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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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REPORT ON THE BIOASSAY OF 1,1,2,2-TETRACHLOROETHANE
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 1,1,2,2-tetrachloroethane 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 histopathologic 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).

This report was prepared at METREK, a Division of The MITRE Corporation (8) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (8), the task leader, Dr. M. R. Kornreich (8), and the senior biologist, Ms. P. Walker (8). The final report was reviewed by members of the participating organizations.

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

A bioassay for possible carcinogenicity of technical-grade 1,1,2,2-tetrachloroethane was conducted using Osborne-Mendel rats and B6C3F1 mice. At initiation of the study the rats were approximately 7 weeks old, and the mice were approximately 5 weeks old. 1,1,2,2-Tetrachloroethane in corn oil was administered by gavage, at either of two dosages, to two groups of 50 male and 50 female animals of each species, 5 days a week. Treatment was over a period of 78 weeks, followed by observation periods of 32 weeks for the rats and 12 weeks for the mice. The high and low time-weighted average dosages were, respectively, 108 and 62 mg/kg/day for male rats, 76 and 43 mg/kg/day for female rats, and 282 and 142 mg/kg/day for the mice of both sexes.

For each species, 20 animals of each sex were placed on test as vehicle controls. These animals were intubated with corn oil at the same rate as the high dose animals. Twenty animals of each sex were placed on test as untreated controls for each species. These animals were not intubated.

Among mice, hepatocellular carcinomas were observed in 2/16 (13 percent) male untreated controls, 1/18 (6 percent) male vehicle controls, 13/50 (26 percent) low dose males, 44/49 (90 percent) high dose males, 0/18 female untreated controls, 0/20 female vehicle controls, 30/48 (63 percent) low dose females, and 43/47 (91 percent) of the high dose females. This incidence of hepatocellular carcinoma indicated a highly significant ($P < 0.001$) positive dose-related trend in mice of both sexes.

No statistically significant incidence of neoplastic lesions was observed in male or female rats. However, two hepatocellular carcinomas and one neoplastic nodule, which are rare tumors in the male Osborne-Mendel rat, were observed in the high dose males.

Under the conditions of this study, orally administered 1,1,2,2-tetrachloroethane is a liver carcinogen in B6C3F1 mice of both sexes. The results do not provide conclusive evidence for the carcinogenicity of 1,1,2,2-tetrachloroethane in Osborne-Mendel rats.

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I. INTRODUCTION

1,1,2,2-Tetrachloroethane (NCI No. C03554), an aliphatic chlorinated hydrocarbon, is one of a group of halogenated solvents selected for bioassay by the National Cancer Institute. 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 1,1,2,2-tetrachloroethane.* It is also called acetylene tetrachloride or sym-tetrachloroethane.

1,1,2,2-Tetrachloroethane was the first chlorinated hydrocarbon solvent to be manufactured on a large scale. Originally, it was used primarily as an intermediate in the manufacture of di- , tri- , and tetra- chloroethylene. It was also used as an industrial solvent for cellulose acetate, fats, waxes, greases, rubber, and sulfur (Hardie, 1964). In recent years, however, 1,1,2,2-tetrachloroethane has been largely replaced by less toxic solvents. Only one domestic manufacturer is currently producing 1,1,2,2-tetrachloroethane, and most of it is used at the same location as an intermediate in the manufacture of trichloroethylene and tetrachloroethylene (National Institute for Occupational Safety and Health, 1976). Currently, minor uses of 1,1,2,2-tetrachloroethane include use as a carrier or reaction solvent in the manufacturing processes for other chemicals and use as

*The CAS registry number is 79-34-5

an analytical reagent in polymer characterization tests (National Institute for Occupational Safety and Health, 1976).

Based on production data for the synthesis products of 1,1,2,2-tetrachloroethane, it appears that annual production of this compound is at least 40 million pounds (Stanford Research Institute, 1975).

The National Institute for Occupational Safety and Health (1976) estimates that approximately 5000 workers in the United States are potentially exposed to 1,1,2,2-tetrachloroethane annually. The major concerns in occupational exposure are the potential of 1,1,2,2-tetrachloroethane for causing liver damage as well as gastrointestinal and neurologic disturbances (National Institute for Occupational Safety and Health, 1976).

II. MATERIALS AND METHODS

A. Chemicals

1,1,2,2-Tetrachloroethane was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin. Analysis was performed by Hazleton Laboratories America, Inc., Vienna, Virginia. Gas-liquid chromatography (GLC) showed eight peaks with the major peak comprising over 90 percent of the total area. Infrared (IR) analysis was consistent with the structure of the compound. GLC and IR analyses were repeated 15 and 25 months after the initial analyses. The results were virtually identical with those recorded previously and suggested little or no decomposition over this period.

Throughout this report the term 1,1,2,2-tetrachloroethane is used to represent this material.

B. Dosage Preparation

Fresh solutions of 1,1,2,2-tetrachloroethane in Duke's® corn oil (S. F. Sauer Company) were prepared weekly, sealed, and stored in dark bottles at 34°F. The concentration of 1,1,2,2-tetrachloroethane in corn oil (on a weight/volume basis) was 5 percent for the rat chronic bioassay and ranged from 1 to 4 percent for the mouse chronic bioassay.

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 with the Division of Cancer Treatment, 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 provided filtered air at the 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. The mice were housed by sex in groups of ten 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, while 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.

The 1,1,2,2-tetrachloroethane-dosed and both vehicle and untreated control rats were housed in the same room with rats treated with* allyl chloride (107-05-1), 1,2-dibromoethane (106-93-4), carbon tetrachloride (56-23-5), and chloroform (67-66-3). All mice utilized in the 1,1,2,2-tetrachloroethane bioassay, including controls, were housed in the same room as mice treated with allyl chloride (107-05-1), chloroform (67-66-3), chloropicrin (76-06-2), dibromochloropropane (96-12-8), 1,2-dibromoethane (106-93-4), 1,2-dichloroethane (107-06-2), 1,1-dichloroethane (75-34-3), trichloroethylene (79-01-6), 3-sulfolene (77-79-2), iodoform (75-47-8), methylchloroform (71-55-6), 1,1,2-trichloroethane (79-00-5), tetrachloroethylene (127-18-4), hexachloroethane (67-72-1), carbon disulfide (75-15-0), trichlorofluoromethane (75-69-4), and carbon tetrachloride (56-23-5).

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a mg/kg of body weight basis, utilizing the most recently observed group mean body weight as a guide for determining the dose. Mean

*CAS registry numbers are given in parentheses.

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 1,1,2,2-tetrachloroethane solutions under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

F. Selection of Initial Dose Levels

Subchronic toxicity tests were conducted with both rats and mice in order to estimate the maximum tolerated dosages of 1,1,2,2-tetrachloroethane for administration to treated animals in the chronic studies. Animals of each species were distributed among six groups, each consisting of five males and five females. Intubation was performed 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity. 1,1,2,2-Tetrachloroethane dissolved in corn oil was introduced by gavage to five of the six rat groups at dosages of 56, 100, 178, 316, and 562 mg/kg/day and five of the six mouse groups at dosages of 32, 56, 100, 178, and 316 mg/kg/day. The sixth group of each species served as a vehicle control group receiving only corn oil.

In rats, a dose-related retardation in body weight gain was observed. At 56, 100, and 178 mg/kg/day retardation was 3, 9, and 38 percent in the males and 9, 24 and 41 percent in the females, respectively. One male rat died at 100 mg/kg/day and all five female rats died at 316 mg/kg/day, but no deaths of female rats occurred at

lower dosage levels. The initial high dose selected for the chronic study was 100 mg/kg/day for both male and female rats.

In mice, no retardation of body weight gain and no deaths were observed in any of the test groups. The initial high dose selected for the chronic bioassay was 200 mg/kg/day for both male and 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 low dose, high dose, and vehicle control rats were approximately 7 weeks old at initiation of the experiment. The untreated controls were 5 months younger than the treated rats and placed on study 5 months after the treated rats. The high and low dosages initially utilized for rats of both sexes were 100 and 50 mg/kg/day, respectively. In week 15 the dosages were raised to 65 mg/kg/day for low dose males, and to 130 mg/kg/day for high dose males. In week 26 the dosages were decreased to 40 mg/kg/day for the low dose females and to 80 mg/kg/day for the high dose females. Beginning in week 33 intubation ceased for all high dose rats for 1 week, followed by 4 weeks of dose administration. This pattern of cyclic administration was maintained for the remainder of the treatment period. Low dose rats were not affected by this change. The vehicle control rats

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
1,1,2,2-TETRACHLOROETHANE GAVAGE EXPERIMENT

	INITIAL NUMBER OF ANIMALS	1,1,2,2-TETRACHLOROETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0		109	0
VEHICLE CONTROL	20	0	78	32	0
LOW DOSE	50	50	14		62
		65	64		
		0		32	
HIGH DOSE	50	100	14		108
		130	18		
		130[c]	36	9	
		0		32	
FEMALE					
UNTREATED CONTROL	20	0		109	0
VEHICLE CONTROL	20	0	78	32	0
LOW DOSE	50	50	25		43
		40	53		
		0		32	
HIGH DOSE	50	100	25		76
		80	7		
		80[c]	36	9	
		0		32	

[a] Dosages, given in mg/kg body weight, were 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 treatment at the level indicated.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
1,1,2,2-TETRACHLOROETHANE GAVAGE EXPERIMENT

	INITIAL NUMBER OF ANIMALS	1,1,2,2-TETRACHLOROETHANE 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	13	0
LOW DOSE	50	100	18		142
		150	3		
		200	5		
		150	52		
		0		12	
HIGH DOSE	50	200	18		284
		300	3		
		400	5		
		300	52		
		0		12	
FEMALE					
UNTREATED CONTROL	20	--	--	90	--
VEHICLE CONTROL	20	0	78	13	0
LOW DOSE	50	100	18		142
		150	3		
		200	5		
		150	52		
		0		12	
HIGH DOSE	50	200	18		284
		300	3		
		400	5		
		300	52		
		0		12	

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

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

received corn oil with the same frequency and in amounts equal to that received by the respective female and male high dose groups.

The vehicle control, low dose, and high dose mice were approximately 5 weeks old on the day the first dose was administered. Untreated control mice, born 1 week later than treated mice, were placed on test 1 week after treatment had begun. Male mice received the same dosages as female mice throughout the experiment. Initial dosages for high and low dose mice were 200 and 100 mg/kg/day, respectively. In week 19, dosages were raised to 300 and 150 mg/kg/day, respectively. Three weeks later the dosages were raised again, to 400 and 200 mg/kg/day, respectively. In week 27 the dosages were lowered to 300 mg/kg/day for high dose mice, and to 150 mg/kg/day for low dose mice. Vehicle control mice received corn oil by gavage in amounts and frequencies corresponding to the high dose mice.

Vehicle and untreated control animals of both species were maintained and observed in the same manner as dosed animals.

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

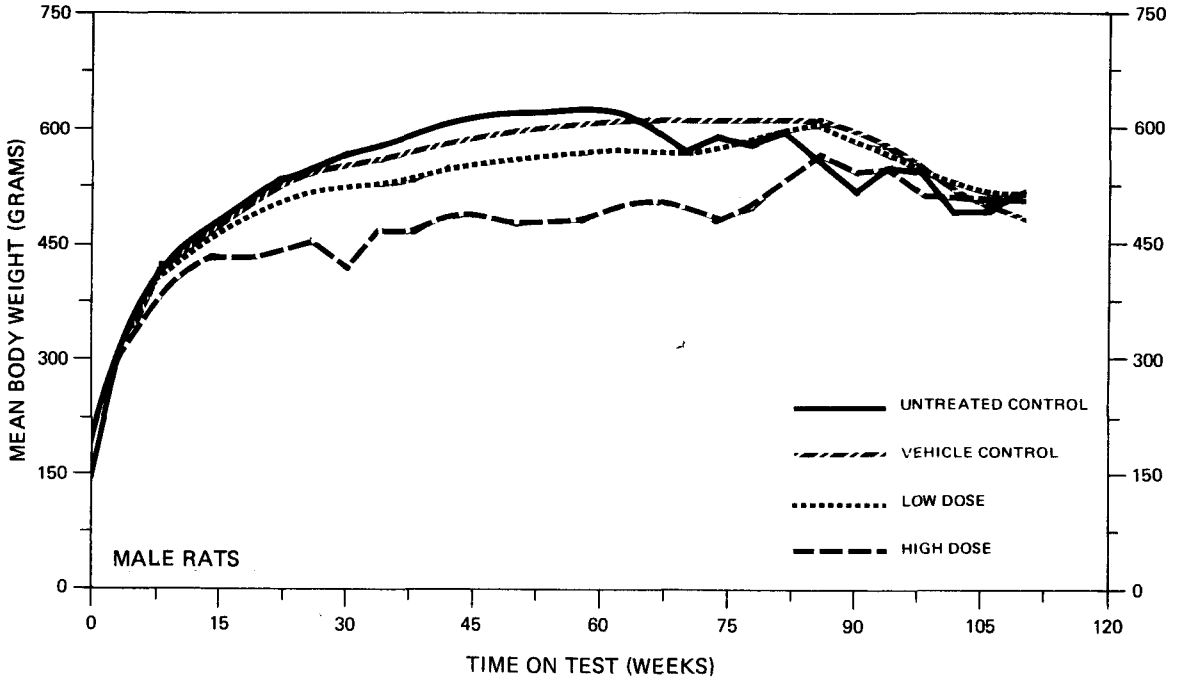
A. Body Weights and Clinical Observations

A dose-related retardation in body weight gain for both male and female rats was observed throughout most of the treatment period (Figure 1). Body weight curves for dosed and control rats tended to converge, however, during the post-treatment observation period.

Clinical signs, including mortality, were observed in the treated female rats early in the study. Deaths occurred in the high dose females as early as week 1, and by week 5 about 20 percent of the animals in this group had died from apparent compound toxicity. A few low and high dose females developed a hunched appearance at the onset of treatment (week 1) with the incidence gradually increasing in all treated groups as the study progressed.

Other signs observed were squinted or reddened eyes (often with a reddish discharge or brown crust) and occasional abdominal urine stains. These signs were observed with greater frequency in the treated groups than in the controls for the duration of compound administration (week 1 through week 78) and were noted at comparable rates in treated and control rats during the last 6 months of the study.

Respiratory signs, characterized by labored respiration, wheezing, and/or nasal discharge, were observed at a low or moderate incidence in all groups during the first year, and increased as the animals aged. As the study approached termination, these signs were



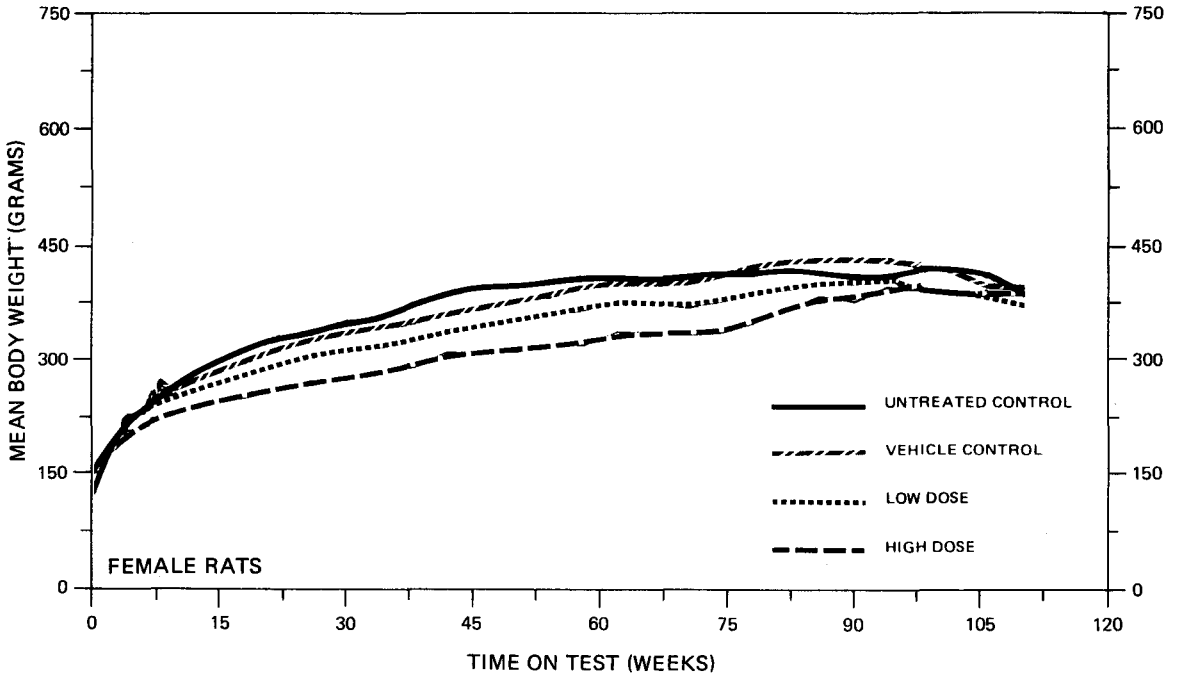


FIGURE 1
GROWTH CURVES FOR 1,1,2,2-TETRACHLOROETHANE CHRONIC STUDY RATS

apparent in a comparatively greater number of treated animals than controls.

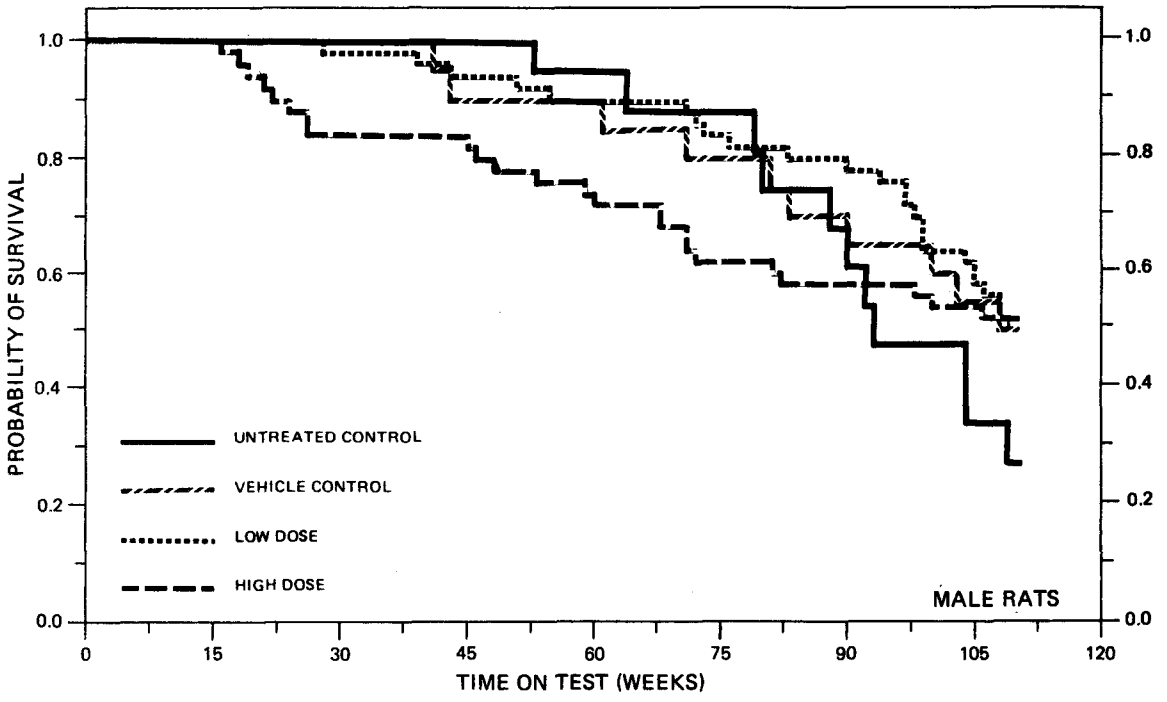
Clinical signs commonly associated with aging were observed with comparable frequency in treated and control animals during the second year of the study. These signs included sores on the body and/or extremities, discoloration of the fur, localized alopecia, bloated appearance, and palpable nodules, tissue masses, or swollen areas.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 1,1,2,2-tetrachloroethane-treated groups are shown in Figure 2.

For male rats the Tarone test for association between increased dosage and elevated mortality was not statistically significant. Survival was relatively good with at least 50 percent of the male rats in the high dose, low dose, and vehicle control groups surviving until termination of the study. Although five animals were sacrificed in week 60, 50 percent of the untreated control group survived at least 90 weeks.

For female rats the Tarone test indicated a significant ($P = 0.005$) association between increased dosage and elevated mortality. A major factor in attaining this level of significance was the death of 10 of the high dose rats in the first 5 weeks of the study: 8 with pneumonia and 2 with no reported lesions. Despite these early losses, 50 percent of the high dose$_{1T}$ group survived more than 92 weeks and 40



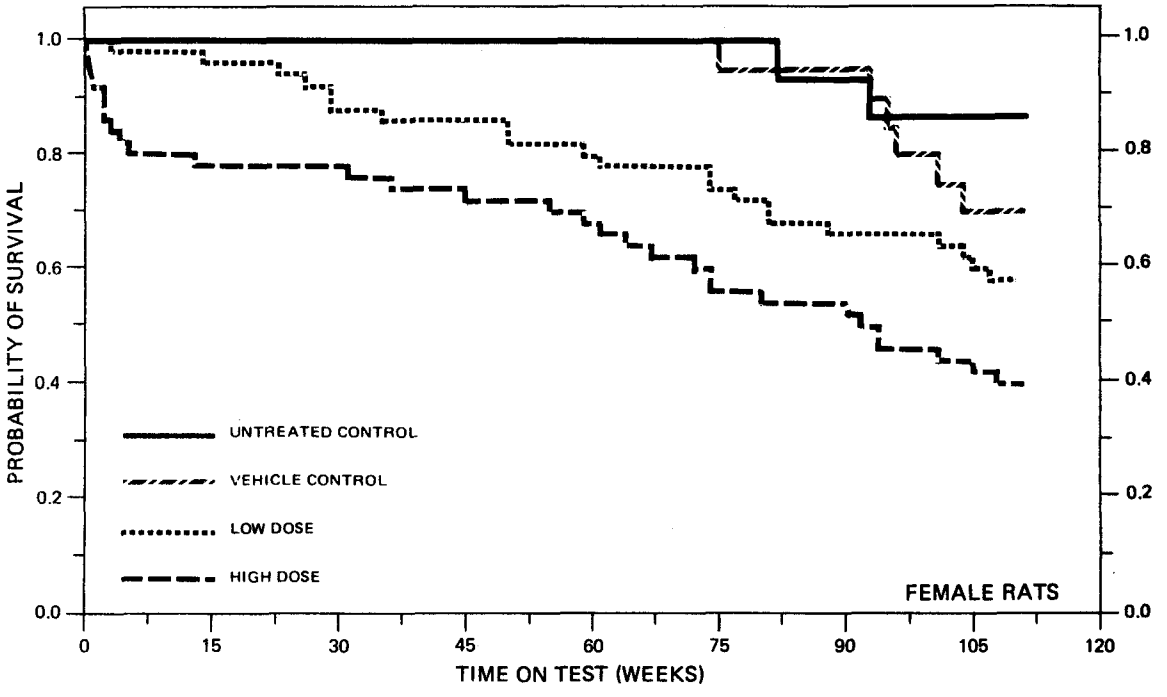


FIGURE 2
SURVIVAL COMPARISONS OF 1,1,2,2-TETRACHLOROETHANE CHRONIC STUDY RATS

percent survived until the end of the study. In the low dose and vehicle control groups 58 and 70 percent, respectively, survived until the end of the study. In the untreated control group, 65 percent survived until the end of the study despite the sacrifice of five animals in week 60. There is no evidence that the early deaths were tumor-related.

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).

Isolated occurrences of several unusual tumors were observed in rats. Hepatocellular carcinomas, rare tumors in the Osborne-Mendel rat, were observed in 2/49 high dose males. Another high dose male (1/49) had a neoplastic liver nodule. One papilloma of the stomach (1/49) and one squamous-cell carcinoma of the stomach (1/49) were observed, each in yet other high dose males. In females only one of these tumor types occurred, a hepatocellular carcinoma (1/20) in an untreated control.

A variety of other neoplasms were observed among both control and chemically treated rats. Each of these other types of tumors have been encountered previously as a spontaneous lesion in the Osborne-Mendel rat. No apparent difference in the frequency of these neoplasms between the control groups and dosed groups was noted in this test. The inflammatory, degenerative, and proliferative lesions

seen in the control and dosed animals were similar in number and kind to those lesions occurring naturally in aged rats.

This pathologic examination provided no convincing evidence for the carcinogenicity of 1,1,2,2-tetrachloroethane in Osborne-Mendel 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 of tumor that was observed in more than 5 percent of any of the 1,1,2,2-tetrachloroethane-dosed groups of either sex is included.

Data from the untreated control groups were not used in the following statistical comparisons because the untreated rats were started on test 5 months after the treated rats and because the survival rate of male untreated rats was low.

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 vehicle control groups for any tumor type for either sex.

Because the observed incidence was higher in the vehicle control than in the dosed groups for certain tumors, the incidence of these tumors in the vehicle control groups was compared to the corresponding spontaneous tumor rates compiled to date for the historical vehicle controls in the NCI Bioassay Program. In female rats, the incidence of fibroadenoma of the mammary gland in the controls from this

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 1,1,2,2-TETRACHLOROETHANE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	1/20(0.05)	2/50(0.04)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.800	0.816
Lower Limit	---	0.045	0.046
Upper Limit	---	46.273	47.195
Weeks to First Observed Tumor	110	97	111
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	0/20(0.00)	0/50(0.00)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	0.255
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	68
Pituitary: Chromophobe Adenoma[b]	5/14(0.35)	5/48(0.10)	5/48(0.10)
P Values[c]	P = 0.036(N)	P = 0.038(N)	P = 0.038(N)
Relative Risk (Vehicle Control)[d]	---	0.292	0.292
Lower Limit	---	0.084	0.084
Upper Limit	---	1.124	1.124
Weeks to First Observed Tumor	90	73	98

TABLE 3
(CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma[b]	3/20(0.15)	0/49(0.00)	2/49(0.04)
P Values[c]	N.S.	P = 0.022(N)	N.S.
Departure from Linear Trend	P = 0.015	---	---
Relative Risk (Vehicle Control)[d]	---	0.000	0.272
Lower Limit	---	0.000	0.025
Upper Limit	---	0.673	2.233
Weeks to First Observed Tumor	83	---	111
Pancreatic Islets: Islet-Cell Adenoma[b]	2/20(0.10)	2/49(0.04)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.408	0.408
Lower Limit	---	0.032	0.032
Upper Limit	---	5.381	5.381
Weeks to First Observed Tumor	110	110	111
Mammary Gland: Adenocarcinoma[b]	2/20(0.10)	2/50(0.04)	0/49(0.00)
P Values[c]	P = 0.045(N)	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.400	0.000
Lower Limit	---	0.032	0.000
Upper Limit	---	5.277	1.372
Weeks to First Observed Tumor	110	39	---

TABLE 3
(CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	1/20(0.05)	1/50(0.02)	0/49(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.400	0.000
Lower Limit	---	0.005	0.000
Upper Limit	---	30.802	7.624
Weeks to First Observed Tumor	110	110	---
All Sites: Hemangiosarcoma[b]	0/20(0.00)	2/50(0.04)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.123	0.255
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	108	110

[a]Dosed groups received time-weighted average doses of 62 and 108 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 vehicle control group when it 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 1,1,2,2-TETRACHLOROETHANE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	1/20(0.05)	2/50(0.04)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
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	111	74	111
Pituitary: Chromophobe Adenoma[b]	3/20(0.15)	11/49(0.22)	6/48(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.497	0.833
Lower Limit	---	0.460	0.204
Upper Limit	---	7.741	4.799
Weeks to First Observed Tumor	101	81	90
Thyroid: Follicular-Cell Carcinoma[b]	0/20(0.00)	1/49(0.02)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.024	0.023
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	108

TABLE 4
(CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Pancreatic Islet: Islet-Cell Adenoma[b]	0/20(0.00)	1/50(0.02)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	---
Lower Limit	---	0.023	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	111	---
Mammary Gland: Adenocarcinoma[b]	0/20(0.00)	1/50(0.02)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.023	0.123
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	67
Mammary Gland: Fibroadenoma[b]	9/20(0.45)	13/50(0.26)	11/50(0.22)
P Values[c]	P = 0.047(N)	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.578	0.489
Lower Limit	---	0.287	0.230
Upper Limit	---	1.316	1.152
Weeks to First Observed Tumor	96	101	67

TABLE 4
(CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	0/20(0.00)	8/50(0.16)	4/48(0.08)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend	P = 0.044	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.952	0.402
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	74	74
All Sites: Hemangiosarcoma[b]	0/20(0.00)	1/50(0.02)	0/50(0.00)
P Values[c]	N.S.	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	---
Lower Limit	---	0.023	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	111	---

[a]Dosed groups received time-weighted average doses of 43 and 76 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 vehicle control group when it 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.

bioassay (9/20 or 45 percent) was significantly higher ($P < 0.05$) than that of the historical controls (39/200 or 20 percent). In male rats, several tumor rates of the controls from this bioassay were significantly higher ($P < 0.05$) than those of the historical controls (Table 5). Because of this phenomenon, several tumors had the appearance of occurring more frequently in control than in dosed animals.

TABLE 5

COMPARISON OF SELECTED TUMOR RATES IN MALE OSBORNE-MENDEL RATS BETWEEN MATCHED VEHICLE CONTROLS AND HISTORICAL VEHICLE CONTROLS

TOPOGRAPHY: MORPHOLOGY	HISTORICAL VEHICLE CONTROLS*	MATCHED VEHICLE CONTROLS*
Pituitary: Chromophobe adenoma	15/200 (7.50)	5/15 (33)
Thyroid: Follicular-cell carcinoma	5/200 (2.50)	3/20 (15)
Pancreatic Islets: Islet-cell adenoma	5/200 (2.50)	2/19 (11)

*Number of tumor-bearing animals/number of animals examined (percent).

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. 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 1,1,2,2-tetrachloroethane that could not be established under the conditions of this test.

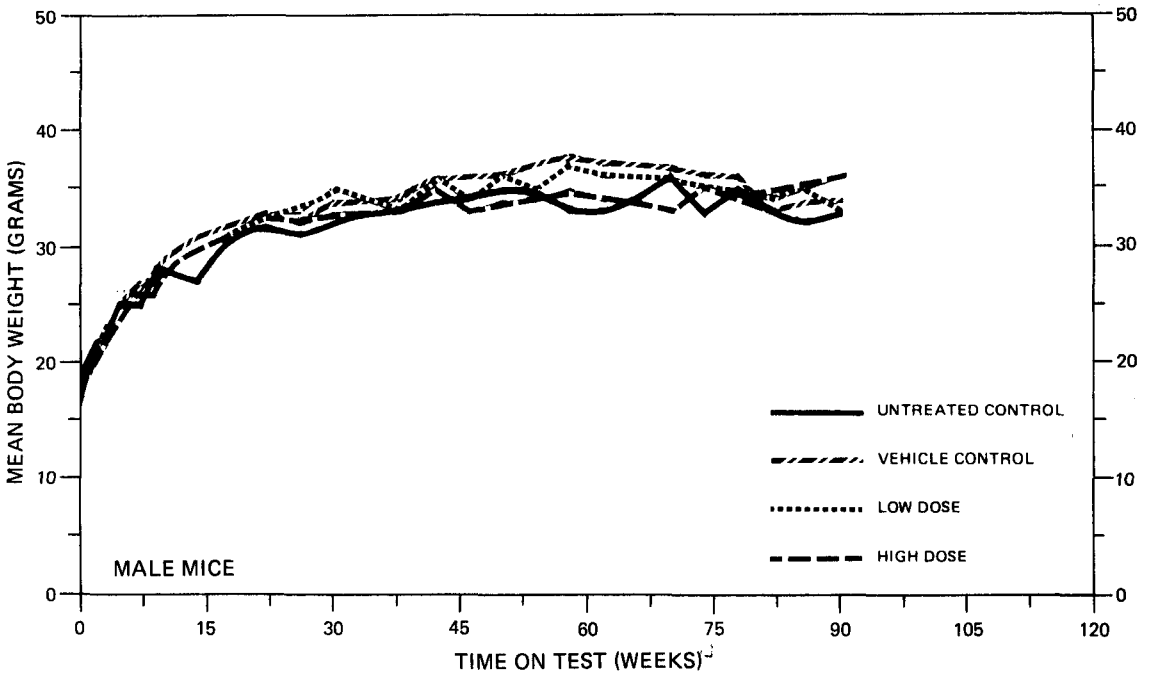
IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

No appreciable difference in body weight gain patterns was observed among female mouse groups (Figure 3). In males, a slight dose-related trend was observed in the vehicle control, low dose, and high dose groups beginning in week 40 and continuing for the duration of the 78-week treatment period.

During the first year of the study, treated mice displayed patterns of behavior and physical appearance that were generally comparable to the control mice. Body sores in the males and generalized or localized alopecia (more prevalent in the females) were the predominant signs observed beginning in week 14. These signs persisted throughout the study. Other clinical signs often observed in group-housed laboratory mice were observed at a comparable rate among treated and control groups. These signs included a hunched appearance, penile, vulvar, or anal irritation with occasional anal prolapse, rough or stained fur, squinted or reddened eyes, and palpable nodules.

Beginning in week 60, pronounced abdominal distension was observed in a few high dose mice. Thereafter, it was noted in an increasing number of high dose females. From cessation of treatment (week 78) until termination of the study, about 95 percent of the high dose females and a few mice in the remaining groups had distended



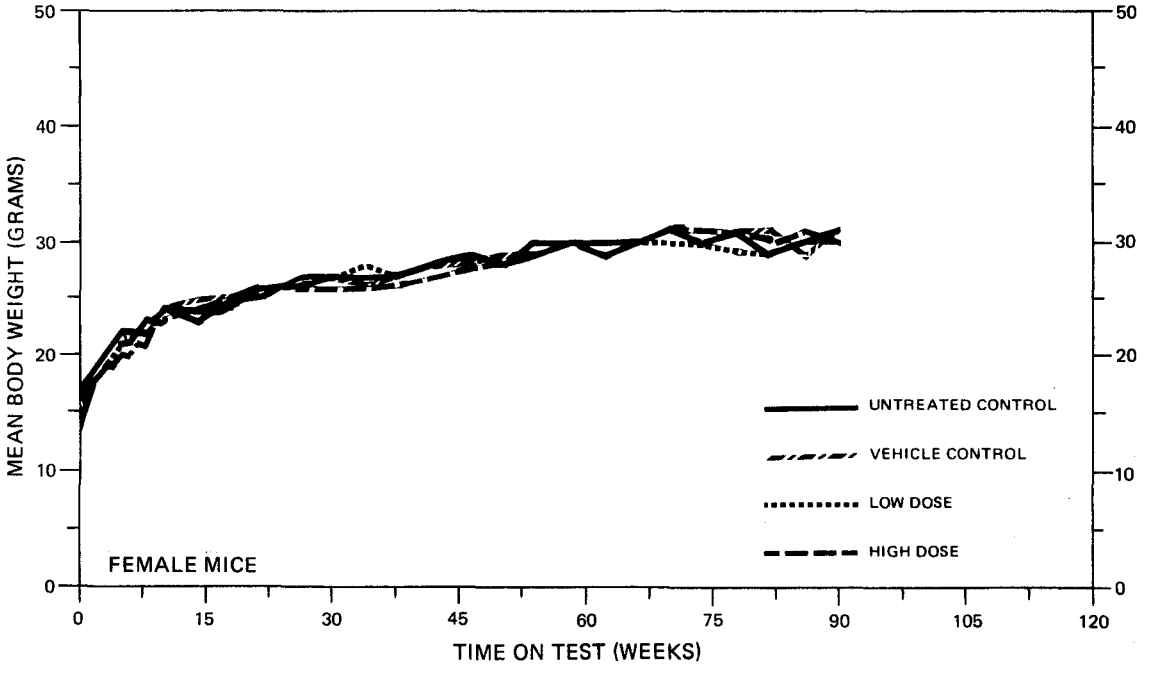


FIGURE 3
GROWTH CURVES FOR 1,1,2,2-TETRACHLOROETHANE CHRONIC STUDY MICE

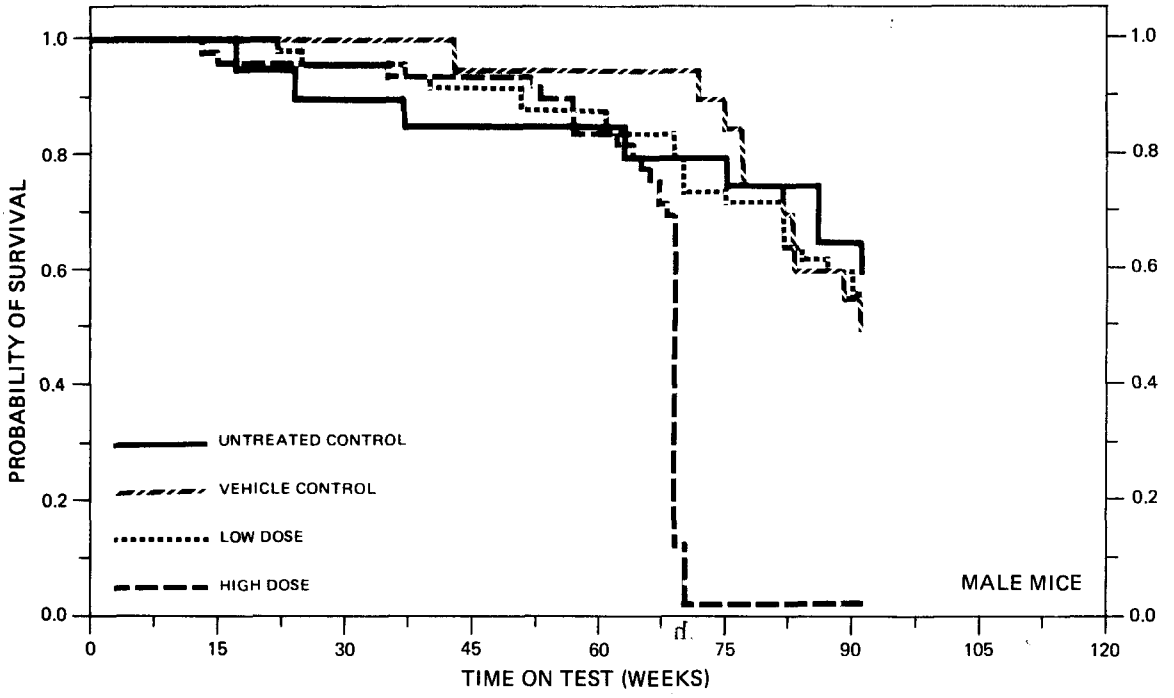
abdomens. Necropsy of these mice revealed liver tumors that were subsequently diagnosed as hepatocellular carcinomas.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 1,1,2,2-tetrachloroethane-treated groups are shown in Figure 4.

For male mice the Tarone test for association between increased dosage and elevated mortality was significant ($P < 0.001$). The departure from linear trend was also significant ($P < 0.001$). Both results are principally due to the death of 33 high dose mice in weeks 69 and 70, leaving only one high dose mouse that survived for the remainder of the study. Subsequent histopathologic examination of these animals revealed acute toxic tubular nephrosis as the apparent cause of death. In addition, hepatocellular carcinomas were evident in most of these mice. At least 50 percent of the animals in the low dose, vehicle control, and untreated control groups survived until the end of the experiment.

For female mice the Tarone test for association between increased dosage and elevated mortality was significant ($P < 0.001$). The departure from linear trend was also significant ($P = 0.003$) due to the relatively severe mortality in the high dose group. However, 50 percent of the high dose group survived more than 82 weeks and 34 percent survived more than 90 weeks. For the low dose, vehicle



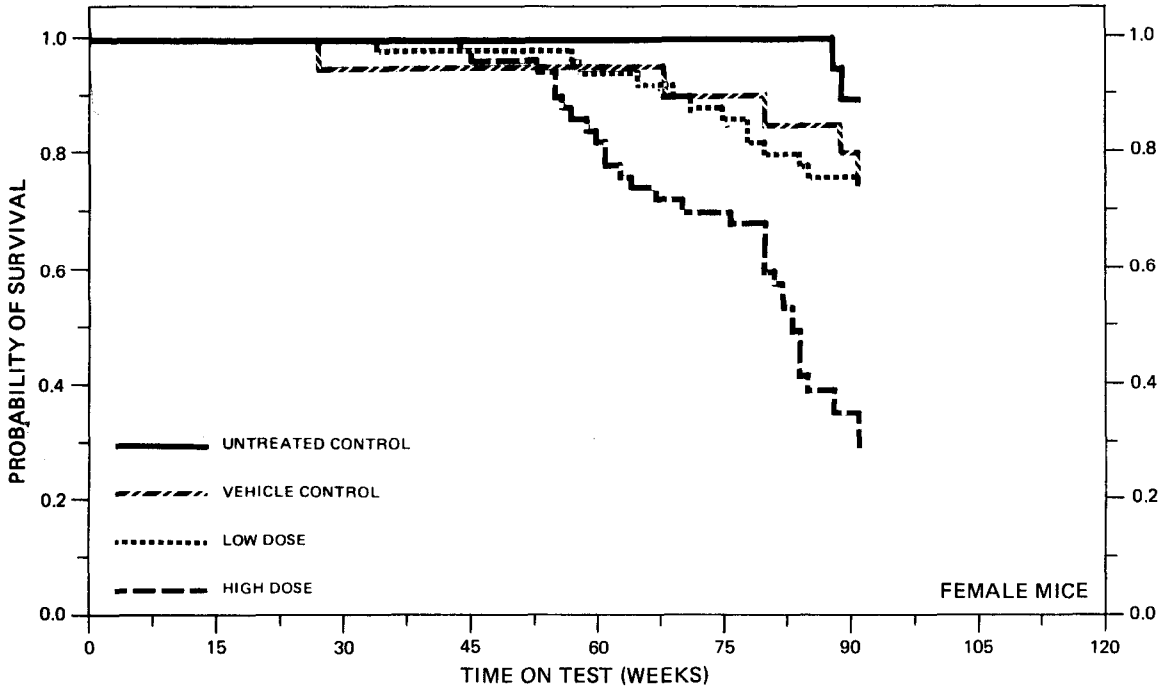


FIGURE 4
SURVIVAL COMPARISONS OF 1,1,2,2-TETRACHLOROETHANE CHRONIC STUDY MICE

control, and untreated control groups 74, 75, and 85 percent, respectively, survived until week 92, the end of the study.

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).

During weeks 69 and 70, 33 high dose male mice died. Hepatocellular carcinomas were present in all but 1 of these 33 male mice. These mice apparently died suddenly, as evidenced by the presence of a large amount of food in the stomach of several of the mice. Sections of stomach and intestine failed to indicate compound-related alterations in the high dose male mice.

Hepatocellular carcinomas occurred in 2/16 untreated control males, 1/18 vehicle control males, 13/50 low dose males, 44/49 high dose males, 30/48 low dose females, 43/47 high dose females, and in no female control animals. The earliest hepatocellular carcinoma was diagnosed in a high dose male mouse dying in week 52, while in the low dose males hepatocellular carcinoma was not diagnosed until week 84. The three high dose male mice that died prior to week 52 had no liver tumors. Therefore, a dose-response relationship was noted in both the incidence of liver tumors and in the time of tumor detection in the male mice. There was metastasis to the lung in one low dose male mouse.

Microscopically, the hepatocellular carcinomas varied greatly in appearance. Some were composed of well-differentiated hepatic cells that had a relatively uniform arrangement of cords, whereas others were composed of anaplastic cells with large hyperchromatic nuclei, often with eosinophilic inclusion bodies and with vacuolated pale cytoplasm. The arrangement of the neoplastic liver cells in the more anaplastic carcinomas varied from short stubby cords to nests of hepatic cells and occasionally pseudo-acinar formation. Mitotic figures were often present. Some of the tumors were characterized by discrete highly anaplastic areas within otherwise well-differentiated tumors. The hepatic neoplasms occurring in the 1,1,2,2-tetrachloroethane-treated mice did not differ morphologically from the spectrum of hepatocellular carcinomas occasionally noted in control mice.

This pathologic evaluation provides evidence for the hepatocarcinogenicity of 1,1,2,2-tetrachloroethane in B6C3F1 mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 6 and 7. The analysis for every type of tumor that was observed in more than 5 percent of any of the 1,1,2,2-tetrachloroethane-dosed groups of either sex is included.

Two control groups were used for statistical analyses: the vehicle control group (designated in this section as the "matched" vehicle control group) and a pooled vehicle control group, combining the vehicle controls from the studies of 1,1,2,2-tetrachloroethane

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 1,1,2,2-TETRACHLOROETHANE[a]

TOPOGRAPHY:MORPHOLOGY	MATCHED VEHICLE CONTROL	POOLED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	1/18(0.06)	1/36(0.03)	2/39(0.05)	2/47(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Vehicle Control)[d]	---	---	0.923	0.766
Lower Limit	---	---	0.052	0.043
Upper Limit	---	---	53.075	44.252
Relative Risk (Pooled Vehicle Control)[d]	---	---	1.846	1.532
Lower Limit	---	---	0.101	0.083
Upper Limit	---	---	105.075	88.440
Weeks to First Observed Tumor	92	---	92	69
Liver: Hepatocellular Carcinoma[b]	1/18(0.05)	3/36(0.08)	13/50(0.26)	44/49(0.90)
P Values[c]	P < 0.001	P < 0.001	P = 0.033**	P < 0.001* P < 0.001**
Departure from Linear Trend	P = 0.022	P = 0.007	---	---
Relative Risk (Matched Vehicle Control)[d]	---	---	4.680	16.163
Lower Limit	---	---	0.805	3.420
Upper Limit	---	---	193.753	525.786
Relative Risk (Pooled Vehicle Control)[d]	---	---	3.120	10.776
Lower Limit	---	---	0.944	4.225
Upper Limit	---	---	16.026	37.023
Weeks to First Observed Tumor	72	---	84	52

TABLE 6
(CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	MATCHED VEHICLE CONTROL	POOLED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
All Sites: Lymphoma[b]	0/18(0.00)	0/36(0.00)	4/50(0.08)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.350	0.231
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Pooled Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.674	0.446
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	82	52

[a]Dosed groups received time-weighted average doses of 142 and 284 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 vehicle control group (*) and the pooled 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 7

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 1,1,2,2-TETRACHLOROETHANE[a]

TOPOGRAPHY:MORPHOLOGY	MATCHED VEHICLE CONTROL	POOLED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	0/20(0.00)	1/40(0.03)	1/46(0.02)	1/44(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.026	0.027
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.870	0.909
Lower Limit	---	---	0.011	0.012
Upper Limit	---	---	66.805	69.770
Weeks to First Observed Tumor	---	---	---	76
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	1/40(0.03)	30/48(0.63)	43/47(0.91)
P Values[c]	P < 0.001	P < 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	4.354	6.805
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Pooled Vehicle Control)[d]	---	---	25.000	36.596
Lower Limit	---	---	4.591	7.490
Upper Limit	---	---	964.569	1119.509
Weeks to First Observed Tumor	---	---	58	53

TABLE 7
(CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	MATCHED VEHICLE CONTROL	POOLED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
All Sites: Lymphoma[b]	0/20(0.00)	2/40(0.05)	7/48(0.15)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend	P = 0.040	---	---	---
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.843	0.266
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Pooled Vehicle Control)[d]	---	---	2.917	1.277
Lower Limit	---	---	0.595	0.154
Upper Limit	---	---	27.579	14.694
Weeks to First Observed Tumor	---	---	80	76

[a] Dosed groups received time-weighted average doses of 142 and 284 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 vehicle control group (*) and the pooled 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.

and chloropicrin. The control mice used for the pool were of the same strain, were housed in the same room, were placed on test at approximately the same time, and were diagnosed by the same pathologists.

For male mice, the Cochran-Armitage tests for a positive association between increased dosage and elevated incidence of hepatocellular carcinoma were highly significant ($P < 0.001$) using either the matched vehicle or pooled vehicle controls. A significant departure from linear trend was noted ($P = 0.022$ using the matched controls, $P = 0.007$ using the pooled controls) due to the extremely sharp increase in tumor incidence among the dosed groups. The Fisher exact tests confirmed the significantly ($P < 0.001$) higher incidence of this tumor in the high dose group compared to either the matched vehicle or pooled vehicle controls, as well as for the low dose group compared to the pooled vehicle control ($P = 0.033$). The spontaneous tumor rate for hepatocellular carcinoma, as observed in the historical vehicle controls at Hazleton Laboratories for male B6C3F1 mice compiled by the NCI Bioassay Program, was 74/612 (12 percent) compared to the rates of 13/50 (26 percent) in the low dose and 44/49 (90 percent) in the high dose 1,1,2,2-tetrachloroethane-treated males. Finally, the lower limit of the 95 percent confidence interval on the relative risk was greater than the value one for the comparison of either of the dosed groups to either of the control groups. These statistical tests indicate that the occurrence of hepatocellular carcinoma in

male mice was associated with oral administration of 1,1,2,2-tetrachloroethane at the dose levels used in this experiment.

Similarly, the incidence of hepatocellular carcinoma was significant in female mice. The Cochran-Armitage tests for positive dose-related trend in proportions were found to be significant ($P < 0.001$) when compared to either the matched vehicle controls or the pooled vehicle controls. The results of the Fisher exact tests confirmed this positive finding: both high and low dose animals demonstrated significant ($P < 0.001$) increases in hepatocellular carcinoma compared to either the matched vehicle controls or the pooled vehicle controls. The spontaneous tumor rate for hepatocellular carcinoma, observed in the historical vehicle controls at Hazleton Laboratories for female B6C3F1 mice, was 8/560 (1 percent) compared to rates of 30/48 (63 percent) in the low dose and 43/47 (91 percent) in the high dose 1,1,2,2-tetrachloroethane-treated females. Finally, the entire range of the 95 percent confidence interval on the relative risk is greater than the value one for the comparison of either of the dosed groups to either of the control groups. These statistical tests indicate that the occurrence of hepatocellular carcinomas in female B6C3F1 mice was associated with the oral administration of 1,1,2,2-tetrachloroethane at the dose levels used in this experiment.

V. DISCUSSION

Under the conditions of this study, administration of 1,1,2,2-tetrachloroethane was associated with a significant increase in the incidence of hepatocellular carcinomas in mice of both sexes. Although a variety of neoplasms were observed in the treated rats, none of these was found to be statistically significant.

Statistical tests indicated a strong association between oral administration of 1,1,2,2-tetrachloroethane and occurrence of hepatocellular carcinomas in both male and female mice. Incidences of hepatocellular carcinoma exhibited a highly significant ($P < 0.001$) positive dose-related trend in mice of both sexes.

No neoplasms were observed in dosed rats at an incidence significantly higher than that observed in controls. 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 may have a low degree of sensitivity to induction of hepatocellular carcinoma by oral administration of chlorinated organic compounds.

Under the conditions of this study, orally administered 1,1,2,2-tetrachloroethane is a liver carcinogen in B6C3F1 mice. The results of this study do not, however, provide evidence for carcinogenicity of 1,1,2,2-tetrachloroethane in Osborne-Mendel rats.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 1,1,2,2-TETRACHLOROETHANE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 1,1,2,2-TETRACHLOROETHANE

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA		1 (5%)		
*SUBCUT TISSUE	(20)	(20)	(50)	(49)
ADENOCARCINOMA, NOS				1 (2%)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
FIBROMA		1 (5%)	2 (4%)	2 (4%)
FIBROSARCOMA	(5%)			
LIPOMA			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
LYMPHOCYTIC LEUKEMIA	1 (5%)			
*SPLEEN	(20)	(19)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
*LIVER	(20)	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
NONE				

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(14)	(14)	(41)	(28)
CARCINOMA,NOS	1 (7%)			
#LIVER	(20)	(20)	(50)	(49)
NEOPLASTIC NODULE				1 (2%)
HEPATOCELLULAR CARCINOMA				2 (4%)
#PANCREAS	(20)	(20)	(49)	(49)
HEMANGIOSARCOMA			1 (2%)	
#STOMACH	(20)	(20)	(50)	(48)
PAPILLOMA, NOS				1 (2%)
SQUAMOUS CELL CARCINOMA				1 (2%)
#SMALL INTESTINE	(20)	(20)	(47)	(49)
FIBROSARCOMA	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(49)
TUBULAR-CELL ADENOMA				1 (2%)
MIXED TUMOR, MALIGNANT			1 (2%)	
HAMARTOMA		1 (5%)		
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(14)	(48)	(48)
CHROMOPHOBE ADENOMA	2 (10%)	5 (36%)	5 (10%)	5 (10%)
#ADRENAL	(20)	(20)	(50)	(49)
CORTICAL CARCINOMA	2 (10%)			
#THYROID	(19)	(20)	(49)	(49)
FOLLICULAR-CELL CARCINOMA	1 (5%)	3 (15%)		2 (4%)
#PARATHYROID	(3)	(20)	(50)	(49)
ADENOMA, NOS			1 (2%)	
#PANCREATIC ISLETS	(20)	(20)	(49)	(49)
ISLET-CELL ADENOMA		2 (10%)	2 (4%)	2 (4%)

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(49)
ADENOCARCINOMA, NOS	1 (5%)	2 (10%)	2 (4%)	
FIBROADENOMA	1 (5%)	1 (5%)	1 (2%)	
*TESTIS	(20)	(20)	(50)	(48)
MESOTHELIOMA, NOS				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(49)
LIPOMA				2 (4%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	11	9	23	25
MORIBUND SACRIFICE		1	1	
SCHEDULED SACRIFICE	5			
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	4	10	26	25
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	11	17	20
TOTAL PRIMARY TUMORS	11	16	19	26
TOTAL ANIMALS WITH BENIGN TUMORS	2	9	11	13
TOTAL BENIGN TUMORS	3	10	12	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	6	7	9
TOTAL MALIGNANT TUMORS	8	6	7	10
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	
TOTAL SECONDARY TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				2
TOTAL UNCERTAIN TUMORS				2
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 1,1,2,2-TETRACHLOROETHANE

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
FIBROMA		1 (5%)	2 (4%)	1 (2%)
LIPOMA				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(50)
RHABDOMYOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
*SUBCUT TISSUE/BACK	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#SPLEEN	(20)	(20)	(49)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(50)
RHABDOMYOSARCOMA			1 (2%)	
MIXED TUMOR, METASTATIC	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
HEPATOCELLULAR CARCINOMA	1 (5%)			

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
MIXED TUMOR, MALIGNANT	1 (5%)	1 (5%)		
HAMARTOMA	2 (10%)		1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(49)	(48)
CHROMOPHOBE ADENOMA	6 (32%)	3 (15%)	11 (22%)	6 (13%)
#ADRENAL	(20)	(20)	(49)	(49)
CORTICAL CARCINOMA			1 (2%)	
PHEOCHROMOCYTOMA				1 (2%)
#THYROID	(20)	(20)	(49)	(50)
FOLLICULAR-CELL CARCINOMA			1 (2%)	1 (2%)
C-CELL ADENOMA	2 (10%)			1 (2%)
C-CELL CARCINOMA	2 (10%)			
#PANCREATIC ISLETS	(20)	(20)	(50)	(50)
ISLET-CELL ADENOMA	1 (5%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOMA, NOS		1 (5%)	1 (2%)	1 (2%)
ADENOCARCINOMA, NOS	2 (10%)		1 (2%)	2 (4%)
FIBROMA				1 (2%)
FIBROADENOMA	2 (10%)	9 (45%)	13 (26%)	11 (22%)
#UTERUS	(20)	(20)	(50)	(48)
ADENOCARCINOMA, NOS			2 (4%)	
ENDOMETRIAL STROMAL POLYP			8 (16%)	4 (8%)
HEMANGIOMA	1 (5%)			
HEMANGIOSARCOMA			1 (2%)	
#OVARY	(20)	(20)	(50)	(48)
CYSTADENOCARCINOMA, NOS	1 (5%)			
GRANULOSA-CELL TUMOR			1 (2%)	1 (2%)
NERVOUS SYSTEM				
NONE				

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	2	6	20	30
MORIBUND SACRIFICE			1	
SCHEDULED SACRIFICE	5			
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	13	14	29	20
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	12	28	23
TOTAL PRIMARY TUMORS	21	15	48	33
TOTAL ANIMALS WITH BENIGN TUMORS	12	11	24	21
TOTAL BENIGN TUMORS	14	14	38	27
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	1	7	5
TOTAL MALIGNANT TUMORS	7	1	9	5
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	
TOTAL SECONDARY TUMORS	1		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	1
TOTAL UNCERTAIN TUMORS			1	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 1,1,2,2-TETRACHLOROETHANE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 1,1,2,2-TETRACHLOROETHANE

	CONTROL (UNTR) 02-M021	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	19	18	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	19	18	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(19)	(18)	(49)	(49)
SQUAMOUS CELL CARCINOMA	1 (5%)			
FIBROSARCOMA	1 (5%)			
*SUBCUT TISSUE	(19)	(18)	(49)	(49)
FIBROMA			1 (2%)	
FIBROSARCOMA			2 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(19)	(18)	(39)	(47)
HEPATOCELLULAR CARCINOMA, METAST			1 (3%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (11%)	1 (6%)	2 (5%)	2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(19)	(18)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (11%)		2 (4%)	1 (2%)
*SUBCUT TISSUE	(19)	(18)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#LIVER	(19)	(18)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	1 (2%)
CIRCULATORY SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M021	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
DIGESTIVE SYSTEM				
#LIVER	(19)	(18)	(50)	(49)
HEPATOCELLULAR CARCINOMA	2 (11%)	1 (6%)	13 (26%)	44 (90%)
HEMANGIOMA		1 (6%)		
HEMANGIOSARCOMA	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(19)	(18)	(39)	(47)
ADENOCARCINOMA, NOS	1 (5%)			
TUBULAR-CELL ADENOMA		1 (6%)		
TUBULAR-CELL ADENOCARCINOMA			1 (3%)	
FIBROSARCOMA	1 (5%)			
ENDOCRINE SYSTEM				
#THYROID	(16)	(17)	(38)	(47)
FOLLICULAR-CELL ADENOMA				1 (2%)
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 02-M021	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	8	10	23	47
MORIBUND SACRIFICE				2
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	12	9	27	1
ANIMAL MISSING		1		
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	4	17	45
TOTAL PRIMARY TUMORS	12	4	23	50
TOTAL ANIMALS WITH BENIGN TUMORS	2	3	3	3
TOTAL BENIGN TUMORS	2	3	3	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	1	17	45
TOTAL MALIGNANT TUMORS	10	1	20	47
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	
TOTAL SECONDARY TUMORS			1	
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 1,1,2,2-TETRACHLOROETHANE

	CONTROL (UNTR) 02-F021	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING	1		1	1
ANIMALS NECROPSIED	19	20	48	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	48	47
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(19)	(20)	(46)	(44)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)			1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(19)	(20)	(48)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			3 (6%)	2 (4%)
#SPLEEN	(19)	(19)	(46)	(46)
HEMANGIOSARCOMA			1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#MESENTERIC L. NODE	(19)	(20)	(46)	(46)
ADENOCARCINOMA, NOS, METASTATIC		1 (5%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(19)	(20)	(48)	(47)
HEPATOCELLULAR CARCINOMA			30 (63%)	43 (91%)
URINARY SYSTEM				
NONE				

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F021	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(15)	(46)	(46)
CHROMOPHOBE CARCINOMA	1 (5%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(19)	(20)	(48)	(47)
ADENOCARCINOMA, NOS			1 (2%)	
#UTERUS	(18)	(20)	(46)	(46)
ADENOCARCINOMA, NOS		1 (5%)		
ENDOMETRIAL STROMAL POLYP			1 (2%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA		1 (5%)		
#OVARY	(18)	(20)	(46)	(46)
CYSTADENOMA, NOS			1 (2%)	
ENDOMETRIAL STROMAL SARCOMA, MET		1 (5%)		
TERATOMA, NOS		1 (5%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(19)	(20)	(48)	(47)
ENDOMETRIAL STROMAL SARCOMA, MET		1 (5%)		
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 02-F021	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	2	5	11	36
MORIBUND SACRIFICE				1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	17	15	37	12
ANIMAL MISSING	1		1	1
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	2	33	43
TOTAL PRIMARY TUMORS	2	3	42	49
TOTAL ANIMALS WITH BENIGN TUMORS	1		2	2
TOTAL BENIGN TUMORS	1		2	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	1	33	43
TOTAL MALIGNANT TUMORS	1	2	40	47
TOTAL ANIMALS WITH SECONDARY TUMORS#		1		
TOTAL SECONDARY TUMORS		3		
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 1,1,2,2-TETRACHLOROETHANE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 1,1,2,2-TETRACHLOROETHANE

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)		1 (2%)	
ULCER, NOS			1 (2%)	
HYPERKERATOSIS		1 (5%)		
ACANTHOSIS		1 (5%)		
*SUBCUT TISSUE	(20)	(20)	(50)	(49)
ABSCESS, NOS		1 (5%)	1 (2%)	
RESPIRATORY SYSTEM				
#TRACHEA	(15)	(19)	(50)	(49)
INFLAMMATION, NOS		1 (5%)	1 (2%)	1 (2%)
#LUNG	(20)	(20)	(50)	(49)
PNEUMONIA, CHRONIC MURINE	16 (80%)	11 (55%)	25 (50%)	32 (65%)
CALCIUM DEPOSIT	1 (5%)	1 (5%)		
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(19)	(50)	(49)
INFLAMMATION, NOS			1 (2%)	
HEMATOPOIESIS	1 (5%)		2 (4%)	
#CERVICAL LYMPH NODE	(19)	(19)	(47)	(47)
INFLAMMATION, NOS	1 (5%)			
#MESENTERIC L. NODE	(19)	(19)	(47)	(47)
INFLAMMATION, NOS				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(49)
CALCIUM DEPOSIT	1 (5%)	1 (5%)	2 (4%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
#MYOCARDIUM	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	2 (10%)			
FIBROSIS				1 (2%)
DEGENERATION, NOS	1 (5%)	1 (5%)	1 (2%)	
#ENDOCARDIUM	(20)	(20)	(50)	(49)
HYPERPLASIA, NOS	1 (5%)			
*AORTA	(20)	(20)	(50)	(49)
MEDIAL CALCIFICATION	2 (10%)	3 (15%)	5 (10%)	
*MESENTERIC ARTERY	(20)	(20)	(50)	(49)
MEDIAL CALCIFICATION	1 (5%)		2 (4%)	
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)			1 (2%)
PELIOSIS HEPATIS			1 (2%)	
METAMORPHOSIS FATTY	2 (10%)		2 (4%)	9 (18%)
FOCAL CELLULAR CHANGE			2 (4%)	1 (2%)
ANGIECTASIS	3 (15%)			
*BILE DUCT	(20)	(20)	(50)	(49)
FIBROSIS				1 (2%)
HYPERPLASIA, NOS	4 (20%)	1 (5%)	1 (2%)	1 (2%)
#PANCREAS	(20)	(20)	(49)	(49)
INFLAMMATION, NOS				1 (2%)
PERIARTERITIS	4 (20%)	3 (15%)	6 (12%)	2 (4%)
#STOMACH	(20)	(20)	(50)	(48)
CALCIUM DEPOSIT	2 (10%)	2 (10%)	4 (8%)	1 (2%)
HYPERKERATOSIS		1 (5%)	1 (2%)	2 (4%)
ACANTHOSIS		1 (5%)	1 (2%)	2 (4%)
#COLON	(19)	(20)	(49)	(49)
NEMATODIASIS	1 (5%)			
PARASITISM			1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(49)
CYST, NOS		1 (5%)		1 (2%)
PYELONEPHRITIS, NOS	1 (5%)			1 (2%)
INFLAMMATION, CHRONIC	15 (75%)	14 (70%)	26 (52%)	19 (39%)
CALCIUM DEPOSIT	1 (5%)		2 (4%)	
#URINARY BLADDER	(19)	(20)	(49)	(47)
INFLAMMATION, NOS	1 (5%)	1 (5%)		1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(14)	(48)	(48)
CYST, NOS			1 (2%)	
ANGIECTASIS	1 (5%)	1 (7%)		
#ADRENAL CORTEX	(20)	(20)	(50)	(49)
DEGENERATION, NOS		1 (5%)	1 (2%)	
ANGIECTASIS	1 (5%)			3 (6%)
#THYROID	(19)	(20)	(49)	(49)
ULTIMOBRANCHIAL CYST	2 (11%)			
FOLLICULAR CYST, NOS			2 (4%)	1 (2%)
HYPERPLASIA, C-CELL	1 (5%)	2 (10%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)		1 (2%)	
#PARATHYROID	(3)	(20)	(50)	(49)
HYPERPLASIA, NOS	2 (67%)	1 (5%)	1 (2%)	
REPRODUCTIVE SYSTEM				
#PROSTATE	(20)	(18)	(40)	(33)
INFLAMMATION, NOS	5 (25%)	2 (11%)	1 (3%)	
*SEMINAL VESICLE	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)	2 (10%)		
#TESTIS	(20)	(20)	(50)	(48)
GRANULOMA, SPERMATIC	1 (5%)			
CALCIUM DEPOSIT		1 (5%)		
ATROPHY, NOS	11 (55%)	8 (40%)	20 (40%)	17 (35%)
*EPIDIDYMIS	(20)	(20)	(50)	(49)
NECROSIS, FAT	1 (5%)		1 (2%)	
ATROPHY, NOS	3 (15%)			

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-011M	LOW DOSE 01-012M	HIGH DOSE 01-013M
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(49)
NECROSIS, FAT				1 (2%)
*PERITONEUM	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)		1 (2%)	
*PERICARDIUM	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	2 (10%)			
*MESENTERY	(20)	(20)	(50)	(49)
PERIARTERITIS	4 (20%)	3 (15%)	4 (8%)	2 (4%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		1	8	8
AUTOLYSIS/NO NECROPSY				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 1,1,2,2-TETRACHLOROETHANE

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
ABSCESS, NOS				1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(15)	(20)	(50)	(50)
INFLAMMATION, NOS		2 (10%)		
#LUNG	(20)	(20)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	18 (90%)	8 (40%)	34 (68%)	38 (76%)
HYPERPLASIA, ADENOMATOUS				1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(49)	(48)
HEMATOPOIESIS		2 (10%)	3 (6%)	2 (4%)
#CERVICAL LYMPH NODE	(20)	(18)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
ANGIECTASIS			1 (2%)	1 (2%)
#MESENTERIC L. NODE	(20)	(18)	(50)	(50)
PERIARTERITIS		1 (6%)		
#THYMUS	(15)	(19)	(45)	(38)
ABSCESS, NOS			1 (2%)	
CIRCULATORY SYSTEM				
#MYOCARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
FIBROSIS	1 (5%)			

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

**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
#ENDOCARDIUM	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS		2 (10%)		
*AORTA	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
CYST, NOS		1 (5%)		
INFLAMMATION, NOS			1 (2%)	1 (2%)
METAMORPHOSIS FATTY	1 (5%)		1 (2%)	4 (8%)
FOCAL CELLULAR CHANGE				1 (2%)
ANGIECTASIS		1 (5%)	1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(20)	(20)	(50)	(50)
NECROSIS, NOS	1 (5%)			
*BILE DUCT	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS		1 (5%)	1 (2%)	1 (2%)
#STOMACH	(20)	(20)	(49)	(49)
INFLAMMATION, NOS	1 (5%)			
ULCER, FOCAL			1 (2%)	
HYPERKERATOSIS	1 (5%)			
ACANTHOSIS	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
CYST, NOS			1 (2%)	
INFLAMMATION, CHRONIC	9 (45%)	2 (10%)	12 (24%)	2 (4%)
CALCIUM DEPOSIT	1 (5%)	1 (5%)		
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(20)	(20)	(49)	(49)
DEGENERATION, NOS		3 (15%)		
ANGIECTASIS	3 (15%)	4 (20%)	5 (10%)	
#THYROID	(20)	(20)	(49)	(50)
FOLLICULAR CYST, NOS		1 (5%)	1 (2%)	1 (2%)
HYPERPLASIA, C-CELL	4 (20%)			
HYPERPLASIA, FOLLICULAR-CELL		1 (5%)		

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
#PARATHYROID	(1)	(20)	(50)	(50)
HYPERPLASIA, NOS	1 (100%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
GALACTOCELE				1 (2%)
*VAGINA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
#UTERUS	(20)	(20)	(50)	(48)
HYDROMETRA	4 (20%)		1 (2%)	4 (8%)
#UTERUS/ENDOMETRIUM	(20)	(20)	(50)	(48)
INFLAMMATION, NOS	1 (5%)		1 (2%)	
HYPERPLASIA, CYSTIC	1 (5%)			1 (2%)
#OVARY	(20)	(20)	(50)	(48)
CYST, NOS		3 (15%)		
NERVOUS SYSTEM				
#BRAIN/MENINGES	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
#CEREBRUM	(20)	(20)	(50)	(50)
HYDROCEPHALUS, NOS				1 (2%)
#BRAIN	(20)	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-011F	LOW DOSE 01-014F	HIGH DOSE 01-015F
BODY CAVITIES				
*PLEURA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)	1 (2%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		1	5	4

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 1,1,2,2-TETRACHLOROETHANE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 1,1,2,2-TETRACHLOROETHANE

	CONTROL (UNTR) 02-M021	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	19	18	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	18	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(19)	(18)	(49)	(49)
EPIDERMAL INCLUSION CYST		1 (6%)		
INFLAMMATION, NOS		1 (6%)		
*SUBCUT TISSUE	(19)	(18)	(49)	(49)
ABSCESS, NOS	1 (5%)		1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(19)	(18)	(39)	(47)
PNEUMONIA, CHRONIC MURINE		2 (11%)		1 (2%)
HEMATOPOIETIC SYSTEM			*	
#SPLEEN	(17)	(18)	(39)	(47)
AMYLOID, NOS	2 (12%)			
AMYLOIDOSIS		1 (6%)	5 (13%)	
#LYMPH NODE	(19)	(18)	(39)	(47)
ANGIECTASIS	1 (5%)			
#MESENTERIC L. NODE	(19)	(18)	(39)	(47)
INFLAMMATION, NOS		4 (22%)	2 (5%)	
CIRCULATORY SYSTEM				
#HEART	(19)	(18)	(39)	(47)
CALCIUM DEPOSIT				1 (2%)

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

**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M021	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
DIGESTIVE SYSTEM				
#LIVER	(19)	(18)	(50)	(49)
THROMBUS, ORGANIZED		1 (6%)		
AMYLOID, NOS	1 (5%)			
HYPERPLASIA, NODULAR		1 (6%)		
#LARGE INTESTINE	(19)	(18)	(39)	(47)
NEMATODIASIS	2 (11%)			
#COLON	(19)	(18)	(39)	(47)
PARASITISM				1 (2%)
URINARY SYSTEM				
#KIDNEY	(19)	(18)	(39)	(47)
HYDRONEPHROSIS			3 (8%)	
PYELONEPHRITIS, NOS		1 (6%)		3 (6%)
INFLAMMATION, CHRONIC	7 (37%)	5 (28%)	13 (33%)	10 (21%)
NEPHROPATHY		4 (22%)		
AMYLOID, NOS	6 (32%)			
AMYLOIDOSIS		4 (22%)	3 (8%)	
CALCIUM DEPOSIT			5 (13%)	1 (2%)
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(19)	(18)	(39)	(47)
ANGIECTASIS				1 (2%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(18)	(18)	(39)	(47)
INFLAMMATION, NOS				1 (2%)
*SEMINAL VESICLE	(19)	(18)	(49)	(49)
INFLAMMATION, NOS		1 (6%)		
#TESTIS	(19)	(18)	(39)	(47)
CALCIUM DEPOSIT			1 (3%)	
ATROPHY, NOS	1 (5%)		3 (8%)	1 (2%)
*EPIDIDYMIS	(19)	(18)	(49)	(49)
GRANULOMA, SPERMATIC			1 (2%)	

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 02-M021	CONTROL (VEH) 02-M011	LOW DOSE 02-M012	HIGH DOSE 02-M013
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MEDIASTINUM	(19)	(18)	(49)	(49)
CYST, NOS	1 (5%)			
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	2	18	4
ANIMAL MISSING/NO NECROPSY		1		
NECROPSY PERF/NO HISTO PERFORMED			1	
AUTO/NECROPSY/HISTO PERF			1	
AUTOLYSIS/NO NECROPSY	1	1	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 1.1.2.2-TETRACHLOROETHANE

	CONTROL (UNTR) 02-F021	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING	1		1	1
ANIMALS NECROPSIED	19	20	48	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	48	47
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(19)	(20)	(46)	(44)
BRONCHOPNEUMONIA, ACUTE	2 (11%)			
PNEUMONIA, CHRONIC MURINE		1 (5%)	6 (13%)	8 (18%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(19)	(19)	(46)	(46)
INFLAMMATION, NOS			1 (2%)	
HEMATOPOIESIS	2 (11%)		1 (2%)	
#LYMPH NODE	(19)	(20)	(46)	(46)
HYPERPLASIA, LYMPHOID	1 (5%)			
#MESENTERIC L. NODE	(19)	(20)	(46)	(46)
INFLAMMATION, NOS		1 (5%)		
ANGIECTASIS				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(19)	(20)	(46)	(44)
THROMBUS, ORGANIZED				2 (5%)
#MYOCARDIUM	(19)	(20)	(46)	(44)
FIBROSIS		1 (5%)	1 (2%)	
#ENDOCARDIUM	(19)	(20)	(46)	(44)
HYPERPLASIA, NOS			1 (2%)	

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-F021	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
*CORONARY ARTERY	(19)	(20)	(48)	(47)
INFLAMMATION, CHRONIC	1 (5%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(19)	(19)	(40)	(39)
CYST, NOS			1 (3%)	
INFLAMMATION, NOS				1 (3%)
#LIVER	(19)	(20)	(48)	(47)
THROMBUS, ORGANIZED			1 (2%)	4 (9%)
PELIOSIS HEPATIS			1 (2%)	
HYPERPLASIA, NODULAR			4 (8%)	1 (2%)
*BILE DUCT	(19)	(20)	(48)	(47)
HYPERPLASIA, NOS		1 (5%)		
#PANCREAS	(19)	(20)	(46)	(46)
CYST, NOS		1 (5%)	2 (4%)	
THROMBUS, ORGANIZED				2 (4%)
INFLAMMATION, NOS				1 (2%)
PERIARTERITIS				1 (2%)
#STOMACH	(19)	(20)	(46)	(46)
INFLAMMATION, NOS		1 (5%)		
HYPERKERATOSIS		2 (10%)		
#LARGE INTESTINE	(19)	(20)	(46)	(46)
NEMATODIASIS		1 (5%)		
URINARY SYSTEM				
#KIDNEY	(19)	(20)	(46)	(46)
HYDRONEPHROSIS				16 (35%)
INFLAMMATION, CHRONIC				5 (11%)
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(18)	(20)	(46)	(46)
ANGIECTASIS				1 (2%)
REPRODUCTIVE SYSTEM				
#UTERUS	(18)	(20)	(46)	(46)
HYDROMETRA			3 (7%)	3 (7%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-F021	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
#UTERUS/ENDOMETRIUM	(18)	(20)	(46)	(46)
INFLAMMATION, NOS		6 (30%)	7 (15%)	
INFLAMMATION, ACUTE	1 (6%)			
HYPERPLASIA, CYSTIC	15 (83%)	9 (45%)	9 (20%)	3 (7%)
#OVARY/OVIDUCT	(18)	(20)	(46)	(46)
INFLAMMATION, NOS			1 (2%)	
#OVARY	(18)	(20)	(46)	(46)
CYST, NOS		5 (25%)	5 (11%)	4 (9%)
FOLLICULAR CYST, NOS	4 (22%)			
INFLAMMATION, NOS		2 (10%)	7 (15%)	
INFLAMMATION, SUPPURATIVE	3 (17%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(19)	(20)	(48)	(47)
HYPERTROPHY, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERICARDIUM	(19)	(20)	(48)	(47)
INFLAMMATION, NOS				1 (2%)
*MESENTERY	(19)	(20)	(48)	(47)
PERIARTERITIS				1 (2%)
ALL OTHER SYSTEMS				
NONE				

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 02-F021	CONTROL (VEH) 02-F011	LOW DOSE 02-F014	HIGH DOSE 02-F015
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	1	8	
ANIMAL MISSING/NO NECROPSY	1		1	1
AUTOLYSIS/NO NECROPSY			1	2

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