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BIOASSAY OF

TETRACHLOROETHYLENE

FOR POSSIBLE CARCINOGENICITY

Carcinogen Bioassay and Program Resources Branch
Carcinogenesis Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

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REPORT ON THE BIOASSAY OF TETRACHLOROETHYLENE
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS PROGRAM, DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

CONTRIBUTORS: This report presents the results of the bioassay of tetrachloroethylene conducted for the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This bioassay was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Bioassay Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3,5); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathology was performed by Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Pathologists from NCI (1) and Tracor Jitco (6) have reviewed selected slides and concur with the overall pathologic evaluation of the study.

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Dr. J. R. Joiner (6) and Mr. W. W. Belew (8), using methods selected for the Bioassay Program by Dr. J. J. Gart (9).

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The following scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. R. A. Squire (1), and Dr. J. M. Ward (1).

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SUMMARY

The bioassay of U.S.P.* -grade tetrachloroethylene for possible carcinogenicity was conducted using Osborne-Mendel rats and B6C3F1 mice. Tetrachloroethylene in corn oil was administered by gavage at either of two dosages to groups of 50 male and 50 female animals of each species, 5 days a week, over a period of 78 weeks followed by an observation period of 32 weeks for rats and 12 weeks for mice.

Initial dosage levels for the chronic bioassay were selected on the basis of a preliminary subchronic toxicity test. Subsequent dosage adjustments were made during the course of the chronic bioassay. The high and low time-weighted average dosages of tetrachloroethylene in the chronic study were 941 and 471 mg/kg/day for the male rats, 949 and 474 mg/kg/day for the female rats, 1072 and 536 mg/kg/day for the male mice, and 772 and 386 mg/kg/day for the female mice.

For each species, 20 animals of each sex were placed on test as vehicle controls. These animals were gavaged with corn oil at the same time that dosed animals were gavaged with tetrachloroethylene mixtures. Twenty animals of each sex were placed on test as untreated controls for each species. These animals received no gavage treatments.

No significant increased incidence of neoplastic lesions was observed in treated rats. In both dosed and control rats, respiratory disease was observed with increasing frequency for the latter part of the first year until termination of the bioassay. Lesions indicative of pneumonia were observed in nearly all rats at necropsy. A high incidence of toxic nephropathy was observed in treated rats. Toxic nephropathy was noted in rats that died early in the study (as early as week 20 for male rats and week 28 for female rats). Mortality of rats was dose-related. Fifty percent of the high dose males had died by week 44 and 50 percent of the high dose females had died by week 66.

In both male and female mice, administration of tetrachloroethylene was associated with a significantly increased incidence of heptocellular carcinoma. Hepatocellular carcinomas were observed in 2/17 (12 percent) untreated control males, 2/20 (10 percent) vehicle control males, 32/49 (65 percent) low dose males, 27/48 (56 percent) high dose males, 2/20 (10 percent) untreated control females, 0/20 vehicle control females, 19/48 (40 percent) low dose females, and 19/48 (40 percent) high dose females. Hepatocellular carcinomas metastasized to the kidney in one untreated control male and to the

*United States Pharmacopoeia.

lung in three low dose males, one low dose female, and one high dose female. Toxic nephropathy, similar to that observed in rats, was also observed in treated but not control mice.

Fisher exact tests indicated a highly significant increased incidence of hepatocellular carcinoma for each dosed group compared to each control group. Cochran-Armitage tests showed a highly significant positive association between increased dosage and elevated tumor incidence. Time-adjusted analyses, based on Kaplan and Meier survival curves, indicated that the estimated probability of observing hepatocellular carcinoma by week 91 was 1.00 in a dosed male mouse and 0.938 in a dosed female mouse.

The results of the bioassay of tetrachloroethylene in Osborne-Mendel rats do not allow an evaluation of the carcinogenicity of this compound due to the high rate of early death among the treated animals. However, under the condition of this study, tetrachloroethylene is a liver carcinogen in B6C3F1 mice of both sexes.

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I. INTRODUCTION

Tetrachloroethylene (NCI No. C04580) is one of a group of halogenated organic solvents selected by the National Cancer Institute (NCI) for inclusion in the Carcinogenesis Bioassay Program. These solvents were selected on the basis of large-scale production, extensive use, and lack of adequate chronic toxicity data.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is tetrachloroethylene.* It is also called perchloroethylene and carbon dichloride.

Annual domestic production of tetrachloroethylene in 1974 was approximately 734 million pounds (U.S. International Trade Commission, 1976). The 1974 consumption of the chemical was as follows: 69 percent in the textile and dry-cleaning industries; 16 percent for metal cleaning and degreasing; 12 percent as a chemical intermediate (e.g., fluorocarbon synthesis); and 3 percent for miscellaneous uses (Fishbein, 1976). The last category includes paint removers and other specialty solvent formulations, as well as a very small quantity for medicinal use as an antihelminthic (e.g., treatment of hookworm infestations) (Senewiratne et al., 1975).

Human exposure to tetrachloroethylene is extensive. Approximately 85 percent of the compound consumed is used in a dispersive manner (Stanford Research Institute, 1975). The greatest human

*The CAS registry number is 127-18-4.

exposure takes place in dry-cleaning establishments using tetrachloroethylene, especially when ventilation is inadequate (Fishbein, 1976). Employees of tetrachloroethylene manufacturers and of the industries consuming the chemical may also be directly exposed to the vapors or liquid. Tetrachloroethylene appears to be a widespread environmental contaminant, found in air, water, and food (McConnell et al., 1975). Worldwide air emissions of tetrachloroethylene were estimated at nearly 2.8×10^5 tons in 1974 (Chemical Information Services, 1975), and atmospheric concentrations normally range between 1 and 10 ng/liter (McConnell et al., 1975). Concentrations of the chemical in foodstuffs have been reported as high as 13 mg/kg in butter (McConnell et al., 1975). Tetrachloroethylene was found in New Orleans drinking water and in the plasma of persons ingesting that water (no levels were given) (Dowty et al., 1975). Chlorination at sewage treatment plants slightly raises tetrachloroethylene levels in water (Fishbein, 1976). Human tissues (body fat) have been found to contain as much as 29 mg/kg wet weight of tetrachloroethylene (McConnell et al., 1975). The mean biological half-life of the compound in man, estimated by measuring the total of tetrachloroethylene and tetrachloroethylene metabolites in urine, is 144 hours (Ikeda and Imamura, 1973). Tetrachloroethylene is degraded fairly rapidly in the environment without significant bioaccumulation (McConnell et al., 1975).

Depression of the central nervous system, the primary physiologic effect of acute or chronic inhalation, was noted in humans exposed to

200 ppm of the chemical (Rowe et al., 1952). Recovery was complete within an hour after exposure to concentrations as high as 1000 ppm for two minutes. Only one of six persons exposed to 100 ppm of tetrachloroethylene for an hour experienced effects attributable to that concentration of vapor (Rowe et al., 1952). Symptoms of acute and fatal intoxication from tetrachloroethylene result from action on the nervous system and include tremor, convulsions, paralysis, mental confusion, and coma (Sax, 1975). Subacute exposures produce irritation of the eyes, nose, and throat, headaches, fatigue, nausea, vomiting, and mental confusion (Sax, 1975).

II. MATERIALS AND METHODS

A. Chemicals

Three batches of U.S.P.-grade tetrachloroethylene were purchased by Hazleton Laboratories America, Inc., Vienna, Virginia, from Aldrich Chemical Company, Milwaukee, Wisconsin. The manufacturer's suggested minimum purity was 99 percent. Gas-liquid chromatography showed the major component comprising over 99 percent of the total peak area and one minor impurity having a greater retention time than the major component. Infrared analysis was consistent with that found in the literature. These results suggested a compound with a purity over 99 percent with at least one minor impurity.

Throughout this report the term tetrachloroethylene is used to represent this U.S.P.-grade material.

B. Dosage Preparation

Fresh solutions of tetrachloroethylene and Duke's® corn oil (S. F. Sauer Company) were prepared weekly, sealed, and stored at 34°F. These tetrachloroethylene solutions were considered generally stable for 10 days under the indicated storage conditions. The concentrations of tetrachloroethylene in corn oil were 6, 8, 9, and 11 percent for mice and 50 and 60 percent for rats.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon

tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts of the Division of Cancer Treatment at the National Cancer Institute. The Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various treatment and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 12 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle. The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors, while mice were housed by sex in groups of 10 in solid-bottom polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Shurfire) were provided once each week for mice. Rats received sanitized cages with no bedding with the same

frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles were provided three times a week. Food (Wayne Lab-Blox , Allied Mills, Inc.) and water were available ad libitum.

Tetrachloroethylene-treated rats and their untreated controls were housed in the same room with* 1,1,2-trichloroethane (79-00-5)-treated rats. Vehicle control rats for the tetrachloroethylene bioassay were housed in another room with rats treated with dibromochloropropane (96-12-8), 1,2-dichloroethane (107-06-2), trichloroethylene (79-01-6), 1,1-dichloroethane (75-34-3), and carbon disulfide (75-15-0). Tetrachloroethylene-treated and both vehicle and untreated control mice were maintained in the same room as mice receiving 1,1,2,2-tetrachloroethane (79-34-5), allyl chloride (107-05-11), chloroform (67-66-3), chloropicrin (76-06-2), 1,2-dichloroethane (107-06-2), 1,1-dichloroethane (75-34-3), 3-sulfolene (77-79-21), iodoform (75-47-8), methylchloroform (71-55-6), 1,1,2-trichloroethane (79-00-5), hexachloroethane (67-72-1), carbon disulfide (75-15-0), trichlorofluoromethane (75-69-4), carbon tetrachloride (56-23-5), trichloroethylene (79-01-6), 1,2-dibromoethane (106-93-4), and dibromochloropropane (96-12-8).

*CAS registry numbers are given in parentheses.

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a mg/kg body weight basis utilizing the most recently observed group mean body weight as a guide for determining the dose. Mean body weights for each group were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. All animals of one sex within a treatment group received the same dose. Animals were gavaged with test solutions under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

F. Selection of Initial Dose Levels

In order to establish the maximum tolerated dosages of tetrachloroethylene for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Six groups, each consisting of five males and five females, were utilized for each animal species. Tetrachloroethylene dissolved in corn oil was administered by gavage to five of the six rat groups at dosages of 316, 562, 1000, 1780, and 3160 mg/kg/day and to five of the six mouse groups at dosages of 562, 1000, 1780, 3160, and 5620 mg/kg/day. The sixth group of each species served as a control group and was gavaged only with corn oil. Intubation occurred 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity.

A dosage inducing no mortality and resulting in a retardation in body weight gain of approximately 20 percent was to be selected

as the initial high dose. When weight gain criteria were not applicable, mortality data alone were utilized.

All the rats, both male and female, dosed with 1000 mg/kg/day or less survived the entire 6-week treatment period and the 2-week observation period, while deaths were observed at higher dose levels. As weight gain retardation was not noted in the animals treated with 1000 mg/kg/day or less, the high dosage selected for the chronic bioassay for male and female rats was 1000 mg/kg/day.

The male mice receiving 562 mg/kg/day experienced no reduction in weight gain relative to controls, while the male mice receiving 1000 mg/kg/day experienced a 22 percent reduction in weight gain relative to controls. An initial high dosage of 900 mg/kg/day was selected for the chronic bioassay of male mice. Female mice receiving 562 mg/kg/day gained 70 percent of the weight gained by controls, while the female mice receiving 1000 mg/kg/day gained 85 percent of the weight gained by controls. An initial high dosage of 600 mg/kg/day was selected for the chronic bioassay of female mice.

G. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, dosages administered, duration of treated and untreated observation periods, and the time-weighted average dosages) are summarized in Tables 1 and 2.

The high dose, low dose, and untreated control rats were approximately 7 weeks old at the time they were placed on test. The

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
TETRACHLOROETHYLENE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	TETRACHLORO-ETHYLENE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0		110	0
VEHICLE CONTROL	20	0	78	32	0
LOW DOSE	50	500	19		471
		700	6		
		500	20		
		500[c]	26	7	
		0		32	
HIGH DOSE	50	1000	19		941
		1400	6		
		1000	20		
		1000[c]	26	7	
		0		32	
FEMALE					
UNTREATED CONTROL	20	0		110	0
VEHICLE CONTROL	20	0	78	32	0
LOW DOSE	50	500	16		474
		600	3		
		700	6		
		500	20		
		500[c]	26	7	
		0		32	
HIGH DOSE	50	1000	16		949
		1200	3		
		1400	6		
		1000	20		
		1000[c]	26	7	
		0		32	

[a] Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma(\text{dosage X number of weeks received})}{\Sigma(\text{weeks receiving treatment})}$

[c] These dosages were cyclically administered with a pattern of 1 dose-free week followed by 4 weeks (5 days per week) of dosage at the level indicated.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
TETRACHLOROETHYLENE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	TETRACHLORO-ETHYLENE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0		90	0
VEHICLE CONTROL	20	0	78	12	0
LOW DOSE	50	450 550 0	11 67	 12	536
HIGH DOSE	50	900 1100 0	11 67	 12	1072
FEMALE					
UNTREATED CONTROL	20	0		90	0
VEHICLE CONTROL	20	0	78	12	0
LOW DOSE	50	300 400 0	11 67	 12	386
HIGH DOSE	50	600 800 0	11 67	 12	772

[a] Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma \text{(dosage X number of weeks received)}}{\Sigma \text{(weeks receiving treatment)}}$

vehicle control rats were approximately 4 weeks older than the other rats and, therefore, were started on test 4 weeks earlier. The high and low doses of tetrachloroethylene initially utilized for both males and females were 1000 and 500 mg/kg/day, respectively. After 16 weeks on test the female rats appeared to be tolerating the chemical, so their high dose was increased to 1200 mg/kg/day. At the end of week 19, high doses for both sexes were increased to 1400 mg/kg/day. Because of toxic effects evidenced during week 25, the dosage administered to the high dose females was decreased in week 26 to the original level of 1000 mg/kg/day. The low doses were adjusted accordingly, so that they consistently remained one-half the high dose. In week 46 intubation ceased for all treated animals for 1 week, followed by 4 weeks of dose administration. This pattern continued for the remainder of the treatment period. An untreated period of 32 weeks followed the 78-week treatment period in order to observe any delayed toxicity or tumor development.

The high dose, low dose, and untreated control mice were approximately 5 weeks old at the time they were placed on test. The vehicle control mice were approximately 2 weeks older than the other mice and were started on test correspondingly earlier. The high and low doses initially utilized for males and females, respectively, were 900 and 450 mg/kg/day and 600 and 300 mg/kg/day. After 11 weeks, the animals appeared to be tolerating the chemical, so the high and low doses were, respectively, increased to 1100 and 550 mg/kg/day for male mice

and 800 and 400 mg/kg/day for female mice. Treatment continued at this level for the remainder of the 78-week treatment period and was followed by approximately 12 weeks of observation.

H. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected daily for mortality. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. The presence of tissue masses was determined by observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by exsanguination under sodium pentobarbital anesthesia, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, or gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice) and bile duct, pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid,

parathyroid, pancreatic islets, testis, prostate, brain, uterus, mammary gland, and ovary.

Tissues for which slides were prepared were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

I. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and used Tarone's (1975) extensions of Cox's methods for testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g.,

lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from

the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

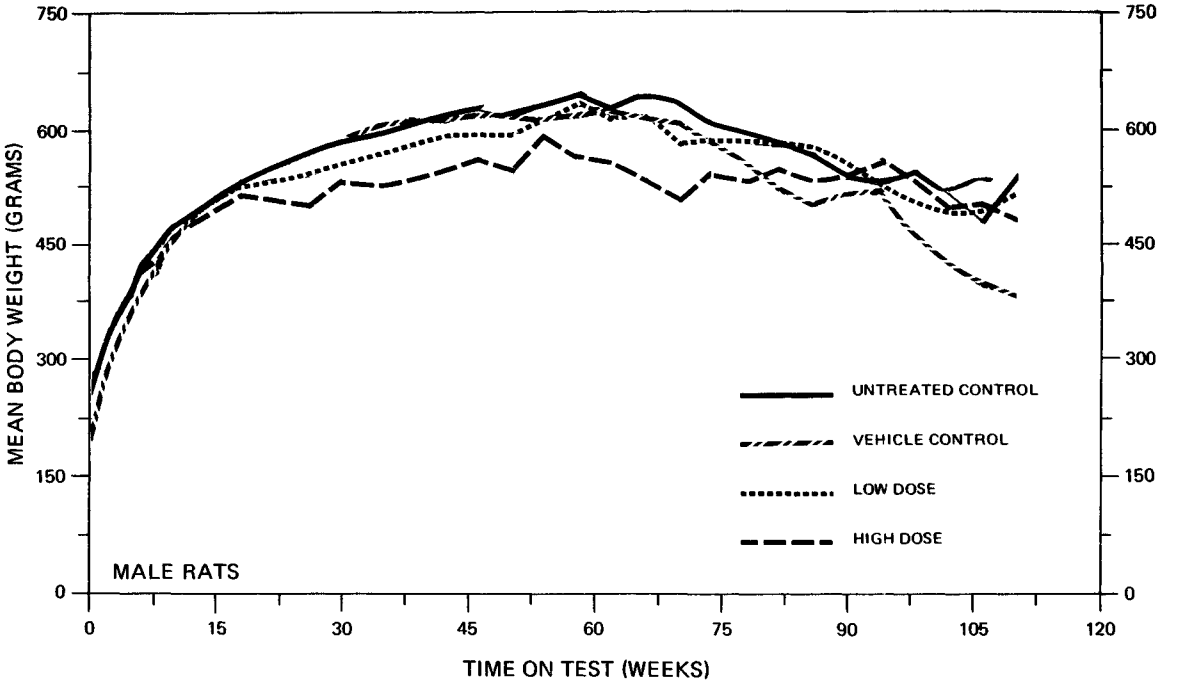
III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

During the first year of the study, treated rats gained less weight than did their untreated controls. However, the differences in weight gain did not exceed 13 percent. Throughout the second year, treated animals continued to gain less weight than did the untreated controls, but the disparity never exceeded 19 percent (Figure 1).

No characteristic signs of the toxic effects of the compound were observed during the first 6 weeks of the study. Clinical signs were observed with slightly greater frequency in the treated rats of both sexes than in the respective control rats from week 7 through week 46. However, during the remainder of the study these signs were noted at comparable rates in treated and control animals.

As the study progressed, a hunched appearance, first noted in a few animals during week 7, was observed with gradually increasing frequency in the treated groups, particularly in the high dose females. Urine staining on the lower abdomen was a predominant clinical sign in the treated groups from week 26 to termination of the study. The greatest incidence of this was observed in the high dose females. Other signs observed with comparable frequency in control and treated rats included roughening and/or staining of the fur; eyes squinted or showing a reddish discharge or crust; body sores, particularly on the tail; and localized alopecia of the body or extremities. Isolated observations included circling in one low



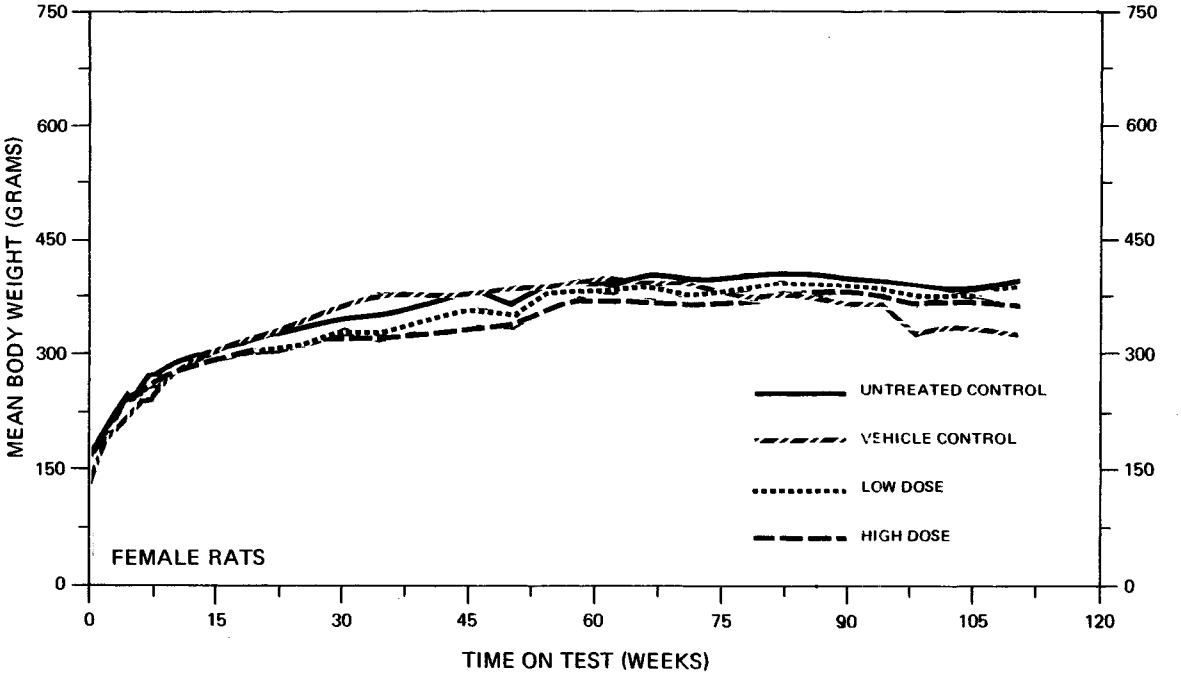


FIGURE 1
GROWTH CURVES FOR TETRACHLOROETHYLENE CHRONIC STUDY RATS

dose male in week 42, salivation in several high dose males and females during weeks 34 through 42 of the study, and reddish vaginal discharge in one high dose female from week 50 though week 58.

Respiratory signs, characterized by dyspnea, wheezing, and/or reddish nasal discharge, were noted in treated and control rats during the latter part of the first year with the incidence increasing for all groups as the animals aged. In week 110, most of the surviving animals had a hunched appearance, sores on the body, and dyspnea.

The first palpable nodule was noted during the latter part of the first year in the axilla of a high dose female. Several palpable nodules, tissue masses, or wart-like lesions were noted in all groups during the second year of the study.

B. Survival

The estimated probabilities of survival for male and female rats in the control and tetrachloroethylene-dosed groups are shown in Figure 2.

For both male and female rats, the Tarone test indicated a statistically significant association ($P < 0.001$) between increased dosage and elevated mortality. For both sexes this association was particularly marked after 30 weeks.

Fifty percent of the high dose males died by week 44, and 50 percent of the high dose females died by week 66. By comparison, the median survival for each of the control groups was over 88 weeks for

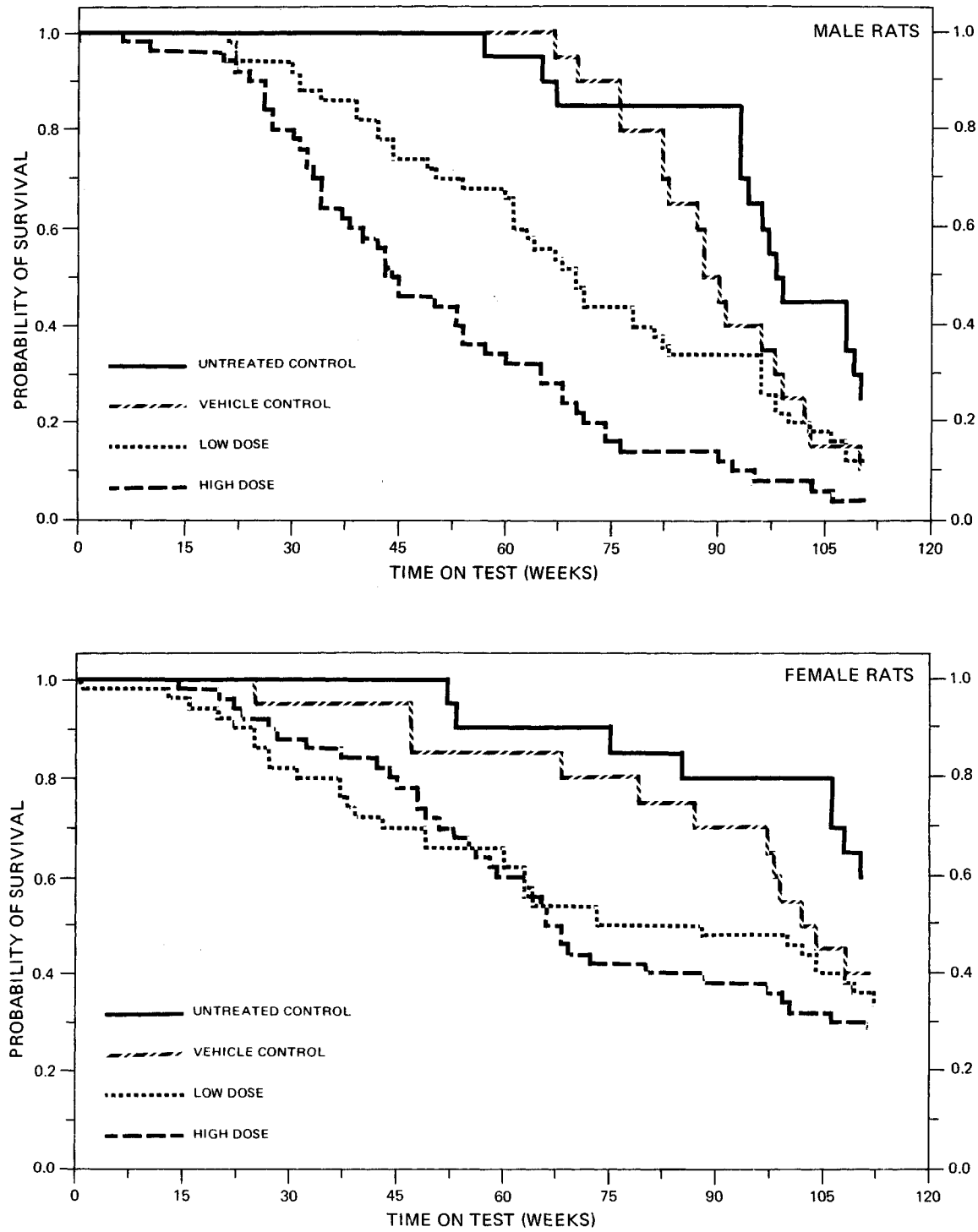


FIGURE 2
SURVIVAL COMPARISONS OF TETRACHLOROETHYLENE CHRONIC STUDY RATS

the males and over 102 weeks for the females. The early deaths and their significant association with dose levels imply that optimum dosage was exceeded in the rats. These unusually early deaths were not associated with observed tumors.

C. Pathology

Histopathologic findings on neoplasms in rats are tabulated in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are tabulated in Appendix C (Tables C1 and C2).

Toxic nephropathy was noticed early in the study and occurred in 43/49 low dose males, 47/50 high dose males, 29/50 low dose females, 39/50 high dose females, and in no control animals. Microscopically, toxic nephropathy was characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium. Some affected tubules were empty, others were filled with hyalin casts. In occasional tubules, the damaged cells were replaced by enlarged darkstaining regenerative tubular epithelial cells. At this stage the kidney often had infiltration of inflammatory cells, fibrosis, and focal mineralization.

Renal neoplasms were either malignant mixed tumors or hamartomas.* Malignant mixed tumors occurred in 1/19 untreated control males, 2/20 vehicle control males, 1/49 low dose males, and 0/50 high

*Nonneoplastic proliferative lesions composed of lipocytes, tubular structures, and fibroblasts in varying proportions.

dose males. One high dose female (1/50) was the only female in which these malignant mixed tumors were observed. Hamartomas occurred in 1/20 vehicle control males, 1/50 high dose males, and 1/20 untreated control females. They were not detected in any other animals. Malignant mixed tumors were composed predominantly of spindled cells and immature fat cells with nuclear variability (atypia) and occasional mitotic figures present. The cells comprising the epithelial component (embryonic renal tubules) of the malignant neoplasms were not appreciably different from those present in the hamartomas. The malignant mixed tumors were not well-circumscribed. There was extensive invasion and destruction of the adjacent renal tissue and the neoplasm often extended beyond the renal capsule to involve the surrounding abdominal viscera. The hamartomas were composed of a mixture of mature fat cells, occasional renal tubules that were embryonic in appearance, and spindled cells. These lesions were generally circumscribed from the surrounding renal parenchyma.

Other inflammatory, degenerative, and proliferative lesions observed in control and test animals were similar in number and kind to those spontaneous lesions found in aged rats.

No pathologic evidence of the carcinogenicity of tetrachloroethylene was noted; however, tetrachloroethylene caused toxic nephropathy in the kidneys of the male and female rats.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis for every type

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH TETRACHLOROETHYLENE[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
All Sites: Hemangiosarcoma[b]	2/20(0.10)	1/20(0.05)	2/50(0.04)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk(Untreated Control)[d]	---	---	0.400	0.200
Lower Limit	---	---	0.032	0.007
Upper Limit	---	---	5.277	3.681
Relative Risk(Vehicle Control)[d]	---	---	0.800	0.400
Lower Limit	---	---	0.045	0.005
Upper Limit	---	---	46.273	30.802
Weeks to First Observed Tumor	93	70	67	103
Pituitary: Chromophobe Adenoma or Carcinoma[b]	4/19(0.21)	0/20(0.00)	1/49(0.02)	0/44(0.00)
P Values[c]	P = 0.002(N)	N.S.	P = 0.019*(N)	P = 0.007*(N)
Departure from Linear Trend	P = 0.036	---	---	---
Relative Risk(Untreated Control)[d]	---	---	0.097	0.000
Lower Limit	---	---	0.002	0.000
Upper Limit	---	---	0.913	0.459
Relative Risk(Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.023	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	93	---	112	---
Pituitary: Chromophobe Adenoma[b]	3/19(0.16)	0/20(0.00)	1/49(0.02)	0/44(0.00)
P Values[c]	P = 0.008(N)	N.S.	N.S.	P = 0.024*(N)
Relative Risk(Untreated Control)[d]	---	---	0.129	0.000
Lower Limit	---	---	0.003	0.000
Upper Limit	---	---	1.517	0.709
Relative Risk(Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.023	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	93	---	112	---

[a] Dosed groups received time-weighted average doses of 471 and 949 mg/kg by gavage.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] Beneath the incidence of each of the controls is the probability level for the Cochran-Armitage test for dose-related trend in proportions when it is below 0.05, otherwise N.S. - not significant. Departure from linear trend is noted when it is below 0.05 for any comparison. Beneath the dose group incidence is the probability level for the Fisher exact (conditional) test for the comparison of that dose group with the tetrachloroethylene untreated control group (*) and the vehicle control group (**) when either is below 0.05, otherwise N.S. - not significant.

(N) Less incidence in the dose group(s) than in a control group results in a negative indication.

[d] Relative Risk of the treated group versus the control group is shown along with the lower and upper limit of the 95% confidence interval for that Relative Risk.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH TETRACHLOROETHYLENE[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	3/20(0.15)	3/20(0.15)	7/50(0.14)	7/50(0.14)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk(Untreated Control)[d]	---	---	0.933	0.933
Lower Limit	---	---	0.245	0.245
Upper Limit	---	---	5.215	5.215
Relative Risk(Vehicle Control)[d]	---	---	0.933	0.933
Lower Limit	---	---	0.245	0.245
Upper Limit	---	---	5.215	5.215
Weeks to First Observed Tumor	106	---	112	97
All Sites: Hemangiosarcoma[b]	0/20(0.00)	0/20(0.00)	1/50(0.02)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk(Untreated Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.022	---
Upper Limit	---	---	Infinite	---
Relative Risk(Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.022	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	60	---
Pituitary: Chromophobe Adenoma[b]	8/20(0.40)	4/20(0.20)	9/50(0.18)	6/50(0.12)
P Values[c]	P = 0.009(N)	N.S.	N.S.	P = 0.012*(N)
Relative Risk(Untreated Control)[d]	---	---	0.450	0.300
Lower Limit	---	---	0.191	0.104
Upper Limit	---	---	1.177	0.871
Relative Risk(Vehicle Control)[d]	---	---	0.900	0.600
Lower Limit	---	---	0.294	0.165
Upper Limit	---	---	3.660	2.659
Weeks to First Observed Tumor	85	85	73	97

[a] Dosed groups received time-weighted average doses of 474 and 949 mg/kg by gavage.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] Beneath the incidence of each of the controls is the probability level for the Cochran-Armitage test for dose-related trend in proportions when it is below 0.05, otherwise N.S. - not significant. Departure from linear trend is noted when it is below 0.05 for any comparison. Beneath the dose group incidence is the probability level for the Fisher exact (conditional) test for the comparison of that dose group with the tetrachloroethylene untreated control group (*) and the vehicle control group (**) when either is below 0.05, otherwise N.S. - not significant.

(N) Less incidence in the dose group(s) than in a control group results in a negative indication.

[d] Relative Risk of the treated group versus the control group is shown along with the lower and upper limit of the 95% confidence interval for that Relative Risk.

of tumor that was observed in more than 5 percent of any of the tetrachloroethylene-dosed groups of either sex is included.

Neither the Cochran-Armitage tests nor the Fisher exact tests indicated any statistically significant increase in the proportion of tumors found in dosed groups over that found in either control group for any tumor type for either sex. This experiment, therefore, provides no evidence of the carcinogenicity of tetrachloroethylene in rats.

To provide additional insight, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. The implication of such intervals is that in 95 percent of a large number of identical experiments, the true ratio of the tumor rate of the dosed group to that of the control group would be inside the interval as calculated from this experiment. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of a significantly increased rate of tumor incidence induced in rats by tetrachloroethylene that could not be established under the conditions of this test.

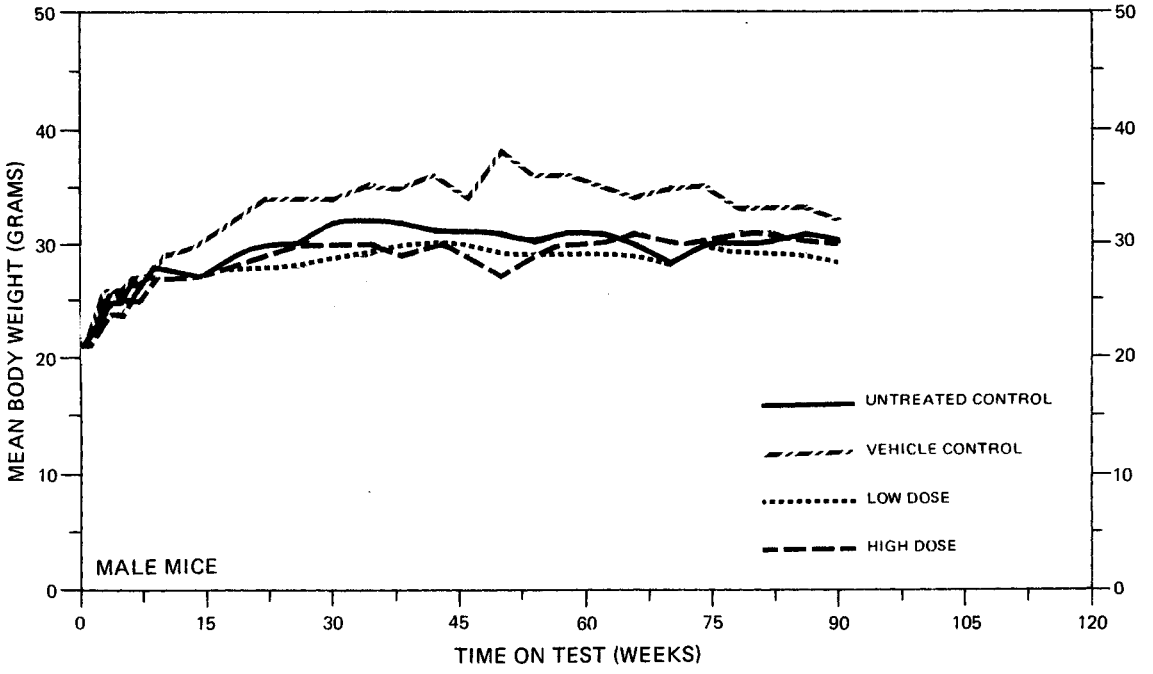
IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

There were no appreciable differences in mean body weight gain between dosed mice and untreated mice of either sex during this bioassay (Figure 3). Dosed male mice did, however, gain less weight than vehicle control males after the first three months, and dosed female mice did gain less than vehicle control females during the second year of the bioassay.

Appearance and behavior were generally similar for control and treated mice during the first 26 weeks of the study. Signs often observed in group-housed laboratory mice were noted with a slightly greater frequency in the treated mice of both sexes than in the respective control animals during the remainder of the first year. These signs included body sores (particularly in the males), anal or penile irritation, rough or stained fur, and generalized or localized alopecia.

A greater number of treated mice of both sexes showed a hunched appearance from week 42 through week 62. Thereafter, surviving test animals exhibited a hunched appearance at a comparable frequency to the controls. A low incidence of bloating or abdominal distension was noted in the treated groups during the second year of the study. Nodules were palpated on the ventral region of a few animals as early as week 6; however, most of these palpable nodules were not persistent



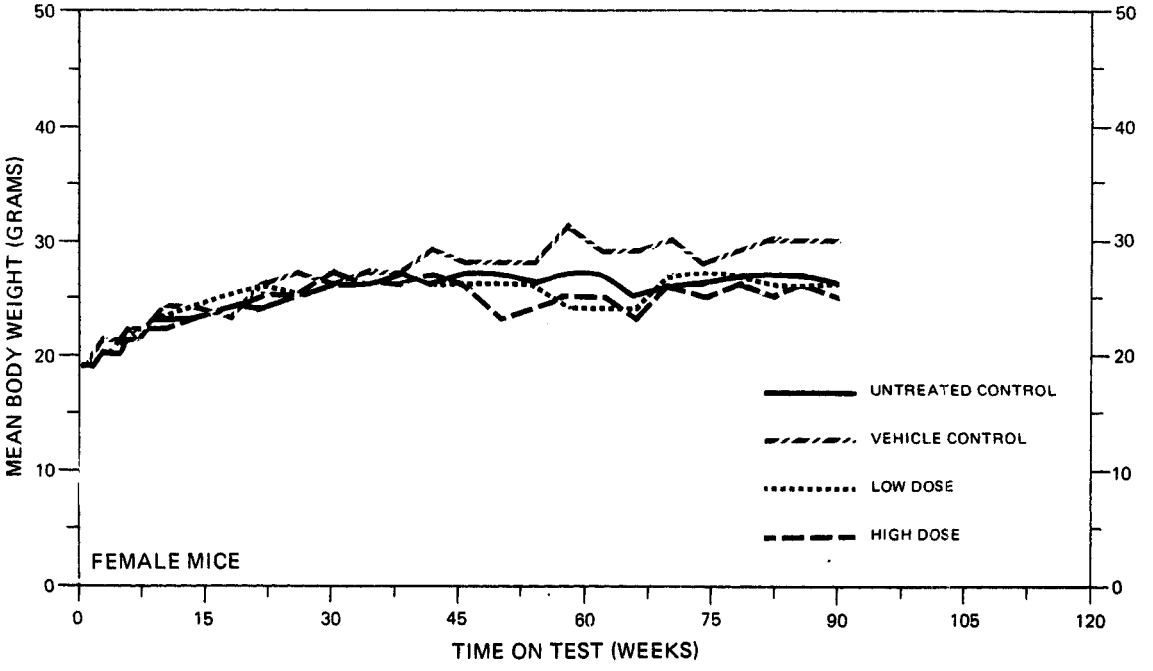


FIGURE 3
GROWTH CURVES FOR TETRACHLOROETHYLENE CHRONIC STUDY MICE

and were probably abscesses that drained and healed during the course of the study.

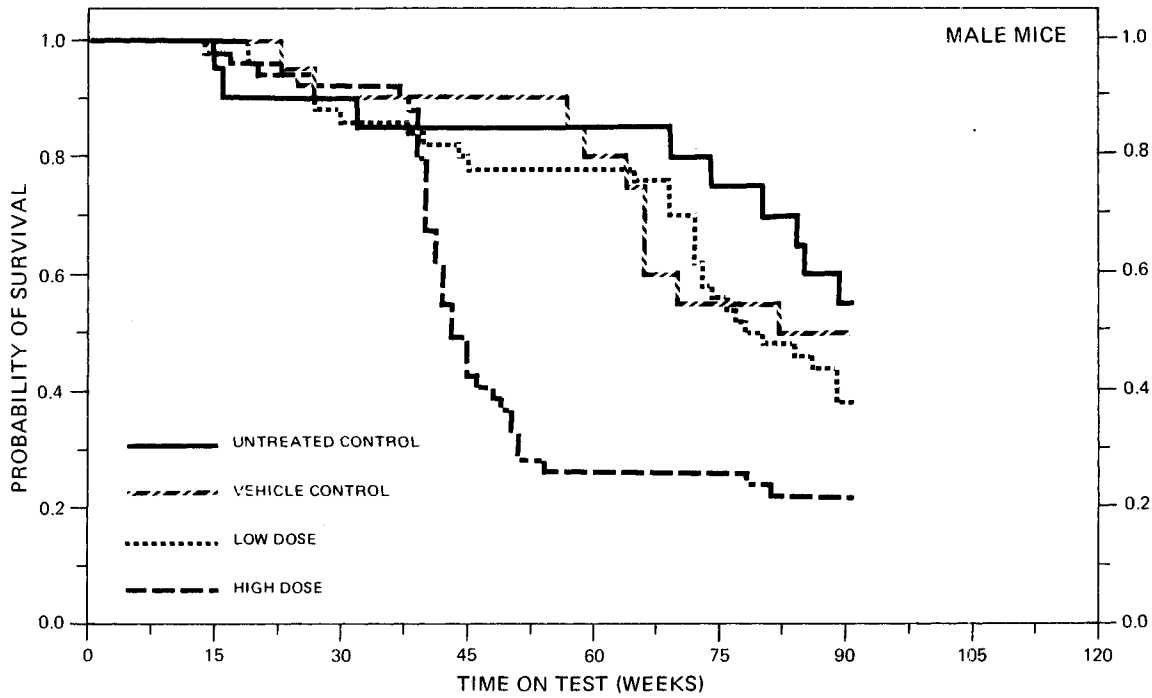
B. Survival

The estimated probabilities of survival for male and female mice in the control and tetrachloroethylene-dosed groups are shown in Figure 4.

For mice of both sexes the Tarone test indicated a significant ($P < 0.001$) association between increased dosage of tetrachloroethylene and elevated mortality. Fifty percent of each control group of male mice survived to termination of the experiment (over 90 weeks), compared to a median survival of 78 weeks in the low dose males and 43 weeks in the high dose males. In female mice, the median survival for both vehicle and untreated controls was over 90 weeks (termination of the experiment) compared to 62 weeks in the low dose group and 50 weeks in the high dose group. As may be seen in Figure 4, the survival curves for the high dose groups of both sexes were substantially lower than the control group curves after 40 to 45 weeks. While the early mortality in mice may indicate that the optimum dose was exceeded, it must also be noted that liver tumors were found in substantial numbers of the mice of both sexes that died early in the experiment.

C. Pathology

Histopathologic findings on neoplasms in mice are tabulated in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are tabulated in Appendix D (Tables D1 and D2).



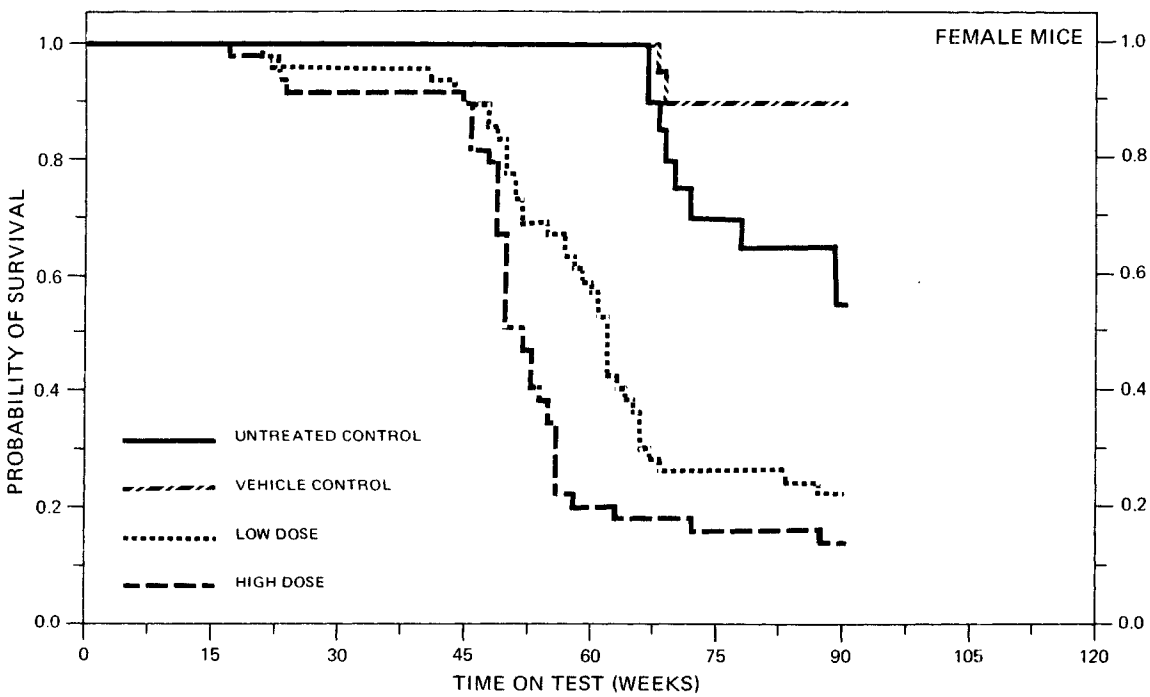


FIGURE 4
SURVIVAL COMPARISONS OF TETRACHLOROETHYLENE CHRONIC STUDY MICE

Hepatocellular carcinomas occurred in 2/17 (12 percent) untreated control males, 2/20 (10 percent) vehicle control males, 32/49 (65 percent) low dose males, 27/48 (56 percent) high dose males, 2/20 (10 percent) untreated control females, 0/20 vehicle control females, 19/48 (40 percent) low dose females, and 19/48 (40 percent) high dose females. Hepatocellular carcinomas metastasized to the kidney in 1/18 untreated control males and to the lung in 3/49 low dose males, 1/49 low dose females, and 1/48 high dose females.

The hepatocellular carcinomas varied greatly in appearance. Some lesions consisted of well-differentiated hepatocytes that were arranged in relatively uniform hepatic cords. Other hepatocellular carcinomas had very anaplastic cells with large hyperchromatic nuclei, often with inclusion bodies and with vacuolated, pale cytoplasm. Arrangement of the neoplastic cells varied from short stubby cords to nests of hepatic cells and occasionally acinar formation. Mitotic figures were often present. Some of the tumors were characterized by discrete areas of highly anaplastic cells. The hepatic neoplasms occurring in the control mice were not different in appearance from those noted in the mice receiving tetrachloroethylene.

Nonneoplastic hepatic cell proliferation (foci of altered hepatic cells) was found only in 3/48 high dose male mice.

Tetrachloroethylene also caused toxic nephropathy in 40/49 low dose males, 45/48 high dose males, 46/48 low dose females, and 48/48 high dose females. This condition was not observed in control

animals. The toxic effect of this chemical on the morphology of the epithelium of the proximal convoluted tubules was similar to that seen in the treated rats.

Chronic murine pneumonia occurred frequently. Other nonneoplastic lesions, such as degeneration and inflammation of various tissues, occurred in the treated and control animals in a relatively low incidence.

Results of this pathologic examination indicate that tetrachloroethylene is hepatocarcinogenic and also causes toxic nephropathy in the kidneys of both male and female mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis for every type of tumor that was observed in more than 5 percent of any of the tetrachloroethylene-dosed groups of either sex is included.

Two control groups were used in the standard statistical analyses: the untreated control group and the vehicle control group. The specific tumor incidences of these control groups were compared to the corresponding spontaneous tumor rates for the historical controls compiled to date on B6C3F1 mice by this bioassay program. No significant differences were observed.

In male mice, hepatocellular carcinomas were found in large numbers in the dosed groups. The Cochran-Armitage tests for positive dose-related trend were highly significant using either the untreated

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH TETRACHLOROETHYLENE[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	2/17(0.12)	2/20(0.10)	32/49(0.65)	27/48(0.56)
P Values[c]	P = 0.018	P = 0.006	P < 0.001* P < 0.001**	P = 0.001 P < 0.001**
Departure from Linear Trend	P = 0.002	P = 0.001	---	---
Relative Risk(Untreated Control)[d]	---	---	5.551	4.781
Lower Limit	---	---	1.709	1.440
Upper Limit	---	---	42.979	37.964
Relative Risk(Vehicle Control)[d]	---	---	6.531	5.625
Lower Limit	---	---	1.972	1.660
Upper Limit	---	---	50.795	44.815
Weeks to First Observed Tumor	91	90	27	40
Lung: Alveolar/Bronchiolar Adenoma[b]	2/18(0.11)	0/20(0.00)	3/49(0.06)	0/48(0.00)
P Values[c]	P = 0.036(N)	N.S.	N.S.	N.S.
Departure from Linear Trend	---	P = 0.047	---	---
Relative Risk(Untreated Control)[d]	---	---	0.551	0.000
Lower Limit	---	---	0.071	0.000
Upper Limit	---	---	6.284	1.259
Relative Risk(Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.255	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	84	---	91	---
Hematopoietic System: Malignant Lymphoma[b]	1/18(0.06)	2/20(0.10)	0/49(0.00)	0/48(0.00)
P Values[c]	N.S.	P = 0.026(N)	N.S.	N.S.
Relative Risk(Untreated Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	6.864	7.004
Relative Risk(Vehicle Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	1.372	1.400
Weeks to First Observed Tumor	91	66	---	---

TABLE 5
(CONCLUDED)

[a]Dosed groups received time-weighted average doses of 536 and 1072 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]Beneath the incidence of each of the controls is the probability level for the Cochran-Armitage test for dose-related trend in proportions when it is below 0.05, otherwise N.S. - not significant. Departure from linear trend is noted when it is below 0.05 for any comparison. Beneath the dose group incidence is the probability level for the Fisher exact (conditional) test for the comparison of that dose group with the untreated control group (*) and the vehicle control group (**) when either is below 0.05, otherwise N.S. - not significant.

(N) Less incidence in the dose group(s) than in a control group results in a negative indication.

[d]Relative Risk of the treated group versus the control group is shown along with the lower and upper limit of the 95% confidence interval for that Relative Risk.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH TETRACHLOROETHYLENE[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	2/20(0.10)	0/20(0.00)	19/48(0.40)	19/48(0.40)
P Values[c]	P = 0.033	P = 0.006	P = 0.014* P < 0.001**	P = 0.014* P < 0.001**
Departure from Linear Trend	---	P = 0.030	---	---
Relative Risk(Untreated Control)[d]	---	---	3.958	3.958
Lower Limit	---	---	1.109	1.109
Upper Limit	---	---	32.790	32.790
Relative Risk(Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	2.656	2.656
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	91	---	41	50
Lung: Alveolar/Bronchiolar Adenoma[b]	1/20(0.05)	0/20(0.00)	0/48(0.00)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk(Untreated Control)[d]	---	---	0.000	0.426
Lower Limit	---	---	0.000	0.006
Upper Limit	---	---	7.780	32.720
Relative Risk(Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.023
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	91	---	---	91

TABLE 6
(CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	0/20(0.00)	4/20(0.20)	0/48(0.00)	1/48(0.02)
P Values[c]	N.S.	P = 0.010(N)	P = 0.006**(N)	P = 0.024**(N)
Relative Risk(Untreated Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.024
Upper Limit	---	---	---	Infinite
Relative Risk(Vehicle Control)[d]	---	---	0.000	0.104
Lower Limit	---	---	0.000	0.002
Upper Limit	---	---	0.444	0.982
Weeks to First Observed Tumor	---	69	---	91

[a]Dosed groups received time-weighted average doses of 386 and 772 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]Beneath the incidence of each of the controls is the probability level for the Cochran-Armitage test for dose-related trend in proportions when it is below 0.05, otherwise N.S. - not significant. Departure from linear trend is noted when it is below 0.05 for any comparison. Beneath the dose group incidence is the probability level for the Fisher exact (conditional) test for the comparison of that dose group with the untreated control group (*) and the vehicle control group (**) when either is below 0.05, otherwise N.S. - not significant.

(N) Less incidence in the dose group(s) than in a control group results in a negative indication.

[d]Relative Risk of the treated group versus the control group is shown along with the lower and upper limit of the 95% confidence interval for that Relative Risk.

controls (P = 0.018) or the vehicle controls (P = 0.006). The departures from linear trend were also significant (P = 0.002 and P = 0.001, using the untreated control and the vehicle control, respectively) because of the large proportions of dosed animals with this tumor. Additionally, the Fisher exact tests comparing incidences among the control and dosed groups all confirmed this positive finding: untreated control to low dose ($P < 0.001$), vehicle control to low dose ($P < 0.001$), untreated control to high dose (P = 0.001), and vehicle control to high dose ($P < 0.001$). Finally, the entire region of the 95 percent confidence interval on the relative risk of the dosed group(s) to the control group(s) was greater than the value one.

The first of the hepatocellular carcinomas to be detected in male mice at necropsy was found in week 27 in the low dose group, compared to week 40 in the high dose group and weeks 90 and 91 in the vehicle and untreated control groups. An additional time-adjusted analysis was performed to estimate the probability of observing a hepatocellular carcinoma in a necropsied male mouse. Based on Kaplan and Meier techniques, the probability of observing a hepatocellular carcinoma by week 91 was estimated to be 1.00 for a high dose male mouse.

These statistical results indicate that the occurrence of hepatocellular carcinomas in male mice was associated with the administration of tetrachloroethylene at the dose levels of this

experiment. There were no other tumors of male mice for which statistical tests indicated a positive association between tetrachloroethylene administration and tumor incidence.

The incidence of hepatocellular carcinoma was also highly significant in female mice. The Cochran-Armitage tests for positive dose-related trend in proportions were found to be significant compared both to the untreated control ($P = 0.033$) and to the vehicle control ($P = 0.006$). A departure from linear trend ($P = 0.030$) was noted with the vehicle controls due to the sharp increase of the incidence of hepatocellular carcinomas in the dosed groups. The results of the Fisher exact tests confirmed this positive finding: both the low and high dose animals demonstrated significant tumor increases as compared to either the untreated controls ($P = 0.014$) or the vehicle controls ($P < 0.001$). Finally, the lower limits of the 95 percent confidence interval of the relative risk of the dosed group(s) versus the control group(s) were greater than one.

The first of the hepatocellular carcinomas to be detected in female mice at necropsy was found in week 41 in the low dose group, compared to week 50 in the high dose group and week 91 in the untreated control group. An additional time-adjusted analysis was performed to estimate the probability of observing a hepatocellular carcinoma in a necropsied female mouse. Based on adjusted Kaplan and Meier techniques, the probability of observing hepatocellular

carcinoma by week 91 was estimated to be 0.938 for a high dose female mouse.

These statistical results indicate that the occurrence of hepatocellular carcinomas in female mice was associated with the administration of tetrachloroethylene at the dose levels used in this experiment. There were no other tumors of female mice for which statistical tests indicated a positive association between tetrachloroethylene administration and tumor incidences.

In addition to the previous analyses, the incidence of hepatocellular carcinomas in dosed mice was compared to the incidence in pooled controls. A pooled group of untreated controls was formed by combining the untreated controls from the tetrachloroethylene study with the untreated controls from the studies of methylchloroform, 1,1-dichloroethane, and chloroform. Vehicle controls from the same four studies were also combined to form a pooled vehicle control. These pooled controls were of the same strain and were placed on test in the same room during a time span exceeding a year. The results of these analyses are presented in Tables 7 and 8.

The Cochran-Armitage tests indicated a significant positive dose-related trend ($P < 0.001$) in both sexes using either of the pooled control groups. The significant departures from linear trend ($P < 0.001$ in the male mice for both pooled untreated and pooled vehicle controls, $P = 0.011$ in female mice using the pooled untreated controls, and $P = 0.006$ in female mice using the pooled vehicle

TABLE 7

ANALYSES OF THE INCIDENCE OF HEPATOCELLULAR CARCINOMA
IN MALE MICE TREATED WITH TETRACHLOROETHYLENE[a]

TOPOGRAPHY: MORPHOLOGY	POOLED UNTREATED CONTROL	POOLED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	7/84(0.08)	7/97(0.07)	32/49(0.65)	27/48(0.56)
P Values[c]	P < 0.001	P < 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend	P < 0.001	P < 0.001	---	---
Relative Risk(Pooled Untreated Control)[d]	---	---	7.837	6.750
Lower Limit	---	---	3.811	3.177
Upper Limit	---	---	18.041	16.153
Relative Risk(Pooled Vehicle Control)[d]	---	---	9.050	7.795
Lower Limit			4.384	3.654
Upper Limit	---	---	20.868	18.687
Weeks to First Observed Tumor	---	---	27	40

[a]Dosed groups received time-weighted average doses of 536 and 1072 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]Beneath the incidence of each of the controls is the probability level for the Cochran-Armitage test for dose-related trend in proportions when it is below 0.05, otherwise N.S. - not significant. Departure from linear trend is noted when it is below 0.05 for any comparison. Beneath the dose group incidence is the probability level for the Fisher exact (conditional) test for the comparison of that dose group with the pooled untreated control group (*) and the pooled vehicle control group (**) when either is below 0.05.

[d]Relative Risk of the treated group versus the control group is shown along with the lower and upper limit of 95% confidence interval for that Relative Risk.

TABLE 8

ANALYSES OF THE INCIDENCE OF HEPATOCELLULAR CARCINOMA
IN FEMALE MICE TREATED WITH TETRACHLOROETHYLENE[a]

TOPOGRAPHY: MORPHOLOGY	POOLED UNTREATED CONTROL	POOLED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	4/97(0.04)	2/99(0.02)	19/48(0.40)	19/48(0.40)
P Values[c]	P < 0.001	P < 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend	P = 0.011	P = 0.006	---	---
Relative Risk(Pooled Untreated Control)[d]	---	---	9.599	9.599
Lower Limit	---	---	3.425	3.425
Upper Limit	---	---	35.988	35.988
Relative Risk(Pooled Vehicle Control)[d]	---	---	19.594	19.594
Lower Limit	---	---	5.024	5.024
Upper Limit	---	---	164.707	164.707
Weeks to First Observed Tumor	---	---	41	50

[a]Dosed groups received time-weighted average doses of 386 and 772 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]Beneath the incidence of each of the controls is the probability level for the Cochran-Armitage test for dose-related trend in proportions when it is below 0.05, otherwise N.S. - not significant. Departure from linear trend is noted when it is below 0.05 for any comparison. Beneath the dose group incidence is the probability level for the Fisher exact (conditional) test for the comparison of that dose group with the pooled untreated control group (*) and the pooled vehicle control group (**) when either is below 0.05.

[d]Relative Risk of the treated group versus the control group is shown along with the lower and upper limit of the 95% confidence interval for that Relative Risk.

controls) were due to the sharp increase in the incidence of hepatocellular carcinomas in the dosed groups. Finally, the Fisher exact tests also provided evidence of the existence of a positive dose-response relationship, since every comparison of a dosed group to a pooled control was highly significant ($P < 0.001$).

V. DISCUSSION

Under the conditions of this study, administration of tetrachloroethylene was associated with a significantly increased incidence of hepatocellular carcinomas in both low and high dose groups of male and female mice. Because of inadequate survival, the bioassay on rats must be considered inconclusive.

Statistical tests indicated a strong association between administration of tetrachloroethylene and the occurrence of hepatocellular carcinomas in both male and female mice. Incidence of hepatocellular carcinomas exhibited a significant positive dose-related trend in mice of both sexes. Hepatocellular carcinomas appeared early in dosed mice. The first hepatocellular carcinoma observed at necropsy occurred in a male low dose mouse that died during week 27. No hepatocellular carcinomas were observed in control mice dying before week 90. A time-adjusted analysis, based on Kaplan and Meier techniques, estimated that the probability of observing hepatocellular carcinoma by week 91 was 1.00 for a high dose male mouse and 0.938 for a high dose female mouse. A small number of hepatocellular carcinomas in tetrachloroethylene-treated mice of both sexes metastasized to the lung, while a single hepatocellular carcinoma in an untreated control male metastasized to the kidney.

No other tumors were observed in male or female mice for which statistical tests indicated a positive association between tetrachloroethylene treatment and tumor incidence.

Mice were housed in a room where other bioassays for carcinogenicity were being performed; however, stringent measures were taken to prevent cross-contamination of animals. The low incidence of neoplasms in control mice suggests that no significant extraneous exposure to carcinogens occurred.

No significant increase in tumor incidence was observed among rats treated with tetrachloroethylene, but because of a high rate of early deaths in treated rats the results of this bioassay do not allow an evaluation of the carcinogenicity of this compound. Mortality rates for rats were dose-related. Fifty percent of the high dose male rats had died by week 44 and 50 percent of the high dose females had died by week 66. Toxic nephropathy was observed in rats that died early in the study (as early as week 20 for male rats and week 28 for female rats). Lesions indicative of pneumonia were observed at necropsy in nearly all rats in this bioassay.

In bioassays using the same strain of rats following a similar protocol and conducted by the same laboratory, only a low incidence (about 5 percent) of hepatocellular carcinoma was observed in rats receiving carbon tetrachloride (considered a positive control) (National Cancer Institute, 1976). It appears, therefore, that the Osborne-Mendel rat has a low degree of sensitivity to induction of hepatocellular carcinoma by chlorinated organic compounds.

The results of this study indicate that tetrachloroethylene is a liver carcinogen in B6C3F1 mice of both sexes. The lack of an

observable carcinogenic effect in rats may be due to poor survival of high dose rats and to a low degree of susceptibility to hepatocellular carcinoma in the Osborne-Mendel rat. The toxic effect of tetrachloroethylene on the kidney was evident in both species. Toxic nephropathy was observed in 79 percent of the dosed rats and 93 percent of the dosed mice.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, Chapter 14. J. Wiley & Sons, New York, 1971.

Berenblum, I., editor, Carcinogenicity Testing. International Union Against Cancer, Technical Report Series, Vol. 2. International Union Against Cancer, Geneva, 1969.

Chemical Abstracts Service, The Chemical Abstracts Service (CAS) Ninth Collective Index, Volumes 76-85, 1972-1976. American Chemical Society, Washington, D.C., 1977.

Chemical Information Services, Stanford Research Institute. Menlo Park, California, 1975.

Cox, D.R., Analysis of Binary Data, Chapters 4 and 5. Methuen and Co., Ltd., London, 1970.

Cox, D.R., "Regression Models and Life-Tables." Journal of the Royal Statistical Society, Series "B" 34:187-220, 1972.

Dowty, B., D. Carlisle, and J.L. Laseter, "Halogenated Hydrocarbons in New Orleans Drinking Water and Blood Plasma." Science 187(4171):75-77, 1975.

Fishbein, L., "Industrial Mutagens and Potential Mutagens. I. Halogenated Aliphatic Derivatives." Mutation Research 32:267-308, 1976.

Gart, J.J., "The Comparison of Proportion: A Review of Significance Tests, Confidence Limits, and Adjustments for Stratification." International Statistical Institute Review 39:148-169, 1971.

Ikeda, M. and T. Imamura, "Biological Half-Life of Trichloroethylene and Tetrachloroethylene in Human Subjects." International Archives of Occupational Health 31(3):209, 1973.

Kaplan, E.L., and P. Meier, "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association 53:457-481, 1958.

Linhart, M.S., J.A. Cooper, R.L. Martin, N.P. Page, and J.A. Peters, "Carcinogenesis Bioassay Data System." Computers and Biomedical Research 7:230-248, 1974.

McConnell, G., D.M. Ferguson, and C.R. Pearson, "Chlorinated Hydrocarbons and the Environment." Endeavor 34:13-27, 1975.

Miller, R.G., Simultaneous Statistical Inference. McGraw-Hill Book Co., New York, 1976.

National Cancer Institute, "Carcinogenesis Bioassay of Trichloroethylene." Carcinogenesis Technical Report Series No. 2, NCI-CG-TR-2, DHEW Publication No. (NIH)76-802, 1976.

Reuber, M.D., and E.L. Glover, "Cirrhosis and Carcinoma of the Liver in Male Rats Given Subcutaneous Carbon Tetrachloride." Journal of the National Cancer Institute 44:419-423, 1970.

Rowe, V.K., D.D. McCollister, H.C. Spencer, E.M. Adams, and D.D. Irish, "Vapor Toxicity of Tetrachloroethylene for Laboratory Animals and Human Subjects." American Medical Association Archives of Industrial Hygiene and Occupational Medicine 5:566-579, 1952.

Saffiotti, U., R. Montesano, A.R. Sellakumar, F. Cefis, and D.G. Kaufman, "Respiratory Tract Carcinogenesis in Hamsters Induced by Different Numbers of Administration of Benzo (a) Pyrene and Ferric Oxide." Cancer Research 32:1073-1079, 1972.

Sax, N.I., Dangerous Properties of Industrial Materials. Van Nostrand Reinhold Company, New York, 1975.

Senewiratne, B., J. Hettiarachchi, and K. Senewiratne, "A Comparative Study of the Relative Efficacy of Pyrantel Pamoate, Bephenium Hydroxynaphthoate and Tetrachloroethylene in the Treatment of Necator americanus Infection in Ceylon." Annals of Tropical Medicine and Parasitology 69(2):233-239, 1975.

Stanford Research Institute, Research Program on Hazard Priority Ranking of Manufactured Chemicals: Phase II, Final Report. Menlo Park, California, 1975.

Tarone, R. E., "Tests for Trend in Life-Table Analysis." Biometrika 62:679-682, 1975.

U.S. International Trade Commission, Synthetic Organic Chemicals. United States Production and Sales, 1974. USITC Publication 776, Washington, D.C., 1976.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH TETRACHLOROETHYLENE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 01-141M	CONTROL (VEH) 01-091M	LOW DOSE 01-142M	HIGH DOSE 01-143M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	49	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
FIBROMA	1 (5%)			1 (2%)
HEMANGIOSARCOMA			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(48)	(50)
ADENOSQUAMOUS CARCINOMA		1 (5%)		
HEMATOPOIETIC SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#SPLEEN	(19)	(20)	(49)	(50)
HEMANGIOSARCOMA	2 (11%)	1 (5%)	1 (2%)	
#CERVICAL LYMPH NODE	(19)	(20)	(49)	(49)
ADENOSQUAMOUS CARCINOMA, METASTA		1 (5%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
#KIDNEY	(19)	(20)	(49)	(50)
ADENOSQUAMOUS CARCINOMA, METASTA		1 (5%)		
MIXED TUMOR, MALIGNANT	1 (5%)	2 (10%)	1 (2%)	
HAMARTOMA		1 (5%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-141M	CONTROL (VEH) 01-091M	LOW DOSE 01-142M	HIGH DOSE 01-143M
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(49)	(44)
CHROMOPHOBE ADENOMA	3 (16%)		1 (2%)	
CHROMOPHOBE CARCINOMA	1 (5%)			
#THYROID	(19)	(20)	(48)	(49)
FOLLICULAR-CELL ADENOMA		1 (5%)		
FOLLICULAR-CELL CARCINOMA	1 (5%)			
C-CELL ADENOMA				1 (2%)
#PANCREATIC ISLETS	(19)	(19)	(48)	(50)
ISLET-CELL ADENOMA	2 (11%)		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
FIBROADENOMA	1 (5%)			
NERVOUS SYSTEM				
#BRAIN	(19)	(20)	(49)	(50)
CHROMOPHOBE CARCINOMA, METASTATI	1 (5%)			
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
SPINDLE/GIANT-CELL CARCINOMA		1 (5%)		
ALL OTHER SYSTEMS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-141M	CONTROL (VEH) 01-091M	LOW DOSE 01-142M	HIGH DOSE 01-143M
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	14	18	43	48
MORIBUND SACRIFICE	1		1	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	5	2	6	2
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	5	5	5
TOTAL PRIMARY TUMORS	12	7	5	6
TOTAL ANIMALS WITH BENIGN TUMORS	6	2	2	4
TOTAL BENIGN TUMORS	7	2	2	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	5	3	2
TOTAL MALIGNANT TUMORS	5	5	3	2
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		
TOTAL SECONDARY TUMORS	1	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	20	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
FIBROSARCOMA				1 (2%)
*SUBCUTIISSUE	(20)	(20)	(50)	(50)
FIBROMA				1 (2%)
FIBROSARCOMA	1 (5%)			2 (4%)
LIPOMA			1 (2%)	1 (2%)
HEMANGIOSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
LYMPHOCYTIC LEUKEMIA			1 (2%)	
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#SPLEEN	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)		
#THYMUS	(16)	(15)	(31)	(23)
LIPOMA				1 (4%)
CIRCULATORY SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

*U.S. GOVERNMENT PRINTING OFFICE: 1977 241-161/3124 1-3

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(50)	(33)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
NEOPLASTIC NODULE	1 (5%)			
#PANCREAS	(20)	(18)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
#STOMACH	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
HAMARTOMA	1 (5%)			
#RIGHT KIDNEY	(20)	(20)	(50)	(50)
MIXED TUMOR, MALIGNANT				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(20)	(50)	(50)
CHROMOPHOBE ADENOMA	8 (40%)	4 (20%)	9 (18%)	6 (12%)
#ADRENAL	(20)	(20)	(50)	(50)
CORTICAL CARCINOMA				1 (2%)
MIXED TUMOR, METASTATIC				1 (2%)
#THYROID	(19)	(20)	(49)	(50)
FOLLICULAR-CELL ADENOMA				1 (2%)
C-CELL ADENOMA	2 (11%)			
C-CELL CARCINOMA				1 (2%)
#PANCREATIC ISLETS	(20)	(18)	(50)	(50)
ISLET-CELL ADENOMA	1 (5%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOMA, NOS				1 (2%)
ADENOCARCINOMA, NOS		1 (5%)	1 (2%)	2 (4%)
FIBROMA			1 (2%)	
FIBROADENOMA	3 (15%)	3 (15%)	7 (14%)	7 (14%)

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
#UTERUS	(20)	(19)	(48)	(50)
ADENOCARCINOMA, NOS			1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (5%)			
#OVARY	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
CYSTADENOCARCINOMA, NOS			1 (2%)	
GRANULOSA-CELL CARCINOMA		1 (5%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	8	12	32	36
MORIBUND SACRIFICE			1	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	12	8	17	14
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	13	7	17	15
TOTAL PRIMARY TUMORS	18	10	25	27
TOTAL ANIMALS WITH BENIGN TUMORS	13	6	14	12
TOTAL BENIGN TUMORS	16	7	19	18
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	2	6	7
TOTAL MALIGNANT TUMORS	1	3	6	9
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	2
TOTAL SECONDARY TUMORS			7	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1			
TOTAL UNCERTAIN TUMORS	1			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH TETRACHLOROETHYLENE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M142	HIGH DOSE 02-M143
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				2
ANIMALS NECROPSIED	18	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	20	49	47
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(18)	(20)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST			3 (6%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (11%)		3 (6%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(18)	(20)	(49)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (6%)	1 (5%)		
#LIVER	(17)	(20)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(17)	(20)	(49)	(48)
HEPATOCELLULAR CARCINOMA	2 (12%)	2 (10%)	32 (65%)	27 (56%)
URINARY SYSTEM				
#KIDNEY	(18)	(20)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST	1 (6%)			
TUBULAR-CELL ADENOCARCINOMA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B-1 (CONTINUED)

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M142	HIGH DOSE 02-M143
ENDOCRINE SYSTEM				
#THYROID	(18)	(20)	(49)	(48)
FOLLICULAR-CELL ADENOMA		1 (5%)		1 (2%)
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
#CEREBRUM	(18)	(19)	(49)	(48)
EPENDYMOMA		1 (5%)		
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M142	HIGH DOSE 02-M143
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	9	10	28	38
MORIBUND SACRIFICE			3	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	11	10	19	10
ANIMAL MISSING				2
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	33	27
TOTAL PRIMARY TUMORS	5	6	36	28
TOTAL ANIMALS WITH BENIGN TUMORS	2	1	3	1
TOTAL BENIGN TUMORS	2	1	3	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	5	32	27
TOTAL MALIGNANT TUMORS	3	5	33	27
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		3	
TOTAL SECONDARY TUMORS	1		3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F144	HIGH DOSE 02-F145
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	20	20	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	19	20	48	48
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(48)	(48)
SQUAMOUS CELL CARCINOMA	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(48)	(47)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)			1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(48)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (10%)		1 (2%)
#LUMBAR LYMPH NODE	(20)	(20)	(48)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (5%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(48)	(48)
HEPATOCELLULAR CARCINOMA	2 (10%)		19 (40%)	19 (40%)
URINARY SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F144	HIGH DOSE 02-F145
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(48)	(48)
ADENOCARCINOMA, NOS			1 (2%)	
#OVARY	(20)	(20)	(48)	(47)
GRANULOSA-CELL TUMOR		1 (5%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F144	HIGH DOSE 02-F145
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	9	2	37	41
MORIBUND SACRIFICE			1	1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	11	18	11	7
ANIMAL MISSING				1
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	5	19	19
TOTAL PRIMARY TUMORS	4	5	20	21
TOTAL ANIMALS WITH BENIGN TUMORS	1			1
TOTAL BENIGN TUMORS	1			1
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	4	19	19
TOTAL MALIGNANT TUMORS	3	4	20	20
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	1
TOTAL SECONDARY TUMORS			1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1		
TOTAL UNCERTAIN TUMORS		1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS				
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN				

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH TETRACHLOROETHYLENE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 01-141M	CONTROL (VEH) 01-091M	LOW DOSE 01-142M	HIGH DOSE 01-143M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	49	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (5%)		1 (2%)	
INFLAMMATION, NOS	1 (5%)	1 (5%)		
HYPERKERATOSIS		1 (5%)		
ACANTHOSIS		1 (5%)		
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (5%)			
HEMORRHAGE				1 (2%)
INFLAMMATION, NOS				2 (4%)
ABSCESS, NOS		1 (5%)		1 (2%)
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(20)	(20)	(48)	(50)
ABSCESS, NOS				1 (2%)
#LUNG	(20)	(20)	(48)	(50)
PNEUMONIA, CHRONIC MURINE	16 (80%)	19 (95%)	38 (79%)	31 (62%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(19)	(20)	(49)	(50)
INFLAMMATION, NOS			1 (2%)	
HEMATOPOIESIS	1 (5%)	2 (10%)	2 (4%)	1 (2%)
#CERVICAL LYMPH NODE	(19)	(20)	(49)	(49)
INFLAMMATION, NOS				1 (2%)
#MESENTERIC L. NODE	(19)	(20)	(49)	(49)
PERIARTERITIS		1 (5%)	1 (2%)	
#THYMUS	(16)	(17)	(18)	(10)
INFLAMMATION, NOS		1 (6%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-141M	CONTROL (VEH) 01-091M	LOW DOSE 01-142M	HIGH DOSE 01-143M
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(49)	(50)
CALCIUM DEPOSIT	2 (10%)			
#MYOCARDIUM	(20)	(20)	(49)	(50)
INFLAMMATION, NOS				1 (2%)
FIBROSIS	1 (5%)			
#ENDOCARDIUM	(20)	(20)	(49)	(50)
HYPERPLASIA, NOS	1 (5%)		1 (2%)	
*AORTA	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	3 (15%)		3 (6%)	1 (2%)
*CORONARY ARTERY	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	2 (10%)			
*MESENTERIC ARTERY	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)		2 (4%)	2 (4%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(14)	(17)	(24)	(11)
INFLAMMATION, NOS		1 (6%)		
#LIVER	(20)	(19)	(49)	(49)
INFLAMMATION, NOS	1 (5%)			
ABSCESS, NOS			1 (2%)	1 (2%)
METAMORPHOSIS FATTY	1 (5%)	1 (5%)	4 (8%)	7 (14%)
FOCAL CELLULAR CHANGE			1 (2%)	2 (4%)
ANGIECTASIS			2 (4%)	1 (2%)
#LIVER/CENTRILOBULAR	(20)	(19)	(49)	(49)
DEGENERATION, NOS				1 (2%)
#LIVER/PERIPORTAL	(20)	(19)	(49)	(49)
FIBROSIS				1 (2%)
*BILE DUCT	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)	6 (12%)
#PANCREAS	(19)	(19)	(48)	(50)
PERIARTERITIS		1 (5%)	6 (13%)	3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-141M	CONTROL (VEH) 01-091M	LOW DOSE 01-142M	HIGH DOSE 01-143M
#STOMACH	(20)	(19)	(49)	(48)
ULCER, FOCAL		1 (5%)		
CALCIUM DEPOSIT	3 (15%)	1 (5%)	4 (8%)	2 (4%)
URINARY SYSTEM				
#KIDNEY	(19)	(20)	(49)	(50)
CYST, NOS				2 (4%)
PYELONEPHRITIS, NOS	2 (11%)		3 (6%)	9 (18%)
INFLAMMATION, NOS				1 (2%)
ABSCESS, NOS		1 (5%)		
INFLAMMATION, CHRONIC	13 (68%)	7 (35%)	2 (4%)	4 (8%)
NEPHROPATHY, TOXIC			43 (88%)	47 (94%)
CALCIUM DEPOSIT	1 (5%)		2 (4%)	1 (2%)
#URINARY BLADDER	(19)	(19)	(49)	(49)
CALCULUS, NOS			1 (2%)	2 (4%)
INFLAMMATION, NOS	1 (5%)		1 (2%)	5 (10%)
HYPERPLASIA, EPITHELIAL				1 (2%)
POLYP			2 (4%)	
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(49)	(44)
INFLAMMATION, NOS		1 (5%)		
#THYROID	(19)	(20)	(48)	(49)
CYST, NOS		1 (5%)		
FOLLICULAR CYST, NOS	1 (5%)		3 (6%)	1 (2%)
#PARATHYROID	(19)	(19)	(49)	(50)
HYPERTROPHY, NOS			1 (2%)	
HYPERPLASIA, NOS	1 (5%)		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(19)	(2)	(33)	(25)
INFLAMMATION, NOS	2 (11%)	1 (50%)	4 (12%)	3 (12%)
*SEMINAL VESICLE	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
#TESTIS	(19)	(20)	(41)	(49)
ATROPHY, NOS	8 (42%)	3 (15%)	9 (22%)	5 (10%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-141M	CONTROL (VEH) 01-091M	LOW DOSE 01-142M	HIGH DOSE 01-143M
*EPIDIDYMIS	(20)	(20)	(50)	(50)
NECROSIS, FAT		1 (5%)	2 (4%)	3 (6%)
NERVOUS SYSTEM				
#BRAIN	(19)	(20)	(49)	(50)
HYDROCEPHALUS, NOS			1 (2%)	
INFLAMMATION, NOS			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
BODY CAVITIES				
*PLEURA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS				2 (4%)
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS	2 (10%)	1 (5%)	3 (6%)	3 (6%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			1	1
NECROPSY PERF/NO HISTO PERFORMED			1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
RESPIPATORY SYSTEM				
#TRACHEA	(20)	(16)	(49)	(50)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(20)	(20)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	19 (95%)	20 (100%)	31 (62%)	37 (74%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(20)	(20)	(50)	(50)
METAMORPHOSIS FATTY		6 (30%)		1 (2%)
#SPLEEN	(20)	(20)	(50)	(50)
ABSCESS, NOS				1 (2%)
HEMATOPOIESIS	3 (15%)	1 (5%)	1 (2%)	3 (6%)
CIRCULATORY SYSTEM				
#ENDOCARDIUM	(20)	(20)	(50)	(49)
HYPERPLASIA, NOS	1 (5%)		1 (2%)	
*AORTA	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(50)	(33)
INFLAMMATION, NOS	1 (5%)	1 (5%)		1 (3%)
INFLAMMATION, FOCAL			1 (2%)	
ABSCESS, NOS				1 (3%)
DEGENERATION, NOS				1 (3%)
METAMORPHOSIS FATTY	2 (10%)	1 (5%)	2 (4%)	4 (12%)
FOCAL CELLULAR CHANGE			1 (2%)	
ANGIECTASIS			1 (2%)	1 (3%)
#LIVER/CENTRILOBULAR	(20)	(19)	(50)	(33)
NECROSIS, NOS			1 (2%)	1 (3%)
#LIVER/PERIPORTAL	(20)	(19)	(50)	(33)
FIBROSIS				1 (3%)
*BILE DUCT	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS	2 (10%)			1 (2%)
#PANCREAS	(20)	(18)	(50)	(50)
CYST, NOS		1 (6%)		
ABSCESS, NOS				1 (2%)
PERIARTERITIS			1 (2%)	
ATROPHY, NOS		1 (6%)		
#STOMACH	(20)	(20)	(50)	(50)
ULCER, FOCAL	3 (15%)	1 (5%)		
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
CYST, NOS		1 (5%)		
PYELONEPHRITIS, NOS			1 (2%)	6 (12%)
INFLAMMATION, CHRONIC	6 (30%)	5 (25%)	1 (2%)	
NEPHROPATHY, TOXIC			29 (58%)	38 (76%)
CALCIUM DEPOSIT	1 (5%)		2 (4%)	4 (8%)
HYPERPLASIA, EPITHELIAL			1 (2%)	2 (4%)
#LEFT KIDNEY	(20)	(20)	(50)	(50)
NEPHROPATHY, TOXIC				1 (2%)
#URINARY BLADDER	(20)	(18)	(50)	(49)
CALCULUS, NOS				1 (2%)
INFLAMMATION, NOS				3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(20)	(50)	(50)
ANGIECTASIS			4 (8%)	2 (4%)
#ADRENAL	(20)	(20)	(50)	(50)
CALCIUM DEPOSIT	1 (5%)			
#ADRENAL CORTEX	(20)	(20)	(50)	(50)
DEGENERATION, NOS			1 (2%)	
ANGIECTASIS	5 (25%)	2 (10%)	3 (6%)	7 (14%)
#THYROID	(19)	(20)	(49)	(50)
FOLLICULAR CYST, NOS	2 (11%)		2 (4%)	3 (6%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
NECROSIS, FAT	1 (5%)			
*VAGINA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			1 (2%)
#UTERUS	(20)	(19)	(48)	(50)
HYDROMETRA			2 (4%)	4 (8%)
#UTERUS/ENDOMETRIUM	(20)	(19)	(48)	(50)
INFLAMMATION, NOS	2 (10%)		2 (4%)	1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)	
#OVARY	(20)	(20)	(50)	(50)
CYST, NOS	1 (5%)			
INFLAMMATION, NOS				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 01-141F	CONTROL (VEH) 01-091F	LOW DOSE 01-144F	HIGH DOSE 01-145F
BODY CAVITIES				
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS			1 (2%)	
ALL OTHER SYSTEMS				
THORACIC CAVITY				
ABSCESS, NOS			1	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			8	5

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH TETRACHLOROETHYLENE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M142	HIGH DOSE 02-M143
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				2
ANIMALS NECROPSIED	18	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	20	49	47
INTEGUMENTARY SYSTEM				
*SKIN	(18)	(20)	(49)	(47)
INFLAMMATION, NOS	1 (6%)			
*SUBCUT TISSUE	(18)	(20)	(49)	(47)
EPIDERMAL INCLUSION CYST		2 (10%)		
ABSCESS, NOS		2 (10%)		
RESPIRATORY SYSTEM				
#TRACHEA	(18)	(20)	(49)	(48)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(18)	(20)	(49)	(48)
PNEUMONIA, CHRONIC MURINE	5 (28%)		14 (29%)	29 (60%)
LEUKEMOID REACTION		1 (5%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(18)	(19)	(49)	(48)
LEUKEMOID REACTION		1 (5%)		
#SPLEEN	(18)	(20)	(49)	(48)
AMYLOIDOSIS		3 (15%)		
HEMATOPOIESIS			4 (8%)	1 (2%)
#CERVICAL LYMPH NODE	(18)	(20)	(49)	(30)
INFLAMMATION, NOS	1 (6%)			
#MESENTERIC L. NODE	(18)	(20)	(49)	(30)
INFLAMMATION, NOS	9 (50%)	1 (5%)	8 (16%)	1 (3%)
ANGIECTASIS	2 (11%)	2 (10%)	4 (8%)	1 (3%)
#THYMUS	(18)	(20)	(49)	(30)
ANGIECTASIS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M142	HIGH DOSE 02-M143
CIRCULATORY SYSTEM				
#HEART	(18)	(20)	(49)	(30)
CALCIUM DEPOSIT		2 (10%)		1 (3%)
#MYOCARDIUM	(18)	(20)	(49)	(30)
DEGENERATION, NOS		1 (5%)		
DIGESTIVE SYSTEM				
#LIVER	(17)	(20)	(49)	(48)
THROMBUS, ORGANIZED			1 (2%)	2 (4%)
INFLAMMATION, NOS		2 (10%)		
AMYLOIDOSIS		1 (5%)		
FOCAL CELLULAR CHANGE				3 (6%)
ANGIECTASIS			1 (2%)	
#LIVER/CENTRILOBULAR	(17)	(20)	(49)	(48)
NECROSIS, NOS			2 (4%)	
*BILE DUCT	(18)	(20)	(49)	(47)
DILATATION, NOS			1 (2%)	
#STOMACH	(18)	(20)	(49)	(48)
HYPERKERATOSIS				1 (2%)
ACANTHOSIS				1 (2%)
#COLON	(18)	(20)	(49)	(48)
NEMATODIASIS	1 (6%)		11 (22%)	5 (10%)
*RECTUM	(18)	(20)	(49)	(47)
INFLAMMATION, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(18)	(20)	(49)	(48)
HYDRONEPHROSIS	3 (17%)		1 (2%)	2 (4%)
PYELONEPHRITIS, NOS	1 (6%)	1 (5%)		1 (2%)
INFLAMMATION, CHRONIC		6 (30%)		
NEPHROPATHY, TOXIC			40 (82%)	45 (94%)
AMYLOIDOSIS		4 (20%)		
CALCIUM DEPOSIT		1 (5%)		
ATROPHY, NOS	1 (6%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M142	HIGH DOSE 02-M143
#URINARY BLADDER	(18)	(19)	(49)	(48)
CALCULUS, NOS			1 (2%)	
INFLAMMATION, NOS				1 (2%)
ENDOCRINE SYSTEM				
#THYROID	(18)	(20)	(49)	(48)
FOLLICULAR CYST, NOS			1 (2%)	
REPRODUCTIVE SYSTEM				
#PROSTATE	(18)	(19)	(49)	(48)
INFLAMMATION, NOS				2 (4%)
*SEMINAL VESICLE	(18)	(20)	(49)	(47)
INFLAMMATION, NOS				1 (2%)
#TESTIS	(17)	(19)	(49)	(48)
GRANULOMA, SPERMATIC		1 (5%)		
CALCIUM DEPOSIT		1 (5%)		
ATROPHY, NOS	1 (6%)	3 (16%)	3 (6%)	
*EPIDIDYMIS	(18)	(20)	(49)	(47)
GRANULOMA, SPERMATIC		1 (5%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(18)	(20)	(49)	(47)
PHTHISIS BULBI			1 (2%)	
*EYE/LACRIMAL GLAND	(18)	(20)	(49)	(47)
INFLAMMATION, NOS			1 (2%)	
NECROSIS, NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M142	HIGH DOSE 02-M143
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	6	1	
ANIMAL MISSING/NO NECROPSY				2
AUTO/NECROPSY/HISTO PERF				1
AUTOLYSIS/NO NECROPSY	2		1	1

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH TETRACHLOROETHYLENE

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F144	HIGH DOSE 02-F145
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	20	20	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	48	48
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(48)	(48)
ABSCESS, NOS		1 (5%)		
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(19)	(48)	(47)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(20)	(20)	(48)	(47)
PNEUMONIA, CHRONIC MURINE	7 (35%)		27 (56%)	31 (66%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(48)	(48)
INFLAMMATION, NOS		1 (5%)		
HEMATOPOIESIS	1 (5%)		5 (10%)	1 (2%)
#CERVICAL LYMPH NODE	(20)	(20)	(48)	(48)
ANGIECTASIS			3 (6%)	
#MESENTERIC L. NODE	(20)	(20)	(48)	(48)
INFLAMMATION, NOS	6 (30%)	3 (15%)	3 (6%)	2 (4%)
ANGIECTASIS	2 (10%)		4 (8%)	3 (6%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(20)	(20)	(48)	(47)
FIBROSIS				2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F144	HIGH DOSE 02-F145
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(48)	(48)
THROMBUS, ORGANIZED		1 (5%)	1 (2%)	2 (4%)
INFLAMMATION, NOS			1 (2%)	2 (4%)
PELIOSIS HEPATIS	1 (5%)			
METAMORPHOSIS FATTY			2 (4%)	
#PANCREAS	(20)	(20)	(48)	(48)
INFLAMMATION, NOS	1 (5%)			
#STOMACH	(20)	(20)	(48)	(47)
ULCER, FOCAL				1 (2%)
HYPERKERATOSIS	1 (5%)			
ACANTHOSIS	1 (5%)	1 (5%)		
#COLON	(20)	(20)	(48)	(47)
NEMATODIASIS	4 (20%)		2 (4%)	2 (4%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(48)	(48)
HYDRONEPHROSIS	1 (5%)			
PYELONEPHRITIS, NOS				1 (2%)
NEPHROPATHY, TOXIC			46 (96%)	48 (100%)
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(20)	(20)	(48)	(48)
ANGIECTASIS			1 (2%)	
#THYROID	(20)	(20)	(48)	(47)
FOLLICULAR CYST, NOS	1 (5%)	2 (10%)		
REPRODUCTIVE SYSTEM				
#UTERUS	(20)	(20)	(48)	(47)
HYDROMETRA	4 (20%)	4 (20%)	1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(20)	(48)	(47)
INFLAMMATION, NOS		1 (5%)		2 (4%)
HYPERPLASIA, CYSTIC	3 (15%)	11 (55%)	1 (2%)	
#OVARY	(20)	(20)	(48)	(47)
CYST, NOS	11 (55%)	6 (30%)	11 (23%)	6 (13%)
INFLAMMATION, NOS	1 (5%)		1 (2%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F144	HIGH DOSE 02-F145
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(20)	(20)	(48)	(48)
INFLAMMATION, NOS	1 (5%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(48)	(48)
INFLAMMATION, NOS		1 (5%)		
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		1		
ANIMAL MISSING/NO NECROPSY				1
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY			2	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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