the rat tests.

8.1 Design of Bioassay

8.1.1 Selection of Animal Species and Strain

Since it is well known that species vary in their carcinogenesis response to chemicals, two species are routinely used in the carcinogenesis bioassay program to decrease the possibility of false negative results based on tests in a resistant strain of animals. A clearly positive result in only one test species is a valid indication of the carcinogenic activity of the test compound while failure to detect carcinogenicity in another species only indicates a lower susceptibility of the latter under the conditions of the test.

Rats and mice were selected as the test species because they are genetically standardized, readily available species that reproduce well and can be easily, successfully, and economically maintained. They have been the most extensively used species for carcinogenesis testing.

The Osborne-Mendel strain of rats was chosen because of the experience gained by the Food and Drug Administration where the strain was used for many years as a general purpose test animal. In addition, it had been found by Reuber and Glover (1970) to be sensitive to the carcinogenicity of carbon tetrachloride by subcutaneous administration. The B6C3F1 strain of mice, an F1 hybrid cross of the C57BL/6 female with the C3H/He male, was chosen because it had been extensively and satisfactorily used in the NCI carcinogenesis bioassays.

8.1.2 Route of Exposure

Trichloroethylene was administered by gavage in this study while the main human exposures are by inhalation of vapors and by ingestion through contaminated water and food products. The selected route of exposure is considered relevant to all modes of human exposure because trichloroethylene is readily absorbed and distributed to all organs following ingestion or inhalation. This has been shown in several species, including the rabbit (Gasq, 1936), the dog (Barrett and Johnston, 1939), and the guinea pig (Fabre and Truhaut, 1952). The fact that in this study tumor induction occurred in the liver indicates that trichloroethylene was absorbed and that systemic exposure of tissues occurred.

8.1.3 Selection of Doses and Duration of Exposure

An attempt was made to select the highest dose that could be administered for most of the animal's lifetime without altering the animal's normal longevity from effects other than carcinogenicity (estimated maximum tolerated dose). A lower dose, corresponding to one half of the high dose, was also tested to assure that at least one group would survive well through the test period if unpredicted toxic effects occurred in the high dose group.

The selection of doses for bioassay is made to assure the greatest probability of detecting a carcinogenic effect within an experimental protocol which must use relatively small numbers of animals compared with the large number of human beings exposed.

8.1.4 Methodology

The protocol and methodology of this bioassay generally conformed to recognized methodology for assessing carcinogenicity as adopted by the NCI. While the NCI has revised in several respects its test procedures since the time the present tests were designed (Guidelines for Carcinogenesis Bioassay in Small Rodents, 1975), these changes do not reduce the meaningfulness of this study. The major changes in current NCI protocols as compared with the test procedures used in this study are: (a) More complete and longer prechronic studies are carried out in an effort to predict the MTD more accurately. Prechronic studies are now routinely conducted for 90 days. Histopathological studies are performed on animals from all dose groups, necessary to establish a maximum tolerated dose. Clinicopathological tests are also performed when indicated. Experience has shown that more extensive prechronic tests reduce or eliminate the need to change dose levels during the course of the chronic study. In the past, survival and slight decrease in weight gain were used as the main indicators of the MTD. (b) Larger matched control groups are now also included with each test so that pooling of controls from several compounds is not necessary. In this bioassay 20 matched controls for each sex and species were started. However, 18 chemicals in the case of the mice and 5 chemicals in the case of rats were tested concurrently, and pooling of the controls for the various chemicals, in order to have a larger number of colony control animals, was anticipated.

It has been recommended by several panels on carcinogenesis testing (Berenblum, 1969; FDA Advisory Committee, 1971; Golberg, 1974) that administration of a food additive in a carcinogenesis test might begin prior to conception and continue in the offspring because such treatment would provide a more thorough examination of the carcinogenic potential of test compounds. The present bioassay makes no attempt to measure either transplacental or neonatal carcinogenic effects.

Commercial laboratory diets were fed to the test animals. Recommendations have been made to use semi-synthetic diets of known and constant composition as a step toward uniformity in interpretation of experimental results from different laboratories and to decrease contamination with mycotoxins, pesticides, or other agents. However, problems in preparation and storage,

nutritional adequacy, palatability, and handling have precluded so far their adoption for practical use in these large scale lifetime studies.

8.2 Test Compound Purity

The purity of the trichloroethylene used in the chronic bioassay was greater than 99%, as determined by gas chromatographic total area data and infrared spectra (see Appendix A). In the gas chromatographic analysis, the percentage of each component was determined from the relative area of its gas chromatographic peak. The sum of the area comprising the peaks was considered to total 100%. In the final analytical work, in which the minor components were actually identified, standard samples of each component were used to correct for differences in gas chromatographic detector response. Nonvolatile materials, such as polymers and inorganic salts, would not have been detected by gas chromatography but there is no reason to suspect their presence. Any significant quantity of such impurities would have been detected in the infrared spectra, which, in fact, compare well with reference trichloroethylene spectra.

Inhibitors and stabilizers are commonly added to trichloroethylene used for vapor degreasing. Some of the trace components, identified in Batch #4 by a combination of gas chromatography and mass spectrometry in subsequent analyses, are 1,2-epoxybutane (0.19%), ethyl acetate (0.04%), epichlorohydrin (0.09%), N-methylpyrrole (0.02%), and diisobutylene (0.03%). According to a major manufacturer, these are typical inhibitors in commercial formulations of trichloroethylene used for vapor degreasing.

It is reported that trichloroethylene in the mid-1960s contained substantial quantities of 1,1,2,2-tetrachloroethane, a highly toxic precursor in the acetylene-based manufacturing process, but current technology and the switch to ethylene-based processes now result in a highly pure commercial product (NIOSH, 1973). That conclusion is consistent with the analytical data on the batches used for the bioassay. Analytical work on bioassay Batch #4 confirmed the absence of detectable quantities of 1,1,2,2,-tetrachloroethane (<5 ppm) and 1,1,1,2-tetrachloroethane (<2 ppm).

While the results obtained in the present bioassay could possibly have been influenced by an impurity in the trichloroethylene used, the extremely low amounts of impurities found make this improbable.

8.3 Metabolism, Distribution, and Excretion

The metabolism, distribution, and excretion of trichloroethylene in humans, rats, and mice was reviewed in Criteria for a Recommended Standard... Occupational Exposure to Trichloroethylene (1973), issued by the National Institute for Occupational Safety and Health.

The data describing evidence for the metabolic pathways of trichloroethylene in mice are not as extensive as that available for man and rats. However, the data do indicate similar metabolic pathways for this compound in the 3 species and do not support the concept that metabolic differences among these species might explain the lack of carcinogenic response of the

rat to trichloroethylene as compared with the mouse. Recent data on trichloroethylene metabolism in man are consistent with earlier findings in experimental animals (Ertle et al., 1972; Ikeda et al., 1971, 1972; Ikeda and Ohtsuji, 1972; Ikeda and Inamura, 1973; Kimmerle and Eben, 1973; Nomiyama and Nomiyama, 1971; Parkhouse, 1969; Soucek and Vlachova, 1960; Stewart and Dodd, 1964; Vignoli et al., 1970).

8.4 Toxicology

Depression of the central nervous system is the primary acute toxic effect of trichloroethylene in both humans and animals. This effect was demonstrated in rats by Adams et al. (1951) in short term toxicity studies. In humans, nausea and vomiting, headache, vertigo, dizziness, tinnitis, unsteady walk, fatigue, sleepiness, and even excitement have all been reported in patients and in those persons inadvertently or occupationally exposed. This and other acute and subchronic toxicity of the compound are extensively reviewed in Criteria for a Recommended Standard...Occupational Exposure to Trichloroethylene (1973) issued by the National Institute for Occupational Safety and Health.

Although data on chronic or carcinogenesis studies were not available in the published literature prior to this report, data from subchronic studies indicated that the liver and kidney were target sites of the toxic effects of trichloroethylene.

The effects of this chemical on liver and kidney were noted by Adams et al. (1951) in subchronic inhalation studies using rats as an experimental model. Liver and kidney weights of both male and female rats were increased but no histopathological abnormalities were reported. Increased liver weights were also observed in both guinea pigs and rabbits. In mice, trichloroethylene is not as nephrotoxic as several other chlorinated methane, ethane, and ethylene derivatives (Plaa and Larson, 1965). However, the hepatotoxicity of trichloroethylene has been reported by several authors. It is much less severe than that of carbon tetrachloride, an intensively studied chlorinated methane that was used as a positive control in this bioassay. In a review of trichloroethylene von Oettingen (1955) described hepatic damage which was reported as early as 1932 in dogs. He also quotes Fiessinger and Laur in 1936 as observing "centrolobar degeneration and vacuolization, and in some animals, a picture similar to yellow atrophy of the liver". Clinical dysfunction of the liver in dogs was reported by Seifter (1944). Mice have shown hepatic dysfunction when exposed to trichloroethylene by inhalation for up to 8 weeks (Kylin et al., 1965) or by intraperitoneal injection (Klaassen and Plaa, 1966). In other studies, the hepatotoxicity of trichloroethylene was enhanced by pretreatment with acetone or isopropyl alcohol (Traiger and Plaa, 1974).

Thus, hepatic damage of varying degrees has been found following repeated exposures of short duration to trichloroethylene. These observations establish the need for chronic studies.

8.5 Pathology and Survival

8.5.1 Rats

In the bioassay various neoplastic entities, both benign and malignant, occurred in all rat dosage groups and controls. Some are rather rare types of tumors in rats, such as pilomatrixoma of skin and aortic body tumor, but none was significantly related to treatment with trichloroethylene. No toxic hepatic change nor primary hepatic tumor was observed in the rats.

Chronic respiratory disease occurred without regard to sex or treatment group in rats. The only treatment-related lesion was a chronic nephropathy encountered among most rats of both sexes and at both high and low doses of the compound. This nephropathy was characterized by degenerative and regenerative changes in tubular epithelium with questionable interstitial response. The lesion is dissimilar from the chronic nephropathy so commonly encountered in rats with advancing age and recognized in some rats on this experiment. No treatment-related lesions severe enough to appear responsible for death were detected in the rats. Nevertheless, decreased survival was generally dose-related.

Only a low incidence of both neoplastic nodule and hepatocellular carcinoma was observed in rats receiving carbon tetrachloride, the positive control compound. Survival was slightly better among the carbon tetrachloride-treated than among the trichloroethylene-treated rats.

In this bioassay as in other previous carcinogenic bioassays of chlorinated organic compounds, some chemicals have been identified as liver carcinogens in the mouse, but have produced no observed carcinogenic effect in the rat. The difference in susceptibility to the induction of tumors by certain chemicals in the rat as compared to the mouse may be attributed to many factors and is beyond the scope of these studies.

8.5.2 Mice

In the mice, there was a significant increase in the incidence of hepatocellular carcinomas in both low and high dose males and high dose females ($P < 0.05$) and low dose females ($P = 0.09$). The tumors were found in 12 of 27 mice dying during the experiment and in 19 of 21 high dose male mice killed at termination of the experiment. Low dose male mice as well as high and low dose female mice had good survival rates. With the exception of 3 low dose male mice dying at 81 to 88 weeks, hepatocellular carcinoma was found only in those animals killed at the end of the experiment. The lower probability of tumor observation in female mice may reflect either the lower doses they received or an actual sex difference in response. Thus, trichloroethylene was found to have a dose-related carcinogenic effect on the liver of both sexes of mice. No other tumor was related to treatment.

Only 20 matched vehicle control mice were started for each species and sex in this bioassay; however, the significance of hepatocellular carcinoma in trichloroethylene-treated mice remains similar when compared with data from control mice for other halogenated solvents tested concurrently.

In this study the doses of trichloroethylene administered to the test animals resulted in a greater survival of mice than of rats. The increased mortality in rats may in part have resulted from intercurrent disease as well as from a greater sensitivity to the toxic effects of trichloroethylene.

In the positive control group, hepatocellular carcinoma was observed in practically all mice receiving carbon tetrachloride. Only one of these animals survived until planned termination of the test. Except for high dose male mice, hepatocellular carcinomas were observed at an earlier age among carbon tetrachloride-treated than among trichloroethylene-treated mice. Thus, carbon tetrachloride was a much stronger hepatocarcinogen than was trichloroethylene, under the conditions of these tests.

8.6 Effect of Various Compounds in the Same Room

Several halogenated solvents were being tested simultaneously in the same room, i.e., 5 in the room housing rats and 18 in the room housing mice. This is not expected to change the results significantly; however, no experimental studies of cross contamination or simultaneous administration are available. A protective effect from simultaneous exposure to other, and halogenated solvents would not be expected, and it is highly unlikely that an interaction of possible airborne contaminant amounts of solvents would bring about false positives, considering the high doses of trichloroethylene used.

The species in which tumors were found, i.e., mice, were housed in a room where 17 other chemicals were being tested; however, stringent precautions against cross contamination were employed. The mice were kept in cages with filter tops which limit the amount of expired chemical in the air available for inhalation by other animals, the total air in each room was changed 10 to 15 times per hour, and the mouse racks were transported to another room with a large hood for the daily intubations. Furthermore, the hepatocarcinomas in mice were present at a greater than $P = 0.01$ level of significance and were produced by doses of trichloroethylene of 700 to 2400 mg/kg, which are several thousand-fold greater than any possible contamination could have been. A dose-related effect was observed and, any possible chemical in the general room air did not affect controls. Thus, although this room arrangement is not desirable as is stated in the Guidelines for Carcinogen Bioassay in Small Rodents, there is no evidence the results would have been different with a single compound in a room.

8.7 Relationship to the Toxicity of Carbon Tetrachloride

Carbon tetrachloride was used as a positive control because of its demonstrated ability to produce liver tumors in rats, hamsters, and mice (Reuber and Glover, 1970, Della Porta et al., 1961, Eschenbrenner and Miller, 1946). The doses used were approximately 10-fold less than for trichloroethylene in rats, but were only slightly higher for males and 50% higher for females than for trichloroethylene in mice.

Pathology of the liver was evident in carbon tetrachloride-treated rats. Hepatocellular carcinomas and neoplastic nodules were found in a few rats

of both dose groups and sexes in contrast to the results with trichloroethylene where no tumors and very little non-tumor pathology of the liver were reported. This is particularly significant since the dose of trichloroethylene used was approximately 10 times greater than for carbon tetrachloride.

Hepatocellular carcinomas were found in practically all mice including those dying before termination of the test. The incidence was considerably greater than for trichloroethylene-treated mice (see section 7.7).

Although in mice the MTD values of carbon tetrachloride and trichloroethylene were similar, all except one carbon tetrachloride-treated animal (of both sex and dose groups) died prior to termination at 90 weeks. The survival of the trichloroethylene-treated female mice was excellent, and even 40% of the high dose males survived until termination of the test. Death in the carbon tetrachloride-treated animals could have resulted either from toxicity or carcinogenicity since tumors were observed in practically all animals. These results confirm previous work. Both Klaassen and Plaa (1966) and Gehring (1968) have shown that in mice the hepatotoxicity of carbon tetrachloride is much greater than that of trichloroethylene, both on an absolute basis and in relation to anesthetic effects and to the LD_{50} value.

8.8 Conclusions

The administration of trichloroethylene under the experimental conditions described in this report induced a high incidence of hepatocellular carcinoma in B6C3F1 mice of both sexes. The test in rats is inconclusive: large numbers of rats died prior to planned termination; in addition, the response of this rat strain to the hepatocarcinogenicity of the positive control compound, carbon tetrachloride, appeared relatively low. Although direct extrapolation to man is not possible, the identification, using this methodology, of trichloroethylene as a carcinogen in animals serves as a warning of its possible carcinogenicity in humans.

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APPENDIX A: CHEMISTRY

Chemical and Physical Characteristics

Physical state: Liquid, nonflammable (Patty, 1963; Sax, 1968)
Odor: Resembling chloroform (Patty, 1963)
Melting point: -73°C (Patty, 1963)
Boiling point: 86.7°C (760 mm Hg) (Stecher, 1968)
Solubility: 0.1 g/100 ml water at 20°C; soluble in ether, ethyl alcohol, and chloroform (Patty, 1963); dissolves most fixed and volatile oils (Stecher, 1968)
Odor threshold: 24.1 ppm
Specific gravity: 1.45560 (25°/4°C) (Patty, 1963)
Vapor density: 4.54 (air = 1) (Patty, 1963)
Vapor pressure: 77 mm Hg (25°C) (International Labour Office, 1972)
Refractive index: 1.4777 (20°C) (Patty, 1963)
Percent in "saturated" air: 10.2 (25°C) (Patty, 1963)
Handling precautions: Use with adequate ventilation (Stecher, 1968). Must be stored in sealed, light-resistant containers.

Technical Product and Impurities

Tetrachloroethane has been reported as an impurity in technical trichloroethylene, particularly in that produced by the acetylene-based process (Dreisbach, 1974; NIOSH Criteria Document, 1973). The chemical used for this bioassay contained no detectable quantity of tetrachloroethane.

Manufacturing Processes

In one industrial process, trichloroethylene is produced from acetylene. The process involves addition of chlorine to acetylene to give 1,1,2,2-tetrachloroethane. The more common process since 1972 involves the addition of chlorine to ethylene to give ethylene dichloride and then further chlorination to 1,1,1,2-tetrachloroethane, followed by HCl elimination to yield trichloroethylene (Wiseman, 1972).

Chemical Analysis

Trichloroethylene Batch #1 - January 9, 1973*

Gas Chromatography (Table A1)

Detector: Flame ionization
Recorder range: 1 mv full scale
Column: 3′ x 1/4" od, aluminum, 80-100 mesh Porapak Q
Temperatures (°C): Injection port 205, detector 250, column oven programmed from 60 (2 min) to 205 (20 min) at 6°/min
Flow rates (ml/min): Nitrogen carrier 45, hydrogen 45, air 475
Attenuation: From 1 x 16 to 10^3 x 32
Remarks: About 0.8 µl sample was injected

*Conducted by Hazleton Laboratories, Inc.

Table A1. Analysis of Total Area Data - Batch #1

Component By Retention Time (min)	Area (cm^2)	Total Area[a] (cm^2)	Percent (A/At x 100)	Av. (%)
2.8	0.1	A	0.00067	
3.4	0.1	B	0.00082	0.001
3.3	0.1	C	0.00075	
13.3	0.54	A	0.0036	
13.6	0.34	B	0.0031	0.003
13.8	0.41	C	0.0034	
18.0	118	A	0.79	
18.0	72	B	0.65	0.7
18.4	83	C	0.69	
19.2	8	A	0.053	
19.4	6	B	0.054	0.06
19.8	7	C	0.058	
21.1[b]	14,840	A	99.1	
20.9[b]	10,920	B	99.2	99.1
21.3[b]	11,900	C	99.1	
26.0	13	A	0.087	
26.0	9	B	0.082	0.09
25.5	12	C	0.10	
Total				100.0

[a]A = 14,980
B = 11,010
C = 12,000
[b]Trichloroethylene

Infrared Spectroscopy (Figure A1)

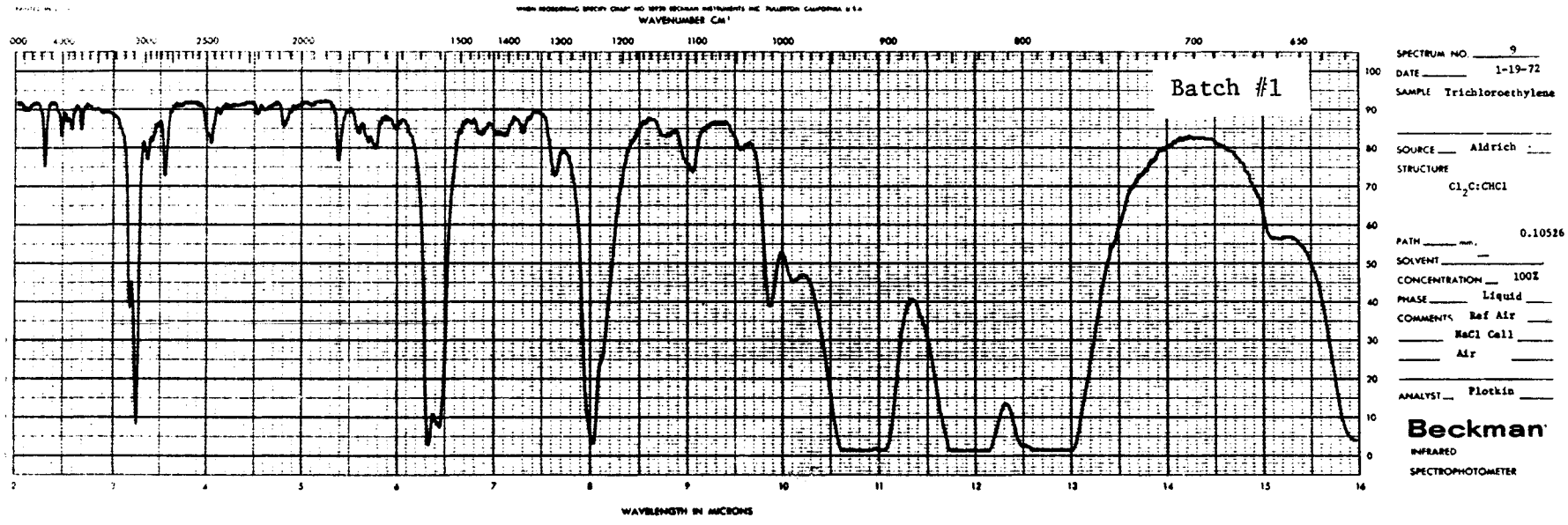

Figure A1. Infrared Spectrum of Trichloroethylene

Trichloroethylene Batch #3 - February 15, 1974*

Gas Chromatography (Table A2)

Same as for Batch #1, except as follows:

Flow rates (ml/min): Hydrogen 60, air 450
Attenuation: From 1 x 16 to 10^3 x 128
Remarks: About 1.0 µl sample was injected

*Conducted by Hazleton Laboratories, Inc.

Table A2. Analysis of Total Area Data - Batch #3

Component By Retention Time (min)	Area (cm^2)	Total Area[a] (cm^2)	Percent (A/At x 100)	Av. (%)
12.7	3.6	A	0.01	
12.6	3.3	B	0.01	0.01
12.7	3.9	C	0.01	
16.8	305	A	0.63	
16.8	284	B	0.62	0.6
17.0	343	C	0.68	
18.2	55	A	0.11	
18.1	52	B	0.12	0.1
18.2	63	C	0.13	
20.2[b]	48,200	A	99.0	
20.2[b]	45,400	B	99.0	99.0
20.2[b]	49,800	C	99.0	
24.2	23	A	0.05	
24.2	21	B	0.05	0.05
24.2	25	C	0.05	
26.0	86	A	0.18	
26.0	79	B	0.17	0.2
26.1	81	C	0.16	
Total				100.0

[a]A = 48,670
B = 45,840
C = 50,320

[b]Trichloroethylene

Infrared Spectroscopy (Figure A2)

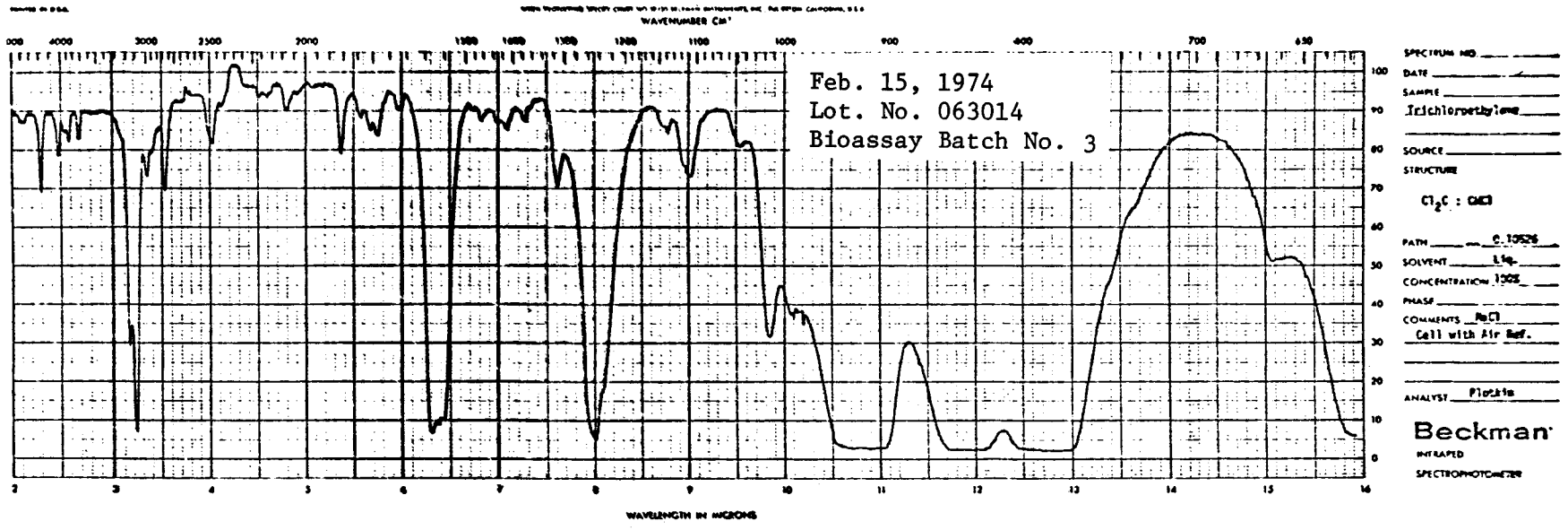

Figure A2. Infrared Spectrum of Trichloroethylene

Trichloroethylene Batch #4 - July 8, 1974*

Gas Chromatography (Table A3)

Same as for Batch #1, except as follows:

Temperatures (°C): Injection port 215, detector 240
Flow rates (ml/min): Hydrogen 65, air 450
Attenuation: From 1 x 16 to 10^4 x 16
Remarks: About 1.2 µl sample was injected

*Conducted by Hazleton Laboratories, Inc.

Table A3. Analysis of Total Area Data - Batch #4

Component By Retention Time (min)	Area (cm^2)	Total Area[a] (cm^2)	Percent (A/At x 100)	Av. (%)
20.7	1.7	A	0.001	
20.7	1.3	B	0.001	0.001
20.6	1.7	C	0.001	
22.8	440	A	0.38	
22.7	370	B	0.36	0.4
22.7	410	C	0.37	
24.1	280	A	0.24	
23.9	230	B	0.22	0.2
23.9	250	C	0.22	
26.4[b]	115,500	A	99.4	
26.2[b]	104,300	B	99.4	99.4
26.2[b]	111,300	C	99.4	
34.8	37	A	0.03	
34.8	33	B	0.03	0.03
34.7	34	C	0.03	
Total				100.0

[a]A = 116,250
B = 104,930
C = 112,000
[b]Trichloroethylene

Infrared Spectroscopy (Figure A3)

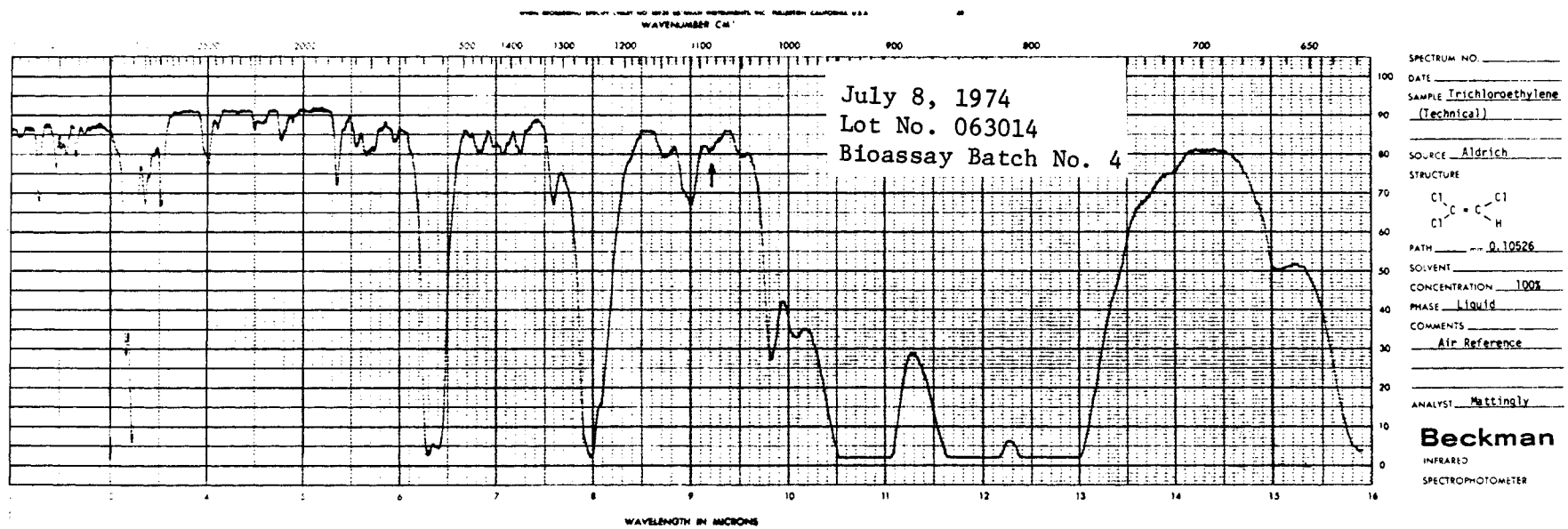

Figure A3. Infrared Spectrum of Trichloroethylene

Identification of Trace Components

July 10, 1975
Bioassay Batch #4*

Analysis Techniques

Temperature-programmed vapor-phase chromatography (vpc) was performed on trichloroethylene in order to obtain relative areas and retention times of the major component and impurities present in the compound. Vapor-phase chromatography-mass spectrometry was performed to obtain the mass peaks of the components present. Vapor-phase chromatography was then repeated on the sample spiked with compounds which had the correct mass and fragmentation properties to confirm enhancement of the impurity peaks. In addition, vpc with electron capture detection was used to analyze for trace amounts of the tetrachloroethanes.

Results - Vapor-Phase Chromatography

Survey System 1: Experimental conditions were as follows: Bendix 2500, 1.8 x 4 mm id Chromosorb column, flame ionization detection, oven temperature programmed from 100 to 250°C at 10°/min.

A major peak and 5 impurities were detected.

Peak	Retention Time (min)	Retention Time (Relative to TCE Peak)	Area (Relative to TCE Peak)	Possible Identity
1	7.0	0.70	0.003	unknown
2	7.9	0.79	0.4	1,2-epoxybutane
3	8.6	0.85	0.3	ethyl acetate
4	10.1	1.00	100	trichloro-ethylene
5	11.5	1.14	0.05	N-methylpyrrole
6	12.9	1.28	0.06	diisobutylene

*Conducted by Midwest Research Institute, Kansas City, MO.

Survey System 2: Experimental conditions: Tracor MT 220, 5% Carbowax 20M TRA on 60-80 mesh Gas-Chrom Q, 1.8 m x 4 mm column, flame ionization detection, oven temperature 40°C.

A major peak and 2 impurites were detected.

Peak	Retention Time (min)	Retention Time (Relative to TCE Peak)	Area (Relative to TCE Peak)	Possible Identity
4	2.4	1.00	100.00	trichloro-ethylene
5	6.0	2.50	0.27	N-methylpyrrole
7	10.9	4.54	0.80	epichlorohydrin

Quantitation and Identity System 1 (Epoxybutane): Experimental conditions: Tracor MT 220, Chromosorb 102, 1.8 m x 4 mm id column, flame ionization detection, oven temperature 100°C.

By addition of known standards to the trichloroethylene sample, it was determined that peak 2 was not due to ethyl vinyl ether, ethyl acetate, tetrahydrofuran, methyl ethyl ketone, or 1,2-epoxyisobutane. However, addition of an authentic sample of 1,2-epoxybutane enhanced the peak. The epoxybutane in trichloroethylene was quantitated against a known standard of epoxybutane.

Peak	Retention Time (min)	Identity	Quantitation (%)
1	-	unknown	
2	18.11	1,2-epoxybutane	0.19
3	22.52	ethyl acetate	

Quantitation and Identity System 2 (Ethyl Acetate): Experimental conditions: Bendix 2500, Chromosorb 102, 1.8 m x 4 mm id, flame ionization detection, oven temperature 135°C.

The vpc-mass data indicated that peak 3 could be ethyl acetate. Addition of an authentic sample of ethyl acetate to the trichloroethylene enhanced this peak. Ethyl acetate in the trichloroethylene was quantitated using an ethyl acetate standard.

Peak	Retention Time (min)	Identity	Quantitation (%)
1	5.7	unknown	
2	7.8	1,2-epoxybutane	
3	9.8	ethyl acetate	0.04

Quantitation and Identity System 3 (N-Methylpyrrole and Trimethylpentene): Experimental conditions: Tracor MT 220, Chromosorb 102, 1.8 m x 4 mm id, flame ionization detection, oven temperature 175°C.

The vpc-mass data indicated that peak 5 could be N-methylpyrrole. Addition of an authentic sample of N-methylpyrrole to the trichloroethylene enhanced this peak.

The vpc-mass data indicated that peak 6 could be diisobutylene (2,2,4-trimethylpentene). Addition of an authentic sample of 2,2,4-trimethylpentene enhanced this peak.

Peaks 5 and 6 were quantitative against the authentic standards.

Peak	Retention Time (min)	Identity	Quantitation (%)
4	4.0	trichloroethylene	
5	6.5	N-methylpyrrole	0.02
6	10.0	trimethylpentene	0.03

Quantitation and Identity System 4 (Epichlorohydrin): Experimental conditions: Tracor MT 220, 5% Carbowax 20M TRA on 60-80 mesh Gas-Chrom Q, 1.8 m x 4 mm, flame ionization detection, oven temperature 40°C.

The vpc-mass data indicated that peak 7 could be epichlorohydrin. Addition of an authentic sample of epichlorohydrin enhanced this peak. The epichlorohydrin present in the trichloroethylene sample was quantitated using an epichlorohydrin standard. On the Chromosorb 102 column, epichlorohydrin has the same retention time as trichloroethylene.

Peak	Retention Time (min)	Identity	Quantitation (%)
4	--	trichloroethylene	
5	8.19	N-methylpyrrole	
7	11.18	epichlorohydrin	0.09

Quantitation and Identity System 5 (Tetrachloroethane): Experimental conditions: Tracor MT 220, Chromosorb 102, 1.8 m x 4 mm id, ^{63}Ni electron capture detection, oven temperature 190°C.

On injection of a 6 µl neat sample of trichloroethyene, Lot No. 063014, no peaks were detected at the retention times of either tetrachloroethane isomer. The concentration of tetrachloroethane in the trichloroethylene (Lot No. 063014) is therefore less than 2 ppm for the 1,1,1,2-isomer and less than 5 ppm for the 1,1,2,2-isomer.

Note: A fresh sample of trichloroethylene (Aldrich Lot No. 090947) did contain a peak at the same retention time as 1,1,1,2-tetrachloroethane. Quantitation against known 1,1,1,2-tetrachloroethane indicated a concentration of 3 ppm.

Standard	Retention Time (min)	Minimum Detectable Amount (ng)
1,1,1,2-Tetrachloroethane	12.0	0.1
1,1,2,2-Tetrachloroethane	16.7	0.3

Vapor-Phase Chromatography-Mass Spectrometry: Experimental conditions: Varian MAT CH-4B interfaced via a Watson-Biemann helium separator to a Micro-Tek 2000 MF gas chromatograph, data processed by Varian 620/i computer, Chromosorb 102 column, 1.8 m x 4 mm id. See Table A4.

Conclusions

Six small impurities were detected in trichloroethylene (Lot No. 063014) by vapor-phase chromatography. Mass spectrometry data indicated that the 5 larger impurities were 1,2-epoxybutane, ethyl acetate, N-methylpyrrole, diisobutylene, and epichlorohydrin. Trichloroethylene samples spiked with authentic samples of the impurities showed enhancement of the corresponding peaks. Quantitation studies indicated the following impurity concentrations: 1,2-epoxybutane, 0.19%; ethyl acetate, 0.04%; N-methylpyrrole, 0.02%; diisobutylene, 0.03%; epichlorohydrin, 0.09%. The first impurity peak (0.003%, relative area) was not detected by mass spectrometry. 1,1,2,2- and 1,1,1,2-tetrachloroethane were not detected by electron capture detection or mass spectrometry; the levels of minimum detection on the electron capture detector for the 2 tetrachloroethane isomers were 5 and 2 ppm, respectively.

Table A4. Vapor-Phase Chromatography-Mass Spectrometry

Peak[a]	Mass	Intensity Relative to Base Peak	Literature Values for: 1,2-Epoxybutane[b] Mass	Intensity Relative to Base Peak
2	28 (N_2)	100		
	42	92	42	100
	41	92	41	93
	27	58	27	39
	72	28	72	34
	29	32	29	30
	39	35	39	28
	71	36	71	28
	57	20	57	20
			Ethyl Acetate[b]	
3	43	100	43	100
	29	43	29	25
	27	23	27	13
	45	49	45	13
	61	49	61	10
	42	16	42	6
	70	30	70	5
	26	8	26	4
	88	15		
			N-Methylpyrrole[b]	
5	81	93	81	100
	80	59	80	80
	39	24	39	37
	42	18	42	30
	53	27	53	28
	28	100 (N_2)	28	17
	55	13	55	17
	27	52	27	15
			Diisobutylene[b]	
6	57	100	57	100
	55	88	55	42
	97	47	97	29
	29	51	29	22
	56	51	56	19
	112	31	112	15
	27	17	27	11
	69	24	69	9
			Epichlorohydrin[b]	
7	57	100	57	100
	27	100	27	39
	29	79	29	31
	49	88	49	25
	31	65	31	22
	62	52	62	18
	28	100 (N_2)	28	16
	51	25	51	8

[a]Peak notation the same as previously indicated.
[b]Eight Peak Index of Mass Spectra, Vol. I (1970), Mass Spectrometry Data Centre, AWRE, Aldermaston, Reading, RG7 4PR, United Kingdom.

Manufacturer's Feed Analysis (Wayne Lab-Blox Meal)
(Allied Mills Inc., Chicago, IL 60606)

Crude protein	(Min.)	24.0%
Crude fat	(Min.)	4.0%
Crude fiber	(Max.)	4.5%

Ingredients

Animal liver meal
Fish meal
Dried whey
Corn and wheat flakes
Ground yellow corn
Soybean meal
Wheat middlings
Cane molasses
Soybean oil
Brewer's dried yeast
Vitamin A palmitate
Irradiated dried yeast (source of vitamin D)
D-Activated animal sterol
Vitamin E supplement
Menadione sodium bisulfite (source of vitamin K activity)
Riboflavin supplement
Niacin
Calcium pantothenate
Choline chloride
Thiamine
Ground limestone
Dicalcium phosphate
Salt
Manganous oxide
Copper oxide
Iron carbonate
Ethylene diamine dihydriodide
Cobalt carbonate
Zinc oxide

Basal Feed Analysis

A study of apparent pesticide residues in basal feed samples was conducted at Gulf South Research Institute under contract to NCI on November 10, 1972. Three samples of feed used at Hazleton were analyzed. No lindane, heptachlor, aldrin, heptachlor epoxide, endrin, DDD, chlordane, methoxychlor, toxaphene, or organophosphate was found. Two of the samples contained 0.00392 and 0.00682 ppm DDE, and 2 contained 0.00629 and 0.02016 ppm DDT. One sample contained 0.03955 ppm Aroclor 1254. The 3 samples contained 0.00249, 0.00141, and 0.00167 ppm dieldrin. The method of analysis was as follows:

A 20 g sample was extracted with 150 ml 6% diethyl ether in hexane on a 25 mm od x 40 cm chromatographic column containing 1" Na_2SO_4. With the stopcock closed, 25 ml extracting solvent was added. The feed sample was added and allowed to settle. The column was filled with extracting solvent and the sample again was allowed to settle. The stopcock was opened and 150 ml extracting solvent was collected in a 500 ml standard taper round-bottom flask. A Synder column was placed on the flask and the extracting solvent was evaporated on a 65-70°C heating mantle. The Snyder column was rinsed with 30 ml hexane and the extract was reduced to about 10 ml. Evaporation continued and the Snyder rinse was repeated a second time. When the extract again was reduced to 10 ml, the heat was removed and the extract was reduced to about 2 ml under vacuum.

The extracted sample was cleaned up on a 25 mm od x 40 cm chromatographic column containing 5" Florisil (activated 15 hours at 135°C) and topped with 1/2" Na_2SO_4. The sample extract was quantitatively transferred to the column with a small portion of hexane. The following extracting solvents were passed through the column and collected:

Fraction A: 175 ml hexane

Fraction B: 200 ml 6% diethyl ether in hexane

Fraction C: 225 ml 15% diethyl ether in hexane

Fraction D: 200 ml 30% diethyl ether in hexane

Each fraction was evaporated as before almost to dryness and the residue was quantitatively transferred to a 10 ml volumetric flask and diluted to volume using hexane. An aliquot was taken for gas-liquid chromatographic analysis. Compounds were identified according to chromatographic retention times only and, therefore, should be considered tentative.

Water Analysis (local artesian well)

(mg/liter except pH)

Calcium	3.8	Cyanide	0.005
Magnesium	1.3	Iron	0.02
Potassium	1.05	Copper	0.005
Sulfate	0.01	Zinc	0.024
Nitrate	2.77	Cadmium	0.006
Nitrite	0.05	Chromium	0.05
Ammonia	0.06	Lead	0.001
Phenol	0.001	Alkalinity	63.1
Chlorine	0.001	Hardness	10.6
Chloride	1.90	pH	6.35 units
Fluoride	0.01		

APPENDIX B: WEIGHTS AND SURVIVAL

Table XIIIa. Mean Body Weights and Survival - Trichloroethylene Subchronic Study - Male Rats

Time Interval (weeks)	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.
	Group 1 (0 mg/kg/day)			Group 2 (562 mg/kg/day)			Group 3 (1000 mg/kg/day)		
0	230	19.4	5/5	230	21.4	5/5	231	21.2	5/5
1	263	21.0	5/5	255	34.5	5/5	259	27.8	5/5
2	295	19.2	5/5	284	40.4	5/5	294	29.8	5/5
3	323	29.4	5/5	319	39.9	5/5	327	30.6	5/5
4	358	26.9	5/5	344	36.7	5/5	359	33.9	5/5
5	373	26.3	5/5	357	36.7	5/5	374	33.1	5/5
6	384	27.2	5/5	362	39.4	5/5	376	31.3	5/5
7	406	28.7	5/5	384	42.0	5/5	406	33.9	5/5
8	417	22.1	5/5	400	39.2	5/5	418	34.1	5/5
Mean av. wt gain (g)	187			170			187		
% of control wt gain	-			90.9			100		
	Group 4 (1730 mg/kg/day)			Group 5 (3160 mg/kg/day)			Group 6 (5620 mg/kg/day)		
0	230	21.0	5/5	230	18.4	5/5	228	20.5	5/5
1	246	14.4	5/5	218	18.8	5/5	193	32.6	3/5
2	278	19.4	5/5	240	23.4	5/5	226	-	1/5
3	310	21.1	5/5	273	30.0	5/5	242	-	1/5
4	342	27.1	5/5	299	34.9	5/5	279	-	1/5
5	355	33.2	5/5	298	40.0	5/5	-	-	0/5
6	364	36.0	5/5	304	43.2	5/5			
7	388	37.5	5/5	344	45.7	5/5			
8	404	37.6	5/5	370	48.4	5/5			
Mean av. wt gain (g)	174			140			51		
% of control wt gain	93			74.9			27.3		

Table XIIIb. Mean Body Weights and Survival - Trichloroethylene Subchronic Study - Female Rats

Time Interval (weeks)	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.
	Group 1 (0 mg/kg/day)			Group 2 (562 mg/kg/day)			Group 3 (1000 mg/kg/day)		
0	168	14.1	5/5	167	10.9	5/5	170	10.6	5/5
1	183	12.6	5/5	178	7.8	5/5	182	12.1	5/5
2	193	26.0	5/5	195	8.8	5/5	197	12.0	5/5
3	218	29.6	5/5	214	9.1	5/5	218	12.7	5/5
4	235	28.5	5/5	230	10.2	5/5	237	16.8	5/5
5	244	29.8	5/5	236	12.1	5/5	238	18.0	5/5
6	249	31.5	5/5	234	12.1	5/5	239	17.5	5/5
7	266	31.6	5/5	248	9.3	5/5	252	18.9	5/5
8	276	28.9	5/5	258	10.5	5/5	260	20.3	5/5
Mean av. wt gain (g)	108			91			90		
% of control wt gain	-			84.3			83.3		
	Group 4 (1730 mg/kg/day)			Group 5 (3160 mg/kg/day)			Group 6 (5620 mg/kg/day)		
0	170	8.3	5/5	170	8.8	5/5	169	14.0	5/5
1	177	9.2	5/5	171	13.3	5/5	178	9.8	2/5
2	183	7.1	5/5	173	19.4	5/5	169	-	1/5
3	202	9.7	5/5	188	24.7	5/5	184	-	1/5
4	227	9.5	5/5	217	23.3	5/5	204	-	1/5
5	226	7.5	5/5	212	21.4	5/5	-	-	0/5
6	223	8.0	5/5	217	19.9	5/5			
7	239	11.2	5/5	229	16.0	5/5			
8	245	14.5	5/5	241	21.7	5/5			
Mean av. wt gain (g)	75			71			35		
% of control wt gain	69.4			65.7			32.3		

Table XIVa. Mean Body Weights and Survival - Trichloroethylene Subchronic Study - Male Mice

Time Interval (weeks)	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.
	Group 1 (0 mg/kg/day)			Group 2 (1000 mg/kg/day)			Group 3 (1780 mg/kg/day)		
0	15	0.9	5/5	15	0.9	5/5	15	0.9	5/5
1	16	0.3	5/5	15	1.4	5/5	16	1.7	5/5
2	18	0.5	5/5	19	1.5	5/5	18	0.8	5/5
3	19	0.3	5/5	20	1.5	5/5	19	0.9	5/5
4	20	0.1	5/5	21	1.4	5/5	20	1.2	5/5
5	20	0.5	5/5	21	1.4	5/5	21	1.3	5/5
6	20	0.4	5/5	22	1.2	5/5	21	1.7	5/5
7	20	0.4	5/5	22	0.9	5/5	21	1.2	5/5
8	21	2.1	5/5	23	1.1	5/5	21	1.5	5/5
Mean av. wt gain (g)	6			8			6		
% of control wt gain	-			133			100		
	Group 4 (3160 mg/kg/day)			Group 5 (5620 mg/kg/day)			Group 6 (10,000 mg/kg/day)		
0	15	0.9	5/5	15	1.0	5/5	15	1.0	5/5
1	16	1.0	5/5	14	0.3	2/5	-	-	0/5
2	18	0.7	5/5	13	3.5	2/5			
3	20	1.0	5/5	18	0.5	2/5			
4	21	1.3	5/5	18	1.3	2/5			
5	22	1.3	5/5	20	1.4	2/5			
6	22	1.5	5/5	20	-	1/5			
7	22	1.4	5/5	20	-	1/5			
8	23	1.2	5/5	20	-	1/5			
Mean av. wt gain (g)	8			5			-		
% of control wt gain	133			83.3			-		

Table XIVb. Mean Body Weights and Survival - Trichloroethylene Subchronic Study - Female Mice

Time Interval (weeks)	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.	Body Weight Mean (g)	Std Dev. (g)	Surv.
	Group 1 (0 mg/kg/day)			Group 2 (1000 mg/kg/day)			Group 3 (1780 mg/kg/day)		
0	11	2.2	5/5	11	2.2	5/5	11	2.2	5/5
1	13	1.6	5/5	11	1.8	5/5	13	1.6	5/5
2	16	1.6	5/5	15	1.1	5/5	14	1.0	5/5
3	17	1.0	5/5	17	1.2	5/5	16	1.1	5/5
4	19	0.6	5/5	18	1.1	5/5	18	0.9	5/5
5	19	0.9	5/5	18	1.4	5/5	18	0.5	5/5
6	20	0.9	5/5	19	1.4	5/5	19	1.0	5/5
7	20	0.6	5/5	18	1.6	5/5	19	0.9	5/5
8	21	0.8	5/5	19	2.0	5/5	20	0.9	5/5
Mean av. wt gain (g)	10			8			9		
% of control wt gain	-			80.0			90.0		
	Group 4 (3160 mg/kg/day)			Group 5 (5620 mg/kg/day)			Group 6 (10,000 mg/kg/day)		
0	11	2.4	5/5	11	2.5	5/5	11	2.6	5/5
1	13	1.5	3/5	13	0.5	2/5	-	-	0/5
2	15	0.5	3/5	13	4.0	2/5			
3	17	1.7	3/5	13	6.9	2/5			
4	20	1.5	3/5	20	-	1/5			
5	20	1.7	3/5	20	-	1/5			
6	20	1.5	3/5	20	-	1/5			
7	21	1.3	3/5	20	-	1/5			
8	21	1.0	3/5	20	-	1/5			
Mean av. wt gain (g)	10			9			-		
% of control wt gain	100			90.0			-		

Table XVa. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Male Rats

Time Interval (weeks)	Vehicle Controls: Body Weight[a] Mean (g)	Vehicle Controls: Body Weight[a] Std Dev. (g)	Vehicle Controls: Food[b] (g)	Vehicle Controls: No. of Animals Weighed	Low Dose: Body Weight Mean (g)	Low Dose: Body Weight Std Dev. (g)	Low Dose: Food (g)	Low Dose: No. of Animals Weighed	High Dose: Body Weight Mean (g)	High Dose: Body Weight Std Dev. (g)	High Dose: Food (g)	High Dose: No. of Animals Weighed
0	193	15.0	0	20	193	15.8	0	50	194	16.7	0	50
1	242	18.7	139	20	240	21.8	145	50	237	22.7	128	50
2	288	20.9	155	20	281	26.4	162	50	269	26.5	157	49
3	312	22.2	162	20	309	21.2	166	50	296	27.9	148	48
4	334	22.6	164	20	329	23.5	164	50	313	34.2	156	48
5	360	24.0	161	20	352	25.4	166	50	340	26.2	161	47
6	387	25.2	162	20	377	27.8	168	50	360	28.7	163	47
7	402	27.6	189	20	382	28.8	196	50	375	27.5	170	46
8	412	31.8	157	20	399	30.6	158	50	381	27.8	152	46
9	437	32.8	155	20	423	32.5	157	50	406	31.2	139	46
10	458	34.2	154	20	433	34.7	162	50	406	32.2	156	46
14	504	39.4	153	20	474	40.4	150	50	446	45.3	140	45
18	535	38.9	161	20	503	41.7	163	48	481	42.5	152	44
22	552	38.0	161	20	519	46.3	158	48	493	43.9	148	43
26	570	43.3	156	20	533	47.1	158	47	500	47.2	150	43
30	587	41.5	155	20	544	48.8	164	46	503	51.3	159	42
34	607	40.3	157	20	564	49.3	159	45	528	49.3	148	40
38	617	46.6	153	20	566	50.5	155	45	535	52.1	143	39
42	612	45.2	175	20	565	47.0	177	44	528	57.2	178	38
46	622	47.7	158	20	575	49.7	151	43	526	52.1	151	36
50	618	64.5	152	20	582	49.0	153	42	528	51.3	142	34
54	616	50.2	149	20	573	47.6	147	40	513	48.3	134	30
58	618	45.2	164	20	576	53.5	158	40	508	52.4	137	27
62	628	49.6	167	20	586	47.5	161	38	507	56.7	165	25
66	615	53.6	156	20	562	46.8	156	37	493	57.2	146	19
70	611	59.8	139	19	567	60.8	139	35	506	52.4	137	17
74	581	65.8	151	18	539	62.7	153	33	485	45.8	151	14
78	559	76.7	153	16	523	67.3	158	31	462	47.2	148	12
82	519	92.4	144	15	503	78.3	159	29	450	55.6	169	11

Table XVa. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Male Rats (continued)

86	500	106.7	136	13	490	88.6	152	24	415	52.2	157	10
90	517	94.6	114	9	482	84.5	124	20	422	53.0	120	9
94	515	69.5	138	8	467	96.3	129	18	415	73.7	136	8
98	459	80.7	120	7	449	97.2	144	16	403	64.7	149	7
102	423	42.2	137	4	420	98.6	141	15	389	72.5	141	6
106	394	37.6	94	3	401	88.9	109	11	418	46.9	142	4
110	382	26.9	91	2	383	101.5	114	8	423	45.3	255	3

[a]Calculated using individual animal weight.
[b]Average weight per animal per week.

Table XVb. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Female Rats

Time Interval (weeks)	Vehicle Controls				Low Dose				High Dose			
	Body Weight[a]		Food[b]	No. of Animals	Body Weight		Food	No. of Animals	Body Weight		Food	No. of Animals
	Mean (g)	Std Dev. (g)	(g)	Weighed	Mean (g)	Std Dev. (g)	(g)	Weighed	Mean (g)	Std Dev. (g)	(g)	Weighed
0	146	11.4	0	20	144	11.0	0	50	144	9.5	0	50
1	169	15.9	110	20	170	13.4	96	50	169	11.7	99	50
2	201	16.1	110	20	183	19.5	122	48	177	21.1	117	50
3	205	14.1	131	20	192	23.7	113	47	196	20.7	110	49
4	216	16.3	133	20	209	18.7	117	46	208	19.9	117	49
5	228	20.0	132	20	220	18.6	127	45	217	22.1	127	49
6	241	25.1	125	20	224	19.2	122	45	226	19.7	118	48
7	242	24.8	153	20	234	19.7	132	44	235	19.8	128	48
8	255	27.9	119	20	240	20.3	113	44	236	18.7	108	48
9	268	26.8	132	20	256	22.0	112	44	251	20.7	112	48
10	280	30.8	130	20	250	21.4	128	44	247	21.0	117	47
14	302	33.8	107	20	271	24.4	98	44	262	26.3	104	47
18	321	37.9	122	20	283	27.9	113	41	276	27.9	112	47
22	330	36.8	119	20	286	31.0	102	37	281	26.5	102	46
26	351	37.6	124	19	293	28.8	110	34	286	30.8	106	45
30	367	39.5	124	19	303	33.9	95	32	304	39.0	93	43
34	382	34.8	128	19	309	33.8	110	31	229	36.3	105	42
38	383	42.7	121	19	309	34.9	104	30	302	38.5	102	41
42	378	52.2	151	19	314	30.7	127	28	306	49.2	130	41
46	382	45.9	127	19	307	30.4	116	28	301	37.1	104	39
50	390	50.9	126	17	312	30.0	114	28	300	42.0	126	39
54	388	51.3	128	17	315	29.8	120	28	307	38.6	113	37
58	396	47.3	135	17	318	34.3	118	27	310	39.7	109	35
62	404	57.4	134	17	318	34.5	129	25	310	39.8	136	34
66	390	54.3	135	17	311	35.7	118	25	304	40.7	116	32
70	399	59.7	116	16	322	46.1	113	23	313	46.1	108	29
74	385	60.4	140	16	303	42.7	127	23	300	45.6	118	24
78	373	58.2	146	16	317	39.9	145	20	317	43.5	135	23
82	382	47.9	143	15	315	43.2	142	20	315	48.1	136	22
86	378	43.4	137	15	311	43.2	131	20	317	51.9	131	22

Table XVb. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Female Rats (continued)

90	364	41.6	101	14	314	33.6	103	19	324	48.9	107	20
94	366	47.7	134	14	313	37.6	123	19	326	55.7	127	20
98	327	61.7	120	13	314	58.3	119	16	321	60.3	129	18
102	336	63.4	134	9	314	66.4	132	15	299	74.3	143	16
106	332	74.9	105	9	308	73.7	114	13	317	70.3	130	13
110	326	80.1	119	8	311	86.0	114	13	311	67.7	136	13

[a]Calculated using individual animal weight.
[b]Average weight per animal per week.

Table XVIa. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Male Mice

Time Interval (weeks)	Vehicle Controls				Low Dose				High Dose			
	Body Weight[a]		Food[b]	No. of Animals Weighed	Body Weight		Food	No. of Animals Weighed	Body Weight		Food	No. of Animals Weighed
	Mean (g)	Std Dev. (g)	(g)		Mean (g)	Std Dev. (g)	(g)		Mean (g)	Std Dev. (g)	(g)	
0	17	0.5	0	20	17	2.0	0	50	17	1.1	0	50
1	20	0.0	24	20	19	1.2	23	50	20	0.5	22	50
2	20	1.2	25	20	21	1.0	26	50	21	0.5	25	50
3	22	0.4	22	20	22	0.9	24	50	22	0.9	25	50
4	23	0.1	22	20	23	0.7	24	50	23	0.7	25	50
5	25	0.4	22	20	24	0.7	25	50	25	0.6	25	50
6	25	0.2	22	20	24	0.5	25	50	24	0.5	24	50
7	25	0.4	25	20	26	0.7	27	50	26	1.1	27	50
8	27	0.3	23	20	26	0.8	26	50	26	0.3	26	50
9	24	1.0	26	20	26	0.8	28	50	26	0.4	29	50
10	27	0.4	22	20	27	1.2	26	50	28	0.4	25	50
14	28	0.1	23	20	28	0.8	27	50	29	0.4	26	49
18	29	1.7	20	20	30	0.9	24	49	31	0.3	23	46
22	30	0.4	28	20	30	1.5	29	48	30	0.8	29	46
26	31	0.2	24	20	31	0.9	28	48	32	0.7	27	42
30	33	0.1	26	20	32	1.0	28	48	32	0.6	28	38
34	34	0.5	26	19	34	1.2	29	47	34	1.1	31	36
38	34	0.5	24	19	35	1.4	29	47	35	0.5	29	35
42	33	0.1	23	18	33	1.1	27	47	35	0.9	30	35
46	34	0.4	26	18	34	0.9	28	47	35	1.6	30	34
50	34	0.5	23	18	34	1.5	27	47	35	0.7	30	34
54	32	0.4	21	18	33	1.0	26	45	34	0.4	30	33
58	33	1.3	27	18	34	1.1	28	44	35	0.6	33	33
62	35	0.5	27	16	34	0.9	30	44	35	0.2	34	30
66	33	0.5	22	15	34	1.5	27	41	34	0.5	32	30
70	33	0.9	31	13	35	1.1	33	41	35	0.5	36	29
74	32	2.7	27	12	34	0.4	34	41	35	0.6	36	27
78	34	0.6	24	8	34	0.8	32	40	35	1.0	39	24

Table XVIa. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Male Mice (continued)

82	33	0.2	33	8	33	0.4	31	38	34	1.2	42	22
86	32	0.1	32	8	32	0.3	32	38	32	1.9	41	22
90	34	0.7	34	8	33	0.7	32	35	34	1.3	38	20

[a]Calculated using individual animal weight.
[b]Average weight per animal per week.

Table XVIb. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Female Mice

Time Interval (weeks)	Vehicle Controls				Low Dose				High Dose			
	Body Weight[a]		Food[b]	No. of Animals Weighed	Body Weight		Food	No. of Animals Weighed	Body Weight		Food	No. of Animals Weighed
	Mean (g)	Std Dev. (g)	(g)		Mean (g)	Std Dev. (g)	(g)		Mean (g)	Std Dev. (g)	(g)	
0	14	0.0	0	20	14	0.6	0	50	14	0.7	0	50
1	17	0.0	22	20	18	0.4	24	50	17	0.6	23	50
2	18	0.3	28	20	18	0.5	28	50	18	0.8	27	50
3	19	0.5	24	20	19	0.3	24	50	19	0.6	23	50
4	19	0.5	30	20	19	0.7	24	50	19	0.7	23	50
5	20	0.5	25	20	20	0.6	24	50	20	0.7	22	50
6	20	0.1	25	20	20	0.3	24	50	19	0.7	23	50
7	21	0.2	32	20	21	0.3	26	50	21	0.5	24	50
8	22	0.9	31	20	21	0.3	27	50	22	0.2	26	50
9	20	0.3	32	20	21	0.7	27	50	21	0.6	26	50
10	22	0.4	23	20	22	0.4	23	50	22	0.6	23	50
14	23	0.4	27	20	23	0.3	23	49	24	0.5	24	49
18	24	0.1	18	20	25	0.9	21	49	25	1.5	20	49
22	25	0.1	27	19	25	0.6	25	49	24	0.6	24	48
26	25	0.2	22	19	26	0.7	23	49	25	0.5	24	47
30	26	0.1	20	19	26	0.4	23	49	26	0.5	24	47
34	27	0.1	24	19	27	0.4	23	48	27	0.4	24	44
38	27	0.6	19	18	27	0.4	22	46	27	0.4	23	43
42	28	0.8	21	18	28	0.5	23	45	27	0.4	35	41
46	28	0.5	21	18	29	0.5	22	45	27	0.3	22	41
50	28	1.1	20	18	28	0.4	21	45	27	0.6	22	41
54	28	1.1	19	18	27	0.5	21	45	26	0.3	22	41
58	29	0.2	22	18	28	0.5	33	44	27	0.4	23	41
62	28	0.5	25	18	28	0.2	25	44	26	0.4	23	41
66	28	0.9	20	18	28	0.7	22	42	27	0.6	21	41
70	29	0.7	23	18	28	0.6	24	42	28	0.7	23	40
74	29	0.6	21	18	29	0.6	24	42	28	0.7	25	40
78	29	0.6	23	18	29	0.7	25	41	28	0.4	26	40

Table XVIb. Mean Body Weights, Food Consumption, and Survival - Trichloroethylene Chronic Study - Female Mice (continued)

82	28	0.5	24	18	28	0.6	25	40	27	0.6	27	40
86	26	0.0	24	17	27	0.6	25	40	25	1.0	25	40
90	28	0.6	28	17	30	0.6	27	40	28	0.7	26	39

[a]Calculated using individual animal weight.
[b]Average weight per animal per week.

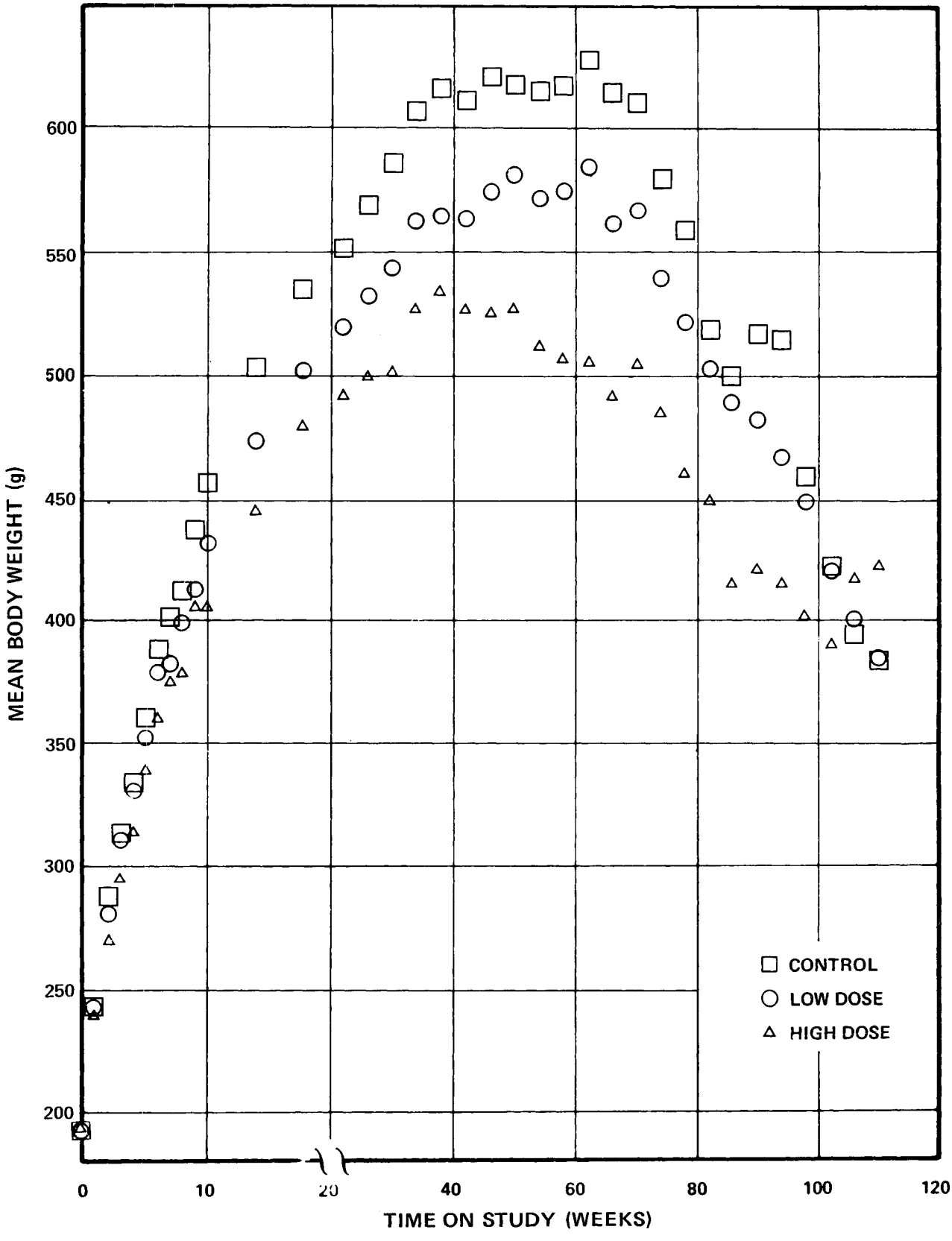

Figure 13a. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Male Rats

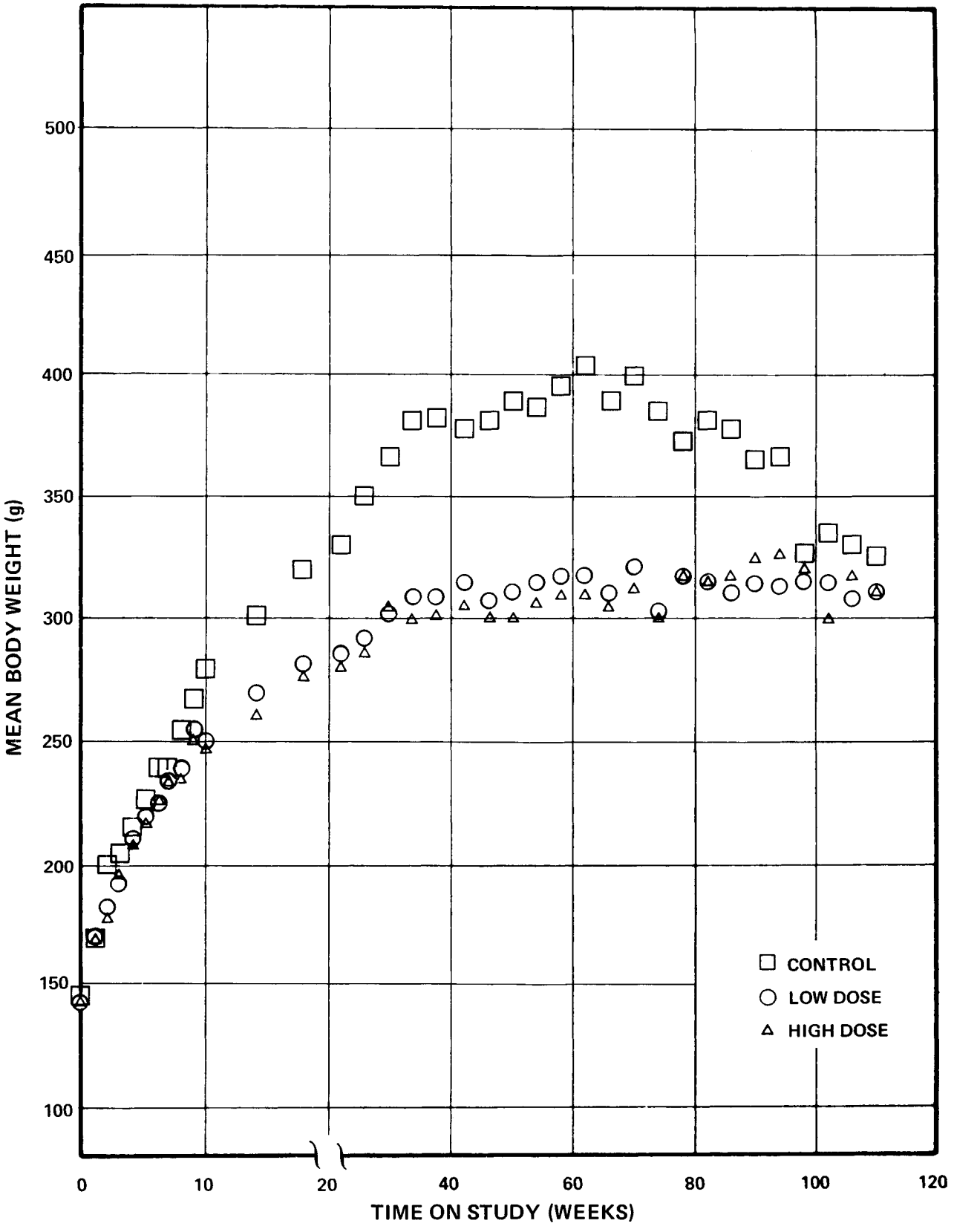

Figure 13b. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Female Rats

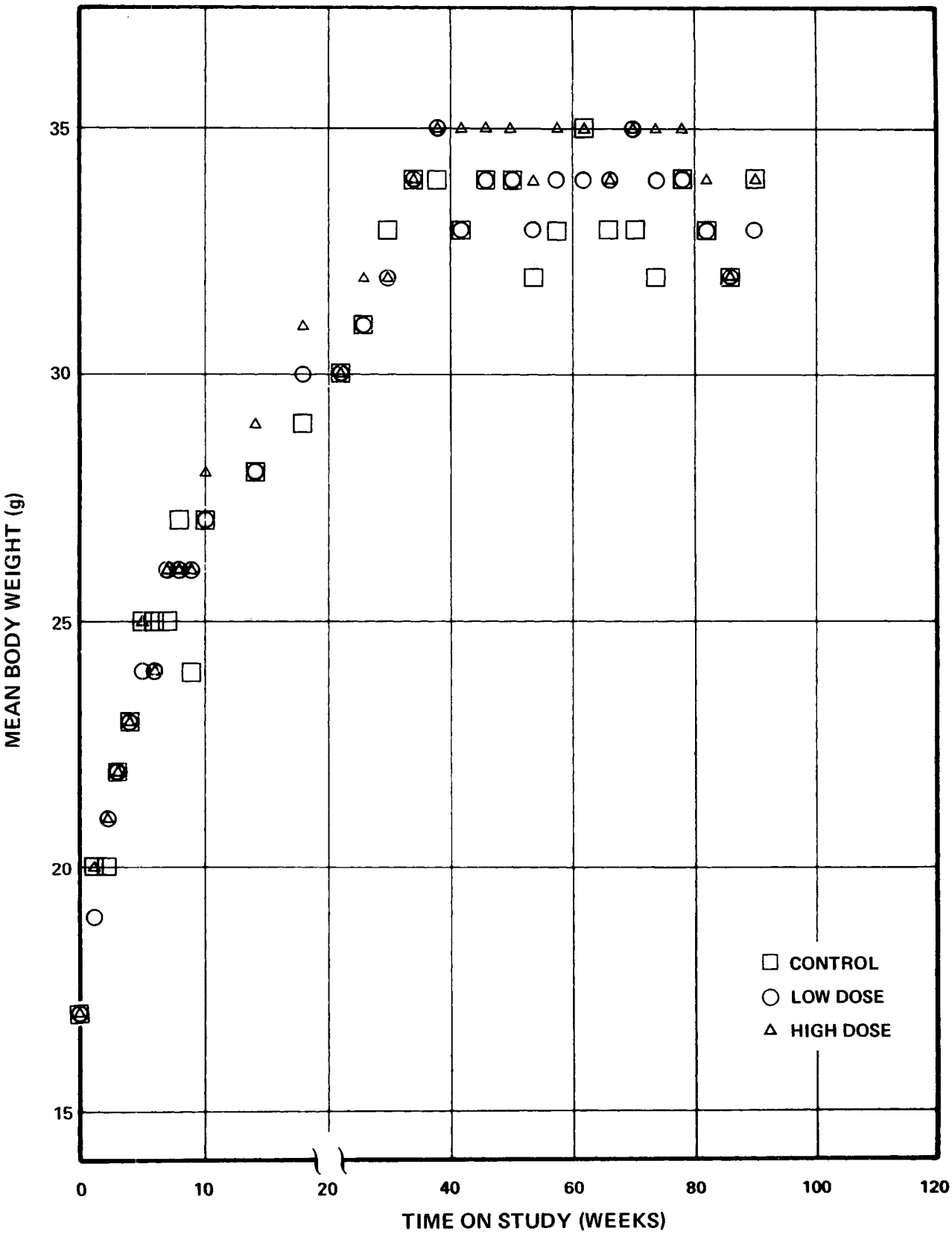

Figure 14a. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Male Mice

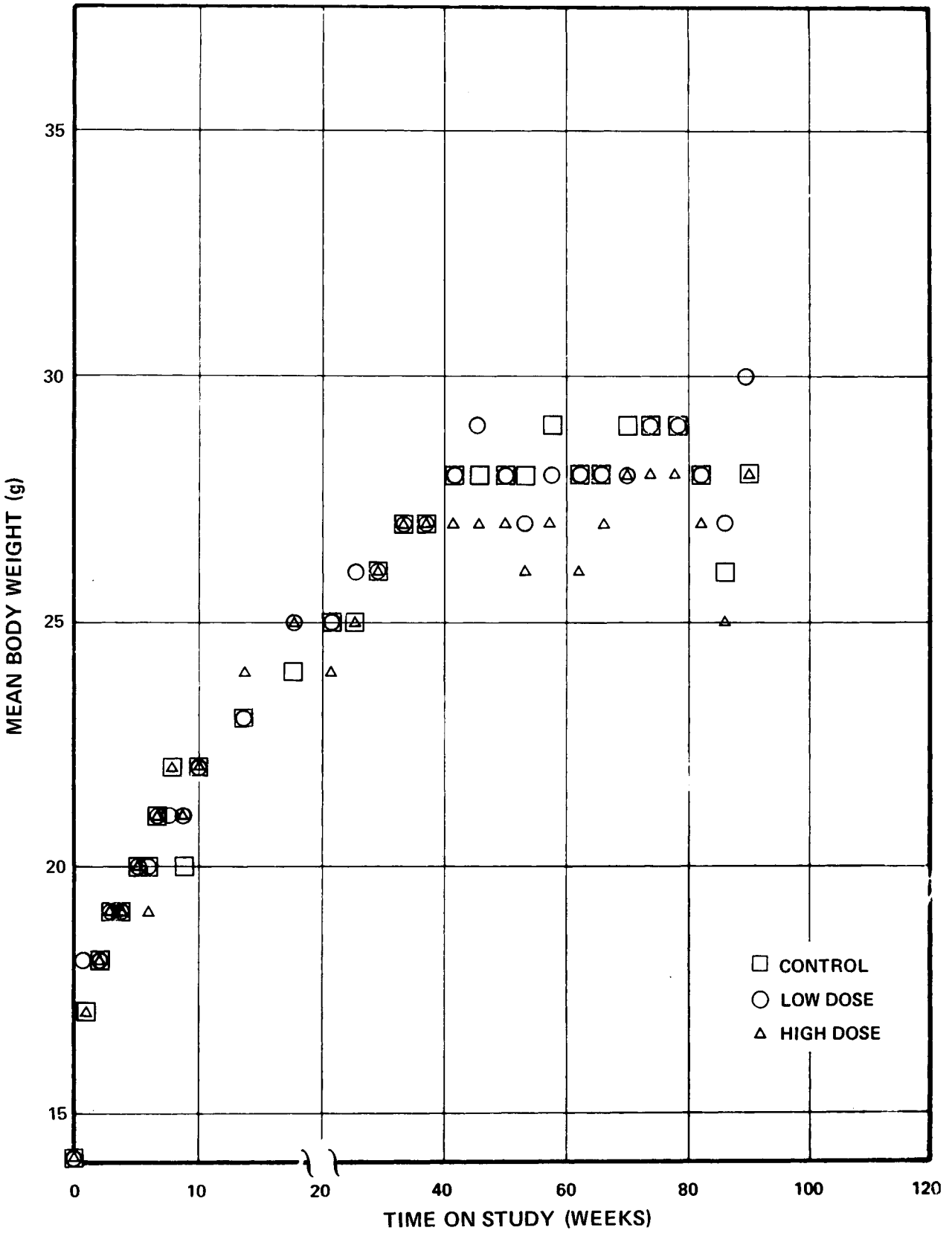

Figure 14b. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Female Mice

APPENDIX C: STATISTICS

Organization of Chronic Data for Statistical Analysis

Statistical analysis begins with examination of the data on survival and pathology of animals in the chronic experiment. These data are presented in detail in the pathology tables in Appendix D. These tables are summarized in this appendix (Tables XVII, XVIIIa, XVIIIb, XIXa, and XIXb). Each animal is listed in its group, identified by its animal number, and arranged in order of the week on study in which it died or was killed or lost. The first column is labeled "Week on Study". An asterisk after the week indicates that the animal's observed lifetime was censored by scheduled or terminal sacrifice, accidental killing, or otherwise lost. Absence of the asterisk indicates that the animal was found dead or was killed while moribund. When mice that were scheduled to be terminally sacrificed at 90 weeks were in fact killed at 91 weeks, 90 weeks is adopted as the week on study of death, so they can be compared with control mice killed at 90 weeks. The second column lists the animal number for reference to the pathology tables. The final column, labeled "Mark", contains letters assigned by the pathologist and the biostatistician in cooperation to sets of pathological diagnoses solely for statistical analysis. The choice of letter is arbitrary, except that more frequent diagnostic sets tend to be assigned to letters early in the alphabet. Each animal is marked if its pathology is included in the set of diagnoses associated with the mark. An animal may have several marks. If the animal has not been evaluated histopathologically, a hyphen appears in the column. A blank space in the column indicates that the animal has been evaluated histopathologically, but has not been marked.

Estimation of Survival Probabilities

The probability that an animal survived each week of the chronic experiment is estimated for each group by the product-limit procedure of Kaplan and Meier (1958). These estimates are listed in Tables XXa, XXb, XXIa, and XXIb in Appendix C. The estimates are also graphed in Figures 2a, 2b, 3a, and 3b. A description of the estimate follows, including a description of the survival tables.

In the survival tables, the first column, labeled j, is the week on study at which death or censoring occurs. The second column, labeled n, is the number of animals at the beginning of week j. The third column, labeled n′, is the number of animals alive at the end of week j. The estimate of the conditional probability of the animal surviving week j, given that it was alive at the beginning of the week, is n′/n. If an animal dies during the week, n′/n is less than one. The number of animals dying during the week is n minus n′. Animals whose lifetimes are censored are removed from the set of surviving animals just before the beginning of the week. This removal does not decrease the estimated conditional probability of survival. The number of animals thus removed is found by subtracting the n of this week from the n′ of the previously listed week. The fourth column, labeled P, is the product of the factors n′/n for all weeks up to and including the current week j. It is the Kaplan-Meier product-limit estimate of the unconditional probability of an animal surviving from the beginning of the chronic experiment through the end of the current week j.

Comparison of Survival Among Groups

A statistical test described by Cox (1972, p. 197), and developed by Mantel (1963, 1966) and Cochran (1954) is used to compare the survival of 2 groups of animals. Table XXc shows results of the test for rats, and Table XXIc shows them for mice. The test accumulates over weeks the observed number of deaths in the higher dosed group minus its expected value under the null hypothesis of equal probability of death in each group. This accumulated statistic is denoted by U in the tables. The test also accumulates the variance of the observed number of deaths. The total variance is denoted by V. A statistic Z is computed by dividing U by the square root of V. Since Z is distributed approximately as a standard normal random variable, the probability of exceeding Z is listed in the column labeled P. Small values of P indicate that the probability of death in the higher dosed group is significantly larger than in the low dosed group at significance level P, indicating longer life for the lower dosed group. The calculation of U and V begins with forming a two-by-two table for each week in which a death has occurred in either group. A typical table is:

	Lower Dose	Higher Dose	Total
Deaths during week	M_0	M_1	M
Survivors of week	N_0-M_0	N_1-M_1	N-M
Animals at risk during week	N_0	N_1	N

The observed number of deaths in the higher dosed group is M_1, and its expected value under the null hypothesis is $E_1=NM_1/N$. Their difference, M_1-E_1, is accumulated over weeks to form the test statistic U. The variance V of the test statistic U is calculated by accumulating a contribution from each table of $(M(N-M)A_1(1-A_1)/(N-1)$, where $A_1=N_1/N$. Four comparisons are made by this test: both dosed groups pooled vs. control, low dose vs. control, high dose vs. control, and high dose vs. low dose.

A dose-response table developed by Tarone (1975) is also applied to the two-by-three table:

	Control	Low Dose	High Dose	Total
Deaths during week	M_0	M_1	M_2	M
Survivors of week	N_0-M_0	N_1-M_1	N_2-M_2	N-M
Animals at risk during week	N_0	N_1	N_2	N
Dosage	d_0	d_1	d_2	

The test statistic U and its variance V are accumulated over weeks. The contribution to U from each table is:

$d_0(M_0-E_0)+d_1(M_1-E_1)+d_2(M_2-E_2)$, where $E_j=MN_j/N$ for j = 0, 1, or 2.

The contribution to V from each table is:

$((d_0^2A_0+d_1^2A_1+d_2^2A_2)-(d_0A_0+d_1A_1+d_2A_2)^2)(M(N-M)/N-1))$, where $A_j=N_j/N$,

for j = 0, 1, or 2.

Estimation of Probabilities of Observing Tumors

The probabilities of observing tumors are estimated by a modification of the product-limit procedure of Kaplan and Meier (1958). This modified estimate is described by Saffiotti et al. (1972). When an animal dies or is killed, it is evaluated histopathologically and marked as observed to have developed the pathology associated with the mark under study or as not yet having developed it. The animal being marked in this context is analogous to the animal having died in the survival context, and the animal not being marked is analogous to having the lifetime of the animal censored by scheduled sacrifice or loss. If histopathological evaluation of the pathology associated with the mark was not performed, the animal is not considered in the analysis of the mark under study. The probability of survival estimated by the product-limit procedure in the survival context corresponds to the probability of not yet having observed a tumor. A more interesting quantity is the probability of having observed a tumor, which is found by subtracting the probability of not having observed a tumor from one. The estimated probabilities of having observed hepatocellular carcinoma of the liver (mark a) for male mice are given in Table XII, and graphed in Figure 11. Figure 12 shows a comparison of incidence of hepatocellular carcinoma in male and female mice.

Comparison of Probabilities of Observing Tumors Among Groups, Adjusting for Age

The statistical tests of Cox (1972) and Tarone (1975) used to compare survival among groups can be modified to compare the probabilities of observing tumors among groups by employing the analogies described above between death in the survival context and observation of a tumor in the context of observing pathology. Specifically, in the two-by-two and two-by-three tables of the section on the comparison of survival among groups, "Deaths during week" is replaced by "animals with observed tumor during week". Tumors cannot be observed while the animals are alive. No distinction is made between the natural death of an animal and the censoring of its lifetime in comparisons of tumor probabilities. Animals in which tumors were not observed at histopathological examination are censored from the group of surviving animals for the next week's comparison.

Calculation and interpretation of the Cox and Tarone tests proceed just as in their use in the survival context. Both tests are one-tailed in the direction of increasing probability of tumor with increasing dose. Small values of P indicate significantly greater probability of tumor in higher dosed animals.

These tests compare animals at the same ages in the groups under comparison, removing biases introduced by differing death rates in control and dosed groups.

Results of these tests are shown in Tables XIIIa-e for rats and XXVIa-e for mice.

Comparison of Probabilities of Observing Tumors Among Groups, by Exact Tests (Not Adjusted for Age)

When the ages of animals at death or sacrifice are ignored, comparison of probabilities of tumors between two groups is performed by the well known Fisher-Irwin exact test, which is a one-tailed test. (See, e.g., Armitage (1971) for a description.) For three groups, with dosages associated with each group, the test, essentially due to Armitage (1971), employs the linear contrast statistic

$$U = d_0M_0 + d_1M_1 + d_2M_2$$

where d_i = ith dosage and M_i = number of animals with the tumor in the ith group.

The exact distribution of U is computed under the null hypothesis that all groups have the same probability of tumor. The probability P that the observed U is equalled or exceeded is given in tables with the observed proportions and percentages of tumors.

To test for overall heterogeneity among three groups not necessarily related to the dosages, the two degree of freedom chi-square statistic for the classical Pearson test for independence is computed from the data and compared with the exact distribution under the null hypothesis as above. Finally, chi-square statistics with one degree of freedom each are used in exact tests partitioning the two degree of freedom statistic into components for a linear trend on a logistic scale and deviation from the linear trend.

Results of these tests are shown in Tables XXIVa-d for rats and Table XXVII for mice.

Table XVII. Identity of Tumor Marks

Mark	Tumor
a	Hepatocellular carcinoma
b	Reticulum-cell sarcoma, lymphosarcoma, or malignant lymphoma
c	Carcinoma or adenocarcinoma of the lung or alveoli
d	Adenoma of the lung
f	Aortic body tumor
g	Fibroadenoma of the mammary glands
h	Hemangiosarcoma of any site
i	Malignant giant-cell tumor of soft tissues or fibrosarcoma of the skin or subcutis
j	Malignant mixed tumor of the kidney
k	Hamartoma of the kidney
l	Follicular adenoma of the thyroid
m	Tubular adenocarcinoma of the kidney
n	Fibroma of the subcutis
p	Follicular adenocarcinoma of the thyroid
q	Squamous cell carcinoma of the subcutis
r	Pilomatrixoma of the skin
t	Chromophobe adenoma of the pituitary
u	Adenocarcinoma of the mammary glands
v	Granulosa-cell carcinoma of the ovaries
w	Adrenal cortical carcinoma
x	Liposarcoma of any site
y	Sarcoma of the endometrium or fibrosarcoma of the uterus
z	Adenoma of the Harderian gland
A	Neurofibroma of any site
B	Adenoma of the kidney
C	Papilloma of the stomach
D	Osteosarcoma
E	Adenocarcinoma of the endometrium
F	Cystadenoma of the ovaries

Table XVIIIa. Data for Statistical Analysis - Trichloroethylene-Treated Male Rats

Control			Low Dose			High Dose		
Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark
67	3		16	28		2	12	
70	11	h	17	36		2	32	
76	14		23	10		5	14	
76	15		27	6		6	4	
82	9		34	35		12	15	
82	13		40	30		17	22	
83	18		42	34		21	6	
87	16		48	3		27	2	
88	5		50	7		31	25	
88	12		53	41		33	24	
90	2	i	60	46		35	40	
91	4		61	39		40	33	
96	19	jl	65	19		42	39	
98	20		67	32		44	3	
99	10	jk	67	44		48	18	
102	17		72	40		49	30	
103	8		74	47		52	5	
110*	1		76	18		52	41	
110*	6		76	23	l	53	37	
110	7	c	80	26	h	54	13	
			80	33		54	17	
			82	5		56	27	
			83	38		58	47	
			83	43		59	9	
			85	1		61	29	
			86	14		62	7	
			86	20		62	38	
			87	29		65	11	p
			88	12		65	28	
			90	15	m	65	45	
			94	25	n	66	49	
			94	49		68	10	
			96	21		70	20	
			97	16		71	16	
			102	9		72	34	r
			103	13		72	50	
			103	27		75	44	
			103	31		76	21	
			104	37		82	19	f
			107	8		83	43	
			107	45		88	31	
			108	4	i	91	36	h
			110*	2	kp	97	42	
			110*	11	q	99	8	
			110*	17		102	35	
			110*	22		103	1	
			110*	24		109	48	
			110	42		110*	23	
			110*	48		110*	26	h
			110*	50		110*	46	

* Animal's observed lifetime censored by scheduled sacrifice, accidental killing or loss. Absence of * means natural death or moribund sacrifice.

- Histopathology not performed.

Table XVIIIb. Data for Statistical Analysis - Trichloroethylene-Treated Female Rats

Control			Low Dose			High Dose		
Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark
25	8		2	24		3	13	
47	16		2*	29	-	5	2	
47	20		2	42		9	32	
68	6	t	3	2	h	21	36	
79	1		5	20		24	49	
87	7		7	47		28	8	
97	11	g	15	1		28	16	
98	15		16	30		30	43	
99	2		16	38		35	40	
102	14	tu	19	11		43	38	
104	19	t	21	12		46	45	
108	12		21	14		50	4	
110*	3	gt	21*	21	-	53	7	
110*	4	bv	22	5		54	41	
110*	5		22	39		58	24	
110*	9		25	17		59	17	
110*	10	g	26	36		63	31	
110*	13		28	35		64	22	
110*	17		33	33		67	28	
110*	18		34	19		69	12	
			40	45		69	27	
			42	22		70	18	
			57	6		70	20	
			60	10		72	14	
			61	44		73	1	
			68	27		73	42	
			69	25		74	39	
			75	15		82	26	
			75	16	b	86	48	
			77	48		89	47	
			86	34		95	21	
			96	23	w	96	50	t
			96	46		101	29	g
			98	32	x	101	35	t
			100	13	n	102	19	
			102	49		103	33	g
			104	40	g	104	34	
			110*	3		110*	3	
			110*	4		110*	5	t
			110*	7	gt	110*	6	b
			110*	8		110*	9	gt
			110*	9		110*	10	g
			110*	18	g	110*	11	
			110*	26	y	110*	15	
			110*	28		110*	23	gt
			110*	31	t	110*	25	
			110*	37		110*	30	gp
			110*	41		110*	37	gy
			110*	43	g	110*	44	
			110	50	g	110*	46	t

* Animal's observed lifetime censored by scheduled sacrifice, accidental killing or loss. Absence of * means natural death or moribund sacrifice.

- Histopathology not performed.

Table XIXa. Data for Statistical Analysis - Trichloroethylene-Treated Male Mice

Control			Low Dose			High Dose		
Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark
32	10		16	10		13	10	
39	9		18	50	b	14	40	
60	8		31*	9		15	49	
61	7		51	30		15*	50	
64	6		53	40		24	19	
66	20		58	8		24	20	
68	5		63	39		25	47	
72	19	a	65	20		25	48	
76	4		65	38		27	46	a
76	18	b	77	19		28	18	a
77	17	i	81	28	b	28	45	
78	3		81	29	ad	29	30	
90*	1	i	86	49	a	30	9	
90*	2		88	7	ad	30	17	a
90*	11	i	88	18		36	8	a
90*	12		90*	1	ad	42	7	
90*	13		90*	2	n	53	39	a
90*	14		90*	3	a	60	5	
90*	15		90*	4	abd	60	6	
90*	16		90*	5	a	61	16	a
			90*	6	a	70	38	a
			90*	11	a	71	15	a
			90*	12	a	72	37	-
			90*	13	a	74	29	a
			90*	14	z	75	4	
			90*	15	ab	75	36	-
			90*	16		78	44	aA
			90*	17	a	83	35	ac
			90*	21	a	88	3	ab
			90*	22		90*	1	a
			90*	23		90*	2	a
			90*	24	a	90*	11	a
			90*	25		90*	12	a
			90*	26	a	90*	13	aB
			90*	27		90*	14	a
			90*	31	a	90*	21	a
			90*	32	a	90*	22	a
			90*	33	a	90*	23	a
			90*	34	a	90*	24	b
			90*	35	a	90*	25	a
			90*	36	a	90*	26	a
			90*	37	ad	90*	27	a
			90*	41	a	90*	28	a
			90*	42		90*	31	d
			90*	43	a	90*	32	a
			90*	44		90*	33	aC
			90*	45		90	34	ai
			90*	46		90*	41	a
			90*	47		90*	42	a
			90*	48	a	90*	43	ah

* Animal's observed lifetime censored by scheduled sacrifice, accidental killing or loss. Absence of * means natural death or moribund sacrifice.

- Histopathology not performed.

Table XIXb. Data for Statistical Analysis - Trichloroethylene-Treated Female Mice

Control			Low Dose			High Dose		
Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark	Week on Study	Animal Number	Mark
20*	10		10	20		14*	10	-
37*	9		32*	10		22*	40	-
83*	8	D	37	19		26*	50	-
90*	1		38	18		32	30	
90*	2		41*	9		32	49	
90*	3	E	55	30		33	39	
90*	4		63	29		38	38	
90*	5		66	40		39	20	
90*	6		76	17	b	40	37	
90*	7	d	81	16	b	69	9	b
90*	11		90*	1	b	88	36	b
90*	12		90*	2		90*	1	b
90*	13		90*	3	ay	90*	2	
90*	14	b	90*	4		90*	3	
90*	15		90*	5		90*	4	
90*	16		90*	6		90*	5	
90*	17		90*	7	a	90*	6	a
90*	18		90*	8		90*	7	
90*	19		90*	11		90*	8	ac
90*	20		90*	12	a	90*	11	
			90*	13		90*	12	a
			90*	14		90*	13	a
			90*	15		90*	14	
			90*	21		90*	15	d
			90*	22		90*	16	
			90*	23		90*	17	
			90*	24		90*	18	b
			90*	25		90*	19	
			90*	26		90*	21	
			90*	27	c	90*	22	b
			90*	28		90*	23	d
			90*	31		90*	24	a
			90*	32	a	90*	25	ac
			90*	33	v	90*	26	a
			90*	34		90*	27	
			90*	35	i	90*	28	
			90*	36	bd	90*	29	
			90*	37		90*	31	
			90*	38	u	90*	32	
			90*	39		90*	33	
			90*	41		90*	34	d
			90*	42	bd	90*	35	
			90*	43	czF	90*	41	abd
			90*	44		90*	42	a
			90*	45		90*	43	
			90*	46		90*	44	a
			90*	47		90*	45	
			90*	48		90*	46	ad
			90*	49		90*	47	
			90*	50		90*	48	

* Animal's observed lifetime censored by scheduled sacrifice, accidental killing or loss. Absence of * means natural death or moribund sacrifice.

- Histopathology not performed.

Table XXa. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Male Rats

Control				Low Dose				High Dose			
j	n	n′	P	j	n	n′	P	j	n	n′	P
0	20	20	1.000	0	50	50	1.000	0	50	50	1.000
67	20	19	.950	16	50	49	.980	2	50	48	.960
70	19	18	.900	17	49	48	.960	5	48	47	.940
76	18	16	.800	23	48	47	.940	6	47	46	.920
82	16	14	.700	27	47	46	.920	12	46	45	.900
83	14	13	.650	34	46	45	.900	17	45	44	.880
87	13	12	.600	40	45	44	.880	21	44	43	.860
88	12	10	.500	42	44	43	.860	27	43	42	.840
90	10	9	.450	48	43	42	.840	31	42	41	.820
91	9	8	.400	50	42	41	.820	33	41	40	.800
96	8	7	.350	53	41	40	.800	35	40	39	.780
98	7	6	.300	60	40	39	.780	40	39	38	.760
99	6	5	.250	61	39	38	.760	42	38	37	.740
102	5	4	.200	65	38	37	.740	44	37	36	.720
103	4	3	.150	67	37	35	.700	48	36	35	.700
110	3	2	.100	72	35	34	.680	49	35	34	.680
				74	34	33	.660	52	34	32	.640
				76	33	31	.620	53	32	31	.620
				80	31	29	.580	54	31	29	.580
				82	29	28	.560	56	29	28	.560
				83	28	26	.520	58	28	27	.540
				85	26	25	.500	59	27	26	.520
				86	25	23	.460	61	26	25	.500
				87	23	22	.440	62	25	23	.460
				88	22	21	.420	65	23	20	.400
				90	21	20	.400	66	20	19	.380
				94	20	18	.360	68	19	18	.360
				96	18	17	.340	70	18	17	.340
				97	17	16	.320	71	17	16	.320
				102	16	15	.300	72	16	14	.280
				103	15	12	.240	75	14	13	.260
				104	12	11	.220	76	13	12	.240
				107	11	9	.180	82	12	11	.220
				108	9	8	.160	83	11	10	.200
				110	8	7	.140	88	10	9	.180
								91	9	8	.160
								97	8	7	.140
								99	7	6	.120
								102	6	5	.100
								103	5	4	.080
								109	4	3	.060
								110	3	3	.060

j = Week on study

n = No. of animals alive at beginning of the week

n′ = No. of animals surviving the week

P = Kaplan-Meier estimate of survival probability

Table XXb. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Female Rats

Control				Low Dose				High Dose			
j	n	n′	P	j	n	n′	P	j	n	n′	P
0	20	20	1.000	0	50	50	1.000	0	50	50	1.000
25	20	19	.950	2	50	48	.960	3	50	49	.980
47	19	17	.850	3	47	46	.940	5	49	48	.960
68	17	16	.800	5	46	45	.919	9	48	47	.940
79	16	15	.750	7	45	44	.899	21	47	46	.920
87	15	14	.700	15	44	43	.878	24	46	45	.900
97	14	13	.650	16	43	41	.837	28	45	43	.860
98	13	12	.600	19	41	40	.817	30	43	42	.840
99	12	11	.550	21	40	38	.776	35	42	41	.820
102	11	10	.500	22	37	35	.734	43	41	40	.800
104	10	9	.450	25	35	34	.713	46	40	39	.780
108	9	8	.400	26	34	33	.692	50	39	38	.760
110	8	8	.400	28	33	32	.671	53	38	37	.740
				33	32	31	.650	54	37	36	.720
j = Week on study				34	31	30	.629	58	36	35	.700
				40	30	29	.608	59	35	34	.680
n = No. of animals alive at beginning of the week				42	29	28	.587	63	34	33	.660
				57	28	27	.566	64	33	32	.640
				60	27	26	.545	67	32	31	.620
				61	26	25	.524	69	31	29	.580
n′ = No. of animals surviving the week				68	25	24	.503	70	29	27	.540
				69	24	23	.482	72	27	26	.520
				75	23	21	.441	73	26	24	.480
P = Kaplan-Meier estimate of survival probability				77	21	20	.420	74	24	23	.460
				86	20	19	.399	82	23	22	.440
				96	19	17	.357	86	22	21	.420
				98	17	16	.336	89	21	20	.400
				100	16	15	.315	95	20	19	.380
				102	15	14	.294	96	19	18	.360
				104	14	13	.273	101	18	16	.320
				110	13	12	.252	102	16	15	.300
								103	15	14	.280
								104	14	13	.260
								110	13	13	.260

Table XXc. Statistical Tests Comparing Estimated Probability of Survival among Control and Trichloroethylene-Treated Rats

Comparison	Male Rats				Female Rats			
	U	V	Z	P	U	V	Z	P
Dose-Response	23.60	51.47	3.29	0.001	8.48	50.64	1.19	0.117
Dosed vs. Control	6.47	18.17	1.52	0.064	7.13	14.55	1.87	0.031
Low Dose vs. Control	0.88	12.44	0.25	0.402	6.33	11.08	1.90	0.028
High Dose vs. Control	11.12	15.07	2.86	0.002	5.50	11.04	1.65	0.049
High Dose vs. Low Dose	13.94	19.86	3.13	0.001	-2.56	17.84	-0.61	0.728

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXIa. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Male Mice

Control				Low Dose				High Dose			
j	n	n′	P	j	n	n′	P	j	n	n′	P
0	20	20	1.000	0	50	50	1.000	0	50	50	1.000
32	20	19	.950	16	50	49	.980	13	50	49	.980
39	19	18	.900	18	49	48	.960	14	49	48	.960
60	18	17	.850	31	48	48	.960	15	48	47	.940
61	17	16	.800	51	47	46	.940	24	46	44	.899
64	16	15	.750	53	46	45	.919	25	44	42	.858
66	15	14	.700	58	45	44	.899	27	42	41	.838
68	14	13	.650	63	44	43	.878	28	41	39	.797
72	13	12	.600	65	43	41	.837	29	39	38	.777
76	12	10	.500	77	41	40	.817	30	38	36	.736
77	10	9	.450	81	40	38	.776	36	36	35	.715
78	9	8	.400	86	38	37	.756	42	35	34	.695
90	8	8	.400	88	37	35	.715	53	34	33	.674
				90	35	35	.715	60	33	31	.633
								61	31	30	.613
								70	30	29	.593
								71	29	28	.572
								72	28	27	.552
								74	27	26	.531
								75	26	24	.490
								78	24	23	.470
								83	23	22	.450
								88	22	21	.429
								90	21	20	.409

j = Week on study

n = No. of animals alive at beginning of the week

n′ = No. of animals surviving the week

P = Kaplan-Meier estimate of survival probability

Table XXIb. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Female Mice

Control				Low Dose				High Dose			
j	n	n′	P	j	n	n′	P	j	n	n′	P
0	20	20	1.000	0	50	50	1.000	0	50	50	1.000
20	20	20	1.000	10	50	49	.980	14	50	50	1.000
37	19	19	1.000	32	49	49	.980	22	49	49	1.000
83	18	18	1.000	37	48	47	.960	26	48	48	1.000
90	17	17	1.000	38	47	46	.939	32	47	45	.957
				41	46	46	.939	33	45	44	.936
				55	45	44	.918	38	44	43	.915
				63	44	43	.897	39	43	42	.894
				66	43	42	.877	40	42	41	.872
				76	42	41	.856	69	41	40	.851
				81	41	40	.835	88	40	39	.830
				90	40	40	.835	90	39	39	.830

j = Week on study

n = No. of animals alive at beginning of the week

n′ = No. of animals surviving the week

P = Kaplan-Meier estimate of survival probability

Table XXIc. Statistical Tests Comparing Estimated Probability of Survival among Control and Trichloroethylene-Treated Mice

	Male Mice				Female Mice			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	6.67	26.11	1.30	0.096	4.29	8.32	1.49	0.068
Dosed vs. Control	-3.02	7.42	-1.11	0.866	2.75	2.27	1.82	0.034
Low Dose vs. Control	-5.72	4.68	-2.64	0.996	2.32	1.65	1.81	0.035
High Dose vs. Control	1.11	8.77	0.37	0.354	2.36	1.66	1.83	0.033
High Dose vs. Low Dose	10.72	10.35	3.33	0.001	0.21	3.99	0.10	0.459

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXII. Tumor Incidence - Trichloroethylene-Treated Rats

	Male Rats			Female Rats		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Mark b Reticulum-cell sarcoma, lymphosarcoma, or malignant lymphoma						
Before 110 weeks	0/17	0/42	0/47	0/12	1/35	0/37
At 110 weeks	0/3	0/8	0/3	1/8	0/13	1/13
Total	0/20	0/50	0/50	1/20	1/48	1/50
Mark g Fibroadenoma of the mammary glands						
Before 110 weeks	0/17	0/42	0/47	1/12	1/35	2/37
At 110 weeks	0/3	0/8	0/3	2/8	4/13	5/13
Total	0/20	0/50	0/50	3/20	5/48	7/50
Mark h Hemangiosarcoma of any site						
Before 110 weeks	1/17	1/42	1/47	0/12	1/35	0/37
At 110 weeks	0/3	0/8	1/3	0/8	0/13	0/13
Total	1/20	1/50	2/50	0/20	1/48	0/50
Mark p Follicular adenocarcinoma of the thyroid						
Before 110 weeks	0/17	0/42	1/47	0/12	0/35	0/37
At 110 weeks	0/3	1/8	0/3	0/8	0/13	1/13
Total	0/20	1/50	1/50	0/20	0/48	1/50
Mark t Chromophobe adenoma of the pituitary						
Before 110 weeks	0/17	0/42	0/47	3/12	0/35	2/37
At 110 weeks	0/3	0/8	0/3	1/8	2/13	4/13
Total	0/20	0/50	0/50	4/20	2/48	6/50
Animals with Tumors (Benign and Malignant)[a]						
Before 110 weeks	4/17	5/42	4/47	4/12	6/35	4/37
At 110 weeks	1/3	2/8	1/3	3/8	6/13	8/13
Total	5/20	7/50	5/50	7/20	12/48	12/50

[a]Includes tumors other than those listed above.

Table XXIIIa. Statistical Tests Comparing Estimated Probability of Observing Reticulum-cell Sarcoma, Lymphosarcoma, or Malignant Lymphoma (Mark b) Control and Trichloroethylene-Treated Rats

	Male Rats				Female Rats			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	0.00	0.00			-0.41	1.77	-0.31	0.620
Dosed vs. Control	0.00	0.00			-0.27	0.54	-0.37	0.644
Low Dose vs. Control	0.00	0.00			-0.21	0.48	-0.30	0.619
High Dose vs. Control	0.00	0.00			-0.24	0.45	-0.36	0.639
High Dose vs. Low Dose	0.00	0.00			0.00	0.50	0.00	0.500

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXIIIb. Statistical Tests Comparing Estimated Probability of Observing Fibroadenoma of the Mammary Glands (Mark g) among Control and Trichloroethylene-Treated Rats

	Male Rats				Female Rats			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	0.00	0.00			1.91	7.09	0.72	0.237
Dosed vs. Control	0.00	0.00			0.64	2.16	0.44	0.330
Low Dose vs. Control	0.00	0.00			0.15	1.55	0.12	0.451
High Dose vs. Control	0.00	0.00			0.88	1.88	0.64	0.259
High Dose vs. Low Dose	0.00	0.00			0.94	2.28	0.62	0.267

Table XXIIIc. Statistical Tests Comparing Estimated Probability of Observing Hemangioma of Any Site (Mark h) among Control and Trichloroethylene-Treated Rats

	Male Rats				Female Rats			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	1.08	1.89	0.79	0.215	-0.26	0.54	-0.35	0.638
Dosed vs. Control	-0.01	0.74	-0.02	0.506	0.17	0.14	0.46	0.324
Low Dose vs. Control	-0.31	0.45	-0.46	0.677	0.30	0.21	0.66	0.255
High Dose vs. Control	0.51	0.75	0.59	0.276	0.00	0.00		
High Dose vs. Low Dose	1.14	0.61	1.45	0.073	-0.52	0.25	-1.04	0.851

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXIIId. Statistical Tests Comparing Estimated Probability of Observing Follicular Adenocarcinoma of the Thyroid (Mark p) among Control and Trichloroethylene-Treated Rats

	Male Rats				Female Rats			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	0.96	0.96	0.98	0.163	0.85	0.60	1.10	0.135
Dosed vs. Control	0.46	0.35	0.77	0.219	0.24	0.18	0.55	0.289
Low Dose vs. Control	0.27	0.20	0.61	0.270	0.00	0.00		
High Dose vs. Control	0.47	0.25	0.93	0.176	0.38	0.24	0.78	0.216
High Dose vs. Low Dose	0.35	0.43	0.53	0.297	0.50	0.25	1.00	0.159

Table XXIIIe. Statistical Tests Comparing Estimated Probability of Observing Chromophobe Adenoma of the Pituitary (Mark t) among Control and Trichloroethylene-Treated Rats

	Male Rats				Female Rats			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	0.00	0.00			0.30	6.54	0.12	0.454
Dosed vs. Control	0.00	0.00			-1.08	1.98	-0.76	0.778
Low Dose vs. Control	0.00	0.00			-1.61	1.36	-1.38	0.916
High Dose vs. Control	0.00	0.00			-0.11	2.14	-0.08	0.531
High Dose vs. Low Dose	0.00	0.00			1.95	1.70	1.50	0.067

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXIVa. Exact Statistical Tests Comparing Proportions of Animals (Not Adjusted for Age) with Observed Hepatocellular Carcinoma of the Liver among Pooled Control and Trichloroethylene-Treated Rats

	Male Rats				Female Rats			
	Veh. Cont.	Low Dose	High Dose	Exact Test	Veh. Cont.	Low Dose	High Dose	Exact Test
Comparison	r/n	r/n	r/n	P	r/n	r/n	r/n	P
Dose-Response	1/99	0/50	0/50		0/98	0/48	0/50	
Veh. Control	1%	0%	0%	1.000	0%	0%	0%	1.000
Dosed vs.	1/99	0/100			0/98	0/98		
Veh. Control	1%	0%		1.000	0%	0%		1.000
Low Dose vs.	1/99	0/50			0/98	0/48		
Veh. Control	1%	0%		1.000	0%	0%		1.000
High Dose vs.	1/99		0/50		0/98		0/50	
Veh. Control	1%		0%	1.000	0%		0%	1.000
High Dose vs.		0/50	0/50			0/48	0/50	
Low Dose		0%	0%	1.000		0%	0%	1.000

Comparison	Chi-square	df	P	Chi-square	df	P
Among High Dose, Low Dose and Vehicle Control	1.02	2	1.000	1.00	2	1.000
Dose-Response Trend Vehicle Control	0.83	1	0.749	1.00	1	1.000
Deviation from Trend Vehicle Control	0.19	1	1.000	0.00	1	1.000

r = Number of animals with observed mark.
n = Number of animals examined histopathologically for the mark.
P = Exact probability of exceeding or equaling observed test statistic under null hypothesis.
df = Degrees of freedom.
See section on statistical methodology for explanation of tests.

Table XXIVb. Exact Statistical Tests Comparing Proportions of Animals (Not Adjusted for Age) with Observed Hepatocellular Carcinoma or Neoplastic Nodule of the Liver among Pooled Control and Trichloroethylene-Treated Rats

	Male Rats				Female Rats			
	Veh. Cont.	Low Dose	High Dose	Exact Test	Veh. Cont.	Low Dose	High Dose	Exact Test
Comparison	r/n	r/n	r/n	P	r/n	r/n	r/n	P
Dose-Response	1/99	0/50	0/50		2/98	0/48	0/50	
Veh. Control	1%	0%	0%	1.000	2%	0%	0%	1.000
Dosed vs.	1/99	0/100			2/98	0/98		
Veh. Control	1%	0%		1.000	2%	0%		1.000
Low Dose vs.	1/99	0/50			2/98	0/48		
Veh. Control	1%	0%		1.000	2%	0%		1.000
High Dose vs.	1/99		0/50		2/98		0/50	
Veh. Control	1%		0%	1.000	2%		0%	1.000
High Dose vs.		0/50	0/50			0/48	0/50	
Low Dose		0%	0%	1.000		0%	0%	1.000

Comparison	Chi-square	df	P	Chi-square	df	P
Among High Dose, Low Dose and Vehicle Control	1.02	2	1.000	2.04	2	0.371
Dose-Response Trend Vehicle Control	0.83	1	0.749	1.67	1	0.310
Deviation from Trend Vehicle Control	0.19	1	1.000	0.37	1	1.000

r = Number of animals with observed mark.
n = Number of animals examined histopathologically for the mark.
P = Exact probability of exceeding or equaling observed test statistic under null hypothesis.
df = Degrees of freedom.
See section on statistical methodology for explanation of tests.

Table XXIVc. Exact Statistical Tests Comparing Proportions of Animals (Not Adjusted for Age) with Observed Hepatocellular Carcinoma of the Liver among Pooled Control and Carbon Tetrachloride-Treated Rats

	Male Rats				Female Rats			
	Veh. Cont.	Low Dose	High Dose	Exact Test	Veh. Cont.	Low Dose	High Dose	Exact Test
Comparison	r/n	r/n	r/n	P	r/n	r/n	r/n	P
Dose-Response	1/99	2/50	2/50		0/98	4/49	1/49	
Veh. Control	1%	4%	4%	0.177	0%	8%	2%	0.174
Dosed vs.	1/99	4/100			0/98	5/98		
Veh. Control	1%	4%		0.187	0%	5%		0.030
Low Dose vs.	1/99	2/50			0/98	4/49		
Veh. Control	1%	4%		0.261	0%	8%		0.011
High Dose vs.	1/99		2/50		0/98		1/49	
Veh. Control	1%		4%	0.261	0%		2%	0.333
High Dose vs.		2/50	2/50			4/49	1/49	
Low Dose		4%	4%	0.691		8%	2%	0.972

Comparison	Chi-square	df	P	Chi-square	df	P
Among High Dose, Low Dose and Vehicle Control	1.82	2	0.601	8.83	2	0.011
Dose-Response Trend Vehicle Control	1.48	1	0.282	1.51	1	0.281
Deviation from Trend Vehicle Control	0.33	1	0.635	7.31	1	0.014

r = Number of animals with observed mark.
n = Number of animals examined histopathologically for the mark.
P = Exact probability of exceeding or equaling observed test statistic under null hypothesis.
df = Degrees of freedom.
See section on statistical methodology for explanation of tests.

Table XXIVd. Exact Statistical Tests Comparing Proportions of Animals (Not Adjusted for Age) with Observed Hepatocellular Carcinoma or Neoplastic Nodule of the Liver among Pooled Control and Carbon Tetrachloride-Treated Rats

	Male Rats					Female Rats				
	Untr. Cont.	Veh. Cont.	Low Dose	High Dose	Exact Test	Untr. Cont.	Veh. Cont.	Low Dose	High Dose	Exact Test
Comparison	r/n	r/n	r/n	r/n	P	r/n	r/n	r/n	r/n	P
Dose-Response Veh. Control		1/99 1%	4/50 8%	3/50 6%	0.070		2/98 2%	6/49 12%	4/49 8%	0.057
Dose-Response Untr. Control	0/20 0%		4/50 8%	3/50 6%	0.353	0/20 0%		6/49 12%	4/49 8%	0.325
Dosed vs. Veh. Control		1/99 1%	7/100 7%		0.033		2/98 2%	10/98 10%		0.016
Dosed vs. Untr. Control	0/20 0%		7/100 7%		0.269	0/20 0%		10/98 10%		0.144
Low Dose vs. Veh. Control		1/99 1%	4/50 8%		0.044		2/98 2%	6/49 12%		0.017
Low Dose vs. Untr. Control	0/20 0%		4/50 8%		0.251	0/20 0%		6/49 12%		0.117
High Dose vs. Veh. Control		1/99 1%		3/50 6%	0.110		2/98 2%		4/49 8%	0.096
High Dose vs. Untr. Control	0/20 0%			3/50 6%	0.358	0/20 0%			4/49 8%	0.245
High Dose vs. Low Dose			4/50 8%	3/50 6%	0.782			6/49 12%	4/49 8%	0.841
Veh. Con. vs. Untr. Control	0/20 0%	1/99 1%			0.832	0/20 0%	2/98 2%			0.689

(continued)

Table XXIVd. Exact Statistical Tests Comparing Proportions of Animals (Not Adjusted for Age) with Observed Hepatocellular Carcinoma or Neoplastic Nodule of the Liver among Pooled Control and Carbon Tetrachloride-Treated Rats (continued)

Comparison	Chi-square	df	P	Chi-square	df	P
Among High Dose, Low Dose and Vehicle Control	4.89	2	0.100	6.39	2	0.046
Dose-Response Trend Vehicle Control	2.98	1	0.128	3.23	1	0.105
Deviation from Trend Vehicle Control	1.90	1	0.203	3.16	1	0.079
Among High Dose, Low Dose and Untreated Control	1.67	2	0.528	2.76	2	0.259
Dose-Response Trend Untreated Control	0.46	1	0.601	0.50	1	0.511
Deviation from Trend Untreated Control	1.21	1	0.333	2.26	1	0.165

r = Number of animals with observed mark.
n = Number of animals examined histopathologically for the mark.
P = Exact probability of exceeding or equaling observed test statistic under null hypothesis.
df = Degrees of freedom.
See section on statistical methodology for explanation of tests.

Table XXV. Tumor Incidence - Trichloroethylene-Treated Mice

	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Mark a	Hepatocellular carcinoma of the liver					
Before 90 weeks	1/12	3/15	12/27	0/3	0/10	0/8
At 90 weeks	0/8	23/35	19/21	0/17	4/40	11/39
Total	1/20	26/50	31/48	0/20	4/50	11/47
Mark b	Reticulum-cell sarcoma, lymphosarcoma, or malignant lymphoma					
Before 90 weeks	1/12	2/15	1/27	0/3	2/10	2/8
At 90 weeks	0/8	2/35	1/21	1/17	3/40	4/39
Total	1/20	4/50	2/48	1/20	5/50	6/47
Mark c	Carcinoma or adenocarcinoma of the lung or alveoli					
Before 90 weeks	0/12	0/15	1/27	0/3	0/10	0/8
At 90 weeks	0/8	0/35	0/21	0/17	2/40	2/39
Total	0/20	0/50	1/48	0/20	2/50	2/47
Mark d	Adenoma of the lung					
Before 90 weeks	0/12	2/15	0/27	0/3	0/10	0/8
At 90 weeks	0/8	3/35	1/21	1/17	2/40	5/39
Total	0/20	5/50	1/48	1/20	2/50	5/47
Marks c or d	Carcinoma, adenocarcinoma, or adenoma of the lung or alveoli					
Before 90 weeks	0/12	2/15	1/27	0/3	0/10	0/8
At 90 weeks	0/8	3/35	1/21	1/17	4/40	7/39
Total	0/20	5/50	2/48	1/20	4/50	7/47
Animals with Tumors (Benign and Malignant)[a]						
Before 90 weeks	3/12	5/15	12/27	1/3	2/10	2/8
At 90 weeks	2/8	25/35	21/21	3/17	12/40	17/39
Total	5/20	30/50	33/48	4/20	14/50	19/47

[a]Includes tumors other than those listed above.

Table XXVIa. Statistical Tests Comparing Estimated Probability of Observing Hepatocellular Carcinoma (Mark a) among Control and Trichloroethylene-Treated Mice

	Male Mice				Female Mice			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	18.57	13.34	5.08	0.000	7.56	6.79	2.90	0.002
Dosed vs. Control	6.72	3.68	3.51	0.000	2.66	1.86	1.95	0.026
Low Dose vs. Control	4.04	2.27	2.68	0.004	1.19	0.79	1.34	0.090
High Dose vs. Control	8.45	4.18	4.13	0.000	3.34	1.90	2.42	0.008
High Dose vs. Low Dose	9.27	6.08	3.76	0.000	3.59	3.08	2.05	0.020

Table XXVIb. Statistical Tests Comparing Estimated Probability of Observing Reticulum-cell Sarcoma, Lymphosarcoma, or Malignant Lymphoma (Mark b) among Control and Trichloroethylene-Treated Mice

	Male Mice				Female Mice			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	-0.40	2.96	-0.23	0.591	2.26	6.07	0.92	0.180
Dosed vs. Control	-0.06	0.80	-0.07	0.527	1.13	1.67	0.88	0.190
Low Dose vs. Control	0.06	0.82	0.06	0.476	0.80	1.21	0.72	0.234
High Dose vs. Control	-0.12	0.62	-0.16	0.563	1.12	1.40	0.95	0.172
High Dose vs. Low Dose	-0.34	1.39	-0.28	0.612	0.57	2.61	0.35	0.362

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXVIc. Statistical Tests Comparing Estimated Probability of Observing Carcinoma or Adenocarcinoma of the Lung or Alveoli (Mark c) among Control and Trichloroethylene-Treated Mice

	Male Mice				Female Mice			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	0.78	0.40	1.23	0.109	1.08	2.06	0.76	0.225
Dosed vs. Control	0.12	0.10	0.36	0.358	0.71	0.56	0.94	0.173
Low Dose vs. Control	0.00	0.00			0.60	0.41	0.93	0.176
High Dose vs. Control	0.26	0.19	0.59	0.277	0.61	0.42	0.94	0.173
High Dose vs. Low Dose	0.62	0.23	1.29	0.099	0.03	0.96	0.03	0.490

Table XXVId. Statistical Tests Comparing Estimated Probability of Observing Adenoma of the Lung (Mark d) among Control and Trichloroethylene-Treated Mice

	Male Mice				Female Mice			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	-0.23	2.37	-0.15	0.560	2.17	3.93	1.09	0.138
Dosed vs. Control	0.73	0.62	0.93	0.177	0.42	1.08	0.40	0.344
Low Dose vs. Control	0.90	0.72	1.07	0.144	-0.11	0.61	-0.14	0.554
High Dose vs. Control	0.28	0.20	0.62	0.268	0.82	1.15	0.76	0.222
High Dose vs. Low Dose	-1.24	1.35	-1.06	0.856	1.54	1.62	1.22	0.112

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXVIe. Statistical Tests Comparing Estimated Probability of Observing Carcinoma, Adenocarcinoma, or Adenoma of the Lung or Alveoli (Mark c or d) among Control and Trichloroethylene-Treated Mice

	Male Mice				Female Mice			
Comparison	U	V	Z	P	U	V	Z	P
Dose-Response	0.55	2.77	0.33	0.370	3.25	5.63	1.37	0.085
Dosed vs. Control	0.85	0.72	1.00	0.160	1.13	1.55	0.90	0.183
Low Dose vs. Control	0.90	0.72	1.07	0.144	0.49	0.97	0.50	0.309
High Dose vs. Control	0.53	0.39	0.85	0.197	1.43	1.48	1.18	0.120
High Dose vs. Low Dose	-0.62	1.59	-0.49	0.688	1.57	2.40	1.01	0.156

U = observed test statistic minus its expected value under the null hypothesis.

V = variance of U.

Z = U divided by square root V.

P = probability that a standard normal random variable is greater than Z.

See appendix on statistical methodology for full definition.

Table XXVII. Exact Statistical Tests Comparing Proportions of Animals (Not Adjusted for Age) with Observed Hepatocellular Carcinoma or Neoplastic Nodule of the Liver among Pooled Control and Trichloroethylene-Treated Mice

	Male Mice					Female Mice				
	Untr. Cont.	Veh. Cont.	Low Dose	High Dose	Exact Test	Untr. Cont.	Veh. Cont.	Low Dose	High Dose	Exact Test
Comparison	r/n	r/n	r/n	r/n	P	r/n	r/n	r/n	r/n	P
Dose-Response Veh. Control		5/77 6%	26/50 52%	31/48 65%	0.000		1/80 1%	4/50 8%	11/47 23%	0.000
Dose-Response Untr. Control	5/70 7%		26/50 52%	31/48 65%	0.000	2/76 3%		4/50 8%	11/47 23%	0.000
Dosed vs. Veh. Control		5/77 6%	57/98 58%		0.000		1/80 1%	15/97 15%		0.001
Dosed vs. Untr. Control	5/70 7%		57/98 58%		0.000	2/76 3%		15/97 15%		0.004
Low Dose vs. Veh. Control		5/77 6%	26/50 52%		0.000		1/80 1%	4/50 8%		0.072
Low Dose vs. Untr. Control	5/70 7%		26/50 52%		0.000	2/76 3%		4/50 8%		0.169
High Dose vs. Veh. Control		**5/77 6%**		**31/48 65%**	**0.000**		**1/80 1%**		**11/47 23%**	0.000
High Dose vs. Untr. Control	**5/70 7%**			**31/48 65%**	**0.000**	**2/76 3%**			**11/47 23%**	0.000
High Dose vs. Low Dose			**26/50 52%**	**31/48 65%**	0.145			**4/50 8%**	**11/47 23%**	0.034
Veh. Con. vs. Untr. Control	5/70 7%	5/77 6%			0.686	2/76 3%	1/80 1%			0.887

(continued)

Table XXVII. Exact Statistical Tests Comparing Proportions of Animals (Not Adjusted for Age) with Observed Hepatocellular Carcinoma or Neoplastic Nodule of the Liver among Pooled Control and Trichloroethylene-Treated Mice (continued)

Comparison	Chi-square	df	P	Chi-square	df	P
Among High Dose, Low Dose and Vehicle Control	52.02	2	0.000	17.76	2	0.000
Dose-Response Trend Vehicle Control	47.85	1	0.000	16.96	1	0.000
Deviation from Trend Vehicle Control	4.16	1	0.041	0.80	1	0.367
Among High Dose, Low Dose and Untreated Control	47.31	2	0.000	14.41	2	0.001
Dose-Response Trend Untreated Control	43.43	1	0.000	13.41	1	0.000
Deviation from Trend Untreated Control	3.89	1	0.049	0.99	1	0.344

r = Number of animals with observed mark.
n = Number of animals examined histopathologically for the mark.
P = Exact probability of exceeding or equaling observed test statistic under null hypothesis.
df = Degrees of freedom.
See section on statistical methodology for explanation of tests.

APPENDIX D: PATHOLOGY

Table XXVIIIa. Numbers of Tissues Examined - Rats

Organ	Controls		Males		Females	
	Males	Females	Low Dose	High Dose	Low Dose	High Dose
Brain	20	20	50	49	48	49
Spinal Cord						
Pituitary	20	20	47	47	47	49
Thyroid	20	20	50	48	46	50
Adrenal	20	20	50	49	47	49
Heart	20	20	50	50	48	50
Lung	20	20	50	50	48	50
Spleen	20	20	49	48	47	50
Liver	20	20	50	50	48	50
Kidney	20	20	50	50	48	50
Stomach	20	20	49	49	47	50
Small Intestine	18	19	49	47	46	50
Large Intestine	19	20	50	50	46	50
Pancreas	20	18	50	48	48	49
Ovary/Testes	20	20	49	47	48	49
Uterus/Prostate	16	20	37	27	48	49
Vagina/Seminal Vesicle		2	4	1		1
Salivary Gland	18	16	33	14	25	24
Lymph Node	20	20	49	39	41	44
Urinary Bladder	20	18	46	46	42	43
Gallbladder						
Nerve						
Muscle						
Eye					1	1
Bone	20	20	50	50	48	48
Mammary Gland	20	20	50	46	45	48
Esophagus	19	19	49	50	47	48
Trachea	20	20	50	48	48	50
Thymus-Cervical Lymph Node	17	15	31	15	22	16
Unusual Lesion			2		1	
Tissue Mass	6	4	5	7	7	9
Aorta			1			
Total Animals Examined	20	20	50	50	48	50

Table XXVIIIb. Numbers of Tissues Examined - Mice

Organ	Controls		Males		Females	
	Males	Females	Low Dose	High Dose	Low Dose	High Dose
Brain	20	20	50	48	50	47
Spinal Cord						
Pituitary	16	16	35	34	44	43
Thyroid	18	20	50	47	46	45
Adrenal	20	20	50	47	49	47
Heart	20	20	50	48	49	47
Lung	20	20	50	48	50	47
Spleen	20	20	50	48	49	47
Liver	20	20	50	48	50	47
Kidney	20	20	50	48	50	47
Stomach	20	20	49	48	49	46
Small Intestine	19	20	50	48	48	47
Large Intestine	20	20	48	47	49	47
Pancreas	20	20	49	47	49	47
Ovary/Testes	20	20	50	48	47	47
Uterus/Prostate	18	20	47	47	48	47
Vagina/Seminal Vesicle				3		
Salivary Gland	15	18	49	39	47	47
Lymph Node	20	19	47	45	49	47
Urinary Bladder	20	19	48	47	48	44
Gallbladder	16	16	36	15	39	34
Nerve						
Muscle						
Eye			2	1	2	
Bone	20	20	50	48	49	47
Mammary Gland	20	20	50	48	49	47
Thymus	19	20	43	42	46	43
Trachea	19	20	49	48	49	46
Esophagus	18	20	50	48	49	47
Unusual Lesion	3	1	5	5	4	1
Total Animals Examined	20	20	50	48	50	47

Tumor Summary Tables for Rats and Mice

Tables XXIXa and XXXa were designed to summarize only the number of primary tumors in each organ of each system. These tables delineate each system, each organ within each system, and the type of tumors within each organ. The counts for each of these 3 categories, that is, the numbers of animals with tumors in both system and organ and the numbers of a particular tumor within each organ, are indented in a hierarchal manner in the same manner as are the categories in the left hand column. If an animal has more than one type of tumor within a given system the total number of animals with tumors in that system may be less than the sum of the organ counts (the number of animals with tumors in a particular organ within that system). For example, 7 high dose female rats have mammary gland tumors and 1 has a tumor of the uterus/endometrium. But since the latter tumor appeared in an animal that also had a mammary gland tumor, the total number of high dose female rats with tumors of the reproductive system is 7, not 8.

In the summary, animals examined represent the number of animals started on test in a specific group less the number of animals with information missing (animal lost or autolyzed) in the group. The number of animals with tumors may be less than the number of animals with benign tumors plus the number of animals with malignant tumors since an animal may have both a benign and a malignant tumor.

Tables XXIXb and XXXb were designed to summarize the number of tumors present in each anatomic site, that is, in each organ of each system regardless of their origin. Thus, all sites of metastatic tumors which appear in more than one organ are included. These tables are organized in the same manner as are Tables XXIXa and XXXa. The counts differ only in that both system and organ counts represent number of animals with tumor in a specific system or organ irrespective of the origin of the tumor. For example, in low dose male rats a hemangiosarcoma of the subcutaneous tissue of the integumentary system is included in Table XXX but not in Table XXIX because although the tumor is present in this tissue it is not a primary tumor of the tissue and originated elsewhere. The tumor summaries for each table are identical except that Table XXX contains the additional counts of total metastatic tumors and animals with metastatic tumors.

Table XXIXa. Primary Tumors by Site of Origin - Trichloroethylene-Treated Rats

Organ System	Male Rats			Female Rats		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM		3	1		2	
Skin			1			
Pilomatrixoma			1			
Subcutaneous Tissue		3			2	
Liposarcoma					1	
Fibroma		1			1	
Fibrosarcoma		1				
Squamous-Cell Carcinoma		1				
RESPIRATORY SYSTEM	1					
Lung	1					
Adenosquamous Carcinoma	1					
CIRCULATORY SYSTEM	1	1	2		1	
Subcutaneous Tissue		1				
Hemangiosarcoma		1				
Multiple Organs					1	
Hemangiosarcoma					1	
Pancreas			1			
Hemangiosarcoma			1			
Spleen	1		1			
Hemangiosarcoma	1		1			
DIGESTIVE SYSTEM						
None						

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Table XXIXa (continued). Primary Tumors by Site of Origin - Trichloroethylene-Treated Rats

Organ System	Male Rats			Female Rats		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
URINARY SYSTEM	2	2				
Kidney	2	2				
Malignant Mixed Tumor	2					
Tubular Adenocarcinoma		1				
Hamartoma	1	1				
ENDOCRINE SYSTEM	1	2	1	4	3	7
Pituitary				4	2	6
Chromophobe Adenoma				4	2	6
Adrenal					1	
Adrenal Cortical Carcinoma					1	
Thyroid	1	2	1			1
Follicular-Cell Adenoma	1	1				
Follicular-Cell Adenocarcinoma		1	1			1
HEMATOPOIETIC SYSTEM				1	1	1
Multiple Organs					1	
Reticulum-Cell Sarcoma					1	
Spleen				1		
Reticulum-Cell Sarcoma				1		
Thymus						1
Reticulum-Cell Sarcoma						1
REPRODUCTIVE SYSTEM				5	6	7
Mammary Gland				4	5	7
Fibroadenoma				3	5	7
Adenocarcinoma				1		
Uterus/Endometrium					1	1
Sarcoma					1	1
Ovary				1		
Granulosa-Cell Carcinoma				1		

Continued on Next Page

Table XXIXa (continued). **Primary Tumors** by Site of Origin - Trichloroethylene-Treated Rats

Organ System	Male Rats			Female Rats		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
NERVOUS SYSTEM			1			
Heart			1			
Aortic Body Tumor			1			
MUSCULOSKELETAL SYSTEM						
None						
ALL OTHER SYSTEMS	1					
Abdomen	1					
Giant-Cell Tumor, Malignant	1					
PRIMARY TUMOR SUMMARY						
Animals Examined	20	50	50	20	48	50
Animals with Benign Tumors	2	3	2	6		11
Total Benign Tumors	2	3	2	7	8	13
Animals with Malignant Tumors	5	5	3	2	5	3
Total Malignant Tumors	5	5	3	3	6	3
Animals with Tumors	5	7	5	7	12	12

Table XXIXb. Tumors by Anatomic Site - Trichloroethylene-Treated Rats

Organ System	Male Rats			Female Rats		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM		4	1		2	
Skin			1			
Pilomatrixoma			1			
Subcutaneous Tissue		4			2	
Liposarcoma					1	
Hemangiosarcoma		1				
Fibroma		1			1	
Fibrosarcoma		1				
Squamous-Cell Carcinoma		1				
RESPIRATORY SYSTEM	1				1	
Lung	1				1	
Hemangiosarcoma					1	
Adenosquamous Carcinoma	1					
CIRCULATORY SYSTEM			1		1	
Heart			1		1	
Hemangiosarcoma					1	
Aortic Body Tumor			1			
DIGESTIVE SYSTEM			1		1	
Liver					1	
Reticulum-Cell Sarcoma					1	
Pancreas			1			
Hemangiosarcoma			1			

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Table XXIXb (continued). Tumors by Anatomic Site - Trichloroethylene-Treated Rats

Organ System	Male Rats			Female Rats		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
DIGESTIVE SYSTEM			1		1	
Liver					1	
Reticulum-Cell Sarcoma					1	
Pancreas			1			
Hemangiosarcoma			1			
URINARY SYSTEM	3	2				
Kidney	3	2				
Malignant Mixed Tumor	2					
Tubular Adenocarcinoma		1				
Hamartoma	1	1				
Adenosquamous Carcinoma Metast.	1					
ENDOCRINE SYSTEM	1	2	1	4	3	7
Pituitary				4	2	6
Chromophobe Adenoma				4	2	6
Adrenal					1	
Adrenal Cortical Carcinoma					1	
Thyroid	1	2	1			1
Follicular-Cell Adenoma	1	1				
Follicular-Cell Adenocarcinoma		1	1			1
HEMATOPOIETIC SYSTEM	2		1	1	1	1
Spleen	1		1	1		
Hemangiosarcoma	1		1			
Reticulum-Cell Sarcoma				1		
Cervical Lymph Node	1				1	
Reticulum-Cell Sarcoma					1	
Adenosquamous Carcinoma, Metast.	1					
Thymus						1
Reticulum-Cell Sarcoma						1

Continued on Next Page

Table XXIXb (continued). Tumors by Anatomic Site - Trichloroethylene-Treated Rats

Organ System	Male Rats			Female Rats		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM				5	6	7
Mammary Gland				4	5	7
Fibroadenoma				3	5	7
Adenocarcinoma				1		
Uterus/Endometrium					1	1
Sarcoma					1	1
Ovary				1		
Granulosa-Cell Carcinoma				1		
NERVOUS SYSTEM						
None						
MUSCULOSKELETAL SYSTEM						
None						
ALL OTHER SYSTEMS	1					
Abdomen	1					
Giant-Cell Tumor, Malignant	1					
TUMOR SUMMARY						
Animals Examined	20	50	50	20	48	50
Animals with Benign Tumors	2	3	2	6	7	11
Total Benign Tumors	2	3	2	7	8	13
Animals with Malignant Tumors	5	5	3	2	5	3
Total Malignant Tumors	5	5	3	3	6	3
Animals with Metastatic Tumors	1					
Total Metastatic Tumors	2					
Animals with Tumors	5	7	5	7	12	12

Table XXXa. Primary Tumors by Site of Origin - Trichloroethylene-Treated Mice

Organ System	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM	3	1			1	
Skin	1					
Fibrosarcoma	1					
Subcutaneous Tissue	2	1			1	
Fibrosarcoma	2				1	
Fibroma		1				
RESPIRATORY SYSTEM		5	2	1	4	7
Lung		5	2	1	4	7
Adenoma		5	1	1	2	5
Alveolar Adenocarcinoma			1		2	2
CIRCULATORY SYSTEM			1			
Lung			1			
Hemangiosarcoma			1			
DIGESTIVE SYSTEM	1	26	31		4	11
Stomach			1			
Papilloma			1			
Liver	1	26	31		4	11
Hepatocellular Carcinoma	1	26	31		4	11
URINARY SYSTEM			1			
Kidney			1			
Adenoma			1			

Continued on Next Page

Table XXXa (continued). Primary Tumors by Site of Origin - Trichloroethylene-Treated Mice

Organ System	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
ENDOCRINE SYSTEM						
None						
HEMATOPOIETIC SYSTEM	1	4	2	1	5	6
Thymus					1	
Lymphosarcoma					1	
Multiple Organs	1	4	2		3	4
Reticulum-Cell Sarcoma	1	2	1		2	2
Lymphosarcoma		2	1		1	2
Spleen					1	1
Lymphosarcoma					1	1
Cervical Lymph Node						1
Malignant Lymphoma						1
Mesentery Lymph Node				1		
Reticulum-Cell Sarcoma				1		
REPRODUCTIVE SYSTEM				1	4	
Mammary Gland					1	
Adenocarcinoma					1	
Uterus				1	1	
Fibrosarcoma					1	
Adenocarcinoma				1		
Ovary					2	
Granulosa-Cell Carcinoma					1	
Cystadenoma					1	
NERVOUS SYSTEM			1			
Muscle of Back			1			
Neurofibroma			1			

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Table XXXa (continued). Primary Tumors by Site of Origin - Trichloroethylene-Treated Mice

Organ System	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM				1		
Soft Tissue				1		
Osteosarcoma				1		
SPECIAL SENSE ORGANS		1			1	
Harderian Gland		1			1	
Adenoma		1			1	
ALL OTHER SYSTEMS			1			
Abdomen			1			
Fibrosarcoma			1			
PRIMARY TUMOR SUMMARY						
Animals Examined	20	50	48	20	50	47
Animals with Benign Tumors		7	4	1	3	5
Total Benign Tumors		7	4	1	4	5
Animals with Malignant Tumors	5	28	32	3	14	16
Total Malignant Tumors	5	30	36	3	15	19
Animals with Tumors	5	30	33	4	14	19

Table XXXb. **Tumors by Anatomic Site - Trichloroethylene-Treated Mice**

Organ System	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM	3	1	1	1	1	
Skin	1		1			
Fibrosarcoma	1					
Alveolar Adenocarcinoma, Metast.			1			
Subcutaneous Tissue	2	1			1	
Fibrosarcoma	2				1	
Fibroma		1				
Soft Tissue				1		
Osteosarcoma				1		
RESPIRATORY SYSTEM		9	5	1	4	8
Lung		9	5	1	4	8
Adenoma		5	1	1	2	5
Alveolar Adenocarcinoma			1		2	2
Hemangiosarcoma			1			
Reticulum-Cell Sarcoma						1
Lymphosarcoma		1				
Hepatocellular Carcinoma, Metast.		4	3			
CIRCULATORY SYSTEM			1			
Aorta			1			
Alveolar Adenocarcinoma, Metast.			1			
DIGESTIVE SYSTEM	2	28	32		7	14
Stomach			2			1
Papilloma			1			
Reticulum-Cell Sarcoma						1
Fibrosarcoma Metastatic			1			
Ileum		1			1	1
Reticulum-Cell Sarcoma		1				1
Lymphosarcoma					1	

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Table XXXb (continued). Tumors by Anatomic Site - Trichloroethylene-Treated Mice

Organ System	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM	1	2		1	6	
Mammary Gland					1	
Adenocarcinoma					1	
Uterus				1	2	
Fibrosarcoma					1	
Reticulum-Cell Sarcoma					1	
Adenocarcinoma				1		
Ovary					2	
Granulosa-Cell Carcinoma					1	
Cystadenoma					1	
Vagina					1	
Reticulum-Cell Sarcoma					1	
Epididymis		1				
Reticulum-Cell Sarcoma		1				
Prostate	1	2				
Reticulum-Cell Sarcoma	1	1				
Lymphosarcoma		1				
Seminal Vesicle	1					
Reticulum-Cell Sarcoma	1					
NERVOUS SYSTEM						
None						
MUSCULOSKELETAL SYSTEM			1			
Muscle of Back			1			
Neurofibroma			1			
SPECIAL SENSE ORGANS		1			1	
Harderian Gland		1			1	
Adenoma		1			1	

Continued on Next Page

Table XXXb (continued). Tumors by Anatomic Site - Trichloroethylene-Treated Mice

Organ System	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
DIGESTIVE SYSTEM (cont.)						
Pancreas			2			
Reticulum-Cell Sarcoma			1			
Fibrosarcoma Metastatic			1			
Liver	2	28	32		6	12
Hepatocellular Carcinoma	1	26	31		4	11
Reticulum-Cell Sarcoma	1		1		2	
Lymphosarcoma		2				1
URINARY SYSTEM		1	4			2
Kidney		1	4			2
Adenoma			1			
Reticulum-Cell Sarcoma			1			1
Lymphosarcoma		1	1			1
Fibrosarcoma Metastatic			1			
ENDOCRINE SYSTEM			1		1	
Adrenal			1		1	
Lymphosarcoma					1	
Fibrosarcoma Metastatic			1			
HEMATOPOIETIC SYSTEM	1	4	4	1	4	6
Thymus		1			1	
Lymphosarcoma		1			1	
Spleen	1	3	2		3	4
Reticulum-Cell Sarcoma	1	1	1		1	1
Lymphosarcoma		2	1		2	3
Lymph Node	1	2	4	1	2	3
Malignant Lymphoma						1
Lymphosarcoma		2	1		2	2
Reticulum-Cell Sarcoma	1	2	1	1	1	1
Alveolar Adenocarcinoma, Metast.			1			
Fibrosarcoma Metastatic			1			
Bone Marrow		1				
Lymphosarcoma		1				

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Table XXXb (continued). Tumors by Anatomic Site - Trichloroethylene-Treated Mice

Organ System	Male Mice			Female Mice		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
ALL OTHER SYSTEMS			1			
Abdomen			1			
Fibrosarcoma			1			
TUMOR SUMMARY						
Animals Examined	20	50	48	20	50	47
Animals with Benign Tumors		7	4	1	3	5
Total Benign Tumors		7	4	1	4	5
Animals with Malignant Tumors	5	28	32	3	14	16
Total Malignant Tumors	5	30	36	3	15	19
Animals with Metastatic Tumors		4	4			
Total Metastatic Tumors		4	11			
Animals with Tumors	5	30	33	4	14	19

Tables XXXI and XXXII - Individual Pathology

Index

Disposition Code

NATD	Natural Death
TSAC	Terminal Sacrifice
MISS	Missing
MSAC	Moribund Sacrifice
ACCK	Accident

Table XXXIa. Individual Pathology - Trichloroethylene-Treated Male Rats

Control Group (Vehicle)

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
67	NATD	003			LUNG	INFLAMMATICN CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
70	NATD	011	SPLEEN	HEMANGIOSARCOMA	PITUITARY	INFLAMMATION
					BRONCHUS	BRONCHIECTASIS
76	NATD	014			SPLEEN	HEMATOPOIESIS EXTRAMED.
					LUNG	INFLAMMATION CHRONIC
					THYMUS	INFLAMMATION
					SALIVARY GLAND	INFLAMMATION
					KIDNEY	ABSCESS
76	NATD	015			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	INFLAMMATION CHRONIC
82	NATD	009			LUNG	INFLAMMATICN CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
82	NATD	013			LUNG	INFLAMMATION CHRONIC
83	NATD	018			BRONCHUS	BRONCHIECTASIS
					STOMACH	CALCIUM DEPOSITION
					MESENTERIC LYMPH NODE	POLYARTERITIS NODOSA
					PANCREAS	POLYARTERITIS NODOSA
					TESTIS	ATROPHY
87	NATD	016			LUNG	INFLAMMATICN CHRONIC
					TESTIS	ATROPHY
88	NATD	005			LUNG	INFLAMMATICN CHRONIC
88	NATD	012			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	INFLAMMATION CHRONIC
90	NATD	002	ABDOMEN	GIANT-CELL TUMOR, MALIGNANT	LUNG	INFLAMMATICN CHRONIC
					TESTIS	ATROPHY, BILATERAL
91	NATD	004			LUNG	INFLAMMATICN CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	INFLAMMATION CHRONIC
					PROSTATE	INFLAMMATION
					SEMINAL VESICLE	INFLAMMATION
					SUBCUT TISSUE	ABSCESS

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Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

Control Group (Vehicle)

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
96	NATD	019	KIDNEY	MALIGNANT MIXED TUMOR		
			THYROID	FOLLICULAR ADENOMA	LUNG	INFLAMMATION CHRONIC
98	NATD	020			EPIDIDYMIS	FAT NECROSIS WITH ENCAPSULATION
					KIDNEY	INFLAMMATION CHRONIC
99	NATD	010	KIDNEY	MALIGNANT MIXED TUMOR	SPLEEN	HEMATOPOIESIS EXTRAMED.
			KIDNEY	HAMARTOMA	LUNG	INFLAMMATION CHRONIC
102	NATD	017			LUNG	INFLAMMATION CHRONIC
					KIDNEY	INFLAMMATION CHRONIC
					MESENTERIC LYMPH NODE	POLYARTERITIS NODOSA
					LIVER	METAMORPHOSIS FATTY
103	NATD	008			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	001			LUNG	INFLAMMATION CHRONIC
					KIDNEY	INFLAMMATION CHRONIC
					SKIN	ACANTHOSIS
					SKIN	HYPERKERATOSIS
					SKIN	INFLAMMATION
110	TSAC	006			LUNG	INFLAMMATION CHRONIC
					KIDNEY	INFLAMMATION CHRONIC
					THYROID	INFLAMMATION CYSTIC
					BONE MARROW	METAMORPHOSIS FATTY
110	NATD	007	LUNG	CARCINOMA, GLANDULAR AND SQUAMOUS, PROBABLY PRIMARY IN LUNG, WITH MULTIPLE PULMONARY METASTASES	STOMACH	ULCER FOCAL
					BONE MARROW	METAMORPHOSIS FATTY
			KIDNEYS, BILATERAL	MULTIPLE METASTATIC TUMORS		
			CERVICAL LYMPH NODE	METASTASIC TUMORS		

end of male rat control

Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
16	NATD	028				NO SIGNIFICANT DIAGNOSIS
17	NATD	036				NO SIGNIFICANT DIAGNOSIS
23	NATD	010				NO SIGNIFICANT DIAGNOSIS
27	NATD	006				NO SIGNIFICANT DIAGNOSIS
34	NATD	035			KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
40	NATD	030			KIDNEY	NEPHROSIS TOXIC
42	NATD	034			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
48	NATD	003			KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
50	NATD	007			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
53	NATD	041			KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
60	NATD	046			KIDNEY	NEPHROSIS TOXIC
					PERICARDIUM	INFLAMMATION
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
61	NATD	039			PERICARDIUM	INFLAMMATICN
					MYOCARDIUM	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
65	NATD	019			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
67	NATD	032			KIDNEY	NEPHROSIS TOXIC
					BRONCHUS	BRONCHIECTASIS
					BONE MARROW	METAMORPHOSIS FATTY

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Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
67	NATD	044			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
72	NATD	040			LEFT ADRENAL	INFLAMMATICN CYSTIC
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
74	NATD	047			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
76	NATD	018			LIVER	INFLAMMATION CYSTIC
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
76	NATD	023	THYROID	FOLLICULAR ADENOMA	PARATHYROID	HYPERPLASIA
					AORTA	ARTERIOSCLEROSIS
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					STOMACH	CALCIUM DEPOSITION
					PANCREAS	POLYARTERITIS NODOSA
					BONE MARROW	METAMORPHOSIS FATTY
80	NATD	026	SUBCUT TISSUE/NECK	HEMANGIOSARCOMA	ADRENAL	ANGIECTASIS
					KIDNEY	NEPHROSIS TOXIC
					KIDNEY	CAPSULAR ABSCESS
					LUNG	INFLAMMATICN CHRONIC
					STOMACH	ULCER FOCAL
80	NATD	033			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					MESENTERY	POLYARTERITIS NODOSA
					PANCREAS	POLYARTERITIS NODOSA
82	NATD	005			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
83	NATD	038			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TESTIS	ATROPHY
					BONE MARROW	METAMORPHOSIS FATTY
83	NATD	043			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATICN CHRONIC

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Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
85	NATD	001			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TRACHEA	INFLAMMATION
86	NATD	014			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					TESTIS	ATROPHY
					TRACHEA	INFLAMMATION
86	NATD	020			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
87	NATD	029			MYOCARDIUM	DEGENERATION
					ATRIUM	CALCIUM DEPOSITION
					AORTA	ARTERIOSCLEROSIS
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					STOMACH	CALCIUM DEPOSITION
					TESTIS	ATROPHY
					VENTRICLE	CALCIUM DEPOSITION
88	NATD	012			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
					SKIN	ACANTHOSIS
					SKIN	HYPERKERATOSIS
					SKIN	EPIDERMAL INCLUSION CYST
90	NATD	015	KIDNEY	TUBULAR ADENOCARCINOMA, UNILATERAL	SPLEEN	HEMATOPOIESIS EXTRAMED.
					LIVER	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					MESENTERY	POLYARTERITIS NODOSA
					PANCREAS	POLYARTERITIS NODOSA
					RIGHT ADRENAL	CONGENITAL MALFORMATION
94	NATD	025	SUBCUT TISSUE/AXILLA	FIBROMA	MYOCARDIUM	DEGENERATION
					MYOCARDIUM	FIBROSIS
					LIVER	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION

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Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
94	NATD	049			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					SUBCUTANEOUS TISSUE OF HIND LEG	ABSCESS
					EPIDIDYMIS	FAT NECROSIS WITH ENCAPSULATION
96	NATD	021			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TESTIS	ATROPHY
97	NATD	016			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PANCREAS	POLYARTERITIS NODOSA
					BONE MARROW	METAMORPHOSIS FATTY
102	NATD	009			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
103	NATD	013			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
103	NATD	027			ADRENAL	ANGIECTASIS
					ADRENAL	DEGENERATION
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					TESTIS	ATROPHY
103	NATD	031			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
104	NATD	037			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PANCREAS	POLYARTERITIS NODOSA
					TESTIS	ATROPHY
					PROSTATE	INFLAMMATION
107	NATD	008			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TRACHEA	INFLAMMATION
					CERVICAL LYMPH NODE	INFLAMMATION
107	NATD	045			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PANCREAS	POLYARTERITIS NODOSA
					PROSTATE	INFLAMMATION

Continued on next page

Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
108	NATD	004	SUBCUT TISSUE/AXILLA	FIBROSARCOMA	KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TESTIS	ATROPHY
					TESTIS	CALCIUM DEPOSITION
110	TSAC	002	THYROID	FOLLICULAR ADENOCARCINOMA	LIVER	METAMORPHOSIS FATTY
			KIDNEY	HAMARTOMA, MEDULLA, UNILATERAL	LIVER	INFLAMMATION CYSTIC
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TESTIS	ATROPHY
110	TSAC	011	SUBCUT TISSUE/AXILLA	SQUAMOUS CELL CARCINOMA	KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PROSTATE	INFLAMMATION
110	TSAC	017			SPLEEN	HEMATOPOIESIS EXTRAMED.
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PANCREAS	POLYARTERITIS NODOSA
					MESENTERY	POLYARTERITIS NODOSA
					TESTIS	ATROPHY
110	TSAC	022			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TESTIS	ATROPHY
110	TSAC	024			LIVER	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PANCREAS	POLYARTERITIS NODOSA
					TESTIS	ATROPHY
					BONE MARROW	METAMORPHOSIS FATTY
110	NATD	042			KIDNEY	NEPHROSIS TOXIC
					TESTIS	ATROPHY
110	TSAC	048			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					TESTIS	ATROPHY
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	050			MYOCARDIUM	DEGENERATION
					KIDNEY	NEPHROSIS TOXIC
					TESTIS	ATROPHY
					BONE MARROW	METAMORPHOSIS FATTY

end of male rats—low dose

Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
2	NATD	012			PERICARDIUM	INFLAMMATICN
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
2	NATD	032			LUNG	INFLAMMATICN CHRONIC
					PLEURA	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY
5	NATD	014			PERICARDIUM	INFLAMMATICN
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
6	NATD	004			KIDNEY	NEPHROSIS TOXIC
12	NATD	015			LIVER/CENTRILOBULAR	METAMORPHOSIS FATTY
					LIVER	CONGESTION
					KIDNEY	NEPHROSIS TOXIC
17	NATD	022			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
21	NATD	006			KIDNEY	NEPHROSIS TOXIC
27	NATD	002			BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
31	NATD	025			PERICARDIUM	INFLAMMATICN
					BONE MARROW	METAMORPHOSIS FATTY
					MYOCARDIUM	INFLAMMATICN
					KIDNEY	NEPHROSIS TOXIC
33	NATD	024			KIDNEY	NEPHROSIS TOXIC
35	NATD	040			LIVER/CENTRILOBULAR	METAMORPHOSIS FATTY
					LIVER	ANGIECTASIS
40	NATD	033			KIDNEY	NEPHROSIS TOXIC
42	NATD	039			LIVER	HEPATOCYTOMEGALY, FOCAL
					LIVER	ANGIECTASIS
					BONE MARROW	METAMORPHOSIS FATTY
44	NATD	003			KIDNEY	NEPHROSIS TOXIC

Continued on next page

Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
48	NATD	018			BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
49	NATD	030			LIVER	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
52	NATD	005			LIVER	METAMORPHOSIS FATTY
					BRONCHUS	BRONCHIECTASIS
					KIDNEY	NEPHROSIS TOXIC
52	NATD	041			LIVER/CENTRILOBULAR	DEGENERATION
					LIVER	METAMORPHOSIS FATTY
					LIVER	ANGIECTASIS
					BRONCHUS	BRONCHIECTASIS
					BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
					EPIDIDYMIS	FAT NECROSIS WITH ENCAPSULATION
53	NATD	037			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					EPIDIDYMIS	FAT NECROSIS WITH ENCAPSULATION
54	NATD	013			BRONCHUS	BRONCHIECTASIS
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
54	NATD	017			LIVER	ANGIECTASIS
					KIDNEY	NEPHROSIS TOXIC
56	NATD	027			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					THYROID	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
58	NATD	047			LIVER/CENTRILOBULAR	DEGENERATION
					LIVER	METAMORPHOSIS FATTY
					BRONCHUS	BRONCHIECTASIS
					KIDNEY	NEPHROSIS TOXIC
59	NATD	009			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
61	NATD	029			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC

Continued on next page

Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
62	NATD	007			LUNG	INFLAMMATICN CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
62	NATD	038			ADRENAL	ANGIECTASIS
					ADRENAL	DEGENERATION
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					LIVER	INFLAMMATION, DIFFUSE
65	NATD	011	THYROID	FOLLICULAR ADENOCARCINOMA	BRONCHUS	ABSCESS
					BRONCHUS	BRONCHIECTASIS
					PLEURA	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY
					LIVER	ANGIECTASIS
					KIDNEY	NEPHROSIS TOXIC
65	NATD	028			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
65	NATD	045			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					TESTIS	ATROPHY
					BONE MARROW	METAMORPHOSIS FATTY
66	NATD	049			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
68	NATD	010			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
70	NATD	020			KIDNEY	NEPHROSIS TOXIC
					EPIDIDYMIS	FAT NECROSIS WITH ENCAPSULATION
71	NATD	016			KIDNEY	NEPHROSIS TOXIC
72	NATD	034	SKIN	PILOMATRIXOMA	PERICARDIUM	INFLAMMATICN
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC

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Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
72	NATD	050			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					ABDOMEN	FAT NECROSIS WITH ENCAPSULATION
75	NATD	044			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
76	NATD	021			PERICARDIUM	INFLAMMATICN
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
82	NATD	019	HEART	AORTIC BODY TUMOR	LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
83	NATD	043			PITUITARY	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					KIDNEY	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY
88	NATD	031			HEART	THROMBOSIS
					ENDOCARDIUM	INFLAMMATION
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					LUNG	ABSCESS
					KIDNEY	NEPHROSIS TOXIC
91	NATD	036	PANCREAS	HEMANGIOSARCOMA	PERICARDIUM	INFLAMMATICN
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					PROSTATE	INFLAMMATION
97	NATD	042			ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					TESTIS	ATROPHY
99	NATD	008			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC

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Table XXXIa (continued). Individual Pathology - Trichloroethylene-Treated Male Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
102	NATD	035			LUNG	INFLAMMATICN CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
103	NATD	001			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
109	NATD	048			ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					KIDNEY	PYELONEPHRITIS
110	TSAC	023			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
110	TSAC	026	SPLEEN	HEMANGIOSARCOMA	LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
110	TSAC	046			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					TESTIS	ATROPHY

end of male rats—high dose

Table XXXIb. Individual Pathology - Trichloroethylene-Treated Female Rats

Control Group (Vehicle)

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
25	NATD	008			LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
47	NATD	016			PERICARDIUM	INFLAMMATION
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
47	NATD	020			LUNG	INFLAMMATION CHRONIC
					SPLEEN	HEMATOPOIESIS EXTRAMED.
68	NATD	006	PITUITARY	CHROMOPHOBE ADENOMA	LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
79	NATD	001			LUNG	INFLAMMATION CHRONIC
					LUNG	ABSCESS
87	NATD	007			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
97	NATD	011	MAMMARY GLAND	FIBROADENOMA	KIDNEY	INFLAMMATION CHRONIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					STOMACH	ULCER FOCAL
98	NATD	015			LUNG	INFLAMMATION CHRONIC
99	NATD	002			LUNG	INFLAMMATION CHRONIC
102	NATD	014	PITUITARY	CHROMOPHOBE ADENOMA	ADRENAL	ANGIECTASIS
			MAMMARY GLAND	ADENOCARCINOMA	LUNG	INFLAMMATION CHRONIC
104	NATD	019	PITUITARY	CHROMOPHOBE ADENOMA	KIDNEY	INFLAMMATION CHRONIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
108	NATD	012			KIDNEY	INFLAMMATION CHRONIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	003	PITUITARY	CHROMOPHOBE ADENOMA	LUNG	INFLAMMATION CHRONIC
			MAMMARY GLAND	FIBROADENOMA	PLEURA	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY

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Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

Control Group (Vehicle)

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
110	TSAC	004	SPLEEN	RETICULUM CELL SARCOMA	LUNG	INFLAMMATICN CHRONIC
			OVARY	GRANULOSA CELL CARCINOMA		
110	TSAC	005			LUNG	INFLAMMATION CHRONIC
110	TSAC	009			LUNG	INFLAMMATICN CHRONIC
110	TSAC	010	MAMMARY GLAND	FIBROADENOMA	LEFT ADRENAL	ANGIECTASIS
					ADRENAL	DEGENERATION
					LUNG	INFLAMMATION CHRONIC
110	TSAC	013			KIDNEY	INFLAMMATICN CHRONIC
					LUNG	INFLAMMATION CHRONIC
110	TSAC	017			LUNG	INFLAMMATICN CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	018			KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	INFLAMMATION CYSTIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					LIVER	METAMORPHOSIS FATTY
					LIVER	INFLAMMATION
					PANCREAS	ATROPHY
					PANCREAS	INFLAMMATION CYSTIC

end of female rats controls

Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
2	NATD	024			LUNG KIDNEY	INFLAMMATICN CHRONIC NEPHROSIS TOXIC
2	MISS	029				ANIMAL MISSING
2	NATD	042			LUNG KIDNEY	INFLAMMATICN CHRONIC NEPHROSIS TOXIC
3	NATD	002	LUNG HEART	HEMANGIOSARCOMA, HEMANGIOSARCOMA,	KIDNEY	PYELONEPHRITIS
5	NATD	020			PERICARDIUM MYOCARDIUM	INFLAMMATICN INFLAMMATION
7	NATD	047			KIDNEY	NEPHROSIS TOXIC
15	NATD	C01			PERICARDIUM MYOCARDIUM LUNG PLEURA	INFLAMMATICN INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION
16	NATD	030			KIDNEY	NEPHROSIS TOXIC
16	NATD	038			KIDNEY BONE MARROW KIDNEY	CALCIUM DEPOSITION METAMORPHOSIS FATTY NEPHROSIS TOXIC
19	NATD	011			SUBCUT TISSUE	ABSCESS
21	NATD	012			BONE MARROW	METAMORPHOSIS FATTY
21	NATD	014				NO SIGNIFICANT DIAGNOSIS
21	MISS	021				ANIMAL MISSING
22	NATD	005			BONE MARROW	METAMORPHOSIS FATTY
22	NATD	039			LUNG KIDNEY	INFLAMMATICN CHRONIC NEPHROSIS TOXIC
25	NATD	017			BONE MARROW	METAMORPHOSIS FATTY
26	NATD	036			KIDNEY	NEPHROSIS TOXIC

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Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
28	NATD	035			KIDNEY	NEPHROSIS TOXIC
33	NATD	033			KIDNEY	NEPHROSIS TOXIC
34	NATD	019			KIDNEY BONE MARROW	NEPHROSIS TOXIC METAMORPHOSIS FATTY
40	NATD	045			ADRENAL ADRENAL KIDNEY	ANGIECTASIS DEGENERATION NEPHROSIS TOXIC
42	NATD	022			LUNG	INFLAMMATION CHRONIC
57	NATD	006			KIDNEY	NEPHROSIS TOXIC
60	NATD	010			KIDNEY BONE MARROW	NEPHROSIS TOXIC METAMORPHOSIS FATTY
61	NATD	044			KIDNEY BRONCHUS PLEURA	NEPHROSIS TOXIC ABSCESS INFLAMMATION
68	NATD	027			KIDNEY LUNG	NEPHROSIS TOXIC INFLAMMATION CHRONIC
69	NATD	025			KIDNEY LUNG	NEPHROSIS TOXIC INFLAMMATION CHRONIC
75	NATD	015			LUNG	INFLAMMATION CHRONIC
75	NATD	016	LIVER CERVICAL LYMPH NODE	RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA	KIDNEY LUNG	NEPHROSIS TOXIC INFLAMMATION CHRONIC
77	NATD	048			KIDNEY LUNG	NEPHROSIS TOXIC INFLAMMATION CHRONIC
86	NATD	034			KIDNEY LUNG PLEURA	NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION
96	NATD	023	ADRENAL	ADRENAL CORTICAL CARCINOMA	KIDNEY LUNG	NEPHROSIS TOXIC INFLAMMATION CHRONIC
96	NATD	046			KIDNEY LUNG	NEPHROSIS TOXIC INFLAMMATION CHRONIC

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Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
98	NATD	032	SUBCUT TISSUE/CHEST	LIPOSARCOMA	KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
100	NATD	013	SUBCUT TISSUE/NECK	FIBROMA	KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
102	NATD	049			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
104	NATD	040	MAMMARY GLAND	FIBROADENOMA	SPLEEN	HEMATOPOIESIS EXTRAMED.
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
110	TSAC	003			TRACHEA	INFLAMMATION
					TRACHEAL LYMPH NODE	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
110	TSAC	004			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					RIGHT OVARY	CYST
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	007	PITUITARY	CHROMOPHOBE ADENOMA	ADRENAL	ANGIECTASIS
			MAMMARY GLAND	FIBROADENOMA	MYOCARDIUM	FIBROSIS
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
110	TSAC	008			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
110	TSAC	009			ADRENAL	ANGIECTASIS
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					RIGHT OVARY	CYST
110	TSAC	018	MAMMARY GLAND	FIBROADENOMA	RIGHT ADRENAL	ANGIECTASIS
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC

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Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
110	TSAC	026	ENDOMETRIUM	SARCOMA	LEFT ADRENAL	ANGIECTASIS
					ADRENAL	DEGENERATION
					LEFT ADRENAL	INFLAMMATION CYSTIC
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					OVARY	CYST
110	TSAC	028			ADRENAL	ANGIECTASIS
					ADRENAL	DEGENERATION
					BILE DUCT	INFLAMMATION PROLIFERATIVE
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					OVARY	CYST
110	TSAC	031	PITUITARY	CHROMOPHOBE ADENOMA	KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					ENDOMETRIUM	INFLAMMATION
					LEFT OVARY	CYST
					RIGHT EYE	CATARACT
					RETINA	DETACHMENT
110	TSAC	037			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	041			PERICARDIUM	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
110	TSAC	043	MAMMARY GLAND	FIBROADENOMA	KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
110	NATD	050	MAMMARY GLAND	FIBROADENOMA, (MULTIPLE - 2)	KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					UTERUS	INFLAMMATION
					BILE DUCT	INFLAMMATION PROLIFERATIVE

end of female rats—low dose

Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
3	NATD	013			PERICARDIUM	INFLAMMATICN
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
5	NATD	002			PERICARDIUM	INFLAMMATICN
					MYOCARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
9	NATD	032			LUNG	INFLAMMATICN CHRONIC
					BONE MARROW	METAMORPHOSIS FATTY
					KIDNEY	NEPHROSIS TOXIC
21	NATD	036			KIDNEY	CALCIUM DEPOSITION
					BONE MARROW	METAMORPHOSIS FATTY
24	NATD	049			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
28	NATD	008			KIDNEY	NEPHROSIS TOXIC
28	NATD	016			KIDNEY	NEPHROSIS TOXIC
30	NATD	043			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
35	NATD	040			KIDNEY	NEPHROSIS TOXIC
43	NATD	038			UTERUS	RETENTION FLUID
46	NATD	045			LUNG	INFLAMMATICN CHRONIC
					KIDNEY	NEPHROSIS TOXIC
50	NATD	004			LUNG	INFLAMMATICN CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					KIDNEY	CALCIUM DEPOSITION

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Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
53	NATD	007			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
54	NATD	041			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
58	NATD	024			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
59	NATD	017			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
63	NATD	031			PERICARDIUM	INFLAMMATION
					BRONCHUS	BRONCHIECTASIS
					KIDNEY	NEPHROSIS TOXIC
64	NATD	022			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					PERICARDIUM	INFLAMMATION
					MYOCARDIUM	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					KIDNEY	CALCIUM DEPOSITION
					BONE MARROW	METAMORPHOSIS FATTY
67	NATD	028			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
69	NATD	012			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC, MARKED
69	NATD	027			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					KIDNEY	CALCIUM DEPOSITION
					UTERUS	RETENTION FLUID
					BONE MARROW	METAMORPHOSIS FATTY

Continued on next page

Table XXXIb (continued). Individual Pathology - **Trichloroethylene**-Treated Female Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
70	NATD	018			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					SMALL INTESTINE	ULCER FOCAL
70	NATD	020			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
72	NATD	014			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
73	NATD	001			ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
73	NATD	042			BRONCHUS	ABSCESS
					KIDNEY	NEPHROSIS TOXIC
					KIDNEY	CALCIUM DEPOSITION
74	NATD	039			BRONCHUS	BRONCHIECTASIS
					KIDNEY	NEPHROSIS TOXIC
82	NATD	026			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
86	NATD	048			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					MESENTERIC LYMPH NODE	INFLAMMATION
					MESENTERIC LYMPH NODE	INFLAMMATION CYSTIC
89	NATD	047			ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
95	NATD	021			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
96	NATD	050	PITUITARY	CHROMOPHOBE ADENOMA	ADRENAL	ANGIECTASIS
					LIVER	METAMORPHOSIS FATTY
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC

Continued on next page

Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
101	NATD	029	MAMMARY GLAND	FIBROADENOMA	LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
101	NATD	035	PITUITARY	CHROMOPHOBE ADENOMA	ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
102	NATD	019			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
103	NATD	033	MAMMARY GLAND	FIBROADENOMA (MULTIPLE-3)	LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
104	NATD	034			BRAIN	HYDROCEPHALUS
					PERICARDIUM	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
110	TSAC	003			ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					BILE DUCT	DILATATION
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	005	PITUITARY	CHROMOPHOBE ADENOMA	ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	006	THYMUS	RETICULUM CELL SARCOMA	LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					OVARY	INFLAMMATION
110	TSAC	009	PITUITARY	CHROMOPHOBE ADENOMA	ADRENAL	DEGENERATION
			MAMMARY GLAND	FIBROADENOMA	ADRENAL	ANGIECTASIS
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC

Continued on next page

Table XXXIb (continued). Individual Pathology - Trichloroethylene-Treated Female Rats

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
110	TSAC	010	MAMMARY GLAND	FIBROADENOMA (MULTIPLE-2)	ADRENAL	ANGIECTASIS
					MYOCARDIUM	DEGENERATION
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
110	TSAC	011			ADRENAL	ANGIECTASIS
					ADRENAL	DEGENERATION
					LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					FALLOPIAN TUBE	INFLAMMATION
110	TSAC	015			LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	023	PITUITARY	CHROMOPHOBE ADENOMA	LUNG	INFLAMMATION CHRONIC
			MAMMARY GLAND	FIBROADENOMA (MULTIPLE-2)	KIDNEY	NEPHROSIS TOXIC
					KIDNEY	CALCIUM DEPOSITION
110	TSAC	025			KIDNEY	NEPHROSIS TOXIC
					LUNG	INFLAMMATION CHRONIC
					PLEURA	INFLAMMATION
110	TSAC	030	THYROID	FOLLICULAR ADENOCARCINOMA	KIDNEY	NEPHROSIS TOXIC
			MAMMARY GLAND	FIBROADENOMA (MULTIPLE-2)		
110	TSAC	037	MAMMARY GLAND	FIBROADENOMA	PITUITARY	CYST
			ENDOMETRIUM	SARCOMA	PERICARDIUM	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
					SPLEEN	HEMATOPOIESIS EXTRAMED.
					CERVICAL LYMPH NODE	INFLAMMATION CYSTIC
					CERVICAL LYMPH NODE	INFLAMMATION
					LUNG	INFLAMMATION CHRONIC
110	TSAC	044			LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
					UTERUS	INFLAMMATION
					BONE MARROW	METAMORPHOSIS FATTY
110	TSAC	046	PITUITARY	CHROMOPHOBE ADENOMA	LUNG	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC

end of female rats

Table XXXIIa. Individual Pathology - Trichloroethylene-Treated Male Mice

Control Group (Vehicle)

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
32	NATD	010				NO SIGNIFICANT DIAGNOSIS
39	NATD	009			SPLEEN	AMYLOIDOSIS
					KIDNEY	PYELONEPHRITIS
60	NATD	008			KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	HYDRONEPHROSIS
					KIDNEY	AMYLOIDOSIS
61	NATD	007			KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	AMYLOIDOSIS
64	NATD	006			KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	HYDRONEPHROSIS
					SPLEEN	AMYLOIDOSIS
66	NATD	020			MESENTERIC LYMPH NODE	ANGIECTASIS
					SUBCUT TISSUE	ABSCESS
68	NATD	005			KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	AMYLOIDOSIS
					KIDNEY	HYDRONEPHROSIS
					SPLEEN	AMYLOIDOSIS
					LIVER	HYPERPLASIA
					ENDOCARDIUM	HYPERPLASIA
72	NATD	019	LIVER	HEPATOCELLULAR CARCINOMA	SPLEEN	AMYLOIDOSIS
76	NATD	004			KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	HYDRONEPHROSIS
76	MSAC	018	LIVER	RETICULUM CELL SARCOMA		
			SPLEEN	RETICULUM CELL SARCOMA		
			MESENTERIC LYMPHNODE	RETICULUM CELL SARCOMA		
			PROSTATE	RETICULUM CELL SARCOMA		
			SEMINAL VESICLES	RETICULUM CELL SARCOMA		
77	NATD	017	SUBCUT TISSUE/BACK	FIBROSARCOMA	SPLEEN	AMYLOIDOSIS
					KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	AMYLOIDOSIS

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Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

Control Group (Vehicle)

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
78	NATD	003				NO SIGNIFICANT DIAGNOSIS
90	TSAC	001	SKIN OF CHEST	FIBROSARCOMA	KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	HYDRONEPHROSIS
90	TSAC	002			KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	HYDRONEPHROSIS
90	TSAC	011	SUBCUT TISSUE/BACK	FIBROSARCOMA		
90	TSAC	012				NO SIGNIFICANT DIAGNOSIS
90	TSAC	013			SKIN	ACANTHOSIS
					SKIN	INFLAMMATION
90	TSAC	014				NO SIGNIFICANT DIAGNOSIS
90	TSAC	015			KIDNEY	HYDRONEPHROSIS
					KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	AMYLOIDOSIS
90	TSAC	016				NO SIGNIFICANT DIAGNOSIS

end of male mice controls

Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
16	NATD	010				NO SIGNIFICANT DIAGNOSIS
18	NATD	050	THYMUS	LYMPHOSARCOMA	KIDNEY	NEPHROSIS TOXIC
			BRONCHIAL LYMPHNODE	LYMPHOSARCOMA		
			LUNG	LYMPHOSARCOMA		
			KIDNEY	LYMPHOSARCOMA		
			PROSTATE	LYMPHOSARCOMA		
			BONE MARROW	LYMPHOSARCOMA		
			CERVICAL LYMPHNODE	LYMPHOSARCOMA		
			SPLEEN	LYMPHOSARCOMA		
			LIVER	LYMPHOSARCOMA		
31	ACCK	009				NO SIGNIFICANT DIAGNOSIS
51	NATD	030			KIDNEY	NEPHROSIS TOXIC
53	NATD	040			KIDNEY	NEPHROSIS TOXIC
58	NATD	008			HEART	ORGANIZED THROMBUS
					ENDOCARDIUM	INFLAMMATION
					MYOCARDIUM	INFLAMMATION
					KIDNEY	PYELONEPHRITIS
					KIDNEY	HYDRONEPHROSIS
					SPLEEN	AMYLOIDOSIS
					URINARY BLADDER	INFLAMMATION
					PROSTATE	INFLAMMATION
					PANCREAS	ATROPHY
					PANCREAS	INFLAMMATION
					BONE	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
63	NATD	039			KIDNEY	NEPHROSIS TOXIC
65	NATD	020			LIVER	HYPERPLASIA
					KIDNEY	NEPHROSIS TOXIC
65	NATD	038			KIDNEY	NEPHROSIS TOXIC
77	NATD	019			BRONCHUS	ABSCESS
					CERVICAL LYMPH NODE	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
81	NATD	028	SPLEEN	LYMPHOSARCOMA	KIDNEY	NEPHROSIS TOXIC
			LIVER	LYMPHOSARCOMA		

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Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
81	NATD	029	LUNG	ADENOMA	KIDNEY	NEPHROSIS TOXIC
			LIVER	HEPATOCELLULAR CARCINOMA		
86	NATD	049	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
					STOMACH	HYPERKERATOSIS
					STOMACH	ACANTHOSIS
88	NATD	007	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			LUNG	HEPATOCELLULAR CARCINOMA METASTA		
			LUNG	ADENOMA		
88	NATD	018			MESENTERIC LYMPH NODE	ANGIECTASIS
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	001	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			LUNG	ADENOMA		
90	TSAC	002	SUBCUT TISSUE/BACK	FIBROMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	003	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	004	LIVER	HEPATOCELLULAR CARCINOMA	SPLEEN	AMYLOIDOSIS
			LUNG	ADENOMA	KIDNEY	NEPHROSIS TOXIC
			MESENTERIC LYMPHNODE	RETICULUM CELL SARCOMA		
			ILEUM	RETICULUM CELL SARCOMA		
			RENAL LYMPHNODE	RETICULUM CELL SARCOMA		
90	TSAC	005	LIVER	HEPATOCELLULAR CARCINOMA	LIVER	THROMBOSIS
					SPLEEN	HEMATOPOIESIS EXTRAMED.
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	006	LIVER	HEPATOCELLULAR CARCINOMA	MESENTERIC LYMPH NODE	ANGIECTASIS
					KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	011	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			LUNG	HEPATOCELLULAR CARCINOMA METASTA		
90	TSAC	012	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	013	LIVER	HEPATOCELLULAR CARCINOMA	MESENTERIC LYMPH NODE	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	014	HARDERIAN GLAND	ADENOMA	KIDNEY	NEPHROSIS TOXIC

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Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
90	TSAC	015	EPIDIDYMIS	RETICULUM CELL SARCOMA	KIDNEY	NEPHROSIS TOXIC
			PROSTATE	RETICULUM CELL SARCOMA		
			SPLEEN	RETICULUM CELL SARCOMA		
			LIVER	HEPATOCELLULAR CARCINOMA		
			LUNG	HEPATOCELLULAR CARCINOMA METASTA		
90	TSAC	016			KIDNEY	NEPHROSIS TOXIC
90	TSAC	017	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	021	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	022			KIDNEY	NEPHROSIS TOXIC
90	TSAC	023			KIDNEY	NEPHROSIS TOXIC
90	TSAC	024	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	025			KIDNEY	NEPHROSIS TOXIC
90	TSAC	026	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	027			KIDNEY	NEPHROSIS TOXIC
90	TSAC	031	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	032	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	033	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	034	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	035	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	036	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	037	LUNG	ADENOMA	KIDNEY	NEPHROSIS TOXIC
			LIVER	HEPATOCELLULAR CARCINOMA		

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Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
90	TSAC	041	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
					STOMACH	ACANTHOSIS
					STOMACH	HYPERKERATOSIS
					MESENTERIC LYMPH NODE	INFLAMMATION
					RIGHT EYE	CONGENITAL MALFORMATION
					RIGHT EYE	PHTHISIS BULBI
					HARDERIAN GLAND	INFLAMMATION
90	TSAC	042			KIDNEY	NEPHROSIS TOXIC
90	TSAC	043	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			LUNG	HEPATOCELLULAR CARCINOMA METASTA	STOMACH	ACANTHOSIS
					STOMACH	HYPERKERATOSIS
					STOMACH	INFLAMMATION EXUDATIVE
					MESENTERIC LYMPH NODE	INFLAMMATION
90	TSAC	044			KIDNEY	NEPHROSIS TOXIC
90	TSAC	045			KIDNEY	NEPHROSIS TOXIC
					LIVER	HYPERPLASIA
90	TSAC	046			KIDNEY	NEPHROSIS TOXIC
90	TSAC	047			KIDNEY	NEPHROSIS TOXIC
					LIVER	INFLAMMATION
90	TSAC	048	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC

end of male mice—low dose

Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
13	NATD	010			KIDNEY	NEPHROSIS TOXIC
14	NATD	040			KIDNEY	NEPHROSIS TOXIC
15	NATD	049			KIDNEY	NEPHROSIS TOXIC
15	ACCK	050				NO SIGNIFICANT DIAGNOSIS
24	NATD	019			KIDNEY	NEPHROSIS TOXIC
24	NATD	020			LIVER KIDNEY	HYPERPLASIA NEPHROSIS TOXIC
25	NATD	047			KIDNEY	NEPHROSIS TOXIC
25	NATD	048			KIDNEY	NEPHROSIS TOXIC
27	NATD	046	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
28	NATD	018	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
28	NATD	045			KIDNEY	NEPHROSIS TOXIC
29	NATD	030			KIDNEY	INFLAMMATION CHRONIC
30	NATD	009			KIDNEY	NEPHROSIS TOXIC
30	NATD	017	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	INFLAMMATION
36	NATD	008	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
42	NATD	007			KIDNEY	NEPHROSIS TOXIC
53	NATD	039	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
60	NATD	005			KIDNEY	NEPHROSIS TOXIC
60	NATD	006			KIDNEY	NEPHROSIS TOXIC
61	NATD	016	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
70	NATD	038	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
71	NATD	015	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC

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Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
72	NATD	037				AUTOLYSIS
74	NATD	029	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
					LIVER/CENTRILOBULAR	NECROSIS
75	NATD	004			KIDNEY	NEPHROSIS TOXIC
					LIVER/CENTRILOBULAR	NECROSIS
					SALIVARY GLAND	INFLAMMATION CYSTIC
					STOMACH	ACANTHOSIS
					STOMACH	HYPERKERATOSIS
75	NATD	036				AUTOLYSIS
78	MSAC	044	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			TISSUE MUSCLE OF BACK	NEUROFIBROMA		
83	NATD	035	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			LUNG	HEPATOCELLULAR CARCINOMA METASTA		
			LUNG	ALVEOLAR ADENOCARCINOMA		
			BRONCHIAL LYMPH NODE	CARCINOMA METASTATIC		
			SKIN OF CHEST	CARCINOMA METASTATIC		
			AORTA	CARCINOMA METASTATIC		
88	MSAC	003	LIVER	HEPATOCELLULAR CARCINOMA	TESTIS	ATROPHY
			SPLEEN	LYMPHOSARCOMA	HARDERIAN GLAND	INFLAMMATION
			MESENTERIC LYMPHNODE	LYMPHOSARCOMA	KIDNEY	NEPHROSIS TOXIC
			KIDNEY	LYMPHOSARCOMA		
90	TSAC	001	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	002	LIVER	HEPATOCELLULAR CARCINOMA	THYROID	HYPERPLASIA CYSTIC
					KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	HYDRONEPHROSIS
					MESENTERIC LYMPH NODE	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	011	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	012	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	013	KIDNEY	ADENOMA	LIVER	HYPERPLASIA
			LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC

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Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
90	TSAC	014	LUNG	HEPATOCELLULAR CARCINOMA METASTA	KIDNEY	HYDRONEPHFCSIS
			LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	INFLAMMATION CHRONIC
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	021	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	HYDRONEPHFCSIS
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	022	LIVER	HEPATOCELLULAR CARCINOMA	MESENTERIC LYMPH NODE	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	023	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	024	MESENTERIC LYMPHNODE	RETICULUM CELL SARCOMA	KIDNEY	NEPHRCSIS TOXIC
			SPLEEN	RETICULUM CELL SARCOMA		
			PANCREAS	RETICULUM CELL SARCOMA		
			KIDNEY	RETICULUM CELL SARCOMA		
			LIVER	RETICULUM CELL SARCOMA		
90	TSAC	025	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	026	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	027	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	028	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	031	LUNG	ADENOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	032	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			LUNG	HEPATOCELLULAR CARCINOMA METASTA	MESENTERIC LYMPH NODE	ANGIECTASIS
90	TSAC	033	LIVER	HEPATOCELLULAR CARCINOMA	STOMACH	HYPERKERATOSIS
			STOMACH	PAPILLOMA	KIDNEY	NEPHROSIS TOXIC
90	NATD	034	KIDNEY	FIBROSARCOMA, METASTATIC	KIDNEY	NEPHROSIS TOXIC
			LIVER	HEPATOCELLULAR CARCINOMA		
			ABDOMENAL CAVITY	FIBROSARCOMA, PRIMARY		
			ADRENAL	FIBROSARCOMA, METASTATIC		
			PANCREAS	FIBROSARCOMA, METASTATIC		
			MESENTERIC LYMPHNODE	FIBROSARCOMA, METASTATIC		
			STOMACH	FIBROSARCOMA, METASTATIC		

Continued on next page

Table XXXIIa (continued). Individual Pathology - Trichloroethylene-Treated Male Mice

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
90	TSAC	041	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	042	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	043	LIVER LUNG	HEPATOCELLULAR CARCINOMA HEMANGIOSARCOMA	KIDNEY	NEPHROSIS TOXIC

end of male mice—high dose

Table XXXIIb. Individual Pathology - Trichloroethylene-Treated Female Mice

Control Group (Vehicle)

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS		OTHER PATHOLOGY	
			TOPOGRAPHY	MORPHOLOGY	TOPOGRAPHY	MORPHOLOGY
20	ACCK	010				NO SIGNIFICANT DIAGNOSIS
37	ACCK	009			ENDOMETRIUM	HYPERPLASIA CYSTIC
83	ACCK	008	SOFT TISSUES OF BACK	OSTEOSARCOMA		
90	TSAC	001			OVARY	CYST
90	TSAC	002			LUNG UTERUS OVARY OVARY	INFLAMMATION CHRONIC INFLAMMATION CYST INFLAMMATION
90	TSAC	003	ENDOMETRIUM	ADENOCARCINOMA		
90	TSAC	004				NO SIGNIFICANT DIAGNOSIS
90	TSAC	005			ENDOMETRIUM OVARY	HYPERPLASIA CYSTIC CYST
90	TSAC	006			ENDOMETRIUM	HYPERPLASIA CYSTIC
90	TSAC	007	LUNG	ADENOMA		
90	TSAC	011			OVARY ENDOMETRIUM	CYST HYPERPLASIA CYSTIC
90	TSAC	012				NO SIGNIFICANT DIAGNOSIS
90	TSAC	013			ENDOMETRIUM	HYPERPLASIA CYSTIC
90	TSAC	014	MESENTERIC LYMPH NODE	RETICULUM CELL SARCOMA	LUNG ENDOMETRIUM	INFLAMMATION CHRONIC HYPERPLASIA CYSTIC
90	TSAC	015			OVARY	CYST
90	TSAC	016			ENDOMETRIUM	HYPERPLASIA CYSTIC
90	TSAC	017			ENDOMETRIUM	HYPERPLASIA CYSTIC
90	TSAC	018			OVARY ENDOMETRIUM	CYST HYPERPLASIA CYSTIC
90	TSAC	019				NO SIGNIFICANT DIAGNOSIS
90	TSAC	020			ENDOMETRIUM	HYPERPLASIA CYSTIC

end of female mice controls

Table XXXIIb (continued). Individual Pathology - Trichloroethylene-Treated Female Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
10	NATD	020				NO SIGNIFICANT DIAGNOSIS
32	ACCK	010			KIDNEY	NEPHROSIS TOXIC
37	MSAC	019			KIDNEY	NEPHROSIS TOXIC
38	NATD	018				NO SIGNIFICANT DIAGNOSIS
41	ACCK	009			KIDNEY	NEPHROSIS TOXIC
55	NATD	030			UTERUS	INFLAMMATION
63	NATD	029				NO SIGNIFICANT DIAGNOSIS
66	NATD	040			KIDNEY	NEPHROSIS TOXIC
76	NATD	017	LIVER UTERUS CERVICAL LYMPHNODE	RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA	KIDNEY	NEPHROSIS TOXIC
81	NATD	016	SPLEEN MESENTERIC LYMPHNODE ILEUM ADRENAL CERVICAL LYMPHNODE	LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	001	LIVER VAGINA SPLEEN	RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	002			UTERUS KIDNEY	INFLAMMATION NEPHROSIS TOXIC
90	TSAC	003	LIVER UTERUS	HEPATOCELLULAR CARCINOMA FIBROSARCOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	004			ENDOMETRIUM KIDNEY	HYPERPLASIA CYSTIC NEPHROSIS TOXIC
90	TSAC	005			KIDNEY	NEPHROSIS TOXIC
90	TSAC	006			ENDOMETRIUM KIDNEY	HYPERPLASIA CYSTIC NEPHROSIS TOXIC

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Table XXXIIb (continued). Individual Pathology - Trichloroethylene-Treated Female Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
90	TSAC	007	LIVER	HEPATOCELLULAR CARCINOMA	ENDOMETRIUM	HYPERPLASIA CYSTIC
					HARDERIAN GLAND	HYPERPLASIA
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	008			STOMACH	ACANTHOSIS
					STOMACH	HYPERKERATOSIS
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	011			UTERUS	RETENTION FLUID
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	012	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	013			OVARY	CYST
					UTERUS	RETENTION FLUID
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	014			UTERUS	POLYP
					UTERUS	INFLAMMATION
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	015			UTERUS	RETENTION FLUID
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	021			KIDNEY	NEPHROSIS TOXIC
90	TSAC	022			KIDNEY	NEPHROSIS TOXIC
90	TSAC	023			ENDOMETRIUM	HYPERPLASIA CYSTIC
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	024			ENDOMETRIUM	HYPERPLASIA CYSTIC
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	025			ENDOMETRIUM	HYPERPLASIA CYSTIC
					KIDNEY	NEPHROSIS TOXIC
90	TSAC	026			KIDNEY	NEPHROSIS TOXIC
90	TSAC	027	LUNG	ALVEOLAR ADENOCARCINOMA	KIDNEY	INFLAMMATION INTERSTITIAL
					KIDNEY	INFLAMMATION PROLIFERATIVE
					PANCREAS	ATROPHY
					KIDNEY	NEPHROSIS TOXIC

Continued on next page

Table XXXIIb (continued). Individual Pathology - Trichloroethylene-Treated Female Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
90	TSAC	028			ENDOMETRIUM KIDNEY	HYPERPLASIA CYSTIC NEPHROSIS TOXIC
90	TSAC	031			KIDNEY	NEPHROSIS TOXIC
90	TSAC	032	LIVER	HEPATOCELLULAR CARCINOMA	UTERUS KIDNEY	RETENTION FLUID NEPHROSIS TOXIC
90	TSAC	033	OVARY	GRANULOSA CELL CARCINOMA	UTERUS KIDNEY	INFLAMMATION NEPHROSIS TOXIC
90	TSAC	034			ENDOMETRIUM OVARY KIDNEY	HYPERPLASIA CYSTIC CYST NEPHROSIS TOXIC
90	TSAC	035	SUBCUT TISSU/ABDOMEN	FIBROSARCOMA	ENDOMETRIUM KIDNEY	HYPERPLASIA CYSTIC NEPHROSIS TOXIC
90	TSAC	036	LUNG SPLEEN	ADENOMA LYMPHOSARCOMA	KIDNEY	NEPHROSIS TOXIC
90	TSAC	037			ENDOMETRIUM KIDNEY	HYPERPLASIA CYSTIC NEPHROSIS TOXIC
90	TSAC	038	MAMMARY GLAND	ADENOCARCINOMA	OVARY KIDNEY	CYST NEPHROSIS TOXIC
90	TSAC	039			KIDNEY	NEPHROSIS TOXIC
90	TSAC	041			KIDNEY	NEPHROSIS TOXIC
90	TSAC	042	LUNG THYMUS	ADENOMA LYMPHOSARCOMA	OVARY KIDNEY	RETENTION FLUID NEPHROSIS TOXIC
90	TSAC	043	OVARY LUNG HARDERIAN GLAND	CYSTADENOMA ALVEOLAR ADENOCARCINOMA ADENOMA	THYROID KIDNEY	INFLAMMATION CYSTIC NEPHROSIS TOXIC
90	TSAC	044			ENDOMETRIUM THYROID KIDNEY	HYPERPLASIA CYSTIC INFLAMMATION CYSTIC NEPHROSIS TOXIC
90	TSAC	045			UTERUS RIGHT OVARY KIDNEY	RETENTION FLUID CYST NEPHROSIS TOXIC

Continued on next page

Table XXXIIb (continued). Individual Pathology - Trichloroethylene-Treated Female Mice

Low Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
91	TSAC	046			KIDNEY	NEPHROSIS TOXIC
91	TSAC	047			ENDOMETRIUM	HYPERPLASIA CYSTIC
					KIDNEY	NEPHROSIS TOXIC
91	TSAC	048			UTERUS	RETENTION FLUID
					KIDNEY	NEPHROSIS TOXIC
91	TSAC	049			ENDOMETRIUM	HYPERPLASIA CYSTIC
					KIDNEY	NEPHROSIS TOXIC
91	TSAC	050			UTERUS	RETENTION FLUID
					KIDNEY	NEPHROSIS TOXIC

end of female mice—low dose

Table XXXIIb (continued). Individual Pathology - Trichloroethylene-Treated Female Mice

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
14	MISS	010				ANIMAL MISSING
22	MISS	040				ANIMAL MISSING
26	MISS	050				ANIMAL MISSING
32	NATD	030			KIDNEY	NEPHROSIS TOXIC
32	NATD	049			KIDNEY	NEPHROSIS
33	NATD	039			KIDNEY	NEPHROSIS TOXIC
38	NATD	038			KIDNEY	NEPHROSIS TOXIC
39	NATD	020			KIDNEY	NEPHROSIS TOXIC
40	NATD	037			KIDNEY	NEPHROSIS TOXIC
69	NATD	009	SPLEEN	LYMPHOSARCOMA	KIDNEY OVARY	NEPHROSIS TOXIC CYST
88	NATD	036	SPLEEN KIDNEY LUNG STOMACH	RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA		
91	TSAC	001	MESENTERIC LYMPH NODE ILEUM	RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA	KIDNEY	NEPHROSIS TOXIC
91	TSAC	002			KIDNEY LIVER OVARY	NEPHROSIS TOXIC HYPERPLASIA CYST
91	TSAC	003			KIDNEY	NEPHROSIS TOXIC
91	TSAC	004			KIDNEY UTERUS	NEPHROSIS TOXIC RETENTION FLUID
91	TSAC	005			KIDNEY ENDOMETRIUM	NEPHROSIS TOXIC HYPERPLASIA CYSTIC
91	TSAC	006	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
91	TSAC	007			KIDNEY	NEPHROSIS TOXIC
91	TSAC	008	LUNG LIVER	ALVEOLAR ADENOCARCINOMA HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC

Continued on next page

Table XXXIIb (continued). Individual Pathology - Trichloroethylene-Treated Female Mice

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
91	TSAC	011			KIDNEY	NEPHROSIS TOXIC
91	TSAC	012	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY UTERUS	NEPHROSIS TOXIC RETENTION FLUID
91	TSAC	013	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY OVARY	NEPHROSIS TOXIC CYST
91	TSAC	014			KIDNEY ENDOMETRIUM	NEPHROSIS TOXIC INFLAMMATION
91	TSAC	015	LUNG	ADENOMA	KIDNEY	NEPHROSIS TOXIC
91	TSAC	016			KIDNEY	NEPHROSIS TOXIC
91	TSAC	017			MESENTERIC LYMPH NODE UTERUS KIDNEY	ANGIECTASIS RETENTION FLUID NEPHROSIS TOXIC
91	TSAC	018	CERVICAL LYMPH NODE	MALIGNANT LYMPHOMA	KIDNEY	NEPHROSIS TOXIC
91	TSAC	019			KIDNEY	NEPHROSIS TOXIC
91	TSAC	021			KIDNEY UTERUS	NEPHROSIS TOXIC RETENTION FLUID
91	TSAC	022	LIVER KIDNEY SPLEEN	LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA	OVARY UTERUS KIDNEY	CYST RETENTION FLUID NEPHROSIS TOXIC
91	TSAC	023	LUNG	ADENOMA	KIDNEY LIVER	NEPHROSIS TOXIC HYPERPLASIA
91	TSAC	024	LIVER	HEPATOCELLULAR CARCINOMA	BRONCHUS KIDNEY	BRONCHIECTASIS NEPHROSIS TOXIC
91	TSAC	025	LUNG LIVER	ALVEOLAR ADENOCARCINOMA HEPATOCELLULAR CARCINOMA	KIDNEY OVARY	NEPHROSIS TOXIC CYST
91	TSAC	026	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
91	TSAC	027			KIDNEY	NEPHROSIS TOXIC

Continued on next page

Table XXXIIb (continued). Individual Pathology - Trichloroethylene-Treated Female Mice

High Dose Group

WEEKS ON STUDY	DISP CODE	ANIMAL NUMBER	TUMORS TOPOGRAPHY	TUMORS MORPHOLOGY	OTHER PATHOLOGY TOPOGRAPHY	OTHER PATHOLOGY MORPHOLOGY
91	TSAC	028			KIDNEY	NEPHROSIS TOXIC
					ENDOMETRIUM	HYPERPLASIA CYSTIC
					OVARY	CYST
91	TSAC	029			KIDNEY	NEPHROSIS TOXIC
					OVARY	CYST
91	TSAC	031			KIDNEY	NEPHROSIS TOXIC
					UTERUS	RETENTION FLUID
91	TSAC	032			KIDNEY	NEPHROSIS TOXIC
91	TSAC	033			KIDNEY	NEPHROSIS TOXIC
91	TSAC	034	LUNG	ADENOMA	KIDNEY	NEPHROSIS TOXIC
91	TSAC	035			KIDNEY	NEPHROSIS TOXIC
91	TSAC	041	LUNG	ADENOMA	KIDNEY	NEPHROSIS TOXIC
			MESENTERIC LYMPHNODE	LYMPHOSARCOMA		
			SPLEEN	LYMPHOSARCOMA		
			CERVICAL LYMPHNODE	LYMPHOSARCOMA		
			LIVER	HEPATOCELLULAR CARCINOMA		
91	TSAC	042	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
91	TSAC	043			KIDNEY	NEPHROSIS TOXIC
91	TSAC	044	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
					UTERUS	RETENTION FLUID
91	TSAC	045			KIDNEY	NEPHROSIS TOXIC
					UTERUS	RETENTION FLUID
91	TSAC	046	LIVER	HEPATOCELLULAR CARCINOMA	KIDNEY	NEPHROSIS TOXIC
			LUNG	ADENOMA		
91	TSAC	047			KIDNEY	NEPHROSIS TOXIC
					MESENTERIC LYMPH NODE	ANGIECTASIS
					STOMACH	ACANTHOSIS
					STOMACH	HYPERKERATOSIS
					OVARY	CYST
91	TSAC	048			KIDNEY	NEPHROSIS
					OVARY	CYST

end of female mice—high dose

APPENDIX E: POSITIVE CONTROLS

Table XXXIIIa. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Male Rats

Individual Number	Week of Death	Diagnosis
001	82	Portal cirrhosis
		Cholangietasis
		Fatty
002	110	Bile duct proliferation
003	103	Advanced autolysis
004	82	Hepatocellular carcinoma
005	110	Portal cirrhosis
		Bile duct proliferation
		Fatty
		Pigment deposition
006	110	Peliosis
		Bile duct proliferation
		Fibrosis (around bile ducts)
007	13	Centrilobular necrosis
		Fatty
008	106	Portal cirrhosis
		Cholangiectasis
		Fatty
		Bile duct proliferation
009	65	Portal cirrhosis
		Fatty
		Bile duct proliferation
010	95	Cholangiectasis
		Fatty
011	102	Portal cirrhosis
		Fatty
		Bile duct proliferation
012	62	Portal cirrhosis
		Fatty
		Bile duct proliferation
013	73	Fatty (diffuse)
014	44	Periportal necrosis
		Degeneration
		Fatty
		Fibrosis
015	99	Periportal degeneration
		Fibrosis
		Bile duct proliferation
016	107	Portal cirrhosis
		Pigment deposition
017	66	Portal cirrhosis
		Bile duct proliferation
		Fatty
		Neoplastic nodule

Table XXXIIIa. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Male Rats (continued)

018	110	Portal cirrhosis Bile duct proliferation Fatty
019	94	Portal cirrhosis Bile duct proliferation Fatty
020	110	Bile duct proliferation Angiectasis Fatty Regenerative nodules
021	105	Portal cirrhosis Bile duct proliferation Fatty
022	110	Angiectasis Bile duct proliferation Fatty Fibrosis
023	106	Advanced autolysis Portal cirrhosis Fatty
024	110	None
025	107	Portal cirrhosis Bile duct proliferation Regenerative nodules
026	110	Regenerative nodules Fatty Angiectasis
027	63	Portal cirrhosis
028	75	Bile duct proliferation Fibrosis Cholangiectasis
029	110	Bile duct proliferation Fatty Fibrosis
030	90	Myelogenous leukemia
031	110	Portal cirrhosis Bile duct proliferation Regenerative nodules
032	60	Portal cirrhosis Bile duct proliferation Fatty Organizing thrombus Hepatocellular carcinoma Regenerative nodules
033	73	Portal cirrhosis Fatty Bile duct proliferation

Table XXXIIIa. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Male Rats

(continued)

034	71	Portal cirrhosis Bile duct proliferation Fatty Regenerative nodules
035	71	Portal cirrhosis Bile duct proliferation Regenerative nodules
036	82	Portal cirrhosis Bile duct proliferation
037	110	Fatty
038	101	Portal cirrhosis Hepatic abscess
039	108	Portal cirrhosis Bile duct proliferation
040	109	Bile duct proliferation Fibrosis Fatty Regenerative nodules
041	58	Portal cirrhosis Bile duct proliferation
042	30	Portal cirrhosis Bile duct proliferation Fatty
043	110	Portal cirrhosis Bile duct proliferation Fatty Regenerative nodules
044	69	Portal cirrhosis Bile duct proliferation Fatty
045	110	Neoplastic nodule
046	110	Portal cirrhosis Bile duct proliferation Regenerative nodules
047	109	Portal cirrhosis Bile duct proliferation
048	104	Portal cirrhosis Bile duct proliferation
049	36	Reticulum cell sarcoma (multicentric)
050	110	Portal cirrhosis Bile duct proliferation Foci of altered cells Regenerative nodules

Table XXXIIIb. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Male Rats

Individual Number	Week of Death	Diagnosis
001	107	Portal cirrhosis Bile duct proliferation Fatty
002	110	Portal cirrhosis Bile duct proliferation
003	100	Advanced autolysis Portal cirrhosis Bile duct proliferation
004	97	Hepatocellular carcinoma
005	80	Regenerative nodules
006	96	Advanced autolysis Bile duct proliferation Portal cirrhosis
007	96	Portal cirrhosis Bile duct proliferation
008	109	Regenerative nodules
009	91	Portal cirrhosis Bile duct proliferation Hepatitis
010	77	Portal cirrhosis Bile duct proliferation
011	55	Fatty
012	58	Portal cirrhosis Fatty
013	64	Portal cirrhosis Bile duct proliferation
014	81	Advanced autolysis Regenerative nodules
015	78	Portal cirrhosis Bile duct proliferation Fatty
016	61	Portal cirrhosis Bile duct proliferation Fatty
017	110	Portal cirrhosis Bile duct proliferation
018	68	Portal cirrhosis Bile duct proliferation Fatty Neoplastic nodule

Table XXXIIIb. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Male Rats

(continued)

019	40	Portal cirrhosis Fatty
020	97	Portal cirrhosis Bile duct proliferation Cholangiectasis
021	110	Portal cirrhosis Bile duct proliferation Regenerative nodules
022	110	Portal cirrhosis Bile duct proliferation
023	77	Portal cirrhosis Bile duct proliferation
024	55	Portal cirrhosis Fatty Bile duct proliferation
025	104	Lymphocytic leukemia
026	79	Hepatocellular carcinoma
027	90	Portal cirrhosis Bile duct proliferation
028	100	Portal cirrhosis Bile duct proliferation
029	97	Portal cirrhosis Bile duct proliferation Organizing thrombus
030	65	Portal cirrhosis Bile duct proliferation Fatty
031	43	Portal cirrhosis Fatty Bile duct proliferation
032	109	Advanced autolysis Portal cirrhosis Bile duct proliferation
033	98	Portal cirrhosis Bile duct proliferation
034	93	Portal cirrhosis Bile duct proliferation
035	88	Portal cirrhosis Fatty Bile duct proliferation Foci of altered cells Regenerative nodules
036	110	Portal cirrhosis Bile duct proliferation
037	90	Portal cirrhosis Bile duct proliferation

Table XXXIIIb. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Male Rats

(continued)

038	14	Fat deposition, diffuse
039	100	Portal cirrhosis Bile duct proliferation
040	83	Portal cirrhosis Bile duct proliferation
041	109	Advanced autolysis Portal cirrhosis Regenerative nodules
042	73	Portal cirrhosis Bile duct proliferation Fatty
043	77	Portal cirrhosis Bile duct proliferation Fatty
044	110	Portal cirrhosis Bile duct proliferation
045	107	Portal cirrhosis Bile duct proliferation
046	96	Portal cirrhosis Bile duct proliferation
047	98	Portal cirrhosis Bile duct proliferation
048	110	Portal cirrhosis Bile duct proliferation Regenerative nodules
049	54	Portal cirrhosis Fatty
050	85	Portal cirrhosis Bile duct proliferation

Table XXXIIIc. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Female Rats

Individual Number	Week of Death	Diagnosis
001	100	Portal cirrhosis
		Bile duct proliferation
002	110	Neoplastic nodule
003	88	Regenerative nodules
		Bile duct proliferation
004	110	Foci of altered cells
005	71	Regenerative nodules
		Fatty
006	96	Portal cirrhosis
		Bile duct proliferation
007	105	Portal cirrhosis
		Bile duct proliferation
008	61	Fatty
		Portal cirrhosis
		Bile duct proliferation
009	110	Portal cirrhosis
		Bile duct proliferation
		Fatty
		Foci of altered cells
		Regenerative nodules
010	110	Portal cirrhosis
		Regenerative nodules
011	101	Reticulum cell sarcoma
012	110	Portal cirrhosis
		Fatty
013	104	Portal cirrhosis
		Bile duct proliferation
		Fatty
		Neoplastic nodule
014	110	Hepatocellular carcinoma
015	86	Portal cirrhosis
		Fatty
016	107	Portal cirrhosis
		Bile duct proliferation
017	110	Portal cirrhosis
		Bile duct proliferation
		Regenerative nodules
018	110	Portal cirrhosis
		Fatty
		Bile duct proliferation
019	57	Portal cirrhosis
		Fatty
020	110	Portal cirrhosis
		Regenerative nodules

Table XXXIIIc. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Female Rats (continued)

021	94	Portal cirrhosis Bile duct proliferation Fatty
022	110	Portal cirrhosis Bile duct proliferation Regenerative nodules
023	100	Portal cirrhosis Organizing thrombus Pigment deposition Bile duct proliferation
024	88	Portal cirrhosis Regenerative nodules
025	110	Portal cirrhosis Angiectasis Hepatocellular carcinoma Bile duct proliferation
026	110	Portal cirrhosis Foci of altered cells Regenerative nodules
027	76	Portal cirrhosis Fatty Bile duct proliferation Hepatitis Regenerative nodules
028	110	Fatty Bile duct proliferation Regenerative nodules
029	88	Portal cirrhosis Bile duct proliferation Fatty
030	110	Portal cirrhosis Bile duct proliferation Regenerative nodules
031	41	Portal cirrhosis Bile duct proliferation
032	93	Advanced autolysis Portal cirrhosis Bile duct proliferation
033	13	Advanced autolysis
034	94	Portal cirrhosis Fatty
035	73	Portal cirrhosis Bile duct proliferation Fatty
036	91	Portal cirrhosis Bile duct proliferation Angiectasis

Table XXXIIIc. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Female Rats (continued)

037	110	Portal cirrhosis Bile duct proliferation
038	79	Advanced autolysis Portal cirrhosis Fatty
039	104	Advanced autolysis Portal cirrhosis Bile duct proliferation Fatty
040	74	Portal cirrhosis Fatty Bile duct proliferation
041	12	Portal cirrhosis Fatty
042	104	Portal cirrhosis Bile duct proliferation Hepatocellular carcinoma
043	110	Portal cirrhosis Fatty Bile duct proliferation Regenerative nodules
044	110	Portal cirrhosis Fatty
045	110	Portal cirrhosis Fatty Bile duct proliferation
046	58	Portal cirrhosis Fatty
047	39	Portal cirrhosis Bile duct proliferation
048	48	Portal cirrhosis Fatty Neoplastic nodule Hepatocellular carcinoma
049	110	Bile duct proliferation Fatty
050	110	Portal cirrhosis Bile duct proliferation

Table XXXIIId. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Female Rats

Individual Number	Week of Death	Diagnosis
001	110	Portal cirrhosis
		Bile duct proliferation
		Fatty
002	110	Portal cirrhosis
		Fatty
		Regenerative nodules
003	16	Portal cirrhosis
004	71	Portal cirrhosis
		Fatty
005	66	Portal cirrhosis
		Fatty
		Bile duct proliferation
006	110	Portal cirrhosis
		Bile duct proliferation
		Fatty
		Regenerative nodules
007	38	Portal cirrhosis
		Fatty
008	103	Portal cirrhosis
		Bile duct proliferation
009	110	Portal cirrhosis
		Fatty
010	110	Portal cirrhosis
		Bile duct proliferation
		Fatty
		Regenerative nodules
011	110	Portal cirrhosis
		Bile duct proliferation
		Regenerative nodules
012	82	Advanced autolysis
		Portal cirrhosis
		Bile duct proliferation
013	110	Portal cirrhosis
		Bile duct proliferation
014	110	Portal cirrhosis
		Bile duct proliferation
		Neoplastic nodule
015	110	Neoplastic nodule
016	12	Portal cirrhosis
		Fatty
		Bile duct proliferation
017	1	Portal cirrhosis
		Angiectasis
018	48	Portal cirrhosis
		Bile duct proliferation

Table XXXIIId. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Female Rats

(continued)

019	80	Portal cirrhosis Bile duct proliferation
020	62	Portal cirrhosis Bile duct proliferation
021	52	Portal cirrhosis Fatty Bile duct proliferation Regenerative nodules
022	13	Portal cirrhosis Fatty
023	4	Portal cirrhosis Fatty
024	30	Portal cirrhosis Fatty
025	19	Portal cirrhosis Fatty
026	69	Portal cirrhosis Bile duct proliferation Hepatitis
027	110	Portal cirrhosis Bile duct proliferation Neoplastic nodule
028	34	Portal cirrhosis Bile duct proliferation Fatty
029	76	Portal cirrhosis Foci of altered cells Regenerative nodules
030	34	Lost
031	80	Portal cirrhosis Bile duct proliferation Regenerative nodules
032	70	Portal cirrhosis Bile duct proliferation Fatty Regenerative nodules
033	4	Portal cirrhosis Fatty
034	110	Regenerative nodules
035	110	Regenerative nodules
036	33	Portal cirrhosis Bile duct proliferation
037	110	Regenerative nodules
038	99	Advanced autolysis Portal cirrhosis Bile duct proliferation
039	12	Portal cirrhosis (early) Fatty

Table XXXIIId. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Female Rats (continued)

040	95	Portal cirrhosis Bile duct proliferation
041	104	Hepatocellular carcinoma
042	9	Portal cirrhosis Fatty Bile duct proliferation
043	53	Fatty Sinusoidal ectasia
044	29	Portal cirrhosis Bile duct proliferation
045	15	Portal cirrhosis Bile duct proliferation
046	44	Portal cirrhosis Bile duct proliferation Fatty Regenerative nodules
047	1	Fatty
048	50	Portal cirrhosis Bile duct proliferation
049	3	Fatty
050	110	Portal cirrhosis Bile duct proliferation Regenerative nodules

Table XXXIVa. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Male Mice

Individual Number	Week of Death	Diagnosis
001	80	Hepatocellular carcinoma
002	74	Hepatocellular carcinoma
003	72	Hepatocellular carcinoma
004	72	Hepatocellular carcinoma
005	72	Hepatocellular carcinoma
006	66	Hepatocellular carcinoma
007	65	Hepatocellular carcinoma
008	63	Hepatocellular carcinoma
009	50	Hepatocellular carcinoma
010	48	Hepatocellular carcinoma
011	80	Hepatocellular carcinoma
012	75	Hepatocellular carcinoma
013	74	Hepatocellular carcinoma
014	74	Hepatocellular carcinoma
015	73	Hepatocellular carcinoma
016	67	Hepatocellular carcinoma
017	67	Hepatocellular carcinoma
018	65	Hepatocellular carcinoma
019	63	Hepatocellular carcinoma
020	55	Hepatocellular carcinoma
021	82	Hepatocellular carcinoma
022	81	Hepatocellular carcinoma
023	79	Hepatocellular carcinoma
024	76	Hepatocellular carcinoma
025	76	Hepatocellular carcinoma
026	72	Hepatocellular carcinoma
027	70	Hepatocellular carcinoma
028	64	Hepatocellular carcinoma
029	61	Hepatocellular carcinoma
030	60	Hepatocellular carcinoma
031	86	Hepatocellular carcinoma
032	82	Hepatocellular carcinoma
033	81	Hepatocellular carcinoma
034	80	Hepatocellular carcinoma
035	75	Hepatocellular carcinoma
036	74	Hepatocellular carcinoma
037	71	Hepatocellular carcinoma
038	64	Hepatocellular carcinoma
039	54	Hepatocellular carcinoma
040	42	Autolysis

Table XXXIVa. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Male Mice (continued)

041	84	Hepatocellular carcinoma
042	80	Hepatocellular carcinoma
043	77	Hepatocellular carcinoma
044	77	Hepatocellular carcinoma
045	75	Hepatocellular carcinoma
046	72	Hepatocellular carcinoma
047	72	Hepatocellular carcinoma
048	69	Hepatocellular carcinoma
049	64	Hepatocellular carcinoma
050	50	Hepatocellular carcinoma

Table XXXIVb. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Male Mice

Individual Number	Week of Death	Diagnosis
001	75	Hepatocellular carcinoma
002	75	Hepatocellular carcinoma
003	75	Hepatocellular carcinoma
004	66	Hepatocellular carcinoma
005	63	Hepatocellular carcinoma
006	63	Hepatocellular carcinoma
007	60	Hepatocellular carcinoma
008	60	Hepatocellular carcinoma
009	55	Hepatocellular carcinoma
010	52	Hepatocellular carcinoma
011	90	Hepatocellular carcinoma
012	79	Hepatocellular carcinoma
013	77	Hepatocellular carcinoma
014	74	Hepatocellular carcinoma
015	69	Hepatocellular carcinoma
016	64	Hepatocellular carcinoma
017	56	Hepatocellular carcinoma
018	53	Hepatocellular carcinoma
019	42	Hepatocellular carcinoma
020	30	Hepatocellular carcinoma
021	77	Hepatocellular carcinoma
022	74	Hepatocellular carcinoma
023	66	Hepatocellular carcinoma
024	65	Hepatocellular carcinoma
025	62	Hepatocellular carcinoma
026	56	Cannibalized
027	48	Hepatocellular carcinoma
028	48	Autolysis
029	48	Hepatocellular carcinoma
030	26	Hepatocellular carcinoma
031	74	Hepatocellular carcinoma
032	74	Hepatocellular carcinoma
033	70	Hepatocellular carcinoma
034	65	Hepatocellular carcinoma
035	63	Hepatocellular carcinoma
036	60	Hepatocellular carcinoma
037	51	Hepatocellular carcinoma
038	51	Hepatocellular carcinoma
039	47	Hepatocellular carcinoma
040	47	Hepatocellular carcinoma

Table XXXIVb. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Male Mice (continued)

041	73	Hepatocellular carcinoma
042	73	Hepatocellular carcinoma
043	71	Hepatocellular carcinoma
044	70	Hepatocellular carcinoma
045	70	Hepatocellular carcinoma
046	58	Hepatocellular carcinoma
047	56	Hepatocellular carcinoma
048	35	Hepatocellular carcinoma
049	26	Hepatocellular carcinoma
050	16	Portal cirrhosis
		Bile duct proliferation

Table XXXIVc. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Female Mice

Individual Number	Week of Death	Diagnosis
001	68	Hepatocellular carcinoma
		Organizing thrombus
002	77	Hepatocellular carcinoma
003	74	Hepatocellular carcinoma
004	74	Hepatocellular carcinoma
005	70	Hepatocellular carcinoma
006	68	Hepatocellular carcinoma
007	62	Cannibalized
008	62	Hepatocellular carcinoma
009	58	Cannibalized
010	45	Autolysis
011	80	Hepatocellular carcinoma
012	80	Hepatocellular carcinoma
013	79	Hepatocellular carcinoma
014	75	Hepatocellular carcinoma
015	70	Hepatocellular carcinoma
016	68	Hepatocellular carcinoma
		Organizing thrombus
017	65	Hepatocellular carcinoma
018	64	Hepatocellular carcinoma
019	36	Hepatocellular carcinoma
020	29	Autolysis
021	81	Hepatocellular carcinoma
022	80	Hepatocellular carcinoma
023	75	Hepatocellular carcinoma
024	70	Hepatocellular carcinoma
025	66	Hepatocellular carcinoma
026	55	Hepatocellular carcinoma
027	48	Hepatocellular carcinoma
028	46	Hepatocellular carcinoma
029	33	Hepatocellular carcinoma
030	11	Autolysis
031	86	Hepatocellular carcinoma
032	84	Hepatocellular carcinoma
033	79	Hepatocellular carcinoma
034	78	Hepatocellular carcinoma
035	75	Hepatocellular carcinoma
036	66	Autolysis
037	66	Hepatocellular carcinoma
038	61	Hepatocellular carcinoma
039	54	Hepatocellular carcinoma
040	30	Hepatocellular carcinoma

Table XXXIVc. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - Low Dose Female Mice (continued)

041	81	Hepatocellular carcinoma
042	79	Cannibalized
043	78	Cannibalized
044	72	Cannibalized
045	71	Hepatocellular carcinoma
046	71	Hepatocellular carcinoma
047	69	Hepatocellular carcinoma
048	64	Cannibalized
049	55	Hepatocellular carcinoma
050	16	Hepatocellular carcinoma

Table XXXIVd. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Female Mice

Individual Number	Week of Death	Diagnosis
001	92	Hepatocellular carcinoma
002	68	Hepatocellular carcinoma
003	61	Hepatocellular carcinoma
004	61	Hepatocellular carcinoma
005	58	Hepatocellular carcinoma
006	51	Hepatocellular carcinoma
007	34	Lost
008	19	Hepatocellular carcinoma
009	19	Cannibalized
010	14	Toxic hepatitis Cirrhosis Bile duct proliferation Fatty
011	74	Hepatocellular carcinoma
012	66	Hepatocellular carcinoma
013	63	Hepatocellular carcinoma
014	60	Hepatocellular carcinoma
015	57	Hepatocellular carcinoma
016	52	Cannibalized
017	51	Autolysis
018	47	Hepatocellular carcinoma
019	43	Hepatocellular carcinoma
020	42	Hepatocellular carcinoma
021	78	Hepatocellular carcinoma
022	73	Hepatocellular carcinoma
023	71	Hepatocellular carcinoma
024	70	Hepatocellular carcinoma
025	67	Hepatocellular carcinoma
026	67	Hepatocellular carcinoma
027	67	Hepatocellular carcinoma
028	58	Hepatocellular carcinoma
029	54	Hepatocellular carcinoma
030	13	Portal cirrhosis Bile duct proliferation
031	80	Hepatocellular carcinoma
032	74	Hepatocellular carcinoma
033	68	Hepatocellular carcinoma
034	59	Hepatocellular carcinoma
035	57	Hepatocellular carcinoma
036	57	Hepatocellular carcinoma
037	56	Hepatocellular carcinoma
038	41	Hepatocellular carcinoma
039	38	Hepatocellular carcinoma
040	35	Hepatocellular carcinoma

Table XXXIVd. Liver Histopathology for Positive Controls (Carbon Tetrachloride) - High Dose Female Mice (continued)

041	80	Hepatocellular carcinoma
042	78	Hepatocellular carcinoma
043	77	Hepatocellular carcinoma
044	73	Hepatocellular carcinoma
045	67	Hepatocellular carcinoma
046	64	Cannibalized
047	46	Hepatocellular carcinoma
048	43	Hepatocellular carcinoma
049	42	Hepatocellular carcinoma
050	36	Hepatocellular carcinoma

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