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**CARCINOGENESIS BIOASSAY OF
TRICHLOROETHYLENE**

CAS No. 79-01-6

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health



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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
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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.



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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'Aguzzo, 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.

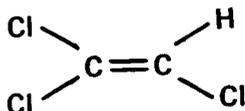
2.0 MATERIALS

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: GYGUIG
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 randomly¹ 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

¹Animals 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

| Group No. | Rats | | | | Mice | | | |
|-----------|---------------------------|----------------------------|-----------------------|---------|---------------------------|----------------------------|-----------------------|---------|
| | Dose (mg/kg) ^a | Concn (mg/ml) ^b | Survival ^c | | Dose (mg/kg) ^a | Concn (mg/ml) ^b | Survival ^c | |
| | | | Males | Females | | | 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 |

^amg Trichloroethylene/kg body weight.

^bmg Trichloroethylene/ml corn oil.

^cAt 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 matched¹ 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 randomly² 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; $6.6 \times 20/1000 = 0.13$ 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.

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

²Animals 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 Diabuta^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 | 650 | 60.0 | 7 | 7 ^c | |
| males and | 750 | 60.0 | 14 | 9 ^c | |
| females | 500 | 60.0 | 23 | 14 ^c | |
| | 500 | 60.0 | 37 | 48 ^d | |
| | no treatment | | 85 | 32 | 549 |
| High dose | 1300 | 60.0 | 7 | 7 ^c | |
| males and | 1500 | 60.0 | 14 | 9 ^c | |
| females | 1000 | 60.0 | 23 | 14 ^c | |
| | 1000 | 60.0 | 37 | 48 ^d | |
| | no treatment | | 85 | 32 | 1097 |
| Mice | | | | | |
| Low dose | 1000 | 15.0 | 5 | 6 ^c | |
| males | 1000 | 10.0 | 11 | 6 ^c | |
| | 1200 | 24.0 | 17 | 66 ^c | |
| | no treatment | | 83 | 12 | 1169 |
| High dose | 2000 | 15.0 | 5 | 6 ^c | |
| males | 2000 | 20.0 | 11 | 6 ^c | |
| | 2400 | 24.0 | 17 | 66 ^c | |
| | no treatment | | 83 | 12 | 2339 |
| Low dose | 700 | 10.0 | 5 | 12 ^c | |
| females | 900 | 18.0 | 17 | 66 ^c | |
| | no treatment | | 83 | 12 | 869 |
| High dose | 1400 | 10.0 | 5 | 6 ^c | |
| females | 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).

^aAge at initial dose or dose change.

^bTime-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.

^cDosing 5 days per week each week.

^dDosing 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.)

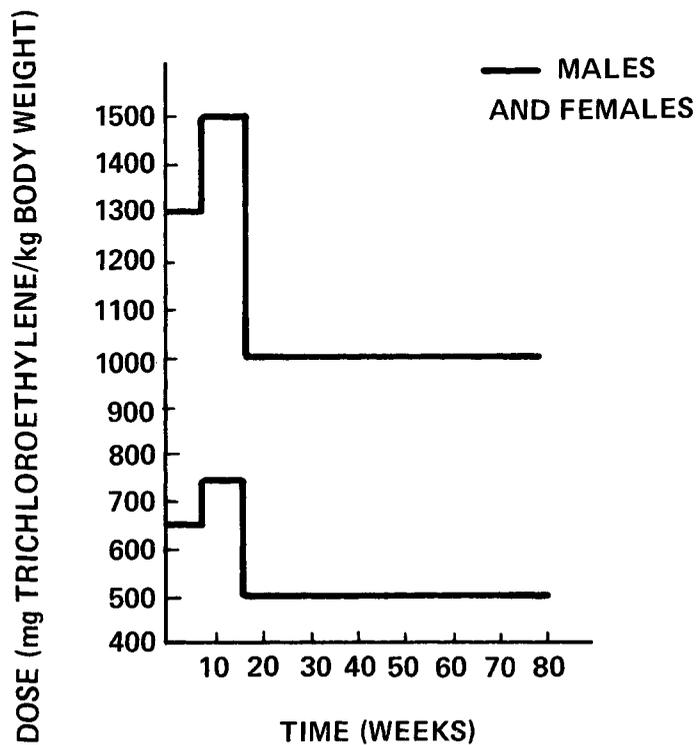


Figure 1a. Dosage Schedule - Chronic Study - Trichloroethylene-Treated Rats

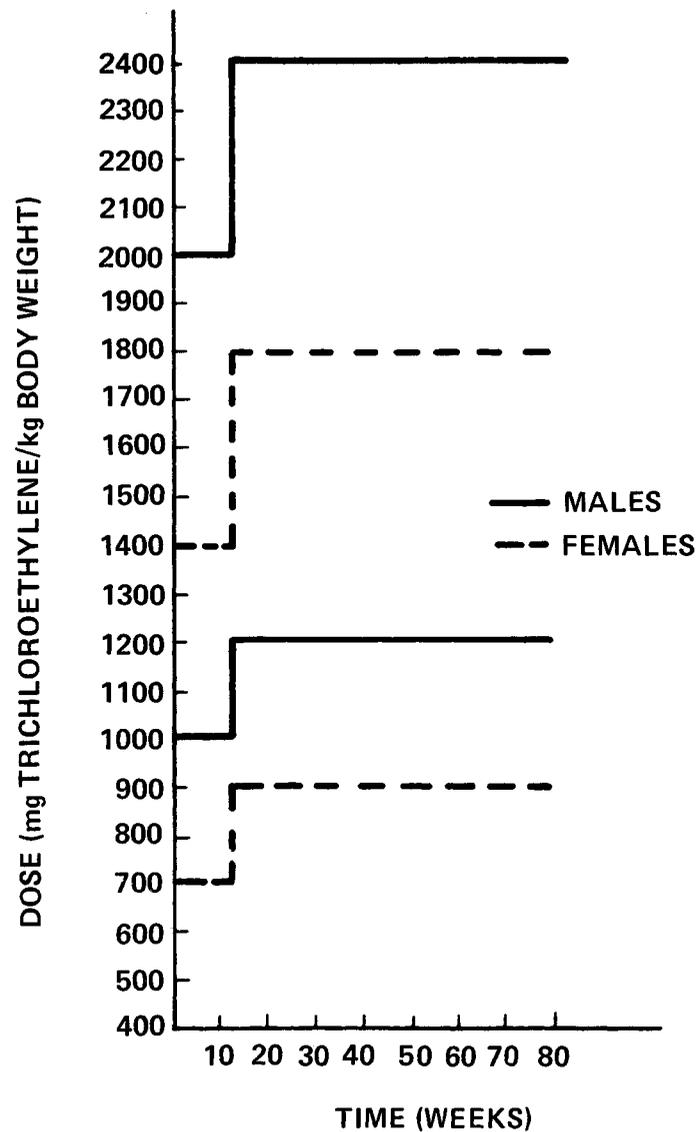


Figure 1b. Dosage Schedule - Chronic Study - Trichloroethylene-Treated Mice

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 throughout 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 |
| High dose males | 50 | 2.5 | 6 | 10 ^c | |
| | 100 | 5.0 | 16 | 68 ^c | |
| | no treatment | | | 84 | 32 |
| Low dose females | 100 | 10.0 | 6 | 14 ^c | |
| | 75 | 7.5 | 20 | 64 ^c | |
| | no treatment | | | 84 | 32 |
| High dose females | 200 | 10.0 | 6 | 14 ^c | |
| | 150 | 7.5 | 20 | 64 ^c | |
| | no treatment | | | 84 | 32 |
| Mice | | | | | |
| Low dose males and females | 1250 | 25.0 | 5 | 78 ^c | |
| | no treatment | | | 83 | 12 |
| High dose males and females | 2500 | 25.0 | 5 | 78 ^c | |
| | no treatment | | | 83 | 12 |

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).

^aAge at initial dose or dose change.

^bTime-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.

^cDosing 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% |

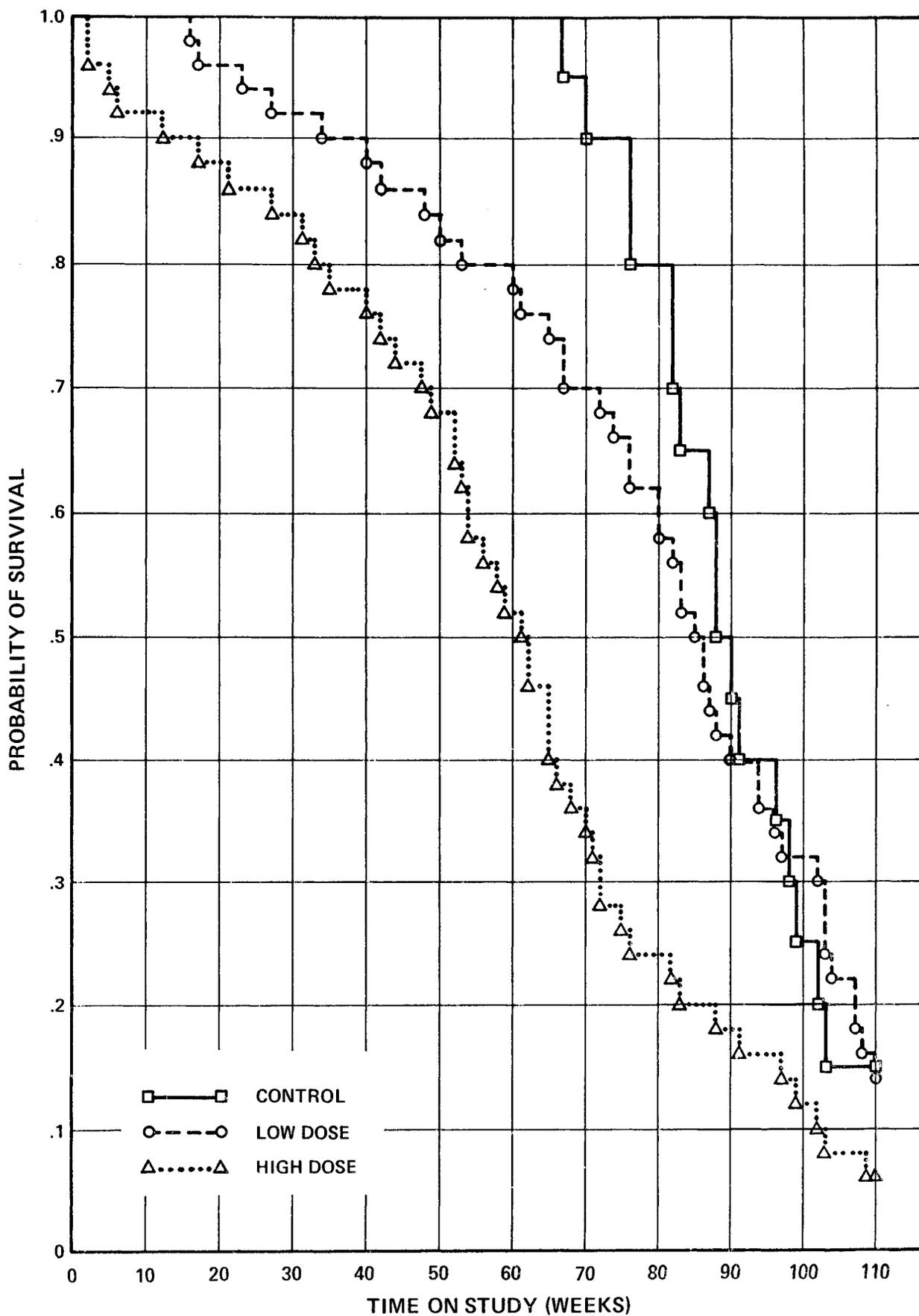


Figure 2a. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Male Rats

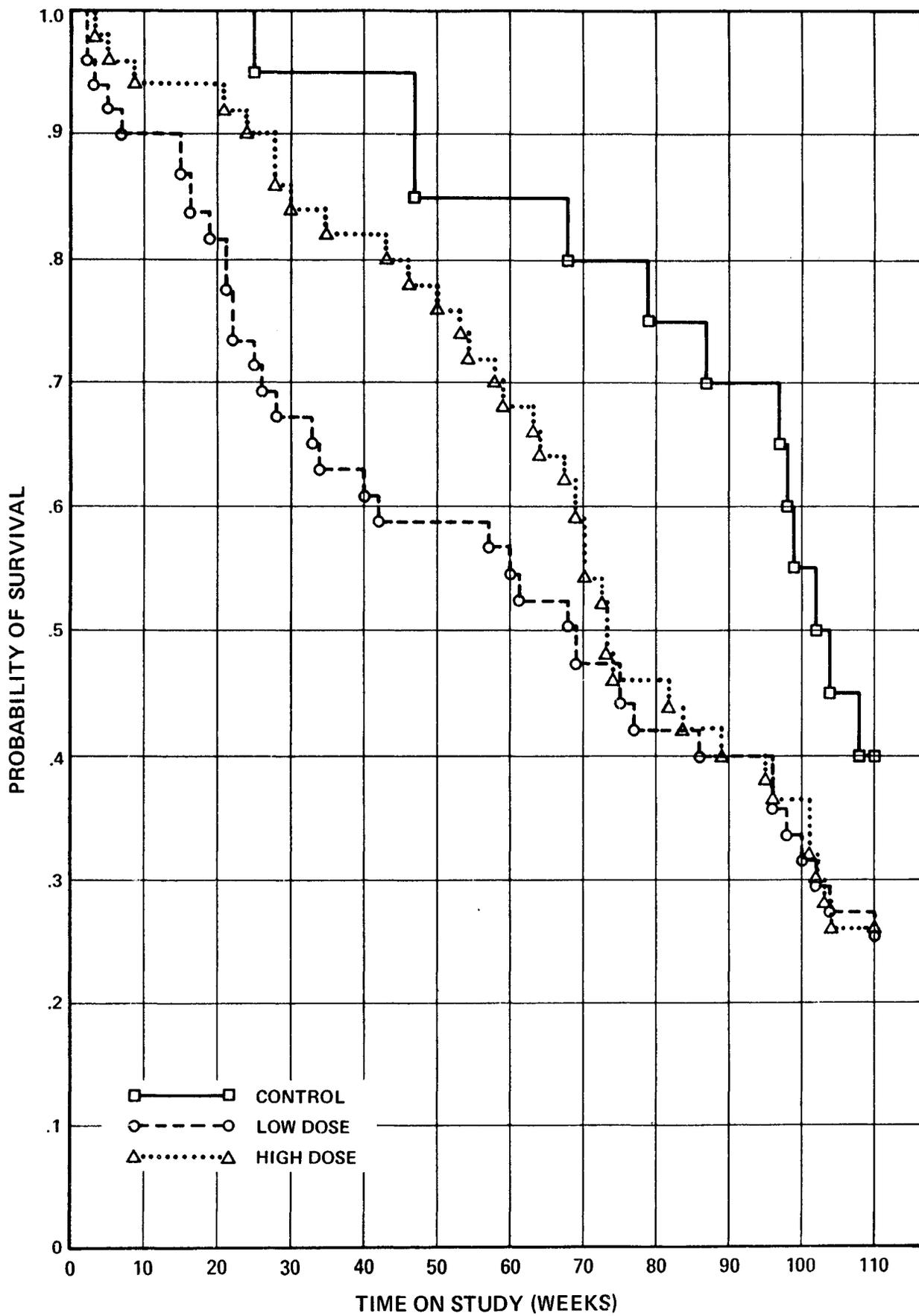


Figure 2b. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Female Rats

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

| Interval | Controls | | Trichloroethylene | | | | Carbon Tetrachloride | | | |
|-----------|----------|-----|-------------------|----|-----------|----|----------------------|----|-----------|----|
| | | | Low Dose | | High Dose | | Low Dose | | High Dose | |
| | 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

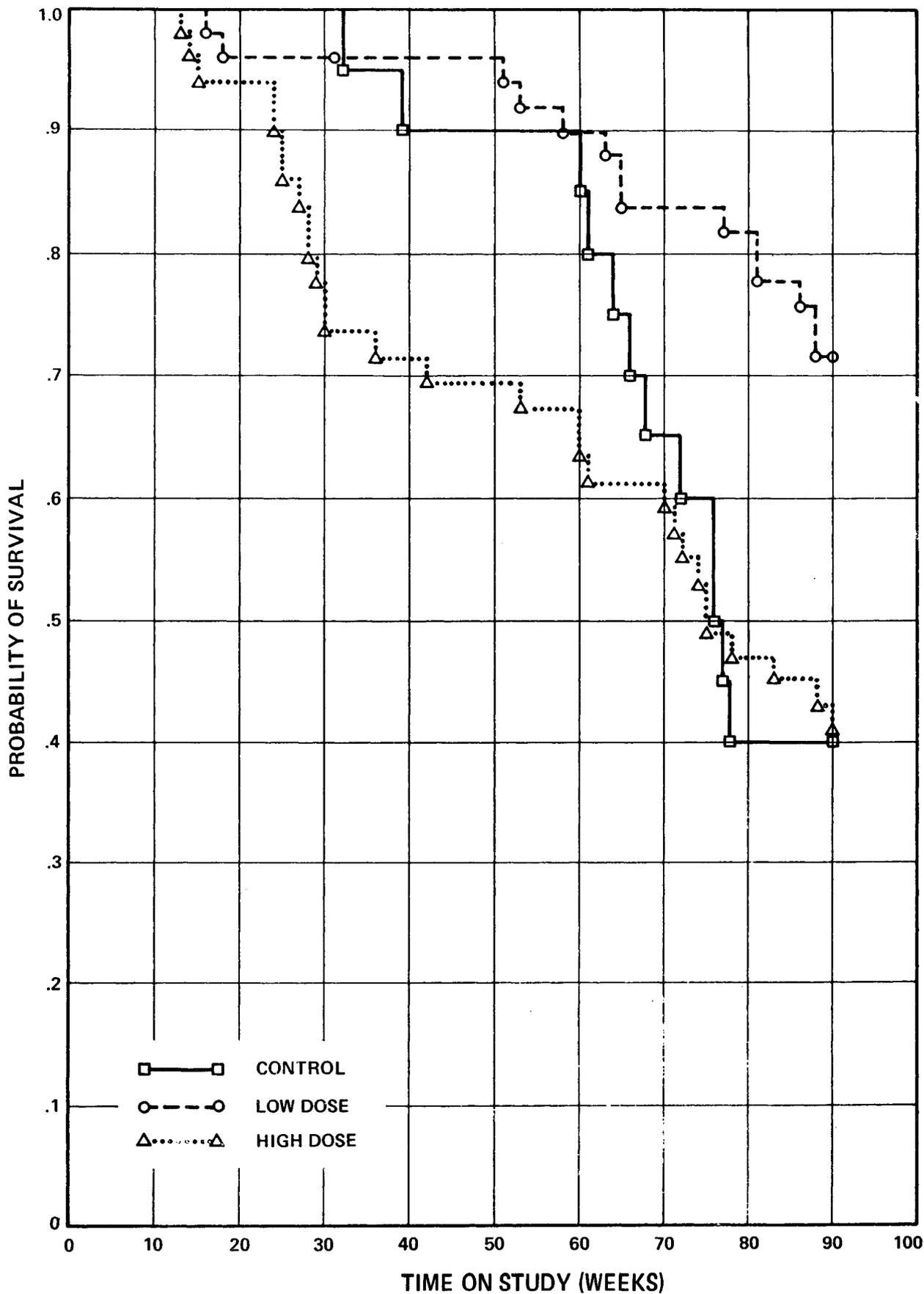


Figure 3a. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Male Mice

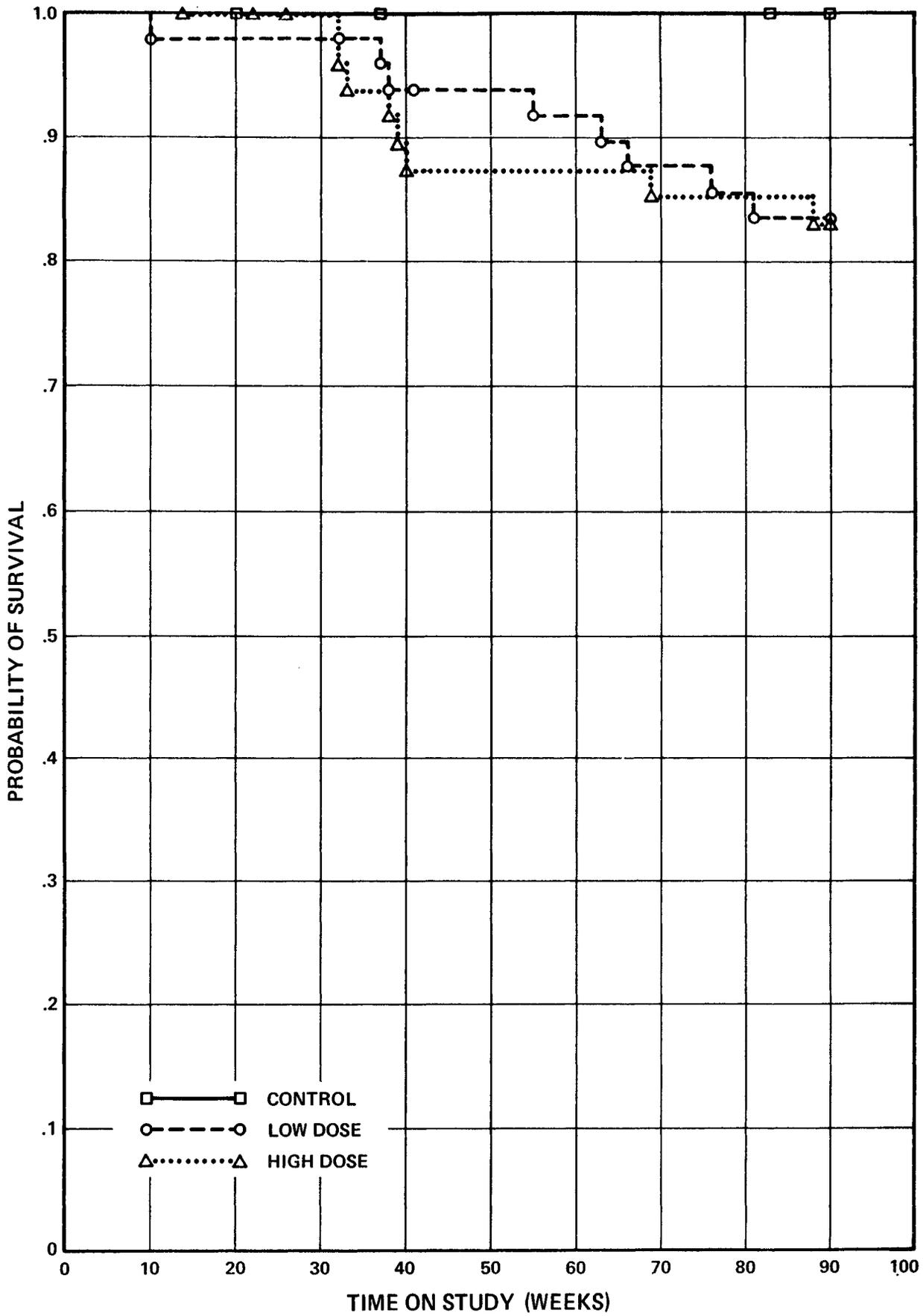


Figure 3b. Product-Limit Estimates of Probability of Survival - Trichloroethylene-Treated Female Mice

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

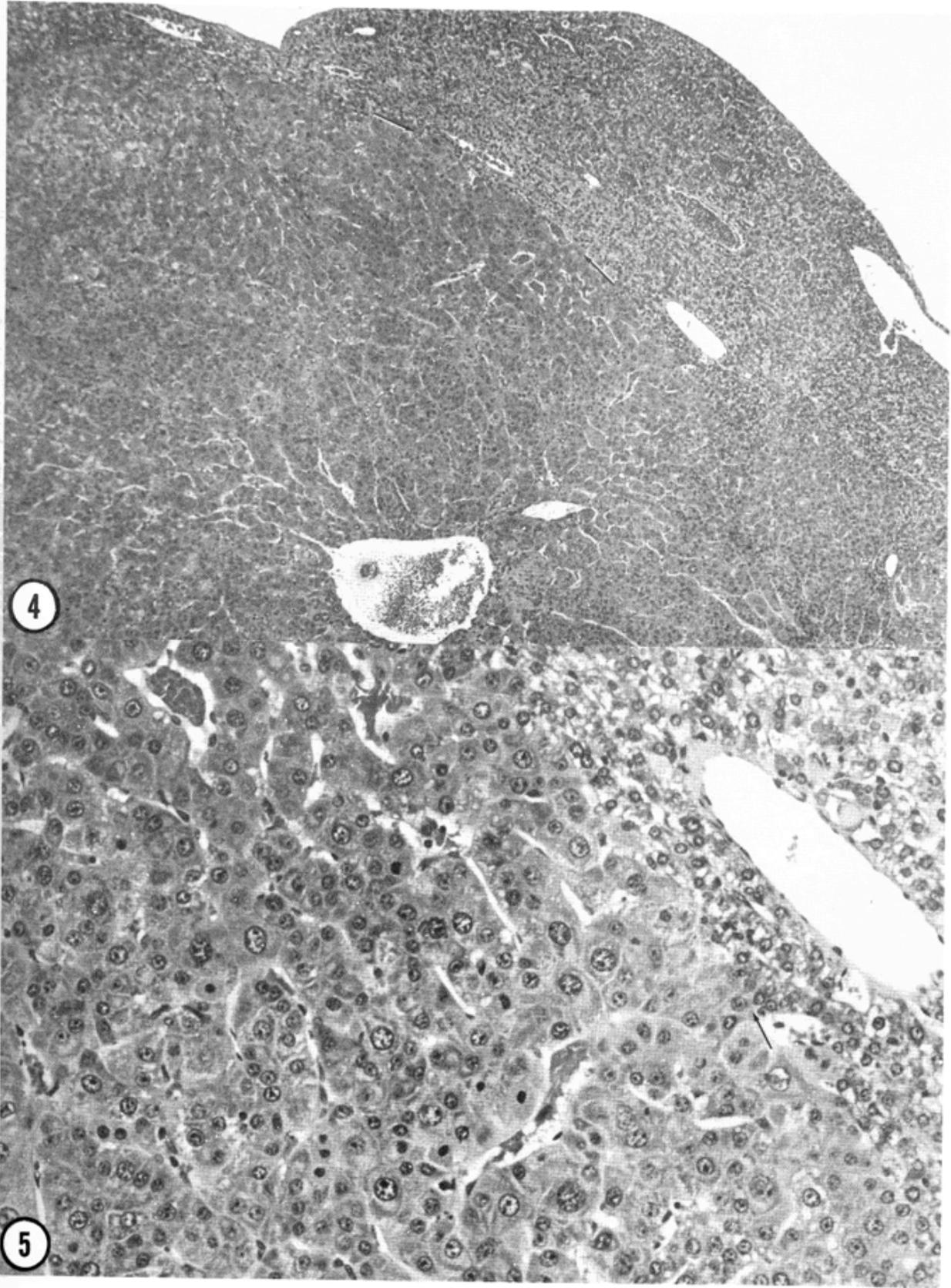
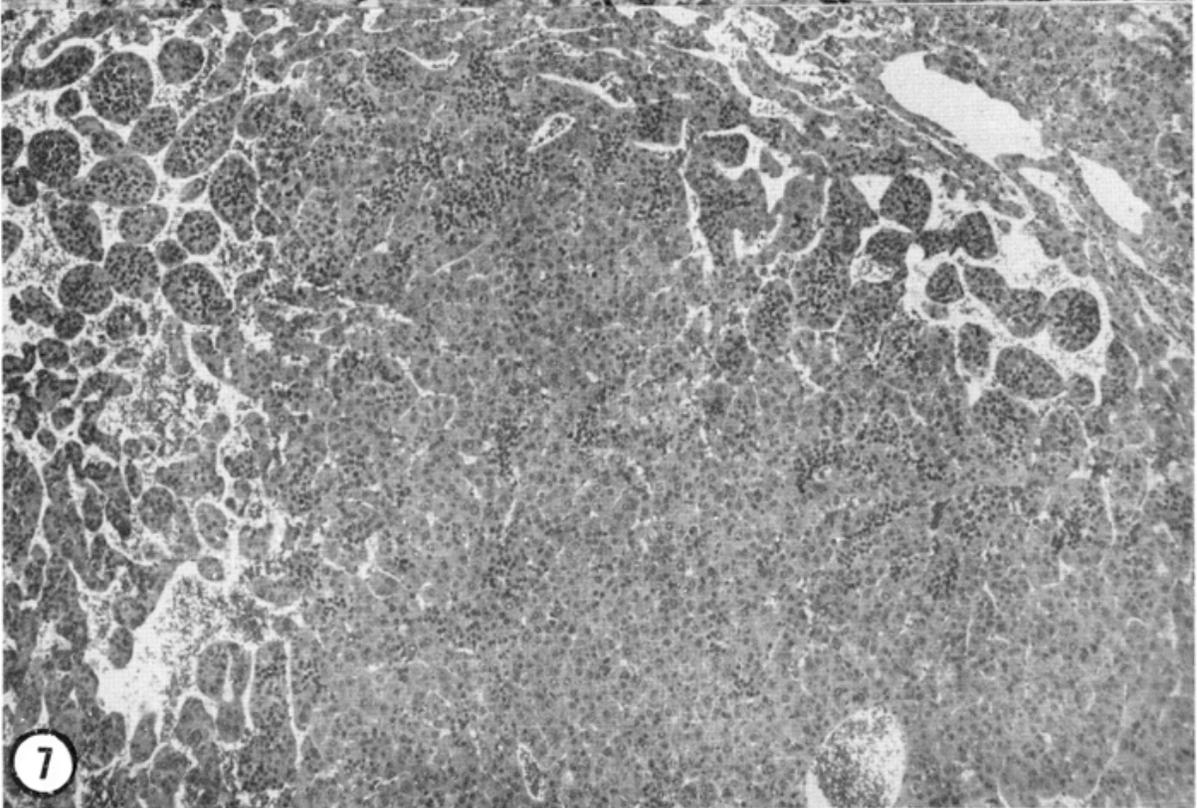
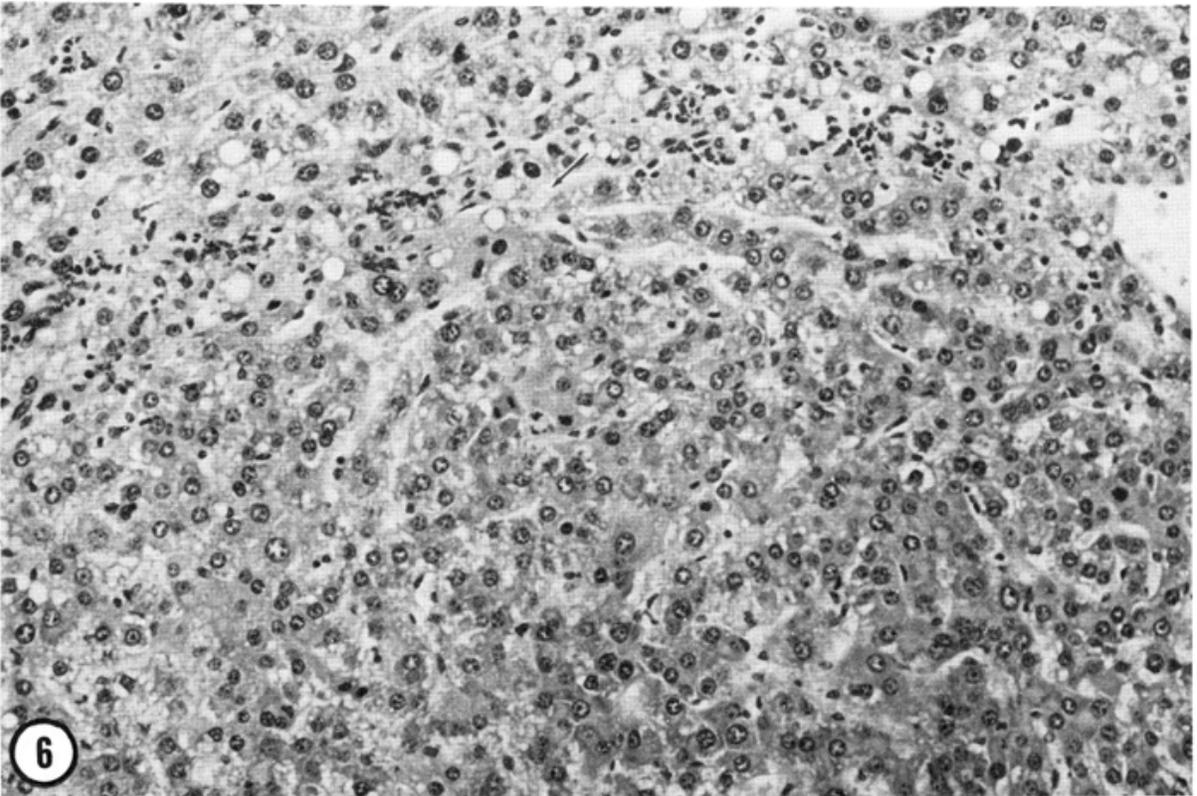
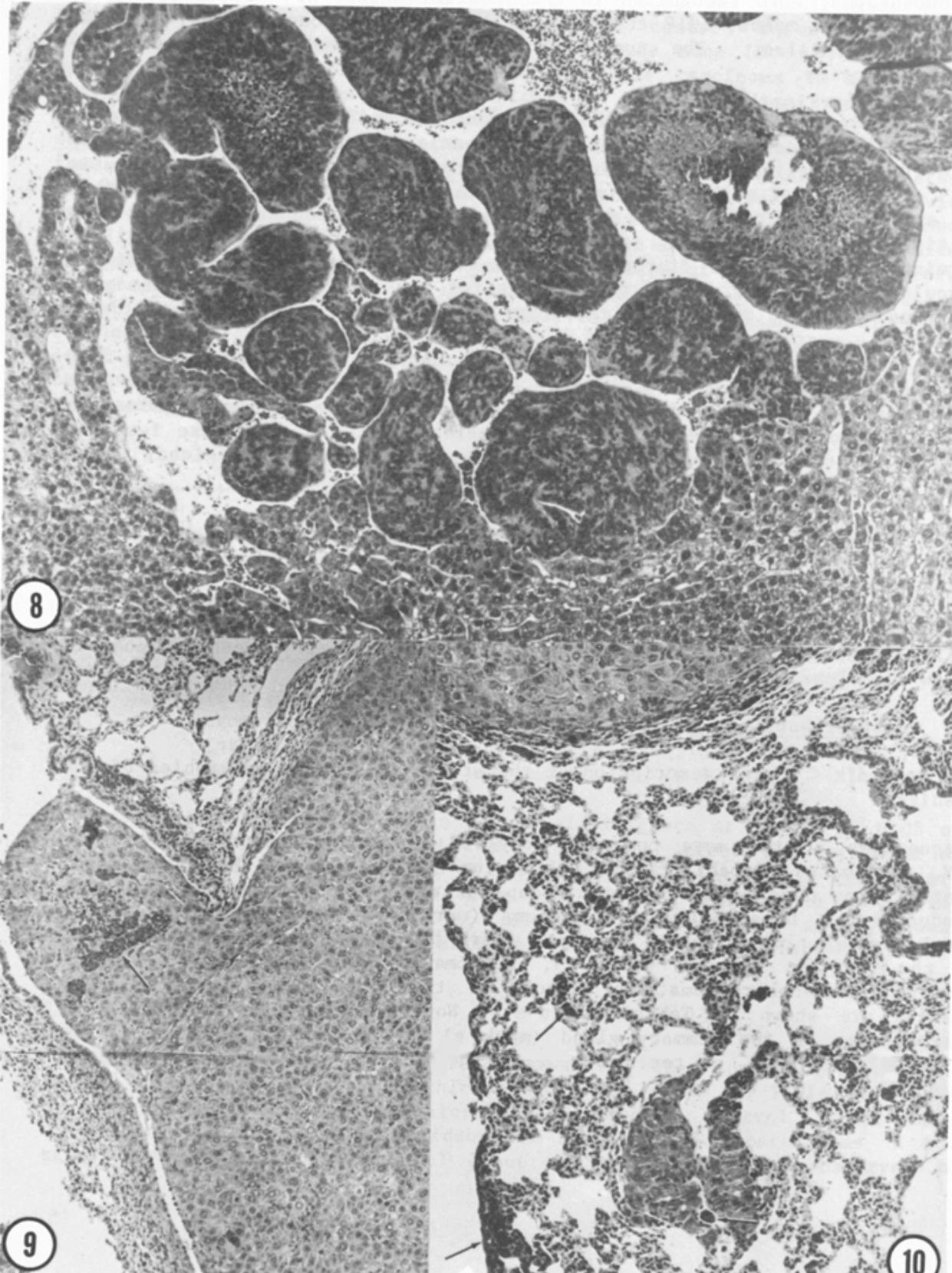


Figure 6. Primary hepatocellular carcinoma, mouse (high dose male #26). The rather anaplastic solid tumor has a recognizable boundary (->) with the pre-existent hepatic parenchyma. Mitoses are abundant. Hematoxylin and eosin, x240

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.



- 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



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

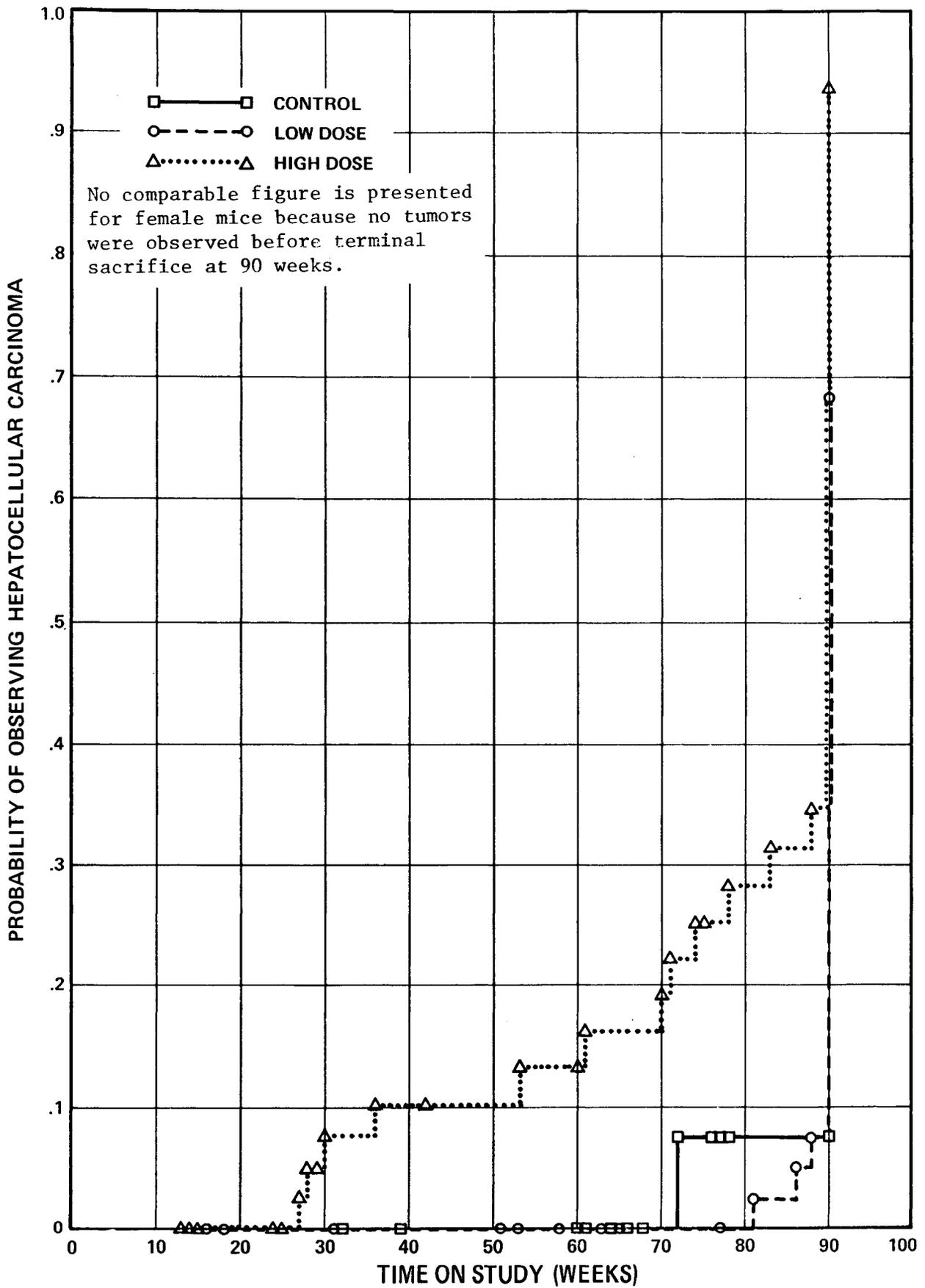


Figure 11. Product-Limit Estimates of Probability of Observing Hepatocellular Carcinoma - Trichloroethylene-Treated Male Mice

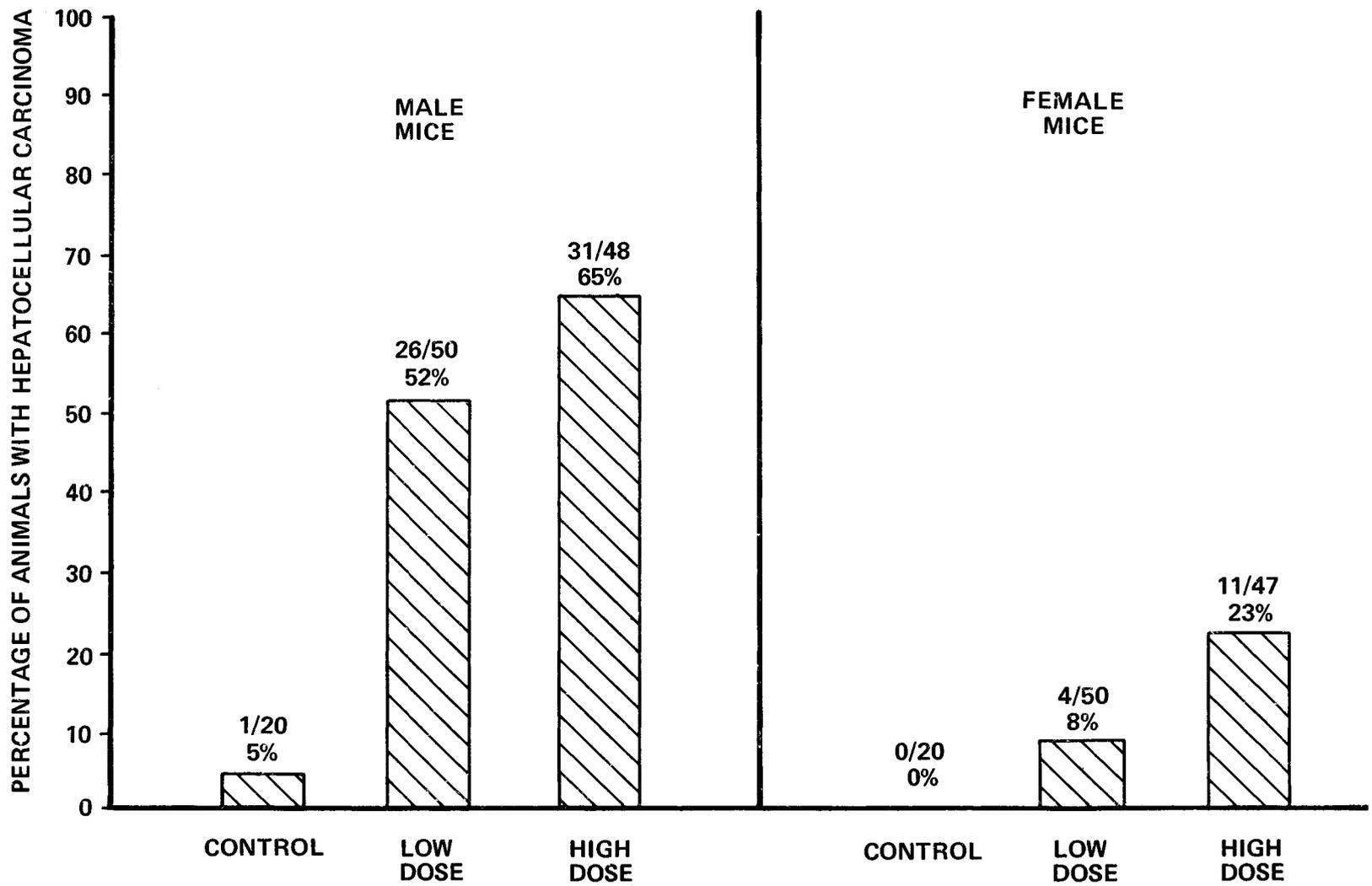


Figure 12. Comparison of Incidence of Hepatocellular Carcinoma in Trichloroethylene-Treated Male and Female Mice

other control groups, thus the significance of hepatocellular 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 |

^aMatched 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

| Interval | Controls | | Trichloroethylene | | | | Carbon Tetrachloride | | | |
|----------|----------|----|-------------------|----|-----------|----|----------------------|----|-----------|----|
| | | | Low Dose | | High Dose | | Low Dose | | High Dose | |
| | 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 XIIIa. Comparison of Hepatocellular Carcinoma Incidence
in Colony Controls - Vehicle-Treated and
Trichloroethylene- and Carbon Tetrachloride-Treated Mice

| Animals | Controls | Trichloroethylene | | Carbon Tetrachloride | |
|---------|----------|-------------------|-----------|----------------------|-----------|
| | | 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

| Animals | Controls | Trichloroethylene | | Carbon Tetrachloride | |
|---------|----------|-------------------|-----------|----------------------|-----------|
| | | 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, tinnitus, 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 LD₅₀ 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 10³ 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 |

^aA = 14,980

B = 11,010

C = 12,000

^bTrichloroethylene

Infrared Spectroscopy (Figure A1)

56

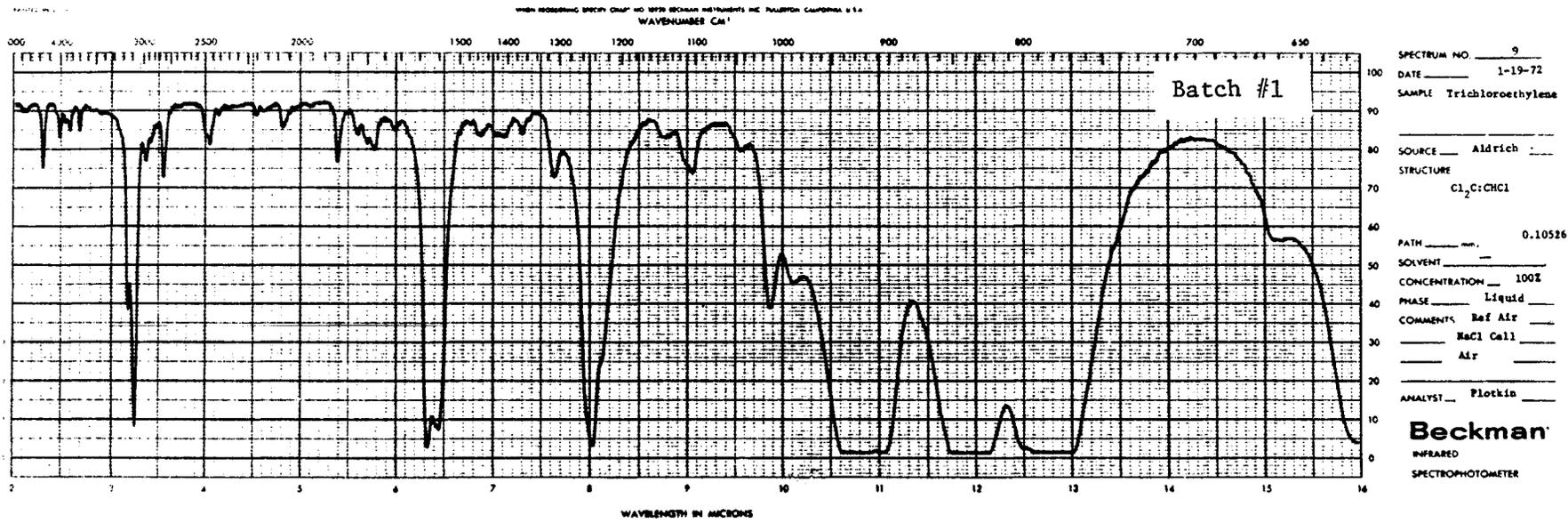


Figure A1. Infrared Spectrum of Trichloroethylene

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 1×16 to $10^3 \times 128$

Remarks: About 1.0 μ l 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 |

^aA = 48,670

B = 45,840

C = 50,320

^bTrichloroethylene

Infrared Spectroscopy (Figure A2)

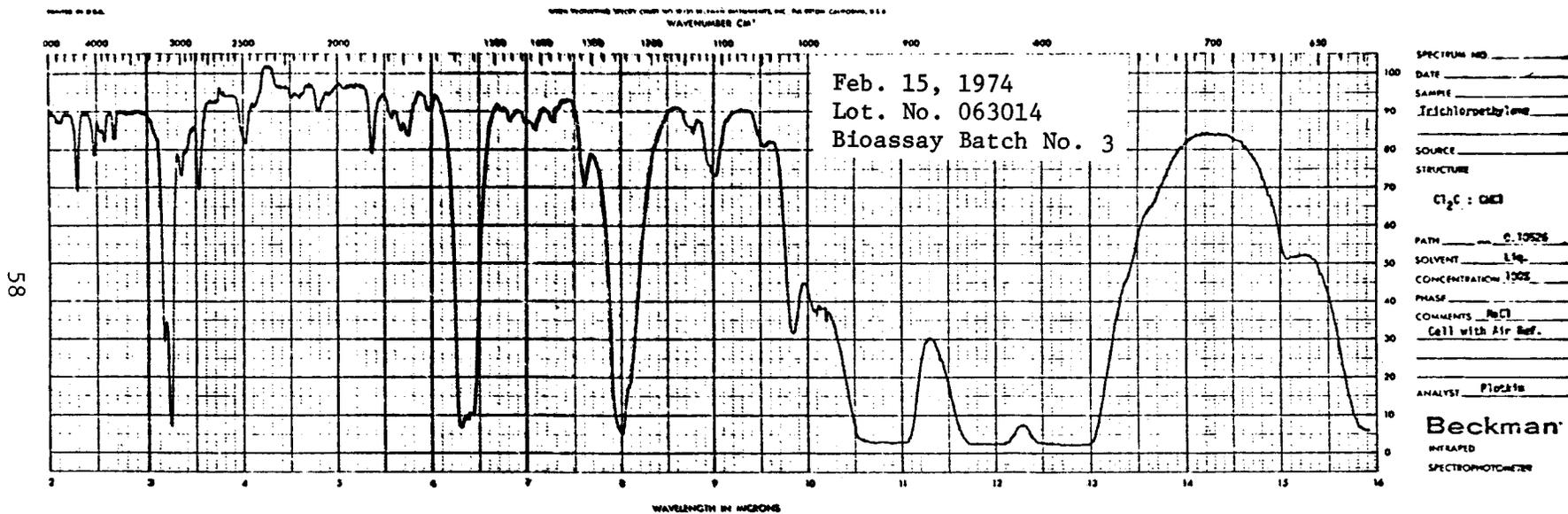


Figure A2. Infrared Spectrum of Trichloroethylene

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 1×16 to $10^4 \times 16$

Remarks: About 1.2 μ l 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 |

^aA = 116,250

B = 104,930

C = 112,000

^bTrichloroethylene

Infrared Spectroscopy (Figure A3)

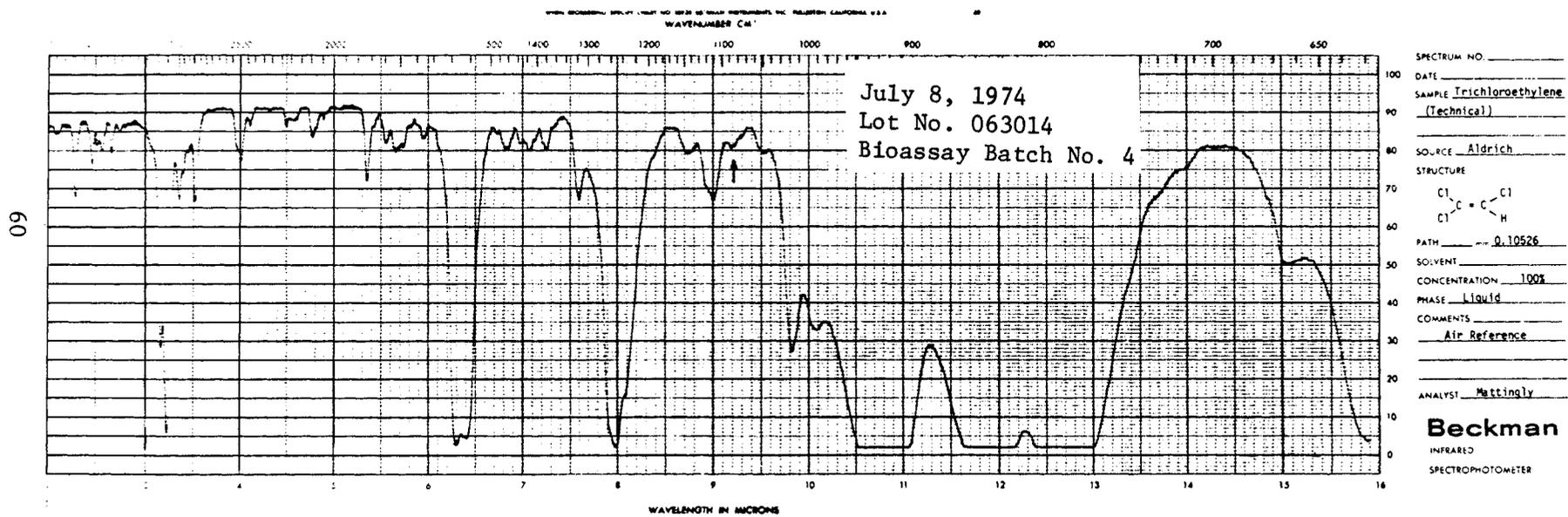


Figure A3. Infrared Spectrum of Trichloroethylene

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 10⁰/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 | trichloroethylene |
| 5 | 11.5 | 1.14 | 0.05 | <u>N</u> -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 impurities 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 | trichloroethylene |
| 5 | 6.0 | 2.50 | 0.27 | <u>N</u> -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 | <u>N</u> -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 | <u>N</u> -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, ⁶³Ni electron capture detection, oven temperature 190°C.

On injection of a 6 µl neat sample of trichloroethylene, 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 |

^aPeak notation the same as previously indicated.

^bEight 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" Na₂SO₄. 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 Snyder 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" Na₂SO₄. 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 | | | Surv. | Body Weight | | | Body Weight | | | | |
|-----------------------|---------------------------------|--------------|--|-------|---------------------------------|--------------|-------|---------------------------------|--------------|-------|--|-----|
| | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | Surv. | Mean (g) | Std Dev. (g) | Surv. | | |
| | <u>Group 1 (0 mg/kg/day)</u> | | | | <u>Group 2 (562 mg/kg/day)</u> | | | <u>Group 3 (1000 mg/kg/day)</u> | | | | |
| 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 | | | |
| | <u>Group 4 (1730 mg/kg/day)</u> | | | | <u>Group 5 (3160 mg/kg/day)</u> | | | <u>Group 6 (5620 mg/kg/day)</u> | | | | |
| 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 | | | Surv. | Body Weight | | | Surv. | Body Weight | | | |
|-----------------------|---------------------------------|--------------|--|-------|---------------------------------|--------------|--|-------|---------------------------------|--------------|--|-----|
| | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | |
| | <u>Group 1 (0 mg/kg/day)</u> | | | | <u>Group 2 (562 mg/kg/day)</u> | | | | <u>Group 3 (1000 mg/kg/day)</u> | | | |
| 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 | | | |
| | <u>Group 4 (1730 mg/kg/day)</u> | | | | <u>Group 5 (3160 mg/kg/day)</u> | | | | <u>Group 6 (5620 mg/kg/day)</u> | | | |
| 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 | 9.2 | | 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 | | | Surv. | Body Weight | | | Body Weight | | | | |
|-----------------------|---------------------------------|--------------|--|-------|---------------------------------|--------------|--|-----------------------------------|--------------|-----|--|-----|
| | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | Mean (g) | Std Dev. (g) | | | |
| | <u>Group 1 (0 mg/kg/day)</u> | | | | <u>Group 2 (1000 mg/kg/day)</u> | | | <u>Group 3 (1780 mg/kg/day)</u> | | | | |
| 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 | | | |
| | <u>Group 4 (3160 mg/kg/day)</u> | | | | <u>Group 5 (5620 mg/kg/day)</u> | | | <u>Group 6 (10,000 mg/kg/day)</u> | | | | |
| 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 | | | Surv. | Body Weight | | | Surv. | Body Weight | | | |
|-----------------------|---------------------------------|--------------|--|-------|---------------------------------|--------------|--|-------|-----------------------------------|--------------|--|-----|
| | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | |
| | <u>Group 1 (0 mg/kg/day)</u> | | | | <u>Group 2 (1000 mg/kg/day)</u> | | | | <u>Group 3 (1780 mg/kg/day)</u> | | | |
| 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 | | | |
| | <u>Group 4 (3160 mg/kg/day)</u> | | | | <u>Group 5 (5620 mg/kg/day)</u> | | | | <u>Group 6 (10,000 mg/kg/day)</u> | | | |
| 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 | | | | Low Dose | | | | High Dose | | | |
|--------------------------|--------------------------|-----------------|--------------------------|------------------------------|-------------|-----------------|-------------|------------------------------|-------------|-----------------|-------------|------------------------------|
| | Body Weight ^a | | Food ^b (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed |
| | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | |
| 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 |

^aCalculated using individual animal weight.

^bAverage 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 (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed |
| | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | | Mean (g) | Std Dev. (g) | | |
| 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 |

^aCalculated using individual animal weight.

^bAverage 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 (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed |
| Mean (g) | Std Dev. (g) | Mean (g) | | | Std Dev. (g) | Mean (g) | | | Std Dev. (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 |

^aCalculated using individual animal weight.

^bAverage weight per animal per week.

Table XVIIb. 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 (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed | Body Weight | | Food (g) | No. of Animals Weighed |
| Mean (g) | Std Dev. (g) | Mean (g) | | | Std Dev. (g) | Mean (g) | | | Std Dev. (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 |

^aCalculated using individual animal weight.

^bAverage weight per animal per week.

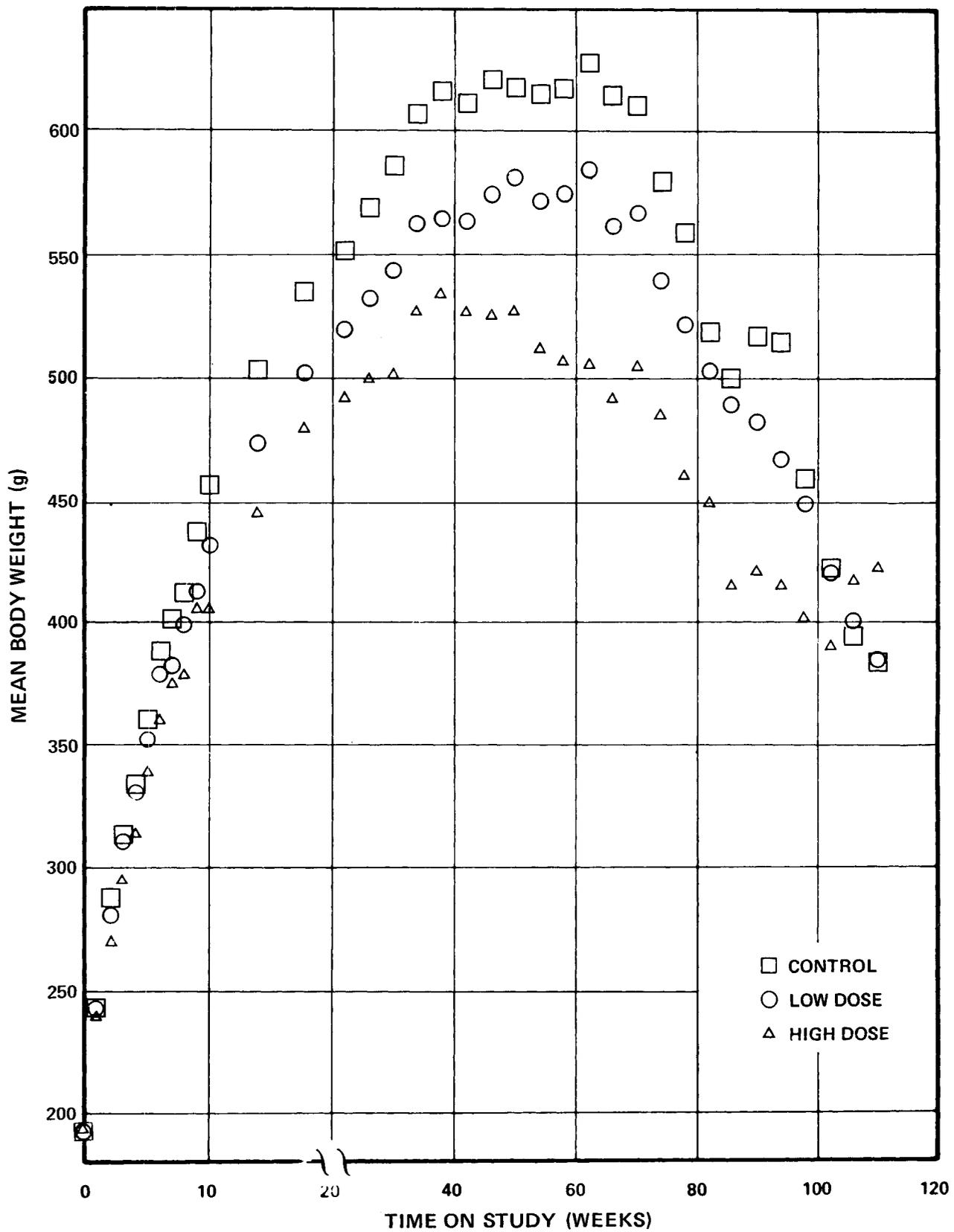


Figure 13a. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Male Rats

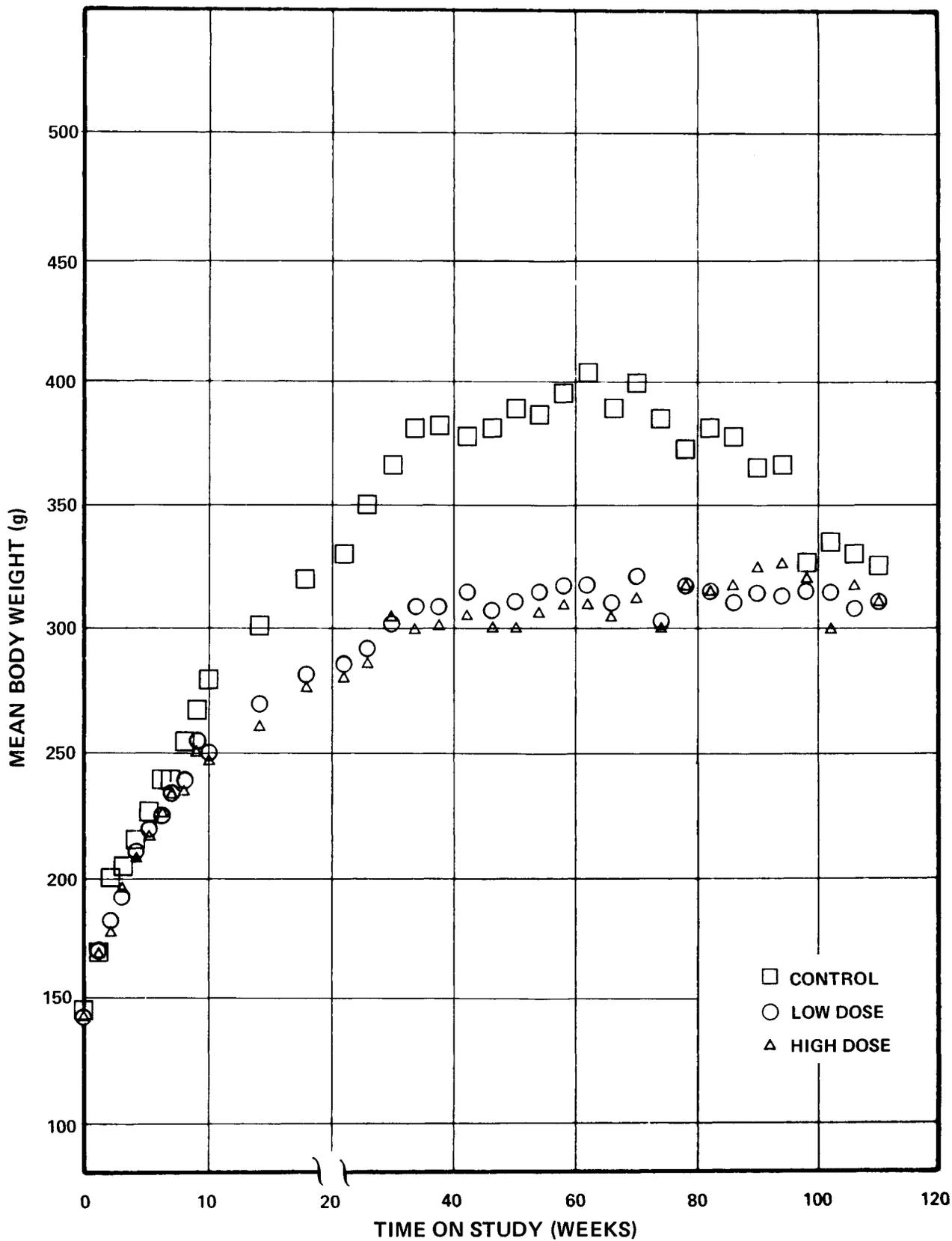


Figure 13b. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Female Rats

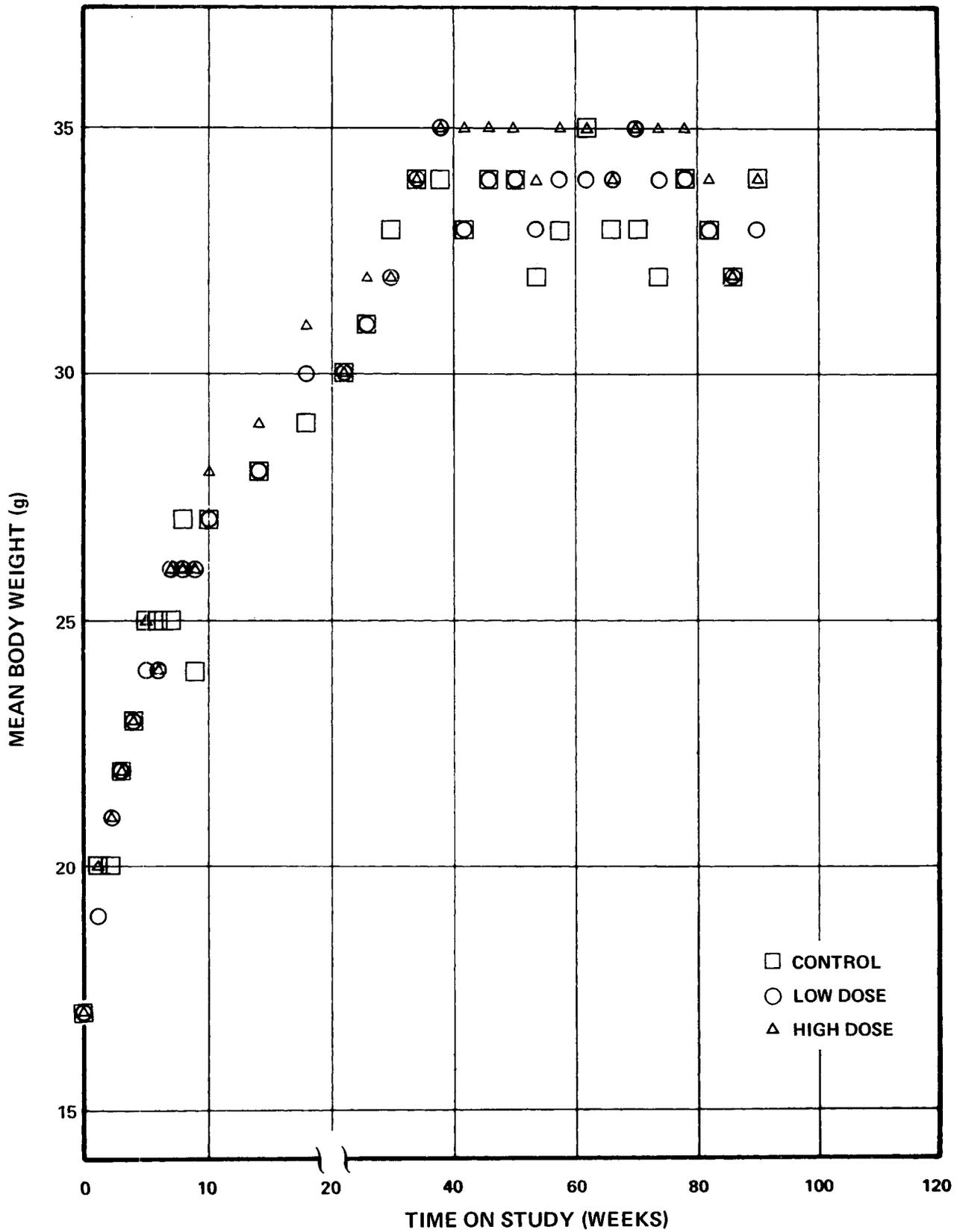


Figure 14a. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Male Mice

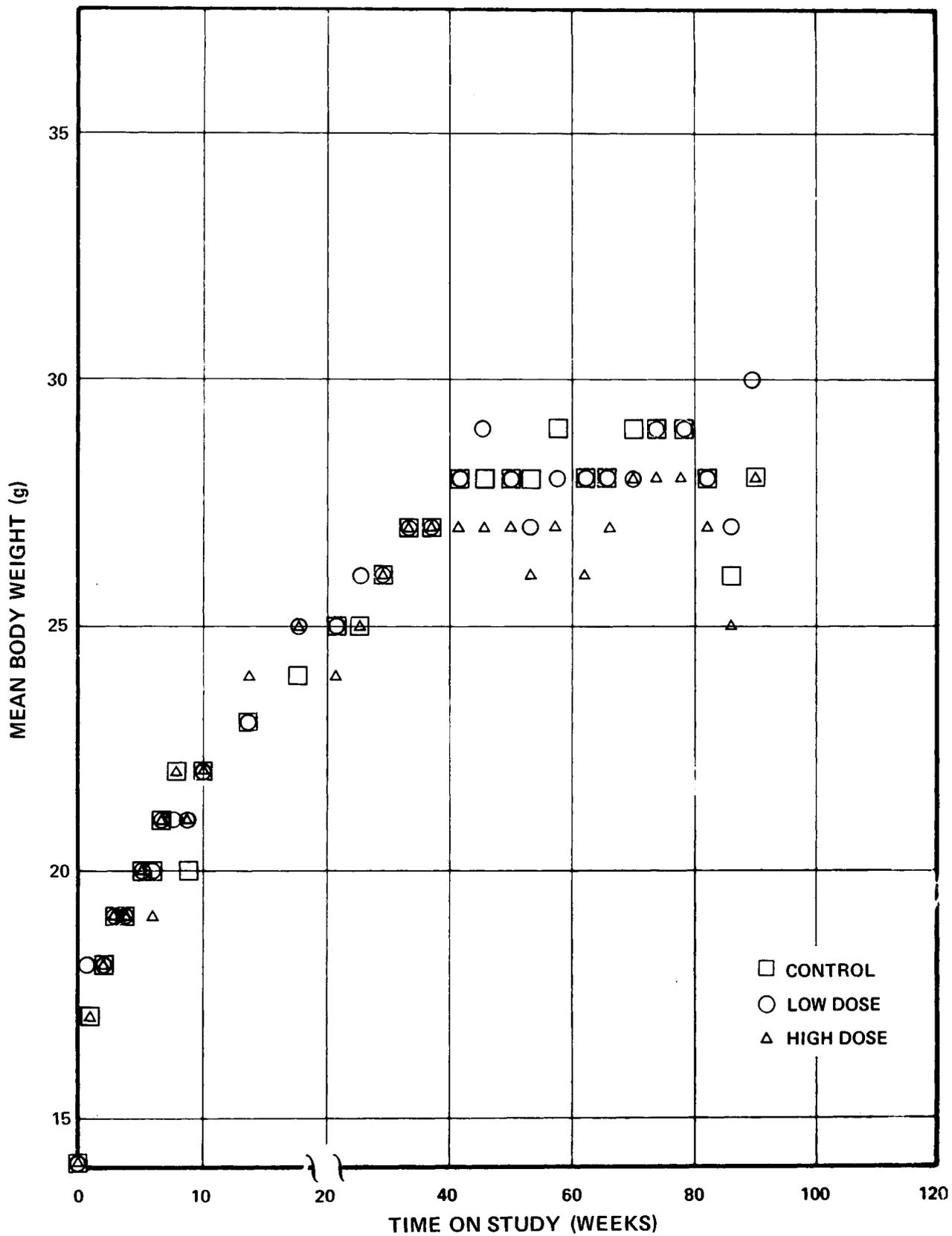


Figure 14b. Mean Body Weight vs. Time on Study - Trichloroethylene-Treated Female Mice

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:

| | <u>Lower Dose</u> | <u>Higher Dose</u> | <u>Total</u> |
|-----------------------------|-------------------|--------------------|--------------|
| 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:

| | <u>Control</u> | <u>Low Dose</u> | <u>High Dose</u> | <u>Total</u> |
|-----------------------------|----------------|-----------------|------------------|--------------|
| 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:

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

The contribution to V from each table is:

$$((d_0^2 A_0 + d_1^2 A_1 + d_2^2 A_2) - (d_0 A_0 + d_1 A_1 + d_2 A_2)^2) (M(N-M)/N-1), \text{ where } A_j = N_j/N,$$

for $j = 0, 1, \text{ or } 2$.

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 = i th dosage and M_i = number of animals with the tumor in the i th 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 | j1 | 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 | |
| * Animal's observed | | | 83 | 38 | | 58 | 47 | |
| lifetime censored | | | 83 | 43 | | 59 | 9 | |
| by scheduled sacri- | | | 85 | 1 | | 61 | 29 | |
| fice, accidental | | | 86 | 14 | | 62 | 7 | |
| killing or loss. | | | 86 | 20 | | 62 | 38 | |
| Absence of * means | | | 87 | 29 | | 65 | 11 | p |
| natural death or | | | 88 | 12 | | 65 | 28 | |
| moribund sacrifice. | | | 90 | 15 | m | 65 | 45 | |
| | | | 94 | 25 | n | 66 | 49 | |
| | | | 94 | 49 | | 68 | 10 | |
| - Histopathology not | | | 96 | 21 | | 70 | 20 | |
| performed. | | | 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 | |

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 | |
| * Animal's observed | | | 57 | 6 | | 70 | 20 | |
| lifetime censored | | | 60 | 10 | | 72 | 14 | |
| by scheduled sacrifice, | | | 61 | 44 | | 73 | 1 | |
| accidental killing or loss. | | | 68 | 27 | | 73 | 42 | |
| Absence of * means | | | 69 | 25 | | 74 | 39 | |
| natural death or | | | 75 | 15 | | 82 | 26 | |
| moribund sacrifice. | | | 75 | 16 | b | 86 | 48 | |
| | | | 77 | 48 | | 89 | 47 | |
| | | | 86 | 34 | | 95 | 21 | |
| | | | 96 | 23 | w | 96 | 50 | t |
| - Histopathology not | | | 96 | 46 | | 101 | 29 | g |
| performed. | | | 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 |

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 |
| * Animal's observed | | | 90* | 15 | | 90* | 14 | |
| lifetime censored | | | 90* | 21 | | 90* | 15 | d |
| by scheduled sacri- | | | 90* | 22 | | 90* | 16 | |
| fice, accidental | | | 90* | 23 | | 90* | 17 | |
| killing or loss. | | | 90* | 24 | | 90* | 18 | b |
| Absence of * means | | | 90* | 25 | | 90* | 19 | |
| natural death or | | | 90* | 26 | | 90* | 21 | |
| moribund sacrifice. | | | 90* | 27 | c | 90* | 22 | b |
| | | | 90* | 28 | | 90* | 23 | d |
| | | | 90* | 31 | | 90* | 24 | a |
| - Histopathology not | | | 90* | 32 | a | 90* | 25 | ac |
| performed. | | | 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 | |

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 |
| j = Week on study | | | | 80 | 31 | 29 | .580 | 54 | 31 | 29 | .580 |
| n = No. of animals | | | | 82 | 29 | 28 | .560 | 56 | 29 | 28 | .560 |
| alive at beginning | | | | 83 | 28 | 26 | .520 | 58 | 28 | 27 | .540 |
| of the week | | | | 85 | 26 | 25 | .500 | 59 | 27 | 26 | .520 |
| n' = No. of animals | | | | 86 | 25 | 23 | .460 | 61 | 26 | 25 | .500 |
| surviving the week | | | | 87 | 23 | 22 | .440 | 62 | 25 | 23 | .460 |
| P = Kaplan-Meier | | | | 88 | 22 | 21 | .420 | 65 | 23 | 20 | .400 |
| estimate of sur- | | | | 90 | 21 | 20 | .400 | 66 | 20 | 19 | .380 |
| vival probability | | | | 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 |

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 | | | | 42 | 29 | 28 | .587 | 63 | 34 | 33 | .660 |
| alive at beginning | | | | 57 | 28 | 27 | .566 | 64 | 33 | 32 | .640 |
| of the week | | | | 60 | 27 | 26 | .545 | 67 | 32 | 31 | .620 |
| | | | | 61 | 26 | 25 | .524 | 69 | 31 | 29 | .580 |
| n' = No. of animals | | | | 68 | 25 | 24 | .503 | 70 | 29 | 27 | .540 |
| surviving the week | | | | 69 | 24 | 23 | .482 | 72 | 27 | 26 | .520 |
| | | | | 75 | 23 | 21 | .441 | 73 | 26 | 24 | .480 |
| P = Kaplan-Meier | | | | 77 | 21 | 20 | .420 | 74 | 24 | 23 | .460 |
| estimate of sur- | | | | 86 | 20 | 19 | .399 | 82 | 23 | 22 | .440 |
| vival probability | | | | 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

| Comparison | Male Mice | | | | Female Mice | | | |
|------------------------|-----------|-------|-------|-------|-------------|------|------|-------|
| | 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 |

^aIncludes 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

| Comparison | Male Rats | | | | Female Rats | | | |
|------------------------|-----------|------|---|---|-------------|------|-------|-------|
| | 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

| Comparison | Male Rats | | | | Female Rats | | | |
|------------------------|-----------|------|---|---|-------------|------|------|-------|
| | 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

| Comparison | Male Rats | | | | Female Rats | | | |
|------------------------|-----------|------|-------|-------|-------------|------|-------|-------|
| | 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 XXIIIId. Statistical Tests Comparing Estimated Probability of Observing Follicular Adenocarcinoma of the Thyroid (Mark p) among Control and Trichloroethylene-Treated Rats

| Comparison | Male Rats | | | | Female Rats | | | |
|------------------------|-----------|------|------|-------|-------------|------|------|-------|
| | 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

| Comparison | Male Rats | | | | Female Rats | | | |
|------------------------|-----------|------|---|---|-------------|------|-------|-------|
| | 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

| Comparison | Male Rats | | | | Female Rats | | | |
|---|------------|-------------|------------|------------|-------------|------------|------------|------------|
| | Veh. Cont. | Low Dose | High Dose | Exact Test | Veh. Cont. | Low Dose | High Dose | Exact Test |
| | r/n | r/n | r/n | P | r/n | r/n | r/n | P |
| Dose-Response Veh. Control | 1/99 1% | 0/50 0% | 0/50 0% | 1.000 | 0/98 0% | 0/48 0% | 0/50 0% | 1.000 |
| Dosed vs. Veh. Control | 1/99 1% | 0/100 0% | | 1.000 | 0/98 0% | 0/98 0% | | 1.000 |
| Low Dose vs. Veh. Control | 1/99 1% | 0/50 0% | | 1.000 | 0/98 0% | 0/48 0% | | 1.000 |
| High Dose vs. Veh. Control | 1/99 1% | | 0/50 0% | 1.000 | 0/98 0% | | 0/50 0% | 1.000 |
| High Dose vs. Low Dose | | 0/50 0% | 0/50 0% | 1.000 | | 0/48 0% | 0/50 0% | 1.000 |
| Comparison | Chi-square | df | P | Chi-square | df | P | | |
| Among High Dose, Low Dose and Vehicle Control | | | | | | | | |
| Dose-Response Trend | 1.02 | 2 | 1.000 | 1.00 | 2 | 1.000 | | |
| Vehicle Control Deviation from Trend | 0.83 | 1 | 0.749 | 1.00 | 1 | 1.000 | | |
| 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

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

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

| Comparison | Male Rats | | | | | Female Rats | | | | |
|-----------------------------|-------------|------------|------------|-------------|------------|-------------|------------|-------------|--------------|------------|
| | Untr. Cont. | Veh. Cont. | Low Dose | High Dose | Exact Test | Untr. Cont. | Veh. Cont. | Low Dose | High Dose | Exact Test |
| | 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 |

^aIncludes 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

| Comparison | Male Mice | | | | Female Mice | | | |
|------------------------|-----------|-------|------|-------|-------------|------|------|-------|
| | 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

| Comparison | Male Mice | | | | Female Mice | | | |
|------------------------|-----------|------|-------|-------|-------------|------|------|-------|
| | 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

| Comparison | Male Mice | | | | Female Mice | | | |
|------------------------|-----------|------|------|-------|-------------|------|------|-------|
| | 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 XXVIId. Statistical Tests Comparing Estimated Probability of Observing Adenoma of the Lung (Mark d) among Control and Trichloroethylene-Treated Mice

| Comparison | Male Mice | | | | Female Mice | | | |
|------------------------|-----------|------|-------|-------|-------------|------|-------|-------|
| | 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

| Comparison | Male Mice | | | | Female Mice | | | |
|------------------------|-----------|------|-------|-------|-------------|------|------|-------|
| | 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

| Comparison | Male Mice | | | | | Female Mice | | | | |
|-----------------------------|-------------|------------|--------------|--------------|------------|-------------|------------|------------|--------------|------------|
| | Untr. Cont. | Veh. Cont. | Low Dose | High Dose | Exact Test | Untr. Cont. | Veh. Cont. | Low Dose | High Dose | Exact Test |
| | 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 | High | Low | High |
| | | | Dose | Dose | Dose | 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 | High | Low | High |
| | | | Dose | Dose | Dose | 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 |
| <u>INTEGUMENTARY SYSTEM</u> | | | | | | |
| Skin | | 3 | 1 | | 2 | |
| Pilomatrixoma | | | 1 | | | |
| Subcutaneous Tissue | | | 1 | | | |
| Liposarcoma | | 3 | | | 2 | |
| Fibroma | | 1 | | | 1 | |
| Fibrosarcoma | | 1 | | | 1 | |
| Squamous-Cell Carcinoma | | 1 | | | | |
| <u>RESPIRATORY SYSTEM</u> | | | | | | |
| Lung | 1 | | | | | |
| Adenosquamous Carcinoma | 1 | | | | | |
| <u>CIRCULATORY SYSTEM</u> | | | | | | |
| Subcutaneous Tissue | 1 | 1 | 2 | | 1 | |
| Hemangiosarcoma | | 1 | | | | |
| Multiple Organs | | 1 | | | | |
| Hemangiosarcoma | | | | | 1 | |
| Pancreas | | | 1 | | | |
| Hemangiosarcoma | | | 1 | | | |
| Spleen | 1 | | 1 | | | |
| Hemangiosarcoma | 1 | | 1 | | | |
| <u>DIGESTIVE SYSTEM</u> | | | | | | |
| 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 | | | | | | |
| Kidney | 2 | 2 | | | | |
| Malignant Mixed Tumor | 2 | | | | | |
| Tubular Adenocarcinoma | | 1 | | | | |
| Hamartoma | 1 | 1 | | | | |
| ENDOCRINE SYSTEM | | | | | | |
| Pituitary | 1 | 2 | 1 | 4 | 3 | 7 |
| 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 | | | | | | |
| Multiple Organs | | | | 1 | 1 | 1 |
| Reticulum-Cell Sarcoma | | | | | 1 | |
| Spleen | | | | 1 | | |
| Reticulum-Cell Sarcoma | | | | 1 | | |
| Thymus | | | | | | 1 |
| Reticulum-Cell Sarcoma | | | | | | 1 |
| REPRODUCTIVE SYSTEM | | | | | | |
| Mammary Gland | | | | 5 | 6 | 7 |
| Fibroadenoma | | | | 4 | 5 | 7 |
| Adenocarcinoma | | | | 3 | 5 | 7 |
| Adenocarcinoma | | | | 1 | | |
| Uterus/Endometrium | | | | | 1 | 1 |
| Sarcoma | | | | | 1 | 1 |
| Ovary | | | | 1 | | |
| Granulosa-Cell Carcinoma | | | | 1 | | |

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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 |
| <u>NERVOUS SYSTEM</u> | | | | | | |
| Heart | | | 1 | | | |
| Aortic Body Tumor | | | 1 | | | |
| <u>MUSCULOSKELETAL SYSTEM</u> | | | | | | |
| None | | | | | | |
| <u>ALL OTHER SYSTEMS</u> | | | | | | |
| Abdomen | 1 | | | | | |
| Giant-Cell Tumor, Malignant | 1 | | | | | |
| <u>PRIMARY TUMOR SUMMARY</u> | | | | | | |
| Animals Examined | 20 | 50 | 50 | 20 | 48 | 50 |
| Animals with Benign Tumors | 2 | 3 | 2 | 6 | 8 | 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 | Control | Male Rats | | Control | Female Rats | |
|-----------------------------|---------|-----------|-----------|---------|-------------|-----------|
| | | Low Dose | High Dose | | Low Dose | High Dose |
| <u>INTEGUMENTARY SYSTEM</u> | | | | | | |
| Skin | | 4 | 1 | | 2 | |
| Pilomatrixoma | | | 1 | | | |
| Subcutaneous Tissue | | 4 | | | 2 | |
| Liposarcoma | | | | | 1 | |
| Hemangiosarcoma | | 1 | | | | |
| Fibroma | | 1 | | | 1 | |
| Fibrosarcoma | | 1 | | | | |
| Squamous-Cell Carcinoma | | 1 | | | | |
| <u>RESPIRATORY SYSTEM</u> | | | | | | |
| Lung | 1 | | | | 1 | |
| Hemangiosarcoma | | | | | 1 | |
| Adenosquamous Carcinoma | 1 | | | | | |
| <u>CIRCULATORY SYSTEM</u> | | | | | | |
| Heart | | | 1 | | 1 | |
| Hemangiosarcoma | | | 1 | | 1 | |
| Aortic Body Tumor | | | 1 | | | |
| <u>DIGESTIVE SYSTEM</u> | | | | | | |
| Liver | | | 1 | | 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 |
| <u>DIGESTIVE SYSTEM</u> | | | | | | |
| Liver | | | 1 | | 1 | |
| Reticulum-Cell Sarcoma | | | | | 1 | |
| Pancreas | | | 1 | | | |
| Hemangiosarcoma | | | 1 | | | |
| <u>URINARY SYSTEM</u> | | | | | | |
| Kidney | 3 | 2 | | | | |
| Malignant Mixed Tumor | 3 | 2 | | | | |
| Tubular Adenocarcinoma | 2 | | | | | |
| Hamartoma | | 1 | | | | |
| Adenosquamous Carcinoma Metast. | 1 | 1 | | | | |
| <u>ENDOCRINE SYSTEM</u> | | | | | | |
| Pituitary | 1 | 2 | 1 | 4 | 3 | 7 |
| Chromophobe Adenoma | | | | 4 | 2 | 6 |
| Adrenal | | | | 4 | 2 | 6 |
| Adrenal Cortical Carcinoma | | | | | 1 | |
| Adrenal Cortical Carcinoma | | | | | 1 | |
| Thyroid | 1 | 2 | 1 | | | 1 |
| Follicular-Cell Adenoma | 1 | 1 | | | | |
| Follicular-Cell Adenocarcinoma | | 1 | 1 | | | 1 |
| <u>HEMATOPOIETIC SYSTEM</u> | | | | | | |
| Spleen | 2 | | 1 | 1 | 1 | 1 |
| Hemangiosarcoma | 1 | | 1 | 1 | | |
| Reticulum-Cell Sarcoma | 1 | | 1 | | | |
| Cervical Lymph Node | 1 | | | 1 | | |
| Reticulum-Cell Sarcoma | | | | | 1 | |
| Adenosquamous Carcinoma, Metast. | 1 | | | | | |
| Thymus | | | | | | 1 |
| Reticulum-Cell Sarcoma | | | | | | 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 |
| <u>REPRODUCTIVE SYSTEM</u> | | | | | | |
| Mammary Gland | | | | 5 | 6 | 7 |
| Fibroadenoma | | | | 4 | 5 | 7 |
| Adenocarcinoma | | | | 3 | 5 | 7 |
| Uterus/Endometrium | | | | 1 | | |
| Sarcoma | | | | | 1 | 1 |
| Ovary | | | | 1 | 1 | 1 |
| Granulosa-Cell Carcinoma | | | | 1 | | |
| <u>NERVOUS SYSTEM</u> | | | | | | |
| None | | | | | | |
| <u>MUSCULOSKELETAL SYSTEM</u> | | | | | | |
| None | | | | | | |
| <u>ALL OTHER SYSTEMS</u> | | | | | | |
| | 1 | | | | | |
| Abdomen | 1 | | | | | |
| Giant-Cell Tumor, Malignant | 1 | | | | | |
| <u>TUMOR SUMMARY</u> | | | | | | |
| 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 |
| <u>INTEGUMENTARY SYSTEM</u> | | | | | | |
| Skin | 3 | 1 | | | 1 | |
| Fibrosarcoma | 1 | | | | | |
| Subcutaneous Tissue | 2 | 1 | | | 1 | |
| Fibrosarcoma | 2 | | | | 1 | |
| Fibroma | | 1 | | | | |
| <u>RESPIRATORY SYSTEM</u> | | | | | | |
| Lung | | 5 | 2 | 1 | 4 | 7 |
| Adenoma | | 5 | 2 | 1 | 4 | 7 |
| Alveolar Adenocarcinoma | | | 1 | 1 | 2 | 5 |
| | | | 1 | | 2 | 2 |
| <u>CIRCULATORY SYSTEM</u> | | | | | | |
| Lung | | | 1 | | | |
| Hemangiosarcoma | | | 1 | | | |
| <u>DIGESTIVE SYSTEM</u> | | | | | | |
| Stomach | 1 | 26 | 31 | | 4 | 11 |
| Papilloma | | | 1 | | | |
| Liver | 1 | 26 | 31 | | 4 | 11 |
| Hepatocellular Carcinoma | 1 | 26 | 31 | | 4 | 11 |
| <u>URINARY SYSTEM</u> | | | | | | |
| Kidney | | | 1 | | | |
| Adenoma | | | 1 | | | |

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

| Organ System | <u>Male Mice</u> | | | <u>Female Mice</u> | | |
|-----------------------------|------------------|----------|-----------|--------------------|----------|-----------|
| | Control | Low Dose | High Dose | Control | Low Dose | High Dose |
| <u>ENDOCRINE SYSTEM</u> | | | | | | |
| None | | | | | | |
| <u>HEMATOPOIETIC SYSTEM</u> | | | | | | |
| Thymus | 1 | 4 | 2 | 1 | 5 | 6 |
| 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 | | |
| <u>REPRODUCTIVE SYSTEM</u> | | | | | | |
| Mammary Gland | | | | 1 | 4 | |
| Adenocarcinoma | | | | | 1 | |
| Uterus | | | | 1 | 1 | |
| Fibrosarcoma | | | | | 1 | |
| Adenocarcinoma | | | | 1 | | |
| Ovary | | | | | 2 | |
| Granulosa-Cell Carcinoma | | | | | 1 | |
| Cystadenoma | | | | | 1 | |
| <u>NERVOUS SYSTEM</u> | | | | | | |
| Muscle of Back | | | 1 | | | |
| Neurofibroma | | | 1 | | | |
| | | | | | | 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 |
| <u>MUSCULOSKELETAL SYSTEM</u> | | | | | | |
| Soft Tissue | | | | 1 | | |
| Osteosarcoma | | | | 1 | | |
| <u>SPECIAL SENSE ORGANS</u> | | | | | | |
| Harderian Gland | | 1 | | | 1 | |
| Adenoma | | 1 | | | 1 | |
| <u>ALL OTHER SYSTEMS</u> | | | | | | |
| Abdomen | | | 1 | | | |
| Fibrosarcoma | | | 1 | | | |
| <u>PRIMARY TUMOR SUMMARY</u> | | | | | | |
| 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 | | | | | | |
| Skin | 3 | 1 | 1 | 1 | 1 | |
| Fibrosarcoma | 1 | | 1 | | | |
| Alveolar Adenocarcinoma, Metast. | 1 | | 1 | | | |
| Subcutaneous Tissue | 2 | 1 | | | 1 | |
| Fibrosarcoma | 2 | | | | 1 | |
| Fibroma | | 1 | | | | |
| Soft Tissue | | | | 1 | | |
| Osteosarcoma | | | | 1 | | |
| RESPIRATORY SYSTEM | | | | | | |
| 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 | | | | | | |
| Aorta | | | 1 | | | |
| Alveolar Adenocarcinoma, Metast. | | | 1 | | | |
| DIGESTIVE SYSTEM | | | | | | |
| Stomach | 2 | 28 | 32 | | 7 | 14 |
| Papilloma | | | 2 | | | 1 |
| Reticulum-Cell Sarcoma | | | 1 | | | |
| Fibrosarcoma Metastatic | | | 1 | | | 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 | <u>Male Mice</u> | | | <u>Female Mice</u> | | |
|-------------------------------|------------------|----------|-----------|--------------------|----------|-----------|
| | Control | Low Dose | High Dose | Control | Low Dose | High Dose |
| <u>REPRODUCTIVE SYSTEM</u> | 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 | | | | | |
| <u>NERVOUS SYSTEM</u> | | | | | | |
| None | | | | | | |
| <u>MUSCULOSKELETAL SYSTEM</u> | | | 1 | | | |
| Muscle of Back | | | 1 | | | |
| Neurofibroma | | | 1 | | | |
| <u>SPECIAL SENSE ORGANS</u> | | 1 | | | 1 | |
| Harderian Gland | | 1 | | | 1 | |
| Adenoma | | 1 | | | 1 | |

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 |
| <u>DIGESTIVE SYSTEM (cont.)</u> | | | | | | |
| 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 |
| <u>URINARY SYSTEM</u> | | | | | | |
| Kidney | | 1 | 4 | | | 2 |
| Adenoma | | 1 | 4 | | | 2 |
| Reticulum-Cell Sarcoma | | | 1 | | | |
| Lymphosarcoma | | 1 | 1 | | | 1 |
| Fibrosarcoma Metastatic | | | 1 | | | |
| <u>ENDOCRINE SYSTEM</u> | | | | | | |
| Adrenal | | | 1 | | 1 | |
| Lymphosarcoma | | | | | 1 | |
| Fibrosarcoma Metastatic | | | 1 | | | |
| <u>HEMATOPOIETIC SYSTEM</u> | | | | | | |
| Thymus | 1 | 4 | 4 | 1 | 4 | 6 |
| Lymphosarcoma | | 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 | | | | |

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 |
| <u>ALL OTHER SYSTEMS</u> | | | 1 | | | |
| Abdomen | | | 1 | | | |
| Fibrosarcoma | | | 1 | | | |
| <u>TUMOR SUMMARY</u> | | | | | | |
| 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

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| Control females | 147 |
| Low dose females | 149 |
| High dose females | 153 |
| Mice | |
| Control males | 158 |
| Low dose males | 160 |
| High dose males | 164 |
| Control females | 168 |
| Low dose females | 169 |
| High dose females | 173 |

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 | | OTHER PATHOLOGY | |
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 67 | NATD | 003 | | | LUNG BONE MARROW | INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 70 | NATD | 011 | SPLEEN | HEMANGIOSARCOMA | PITUITARY BRONCHUS | INFLAMMATION BRONCHIECTASIS |
| 76 | NATD | 014 | | | SPLEEN LUNG THYMUS SALIVARY GLAND KIDNEY | HEMATOPOIESIS EXTRAMED. INFLAMMATION CHRONIC INFLAMMATION INFLAMMATION ABSCESS |
| 76 | NATD | 015 | | | LUNG KIDNEY | INFLAMMATION CHRONIC INFLAMMATION CHRONIC |
| 82 | NATD | 009 | | | LUNG BONE MARROW | INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 82 | NATD | 013 | | | LUNG | INFLAMMATION CHRONIC |
| 83 | NATD | 018 | | | BRONCHUS STOMACH MESENTERIC LYMPH NODE PANCREAS TESTIS | BRONCHIECTASIS CALCIUM DEPOSITION POLYARTERITIS NODOSA POLYARTERITIS NODOSA ATROPHY |
| 87 | NATD | 016 | | | LUNG TESTIS | INFLAMMATION CHRONIC ATROPHY |
| 88 | NATD | 005 | | | LUNG | INFLAMMATION CHRONIC |
| 88 | NATD | 012 | | | LUNG KIDNEY | INFLAMMATION CHRONIC INFLAMMATION CHRONIC |
| 90 | NATD | 002 | ABDOMEN | GIANT-CELL TUMOR, MALIGNANT | LUNG TESTIS | INFLAMMATION CHRONIC ATROPHY, BILATERAL |
| 91 | NATD | 004 | | | LUNG PLEURA KIDNEY PROSTATE SEMINAL VESICLE SUBCUT TISSUE | INFLAMMATION CHRONIC INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION INFLAMMATION 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 | | OTHER PATHOLOGY | |
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 96 | NATD | 019 | KIDNEY THYROID | MALIGNANT MIXED TUMOR FOLLICULAR ADENOMA | LUNG | INFLAMMATION CHRONIC |
| 98 | NATD | 020 | | | EPIDIDYMISS KIDNEY | FAT NECROSIS WITH ENCAPSULATION INFLAMMATION CHRONIC |
| 99 | NATD | 010 | KIDNEY KIDNEY | MALIGNANT MIXED TUMOR HAMARTOMA | SPLEEN LUNG | HEMATOPOIESIS EXTRAMED. INFLAMMATION CHRONIC |
| 102 | NATD | 017 | | | LUNG KIDNEY MESENTERIC LYMPH NODE LIVER | INFLAMMATION CHRONIC INFLAMMATION CHRONIC POLYARTERITIS NODOSA METAMORPHOSIS FATTY |
| 103 | NATD | 008 | | | LUNG PLEURA BONE MARROW | INFLAMMATION CHRONIC INFLAMMATION METAMORPHOSIS FATTY |
| 110 | TSAC | 001 | | | LUNG KIDNEY SKIN SKIN SKIN | INFLAMMATION CHRONIC INFLAMMATION CHRONIC ACANTHOSIS HYPERKERATOSIS INFLAMMATION |
| 110 | TSAC | 006 | | | LUNG KIDNEY THYROID BONE MARROW | INFLAMMATION CHRONIC INFLAMMATION CHRONIC INFLAMMATION CYSTIC METAMORPHOSIS FATTY |
| 110 | NATD | 007 | LUNG KIDNEYS, BILATERAL CERVICAL LYMPH NODE | CARCINOMA, GLANDULAR AND SQUAMOUS, PROBABLY PRIMARY IN LUNG, WITH MULTIPLE PULMONARY METASTASES MULTIPLE METASTATIC TUMORS METASTATIC TUMORS | STOMACH BONE MARROW | ULCER FOCAL METAMORPHOSIS FATTY |

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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 BONE MARROW | NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 40 | NATD | 030 | | | KIDNEY | NEPHROSIS TOXIC |
| 42 | NATD | 034 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 48 | NATD | 003 | | | KIDNEY BONE MARROW | NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 50 | NATD | 007 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 53 | NATD | 041 | | | KIDNEY BONE MARROW | NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 60 | NATD | 046 | | | KIDNEY PERICARDIUM MYOCARDIUM LUNG PLEURA | NEPHROSIS TOXIC INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION |
| 61 | NATD | 039 | | | PERICARDIUM MYOCARDIUM KIDNEY LUNG PLEURA | INFLAMMATION INFLAMMATION NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION |
| 65 | NATD | 019 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 67 | NATD | 032 | | | KIDNEY BRONCHUS BONE MARROW | NEPHROSIS TOXIC BRONCHIECTASIS 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 | | OTHER PATHOLOGY | |
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 67 | NATD | 044 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 72 | NATD | 040 | | | LEFT ADRENAL KIDNEY LUNG BONE MARROW | INFLAMMATION CYSTIC NEPHROSIS TOXIC INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 74 | NATD | 047 | | | KIDNEY LUNG BONE MARROW | NEPHROSIS TOXIC INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 76 | NATD | 018 | | | LIVER KIDNEY LUNG BONE MARROW | INFLAMMATION CYSTIC NEPHROSIS TOXIC INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 76 | NATD | 023 | THYROID | FOLLICULAR ADENOMA | PARATHYROID AORTA KIDNEY LUNG STOMACH PANCREAS BONE MARROW | HYPERPLASIA ARTERIOSCLEROSIS NEPHROSIS TOXIC INFLAMMATION CHRONIC CALCIUM DEPOSITION POLYARTERITIS NODOSA METAMORPHOSIS FATTY |
| 80 | NATD | 026 | SUBCUT TISSUE/NECK | HEMANGIOSARCOMA | ADRENAL KIDNEY KIDNEY LUNG STOMACH | ANGIECTASIS NEPHROSIS TOXIC CAPSULAR ABSCESS INFLAMMATION CHRONIC ULCER FOCAL |
| 80 | NATD | 033 | | | KIDNEY LUNG MESENTERY PANCREAS | NEPHROSIS TOXIC INFLAMMATION CHRONIC POLYARTERITIS NODOSA POLYARTERITIS NODOSA |
| 82 | NATD | 005 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 83 | NATD | 038 | | | KIDNEY LUNG TESTIS BONE MARROW | NEPHROSIS TOXIC INFLAMMATION CHRONIC ATROPHY METAMORPHOSIS FATTY |
| 83 | NATD | 043 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |

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

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

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 |
| 94 | NATD | 049 | | | KIDNEY LUNG SUBCUTANEOUS TISSUE OF HIND LEG EPIDIDYMIS | NEPHROSIS TOXIC INFLAMMATION CHRONIC ABSCESS PAT NECROSIS WITH ENCAPSULATION |
| 96 | NATD | 021 | | | KIDNEY LUNG TESTIS | NEPHROSIS TOXIC INFLAMMATION CHRONIC ATROPHY |
| 97 | NATD | 016 | | | KIDNEY LUNG PANCREAS BONE MARROW | NEPHROSIS TOXIC INFLAMMATION CHRONIC POLYARTERITIS NODOSA METAMORPHOSIS FATTY |
| 102 | NATD | 009 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 103 | NATD | 013 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 103 | NATD | 027 | | | ADRENAL ADRENAL KIDNEY LUNG PLEURA TESTIS | ANGIECTASIS DEGENERATION NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION ATROPHY |
| 103 | NATD | 031 | | | KIDNEY LUNG BONE MARROW | NEPHROSIS TOXIC INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 104 | NATD | 037 | | | KIDNEY LUNG PANCREAS TESTIS PROSTATE | NEPHROSIS TOXIC INFLAMMATION CHRONIC POLYARTERITIS NODOSA ATROPHY INFLAMMATION |
| 107 | NATD | 008 | | | KIDNEY LUNG TRACHEA CERVICAL LYMPH NODE | NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION INFLAMMATION |
| 107 | NATD | 045 | | | KIDNEY LUNG PANCREAS PROSTATE | NEPHROSIS TOXIC INFLAMMATION CHRONIC POLYARTERITIS NODOSA 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 | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|----------------------|---|--|---|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 108 | NATD | 004 | SUBCUT TISSUE/AXILLA | FIBROSARCOMA | KIDNEY LUNG TESTIS TESTIS | NEPHROSIS TOXIC INFLAMMATION CHRONIC ATROPHY CALCIUM DEPOSITION |
| 110 | TSAC | 002 | THYROID KIDNEY | FOLLICULAR ADENOCARCINOMA HAMARTOMA, MEDULLA, UNILATERAL | LIVER LIVER KIDNEY LUNG TESTIS | METAMORPHOSIS FATTY INFLAMMATION CYSTIC NEPHROSIS TOXIC INFLAMMATION CHRONIC ATROPHY |
| 110 | TSAC | 011 | SUBCUT TISSUE/AXILLA | SQUAMOUS CELL CARCINOMA | KIDNEY LUNG PROSTATE | NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION |
| 110 | TSAC | 017 | | | SPLEEN KIDNEY LUNG PANCREAS MESENTERY TESTIS | HEMATOPOIESIS EXTRAMED. NEPHROSIS TOXIC INFLAMMATION CHRONIC POLYARTERITIS NODOSA POLYARTERITIS NODOSA ATROPHY |
| 110 | TSAC | 022 | | | KIDNEY LUNG TESTIS | NEPHROSIS TOXIC INFLAMMATION CHRONIC ATROPHY |
| 110 | TSAC | 024 | | | LIVER KIDNEY LUNG PANCREAS TESTIS BONE MARROW | METAMORPHOSIS FATTY NEPHROSIS TOXIC INFLAMMATION CHRONIC POLYARTERITIS NODOSA ATROPHY METAMORPHOSIS FATTY |
| 110 | NATD | 042 | | | KIDNEY TESTIS | NEPHROSIS TOXIC ATROPHY |
| 110 | TSAC | 048 | | | KIDNEY LUNG TESTIS BONE MARROW | NEPHROSIS TOXIC INFLAMMATION CHRONIC ATROPHY METAMORPHOSIS FATTY |
| 110 | TSAC | 050 | | | MYOCARDIUM KIDNEY TESTIS BONE MARROW | DEGENERATION NEPHROSIS TOXIC ATROPHY 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 LUNG PLEURA | INFLAMMATION CHRONIC INFLAMMATION |
| 2 | NATD | 032 | | | LUNG PLEURA BONE MARROW | INFLAMMATION CHRONIC INFLAMMATION METAMORPHOSIS FATTY |
| 5 | NATD | 014 | | | PERICARDIUM MYOCARDIUM LUNG PLEURA KIDNEY | INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |
| 6 | NATD | 004 | | | KIDNEY | NEPHROSIS TOXIC |
| 12 | NATD | 015 | | | LIVER/CENTRILOBULAR LIVER KIDNEY | METAMORPHOSIS FATTY CONGESTION NEPHROSIS TOXIC |
| 17 | NATD | 022 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 21 | NATD | 006 | | | KIDNEY | NEPHROSIS TOXIC |
| 27 | NATD | 002 | | | BONE MARROW KIDNEY | METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 31 | NATD | 025 | | | PERICARDIUM BONE MARROW MYOCARDIUM KIDNEY | INFLAMMATION METAMORPHOSIS FATTY INFLAMMATION NEPHROSIS TOXIC |
| 33 | NATD | 024 | | | KIDNEY | NEPHROSIS TOXIC |
| 35 | NATD | 040 | | | LIVER/CENTRILOBULAR LIVER | METAMORPHOSIS FATTY ANGIECTASIS |
| 40 | NATD | 033 | | | KIDNEY | NEPHROSIS TOXIC |
| 42 | NATD | 039 | | | LIVER LIVER BONE MARROW | HEPATOCYTCMEGALY, FOCAL ANGIECTASIS METAMORPHOSIS FATTY |
| 44 | NATD | 003 | | | KIDNEY | NEPHROSIS TOXIC |

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

High Dose Group

| WEEKS ON STUDY | DISP ANIMAL CODE NUMBER | TUMORS | | OTHER PATHOLOGY | |
|-------------------|----------------------------|------------|------------|--|--|
| | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 48 | NATD 018 | | | BONE MARROW KIDNEY | METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 49 | NATD 030 | | | LIVER KIDNEY | METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 52 | NATD 005 | | | LIVER BRONCHUS KIDNEY | METAMORPHOSIS FATTY BRONCHIECTASIS NEPHROSIS TOXIC |
| 52 | NATD 041 | | | LIVER/CENTRILOBULAR LIVER LIVER BRONCHUS BONE MARROW KIDNEY EPIDIDYMIS | DEGENERATION METAMORPHOSIS FATTY ANGIECTASIS BRONCHIECTASIS METAMORPHOSIS FATTY NEPHROSIS TOXIC FAT NECROSIS WITH ENCAPSULATION |
| 53 | NATD 037 | | | LUNG PLEURA KIDNEY EPIDIDYMIS | INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC FAT NECROSIS WITH ENCAPSULATION |
| 54 | NATD 013 | | | BRONCHUS LUNG KIDNEY | BRONCHIECTASIS INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 54 | NATD 017 | | | LIVER KIDNEY | ANGIECTASIS NEPHROSIS TOXIC |
| 56 | NATD 027 | | | LUNG PLEURA THYROID KIDNEY | INFLAMMATION CHRONIC INFLAMMATION INFLAMMATION NEPHROSIS TOXIC |
| 58 | NATD 047 | | | LIVER/CENTRILOBULAR LIVER BRONCHUS KIDNEY | DEGENERATION METAMORPHOSIS FATTY BRONCHIECTASIS NEPHROSIS TOXIC |
| 59 | NATD 009 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 61 | NATD 029 | | | LUNG PLEURA KIDNEY | INFLAMMATION CHRONIC INFLAMMATION 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 | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|------------|---------------------------|--|---|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 62 | NATD | 007 | | | LUNG BONE MARROW KIDNEY | INFLAMMATION CHRONIC METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 62 | NATD | 038 | | | ADRENAL ADRENAL LUNG KIDNEY LIVER | ANGIECTASIS DEGENERATION INFLAMMATION CHRONIC NEPHROSIS TOXIC INFLAMMATION, DIFFUSE |
| 65 | NATD | 011 | THYROID | FOLLICULAR ADENOCARCINOMA | BRONCHUS BRONCHUS PLEURA BONE MARROW LIVER KIDNEY | ABSCCESS BRONCHIECTASIS INFLAMMATION METAMORPHOSIS FATTY ANGIECTASIS NEPHROSIS TOXIC |
| 65 | NATD | 028 | | | LUNG KIDNEY BONE MARROW | INFLAMMATION CHRONIC NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 65 | NATD | 045 | | | LUNG KIDNEY TESTIS BONE MARROW | INFLAMMATION CHRONIC NEPHROSIS TOXIC ATROPHY METAMORPHOSIS FATTY |
| 66 | NATD | 049 | | | LUNG KIDNEY BONE MARROW | INFLAMMATION CHRONIC NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 68 | NATD | 010 | | | LUNG PLEURA KIDNEY | INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |
| 70 | NATD | 020 | | | KIDNEY EPIDIDYMIS | NEPHROSIS TOXIC FAT NECROSIS WITH ENCAPSULATION |
| 71 | NATD | 016 | | | KIDNEY | NEPHROSIS TOXIC |
| 72 | NATD | 034 | SKIN | PILOMATRIXOMA | PERICARDIUM MYOCARDIUM LUNG PLEURA KIDNEY | INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION 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 |
| 72 | NATD | 050 | | | LUNG KIDNEY ABDOMEN | INFLAMMATION CHRONIC NEPHROSIS TOXIC FAT NECROSIS WITH ENCAPSULATION |
| 75 | NATD | 044 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 76 | NATD | 021 | | | PERICARDIUM MYOCARDIUM LUNG PLEURA KIDNEY | INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |
| 82 | NATD | 019 | HEART | AORTIC BODY TUMOR | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 83 | NATD | 043 | | | PITUITARY LUNG KIDNEY KIDNEY BONE MARROW | ANGIECTASIS INFLAMMATION CHRONIC NEPHROSIS TOXIC INFLAMMATION METAMORPHOSIS FATTY |
| 88 | NATD | 031 | | | HEART ENDOCARDIUM MYOCARDIUM LUNG LUNG KIDNEY | THROMBOSIS INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC ABSCESS NEPHROSIS TOXIC |
| 91 | NATD | 036 | PANCREAS | HEMANGIOSARCOMA | PERICARDIUM MYOCARDIUM LUNG PLEURA KIDNEY PROSTATE | INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC INFLAMMATION |
| 97 | NATD | 042 | | | ADRENAL LUNG KIDNEY TESTIS | ANGIECTASIS INFLAMMATION CHRONIC NEPHROSIS TOXIC ATROPHY |
| 99 | NATD | 008 | | | LUNG KIDNEY | INFLAMMATION CHRONIC 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 | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|------------|-----------------|-------------------------------------|--|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 102 | NATD | 035 | | | LUNG BONE MARROW KIDNEY | INFLAMMATION CHRONIC METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 103 | NATD | 001 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 109 | NATD | 048 | | | ADRENAL LUNG KIDNEY KIDNEY | ANGIECTASIS INFLAMMATION CHRONIC NEPHROSIS TOXIC PYELONEPHRITIS |
| 110 | TSAC | 023 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 110 | TSAC | 026 | SPLEEN | HEMANGIOSARCOMA | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 110 | TSAC | 046 | | | LUNG KIDNEY TESTIS | INFLAMMATION CHRONIC NEPHROSIS TOXIC 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 | | OTHER PATHOLOGY | |
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 25 | NATD | 008 | | | LUNG BONE MARROW | INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 47 | NATD | 016 | | | PERICARDIUM MYOCARDIUM LUNG PLEURA | INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION |
| 47 | NATD | 020 | | | LUNG SPLEEN | INFLAMMATION CHRONIC HEMATOPOIESIS EXTRAMED. |
| 68 | NATD | 006 | PITUITARY | CHROMOPHOBE ADENOMA | LUNG BONE MARROW | INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 79 | NATD | 001 | | | LUNG LUNG | INFLAMMATION CHRONIC ABSCISS |
| 87 | NATD | 007 | | | LUNG PLEURA | INFLAMMATION CHRONIC INFLAMMATION |
| 97 | NATD | 011 | MAMMARY GLAND | FIBROADENOMA | KIDNEY LUNG PLEURA STOMACH | INFLAMMATION CHRONIC INFLAMMATION CHRONIC INFLAMMATION ULCER FOCAL |
| 98 | NATD | 015 | | | LUNG | INFLAMMATION CHRONIC |
| 99 | NATD | 002 | | | LUNG | INFLAMMATION CHRONIC |
| 102 | NATD | 014 | PITUITARY MAMMARY GLAND | CHROMOPHOBE ADENOMA ADENOCARCINOMA | ADRENAL LUNG | ANGIECTASIS INFLAMMATION CHRONIC |
| 104 | NATD | 019 | PITUITARY | CHROMOPHOBE ADENOMA | KIDNEY LUNG BONE MARROW | INFLAMMATION CHRONIC INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 108 | NATD | 012 | | | KIDNEY LUNG BONE MARROW | INFLAMMATION CHRONIC INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 110 | TSAC | 003 | PITUITARY MAMMARY GLAND | CHROMOPHOBE ADENOMA FIBROADENOMA | LUNG PLEURA BONE MARROW | INFLAMMATION CHRONIC INFLAMMATION 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 | | OTHER PATHOLOGY | |
|----------------|-----------|---------------|-----------------|--|--|--|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 110 | TSAC | 004 | SPLEEN OVARY | RETICULUM CELL SARCOMA GRANULOSA CELL CARCINOMA | LUNG | INFLAMMATION CHRONIC |
| 110 | TSAC | 005 | | | LUNG | INFLAMMATION CHRONIC |
| 110 | TSAC | 009 | | | LUNG | INFLAMMATION CHRONIC |
| 110 | TSAC | 010 | MAMMARY GLAND | FIBROADENOMA | LEFT ADRENAL ADRENAL LUNG | ANGIECTASIS DEGENERATION INFLAMMATION CHRONIC |
| 110 | TSAC | 013 | | | KIDNEY LUNG | INFLAMMATION CHRONIC INFLAMMATION CHRONIC |
| 110 | TSAC | 017 | | | LUNG BONE MARROW | INFLAMMATION CHRONIC METAMORPHOSIS FATTY |
| 110 | TSAC | 018 | | | KIDNEY KIDNEY LUNG PLEURA LIVER LIVER PANCREAS PANCREAS | INFLAMMATION CHRONIC INFLAMMATION CYSTIC INFLAMMATION CHRONIC INFLAMMATION METAMORPHOSIS FATTY INFLAMMATION ATROPHY 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 | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|---------------|--------------------------------------|---|--|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 2 | NATD | 024 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 2 | MISS | 029 | | | | ANIMAL MISSING |
| 2 | NATD | 042 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 3 | NATD | 002 | LUNG HEART | HEMANGIOSARCOMA, HEMANGIOSARCOMA, | KIDNEY | PYELONEPHRITIS |
| 5 | NATD | 020 | | | PERICARDIUM MYOCARDIUM | INFLAMMATION INFLAMMATION |
| 7 | NATD | 047 | | | KIDNEY | NEPHROSIS TOXIC |
| 15 | NATD | 001 | | | PERICARDIUM MYOCARDIUM LUNG PLEURA | INFLAMMATION 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 | INFLAMMATION 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 ANIMAL CODE NUMBER | TUMORS | | OTHER PATHOLOGY | |
|-------------------|----------------------------|----------------------------|-------------------------------------|--|---|
| | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 98 | NATD 032 | SUBCUT TISSUE/CHEST | LIPOSARCOMA | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 100 | NATD 013 | SUBCUT TISSUE/NECK | FIBROMA | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 102 | NATD 049 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 104 | NATD 040 | MAMMARY GLAND | FIBROADENOMA | SPLEEN KIDNEY LUNG | HEMATOPOIESIS EXTRAMED. NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 110 | TSAC 003 | | | TRACHEA TRACHEAL LYMPH NODE KIDNEY LUNG | INFLAMMATION INFLAMMATION NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 110 | TSAC 004 | | | KIDNEY LUNG RIGHT OVARY BONE MARROW | NEPHROSIS TOXIC INFLAMMATION CHRONIC CYST METAMORPHOSIS FATY |
| 110 | TSAC 007 | PITUITARY MAMMARY GLAND | CHROMOPHOBE ADENOMA FIBROADENOMA | ADRENAL MYOCARDIUM KIDNEY LUNG | ANGIECTASIS FIBROSIS NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 110 | TSAC 008 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 110 | TSAC 009 | | | ADRENAL KIDNEY LUNG RIGHT OVARY | ANGIECTASIS NEPHROSIS TOXIC INFLAMMATION CHRONIC CYST |
| 110 | TSAC 018 | MAMMARY GLAND | FIBROADENOMA | RIGHT ADRENAL KIDNEY LUNG | ANGIECTASIS 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 | | OTHER PATHOLOGY | |
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 110 | TSAC | 026 | ENDOMETRIUM | SARCOMA | LEFT ADRENAL ADRENAL LEFT ADRENAL KIDNEY LUNG OVARY | ANGIECTASIS DEGENERATION INFLAMMATION CYSTIC NEPHROSIS TOXIC INFLAMMATION CHRONIC CYST |
| 110 | TSAC | 028 | | | ADRENAL ADRENAL BILE DUCT KIDNEY LUNG OVARY | ANGIECTASIS DEGENERATION INFLAMMATION PROLIFERATIVE NEPHROSIS TOXIC INFLAMMATION CHRONIC CYST |
| 110 | TSAC | 031 | PITUITARY | CHROMOPHOBE ADENOMA | KIDNEY LUNG ENDOMETRIUM LEFT OVARY RIGHT EYE RETINA | NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION CYST CATARACT DETACHMENT |
| 110 | TSAC | 037 | | | KIDNEY LUNG BONE MARROW | NEPHROSIS TOXIC INFLAMMATION CHRONIC METAMORPHOSIS FATY |
| 110 | TSAC | 041 | | | PERICARDIUM KIDNEY LUNG PLEURA | INFLAMMATION NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION |
| 110 | TSAC | 043 | MAMMARY GLAND | FIBROADENOMA | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 110 | NATD | 050 | MAMMARY GLAND | FIBROADENOMA, (MULTIPLE - 2) | KIDNEY LUNG UTERUS BILE DUCT | NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION 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 | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|------------|------------|--|--|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 3 | NATD | 013 | | | PERICARDIUM MYOCARDIUM LUNG PLEURA BONE MARROW KIDNEY | INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 5 | NATD | 002 | | | PERICARDIUM MYOCARDIUM LUNG PLEURA BONE MARROW KIDNEY | INFLAMMATION INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 9 | NATD | 032 | | | LUNG BONE MARROW KIDNEY | INFLAMMATION CHRONIC METAMORPHOSIS FATTY NEPHROSIS TOXIC |
| 21 | NATD | 036 | | | KIDNEY BONE MARROW | CALCIUM DEPOSITION METAMORPHOSIS FATTY |
| 24 | NATD | 049 | | | KIDNEY LUNG | NEPHROSIS TOXIC INFLAMMATION CHRONIC |
| 28 | NATD | 008 | | | KIDNEY | NEPHROSIS TOXIC |
| 28 | NATD | 016 | | | KIDNEY | NEPHROSIS TOXIC |
| 30 | NATD | 043 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 35 | NATD | 040 | | | KIDNEY | NEPHROSIS TOXIC |
| 43 | NATD | 038 | | | UTERUS | RETENTION FLUID |
| 46 | NATD | 045 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 50 | NATD | 004 | | | LUNG PLEURA KIDNEY KIDNEY | INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC CALCIUM DEPOSITION |

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

High Dose Group

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

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

High Dose Group

| WEEKS ON STUDY | DISP CODE | ANIMAL NUMBER | TUMORS | | OTHER PATHOLOGY | |
|----------------|-----------|---------------|------------|---------------------|--|--|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 70 | NATD | 018 | | | LUNG KIDNEY SMALL INTESTINE | INFLAMMATION CHRONIC NEPHROSIS TOXIC ULCER FOCAL |
| 70 | NATD | 020 | | | LUNG KIDNEY BONE MARROW | INFLAMMATION CHRONIC NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 72 | NATD | 014 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 73 | NATD | 001 | | | ADRENAL LUNG KIDNEY BONE MARROW | ANGIECTASIS INFLAMMATION CHRONIC NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 73 | NATD | 042 | | | BRONCHUS KIDNEY KIDNEY | ABSCESS NEPHROSIS TOXIC CALCIUM DEPOSITION |
| 74 | NATD | 039 | | | BRONCHUS KIDNEY | BRONCHIECTASIS NEPHROSIS TOXIC |
| 82 | NATD | 026 | | | LUNG KIDNEY BONE MARROW | INFLAMMATION CHRONIC NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 86 | NATD | 048 | | | LUNG PLEURA KIDNEY MESENTERIC LYMPH NODE MESENTERIC LYMPH NODE | INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC INFLAMMATION INFLAMMATION CYSTIC |
| 89 | NATD | 047 | | | ADRENAL LUNG | ANGIECTASIS INFLAMMATION CHRONIC |
| 95 | NATD | 021 | | | LUNG PLEURA KIDNEY | INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |
| 96 | NATD | 050 | PITUITARY | CHROMOPHOBE ADENOMA | ADRENAL LIVER LUNG KIDNEY | ANGIECTASIS METAMORPHOSIS FATTY INFLAMMATION CHRONIC 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 | | OTHER PATHOLOGY | |
|----------------|-----------|---------------|----------------------------|-------------------------------------|---|---|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 101 | NATD | 029 | MAMMARY GLAND | FIBROADENOMA | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 101 | NATD | 035 | PITUITARY | CHROMOPHOBE ADENOMA | ADRENAL LUNG PLEURA KIDNEY | ANGIECTASIS INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |
| 102 | NATD | 019 | | | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 103 | NATD | 033 | MAMMARY GLAND | FIBROADENOMA (MULTIPLE-3) | LUNG KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 104 | NATD | 034 | | | BRAIN PERICARDIUM LUNG PLEURA KIDNEY | HYDROCEPHALUS INFLAMMATION INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |
| 110 | TSAC | 003 | | | ADRENAL LUNG BILE DUCT KIDNEY BONE MARROW | ANGIECTASIS INFLAMMATION CHRONIC DILATATION NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 110 | TSAC | 005 | PITUITARY | CHROMOPHOBE ADENOMA | ADRENAL LUNG KIDNEY BONE MARROW | ANGIECTASIS INFLAMMATION CHRONIC NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 110 | TSAC | 006 | THYMUS | RETICULUM CELL SARCOMA | LUNG KIDNEY OVARY | INFLAMMATION CHRONIC NEPHROSIS TOXIC INFLAMMATION |
| 110 | TSAC | 009 | PITUITARY MAMMARY GLAND | CHROMOPHOBE ADENOMA FIBROADENOMA | ADRENAL ADRENAL LUNG PLEURA KIDNEY | DEGENERATION ANGIECTASIS INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |

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

High Dose Group

| WEEKS ON STUDY | DISP ANIMAL CODE NUMBER | TUMORS | | OTHER PATHOLOGY | |
|-------------------|----------------------------|------------------------------|--|--|---|
| | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 110 | TSAC 010 | MAMMARY GLAND | FIBROADENOMA (MULTIPLE-2) | ADRENAL MYOCARDIUM LUNG PLEURA KIDNEY | ANGIECTASIS DEGENERATION INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC |
| 110 | TSAC 011 | | | ADRENAL ADRENAL LUNG KIDNEY FALLOPIAN TUBE | ANGIECTASIS DEGENERATION INFLAMMATION CHRONIC NEPHROSIS TOXIC INFLAMMATION |
| 110 | TSAC 015 | | | LUNG PLEURA KIDNEY BONE MARROW | INFLAMMATION CHRONIC INFLAMMATION NEPHROSIS TOXIC METAMORPHOSIS FATTY |
| 110 | TSAC 023 | PITUITARY MAMMARY GLAND | CHROMOPHOBE ADENOMA FIBROADENOMA (MULTIPLE-2) | LUNG KIDNEY KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC CALCIUM DEPOSITION |
| 110 | TSAC 025 | | | KIDNEY LUNG PLEURA | NEPHROSIS TOXIC INFLAMMATION CHRONIC INFLAMMATION |
| 110 | TSAC 030 | THYROID MAMMARY GLAND | FOLLICULAR ADENOCARCINOMA FIBROADENOMA (MULTIPLE-2) | KIDNEY | NEPHROSIS TOXIC |
| 110 | TSAC 037 | MAMMARY GLAND ENDOMETRIUM | FIBROADENOMA SARCOMA | PITUITARY PERICARDIUM KIDNEY SPLEEN CERVICAL LYMPH NODE CERVICAL LYMPH NODE LUNG | CYST INFLAMMATION NEPHROSIS TOXIC HEMATOPOIESIS EXTRAMED. INFLAMMATION CYSTIC INFLAMMATION INFLAMMATION CHRONIC |
| 110 | TSAC 044 | | | LUNG KIDNEY UTERUS BONE MARROW | INFLAMMATION CHRONIC NEPHROSIS TOXIC INFLAMMATION METAMORPHOSIS FATTY |
| 110 | TSAC 046 | PITUITARY | CHROMOPHOBE ADENOMA | LUNG KIDNEY | INFLAMMATION CHRONIC 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 KIDNEY | AMYLOIDOSIS PYELONEPHRITIS |
| 60 | NATD | 008 | | | KIDNEY KIDNEY KIDNEY | INFLAMMATION CHRONIC HYDRONEPHROSIS AMYLOIDOSIS |
| 61 | NATD | 007 | | | KIDNEY KIDNEY | INFLAMMATION CHRONIC AMYLOIDOSIS |
| 64 | NATD | 006 | | | KIDNEY KIDNEY SPLEEN | INFLAMMATION CHRONIC HYDRONEPHROSIS AMYLOIDOSIS |
| 66 | NATD | 020 | | | MESENTERIC LYMPH NODE SUBCUT TISSUE | ANGIECTASIS ABSCESS |
| 68 | NATD | 005 | | | KIDNEY KIDNEY KIDNEY SPLEEN LIVER ENDOCARDIUM | INFLAMMATION CHRONIC AMYLOIDOSIS HYDRONEPHROSIS AMYLOIDOSIS HYPERPLASIA HYPERPLASIA |
| 72 | NATD | 019 | LIVER | HEPATOCELLULAR CARCINOMA | SPLEEN | AMYLOIDOSIS |
| 76 | NATD | 004 | | | KIDNEY KIDNEY | INFLAMMATION CHRONIC HYDRONEPHROSIS |
| 76 | MSAC | 018 | LIVER SPLEEN MESENTERIC LYMPHNODE PROSTATE SEMINAL VESICLES | RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA | | |
| 77 | NATD | 017 | SUBCUT TISSUE/BACK | FIBROSARCOMA | SPLEEN KIDNEY KIDNEY | AMYLOIDOSIS INFLAMMATION CHRONIC AMYLOIDOSIS |

Continued on next page

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

Control Group (Vehicle)

| WEEKS ON STUDY | DISP ANIMAL CODE NUMBER | TUMORS | | OTHER PATHOLOGY | |
|----------------|-------------------------|--------------------|--------------|----------------------------|---|
| | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 78 | NATD 003 | | | | NO SIGNIFICANT DIAGNOSIS |
| 90 | TSAC 001 | SKIN OF CHEST | FIBROSARCOMA | KIDNEY KIDNEY | INFLAMMATION CHRONIC HYDRONEPHROSIS |
| 90 | TSAC 002 | | | KIDNEY KIDNEY | INFLAMMATION CHRONIC HYDRONEPHROSIS |
| 90 | TSAC 011 | SUBCUT TISSUE/BACK | FIBROSARCOMA | | |
| 90 | TSAC 012 | | | | NO SIGNIFICANT DIAGNOSIS |
| 90 | TSAC 013 | | | SKIN SKIN | ACANTHOSIS INFLAMMATION |
| 90 | TSAC 014 | | | | NO SIGNIFICANT DIAGNOSIS |
| 90 | TSAC 015 | | | KIDNEY KIDNEY KIDNEY | HYDRONEPHROSIS INFLAMMATION CHRONIC 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 | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|---|---|---|---|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 16 | NATD | 010 | | | | NO SIGNIFICANT DIAGNOSIS |
| 18 | NATD | 050 | THYMUS BRONCHIAL LYMPHNODE LUNG KIDNEY PROSTATE BONE MARROW CERVICAL LYMPHNODE SPLEEN LIVER | LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA LYMPHOSARCOMA | KIDNEY | NEPHROSIS TOXIC |
| 31 | ACCK | 009 | | | | NO SIGNIFICANT DIAGNOSIS |
| 51 | NATD | 030 | | | KIDNEY | NEPHROSIS TOXIC |
| 53 | NATD | 040 | | | KIDNEY | NEPHROSIS TOXIC |
| 58 | NATD | 008 | | | HEART ENDOCARDIUM MYOCARDIUM KIDNEY KIDNEY SPLEEN URINARY BLADDER PROSTATE PANCREAS PANCREAS BONE KIDNEY | ORGANIZED THROMBUS INFLAMMATION INFLAMMATION PYELONEPHRITIS HYDRONEPHROSIS AMYLOIDOSIS INFLAMMATION INFLAMMATION ATROPHY INFLAMMATION INFLAMMATION NEPHROSIS TOXIC |
| 63 | NATD | 039 | | | KIDNEY | NEPHROSIS TOXIC |
| 65 | NATD | 020 | | | LIVER KIDNEY | HYPERPLASIA NEPHROSIS TOXIC |
| 65 | NATD | 038 | | | KIDNEY | NEPHROSIS TOXIC |
| 77 | NATD | 019 | | | BRONCHUS CERVICAL LYMPH NODE KIDNEY | ABSCESS INFLAMMATION NEPHROSIS TOXIC |
| 81 | NATD | 028 | SPLEEN LIVER | LYMPHOSARCOMA LYMPHOSARCOMA | 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 | | OTHER PATHOLOGY | |
|----------------|-----------|---------------|---|---|---|--|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 81 | NATD | 029 | LUNG LIVER | ADENOMA HEPATOCELLULAR CARCINOMA | KIDNEY | NEPHROSIS TOXIC |
| 86 | NATD | 049 | LIVER | HEPATOCELLULAR CARCINOMA | KIDNEY STOMACH STOMACH | NEPHROSIS TOXIC HYPERKERATOSIS ACANTHOSIS |
| 88 | NATD | 007 | LIVER LUNG LUNG | HEPATOCELLULAR CARCINOMA HEPATOCELLULAR CARCINOMA METASTA ADENOMA | KIDNEY | NEPHROSIS TOXIC |
| 88 | NATD | 018 | | | MESENTERIC LYMPH NODE KIDNEY | ANGIECTASIS NEPHROSIS TOXIC |
| 90 | TSAC | 001 | LIVER LUNG | HEPATOCELLULAR CARCINOMA ADENOMA | KIDNEY | NEPHROSIS TOXIC |
| 90 | TSAC | 002 | SUBCUT TISSUE/BACK | FIBROMA | KIDNEY | NEPHROSIS TOXIC |
| 90 | TSAC | 003 | LIVER | HEPATOCELLULAR CARCINOMA | KIDNEY | NEPHROSIS TOXIC |
| 90 | TSAC | 004 | LIVER LUNG MESENTERIC LYMPHNODE ILEUM RENAL LYMPHNODE | HEPATOCELLULAR CARCINOMA ADENOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA | SPLEEN KIDNEY | AMYLOIDOSIS NEPHROSIS TOXIC |
| 90 | TSAC | 005 | LIVER | HEPATOCELLULAR CARCINOMA | LIVER SPLEEN KIDNEY | THROMBOSIS HEMATOPOIESIS EXTRAMED. NEPHROSIS TOXIC |
| 90 | TSAC | 006 | LIVER | HEPATOCELLULAR CARCINOMA | MESENTERIC LYMPH NODE KIDNEY KIDNEY | ANGIECTASIS INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 90 | TSAC | 011 | LIVER LUNG | HEPATOCELLULAR CARCINOMA HEPATOCELLULAR CARCINOMA METASTA | KIDNEY | NEPHROSIS TOXIC |
| 90 | TSAC | 012 | LIVER | HEPATOCELLULAR CARCINOMA | KIDNEY | NEPHROSIS TOXIC |
| 90 | TSAC | 013 | LIVER | HEPATOCELLULAR CARCINOMA | MESENTERIC LYMPH NODE KIDNEY | INFLAMMATION 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 ANIMAL CODE NUMBER | TUMORS | | OTHER PATHOLOGY | |
|----------------|-------------------------|---|--|------------------|---|
| | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | MORPHOLOGY |
| 90 | TSAC 015 | EPIDIDYMIS PROSTATE SPLEEN LIVER LUNG | RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA HEPATOCELLULAR CARCINOMA HEPATOCELLULAR CARCINOMA METASTA | KIDNEY | NEPHROSIS TOXIC |
| 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 KIDNEY | INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 90 | TSAC 036 | LIVER | HEPATOCELLULAR CARCINOMA | KIDNEY | NEPHROSIS TOXIC |
| 90 | TSAC 037 | LUNG LIVER | ADENOMA HEPATOCELLULAR CARCINOMA | KIDNEY | NEPHROSIS TOXIC |

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

Low Dose Group

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

Continued on next page

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

Continued on next page

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 |
| 90 | TSAC | 014 | LUNG LIVER | HEPATOCELLULAR CARCINOMA METASTA HEPATOCELLULAR CARCINOMA | KIDNEY KIDNEY KIDNEY | HYDRONEPHROSIS INFLAMMATION CHRONIC NEPHROSIS TOXIC |
| 90 | TSAC | 021 | LIVER | HEPATOCELLULAR CARCINOMA | KIDNEY KIDNEY | HYDRONEPHROSIS NEPHROSIS TOXIC |
| 90 | TSAC | 022 | LIVER | HEPATOCELLULAR CARCINOMA | MESENTERIC LYMPH NODE KIDNEY | INFLAMMATION NEPHROSIS TOXIC |
| 90 | TSAC | 023 | LIVER | HEPATOCELLULAR CARCINOMA | KIDNEY | NEPHROSIS TOXIC |
| 90 | TSAC | 024 | MESENTERIC LYMPHNODE SPLEEN PANCREAS KIDNEY LIVER | RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA RETICULUM CELL SARCOMA | KIDNEY | NEPHROSIS TOXIC |
| 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 LUNG | HEPATOCELLULAR CARCINOMA HEPATOCELLULAR CARCINOMA METASTA | KIDNEY MESENTERIC LYMPH NODE | NEPHROSIS TOXIC ANGIECTASIS |
| 90 | TSAC | 033 | LIVER STOMACH | HEPATOCELLULAR CARCINOMA PAPILLOMA | STOMACH KIDNEY | HYPERKERATOSIS NEPHROSIS TOXIC |
| 90 | NATD | 034 | KIDNEY LIVER ABDOMENAL CAVITY ADRENAL PANCREAS MESENTERIC LYMPHNODE STOMACH | FIBROSARCOMA, METASTATIC HEPATOCELLULAR CARCINOMA FIBROSARCOMA, PRIMARY FIBROSARCOMA, METASTATIC FIBROSARCOMA, METASTATIC FIBROSARCOMA, METASTATIC FIBROSARCOMA, METASTATIC | 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 | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|---------------|---|-----------------|-----------------|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | 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 | | OTHER PATHOLOGY | |
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | 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 |
| 169 | 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 |

Continued on next page

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

Low Dose Group

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

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

Low Dose Group

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

end of female mice—low dose

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

High Dose Group

| WEEKS ON STUDY | DISP CODE | ANIMAL NUMBER | TUMORS | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|-------------------------------------|--|--------------------------|--|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | 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 |

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

High Dose Group

| WEEKS ON STUDY | DISP CODE | ANIMAL NUMBER | TUMORS | | OTHER PATHOLOGY | |
|-------------------|--------------|------------------|---------------------------|---|---|---|
| | | | TOPOGRAPHY | MORPHOLOGY | TOPOGRAPHY | 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 |

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

High Dose Group

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