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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-TRICHLOROETHANE FOR POSSIBLE CARCINOGENICITY

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

FOREWORD: This report presents the results of the bioassay of 1,1,2-trichloroethane conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected environmental chemicals have the capacity to produce cancer animals. Negative results, in which the test animals do not have a in greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of 1,1,2-trichloroethane 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 Testing Program.

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Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6) and Dr. J.

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SUMMARY

A bioassay of technical-grade 1,1,2-trichloroethane for possible carcinogenicity was conducted using Osborne-Mendel rats and B6C3F1 mice. 1,1,2-Trichloroethane 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 for a period of 78 weeks, followed by an observation period of up to 35 weeks for rats and up to 13 weeks for mice.

The high and low time-weighted average dosages of 1,1,2-trichloroethane were, respectively, 92 and 46 mg/kg/day for male and female rats, and 390 and 195 mg/kg/day for the male and 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 rate as the high dose group of the same sex. Twenty animals of each sex were placed on test as untreated controls for each species. These animals were not intubated.

No neoplasms were observed at statistically significant incidences in male or female rats.

In both male and female mice, administration of 1,1,2-trichloroethane was associated with a significantly increased incidence of hepatocellular carcinomas. Hepatocellular carcinomas were observed in 2/17 (12 percent) untreated control males, 2/20 (10 percent) vehicle control males, 18/49 (37 percent) low dose males, and 37/49 (76 percent) high dose males. Hepatocellular carcinomas were also observed in 2/20 (10 percent) untreated control females, 0/20 vehicle control females, 16/48 (33 percent) low dose females, and 40/45 (89 percent) high dose females. Both the Fisher exact test comparing tumor incidences of dosed to control groups and the Cochran-Armitage test for positive dose-related trend indicated a highly significant ($P < 0.001$) association between hepatocellular carcinomas in all mouse groups and the administration of 1,1,2-trichloroethane.

A positive dose-related association between administration of 1,1,2-trichloroethane and the incidence of pheochromocytoma of the adrenal gland was indicated by the Cochran-Armitage test for mice of both sexes. Fisher exact tests confirmed these results for high dose female mice but not for other mouse groups. There were no other neoplasms for which statistical tests indicated a positive association between dosage and tumor incidence in mice.

The results of this study do not provide convincing evidence for the carcinogenicity of 1,1,2-trichloroethane in Osborne-Mendel rats.

Under the conditions of this bioassay 1,1,2-trichloroethane is carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas and adrenal pheochromocytomas.

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I. INTRODUCTION

1,1,2-Trichloroethane (NCI No. C04579), 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-trichloroethane.* It is also called vinyltrichloride or beta-trichloroethane.

Production data for 1,1,2-trichloroethane are considered proprietary by the U.S. Federal Trade Commission, since there are only two manufacturers of the chemical. (If three or more companies produce a chemical, production must be reported to the federal government.) However, 90 million pounds of vinylidene chloride were manufactured by dehydrohalogenation of 1,1,2-trichloroethane in 1974 (Stanford Research Institute, 1975), implying a minimum production of approximately 124 million pounds of 1,1,2-trichloroethane in that year. Most 1,1,2-trichloroethane is used as a chemical intermediate in the production of vinylidene chloride (Stanford Research Institute, 1975). Other applications include use in adhesives, in the production of teflon tubing, in lacquer, and in coating formulations (Folkerson, 1977), and as a solvent for fats, oil, waxes, and other products (Hawley, 1971).

*The CAS registry number is 79-00-5.

Exposure of human populations to 1,1,2-trichloroethane occurs primarily through inhalation of vapors released during its manufacture and subsequent use as a chemical intermediate. Since the chemical is readily absorbed through the skin (Hawley, 1971), dermal contact following accidental spills or carbon handling represents an additional route of exposure.

II. MATERIALS AND METHODS

A. Chemicals

One batch of technical-grade 1,1,2-trichloroethane was purchased by Hazleton Laboratories America, Inc., Vienna, Virginia, from Aldrich Chemical Company. The purity of the compound was initially determined by Hazleton using gas-liquid chromatography (GLC) and infrared spectrophotometry. The GLC total-area analysis revealed seven peaks; the major peak accounted for 99.2 percent of the total area. The infrared spectrum of the 1,1,2-trichloroethane was consistent with that expected from the structure of the compound.

Purity determinations were repeated by Hazleton Laboratories seven and thirteen months, respectively, after the initial analysis to assess the stability of the 1,1,2-trichloroethane after storage. The chromatograph from the second GLC analysis showed a peak accounting for 90.8 percent of the total area. In the third analysis the major peak accounted for 95.4 percent of the total area. The infrared spectra were consistent with the first analysis. These results indicate stability of the test compound.

Throughout this report the term 1,1,2-trichloroethane is used to represent this technical-grade material.

B. Dosage Preparation

Fresh solutions of 1,1,2-trichloroethane in Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) were prepared weekly, sealed and stored in dark bottles at 1°C. The concentration of

1,1,2-trichloroethane in corn oil administered to rats ranged from 3.5 to 5.0 percent. The concentration administered to mice ranged from 3.0 to 4.0 percent.

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 treated and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 25°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 ten in solid-bottom polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Pinewood Sawdust Company, Moonachie, New Jersey) 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® meal, Allied Mills, Inc., Chicago, Illinois) and water were available ad libitum.

The rats dosed with 1,1,2-trichloroethane and their untreated controls were housed in the same room with rats intubated with* tetrachloroethylene (127-18-4). Vehicle control rats for the 1,1,2-trichloroethane study were housed in the same room as rats intubated with dibromochloropropane (96-12-8), 1,2-dichloroethane (107-06-2), 1,1-dichloroethane (75-34-3), trichloroethylene (79-01-6), and carbon disulfide (75-15-0).

All mice, including controls, were housed in the same room as mice intubated with 1,1,2,2-tetrachloroethane (79-34-5), chloroform (67-66-3), dibromochloropropane (96-12-8), chloropicrin (76-06-2),

*CAS registry numbers are given in parentheses.

1,2-dichloroethane (107-06-2), 1,1-dichloroethane (75-34-3), allyl chloride (107-05-1), trichloroethylene (79-01-6), 3-sulfolene (77-79-2), iodoform (75-47-8), methylchloroform (71-55-6), 1,2-dibromoethane (106-93-4), 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 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 treated group received the same dose at each administration. Gavage of treated animals was performed 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 estimate the maximum tolerated doses of 1,1,2-trichloroethane for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. A solution of 1,1,2-trichloroethane in corn oil was administered by gavage to five of the six rat groups at dosages of 32, 56, 100, 178, and 316 mg/kg/day and

five of the six mouse groups at dosages of 56, 100, 178, 316, and 562 mg/kg/day. The sixth group of each species served as a control group, receiving only the corn oil. Intubation was performed 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity.

In week 1 of the study, one male rat died at a dosage of 56 mg/kg/day and one female rat died at 100 mg/kg/day. At 56 and 100 mg/kg/day the mean body weight gain, expressed as a percentage of the weight gained by the control animals was, respectively, 96 and 97 percent for males, and 84 and 94 percent for females. The initial high dose selected for both male and female rats in the chronic study was 70 mg/kg/day.

One male mouse died at 316 mg/kg/day and one female died at 178 mg/kg/day. At 178 and 316 mg/kg/day the mean body weight gain, expressed as a percentage of the weight gained by the control animals was, respectively, 101 and 99 percent for males, and 96 and 94 percent for females. The initial high dose selected for both male and female mice in the chronic study was 300 mg/kg/day.

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.

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

	INITIAL NUMBER OF ANIMALS	1,1,2-TRICHLOROETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0	0	111	0
VEHICLE CONTROL	20	0	78	33	0
LOW DOSE	50	35	20		46
		50	58		
		0		34	
HIGH DOSE	50	70	20		92
		100	58		
		0		34	
FEMALE					
UNTREATED CONTROL	20	0	0	111	0
VEHICLE CONTROL	20	0	78	33	0
LOW DOSE	50	35	20		46
		50	58		
		0		34	
HIGH DOSE	50	70	20		92
		100	58		
		0		35	

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

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

TABLE 2
DESIGN SUMMARY FOR B6C3F1 MICE
1,1,2-TRICHLOROETHANE GAVAGE EXPERIMENT

	INITIAL NUMBER OF ANIMALS	1,1,2-TRI-CHLOROETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0	0	91	0
VEHICLE CONTROL	20	0	78	12	0
LOW DOSE	50	150	8		195
		200	70		
		0		12	
HIGH DOSE	50	300	8		390
		400	70		
		0		13	
FEMALE					
UNTREATED CONTROL	20	0	0	91	0
VEHICLE CONTROL	20	0	78	12	0
LOW DOSE	50	150	8		195
		200	70		
		0		13	
HIGH DOSE	50	300	8		390
		400	70		
		0		13	

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

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

1,1,2-Trichloroethane-treated and untreated control rats had a median age of approximately 6 weeks at the start of the study. The vehicle control rats were approximately 8 weeks old on their first day of intubation, which began 4 weeks earlier for the vehicle controls than for the other rat groups. For the first 20 weeks of the experiment, the dosages used for rats were 70 and 35 mg/kg/day of 1,1,2-trichloroethane. Throughout this report the rats initially receiving the former dosage are referred to as the high dose groups and those receiving the latter are referred to as the low dose groups. As the animals appeared to be tolerating the chemical in week 20 of the study, the doses were increased in week 21 to 100 and 50 mg/kg/day for the high and low dose animals, respectively, and these doses were maintained for the remainder of the 78-week dosing period. After the dosing period, observation of the rats continued for up to 35 additional weeks.

The vehicle control and treated mice were approximately 5 weeks old on the day intubation began. Untreated control mice had a median birth date 2 weeks later than the other mouse groups and their observation period lasted a corresponding 2 weeks longer than that of treated mice. The initial dosages of 1,1,2-trichloroethane utilized for the mice were 300 and 150 mg/kg/day. Throughout this report the mice initially receiving the former dosage are referred to as the high dose groups and those receiving the latter are referred to as the low dose groups. High and low doses were increased to 400 and

200 mg/kg/day, respectively, in week 9 because of apparent tolerance to the chemical. These levels were maintained for the remainder of the 78-week dosing period. After the dosing period, observation of the mice continued for up to 13 additional weeks.

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, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder and bile duct (mice), pancreas, esophagus, stomach, small intestine, large

intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, nerves, brain, tunica vaginalis, 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

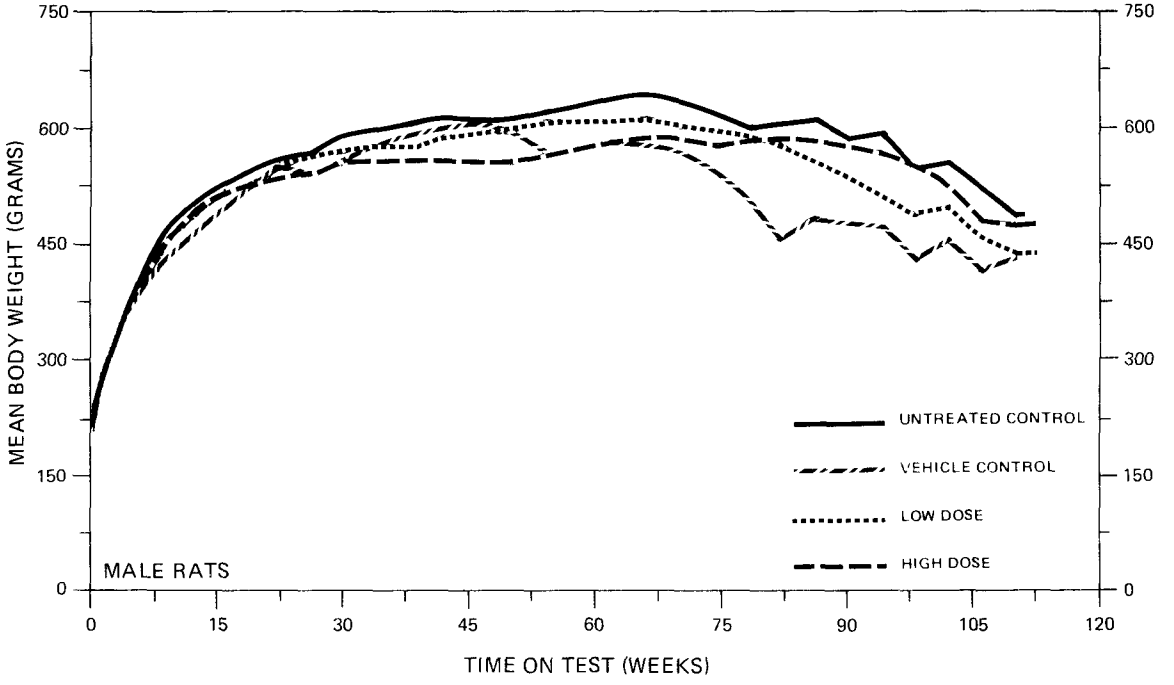
A. Body Weights and Clinical Observations

There were no appreciable differences between the weight gain patterns in the treated and untreated control rats (Figure 1). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

During the first 6 months of the study the appearance and behavior of the treated rats and the untreated controls were generally comparable. Occasional hunched appearance and eye discharges, observed in all groups as early as week 3, were noted in a few more treated than control rats.

As the study progressed, an increasing number of treated rats showed clinical signs which included a hunched appearance, rough fur, urine stains on the abdominal area, dyspnea, and squinted eyes, sometimes with reddish exudate. The incidence and frequency of these signs were similar in low and high dose groups, except that the high dose females showed an elevated incidence of abdominal urine staining from week 26 until intubation ceased in week 78.

Signs of respiratory difficulty characterized by wheezing, dyspnea, and nasal exudate (sometimes bloody in appearance) were noted in treated and control groups at a low or moderate incidence during the latter part of the first year, and this incidence increased as the



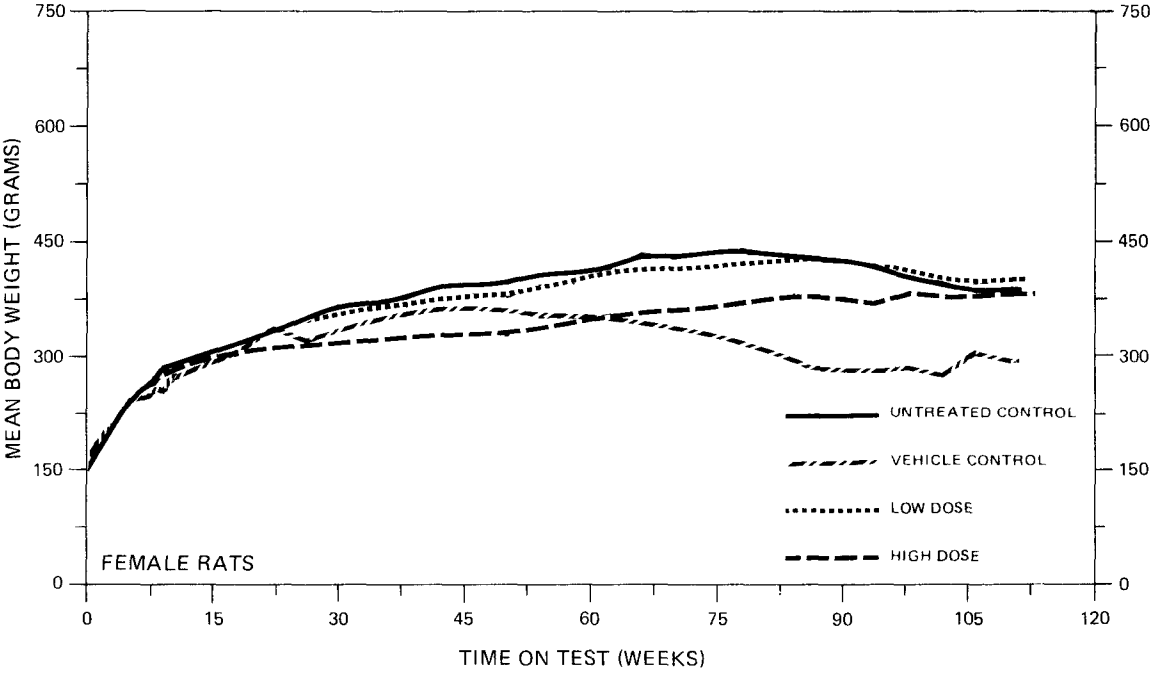


FIGURE 1
GROWTH CURVES FOR 1,1,2-TRICHLOROETHANE CHRONIC STUDY RATS

animals aged. As the study approached termination more treated animals than controls exhibited respiratory difficulty.

Other signs often associated with aging in laboratory rats were observed at a comparable rate in controls and treated rats during the second year of the study. These signs included alopecia, sores on the body and/or extremities, stains on the fur, reddish exudate around the eyes, and intermittent soft feces. Palpable subcutaneous masses and swelling were observed at a comparable rate in treated rats and untreated controls during the last 8 to 10 months of the study.

B. Survival

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

For rats of both sexes the Tarone test for positive association between increased dosage and accelerated mortality was not significant. For both sexes the high dose groups showed poorer survival than the low dose or the untreated control groups until around week 90. The vehicle control groups had unexpectedly poor survival with only 5 percent (1/20) of the males and 20 percent (4/20) of the females surviving until termination of the study.

Among the male rats, at least 50 percent of the high dose, low dose, and untreated control groups survived more than 96 weeks. Among the female rats 50 percent of the high dose, low dose, and untreated

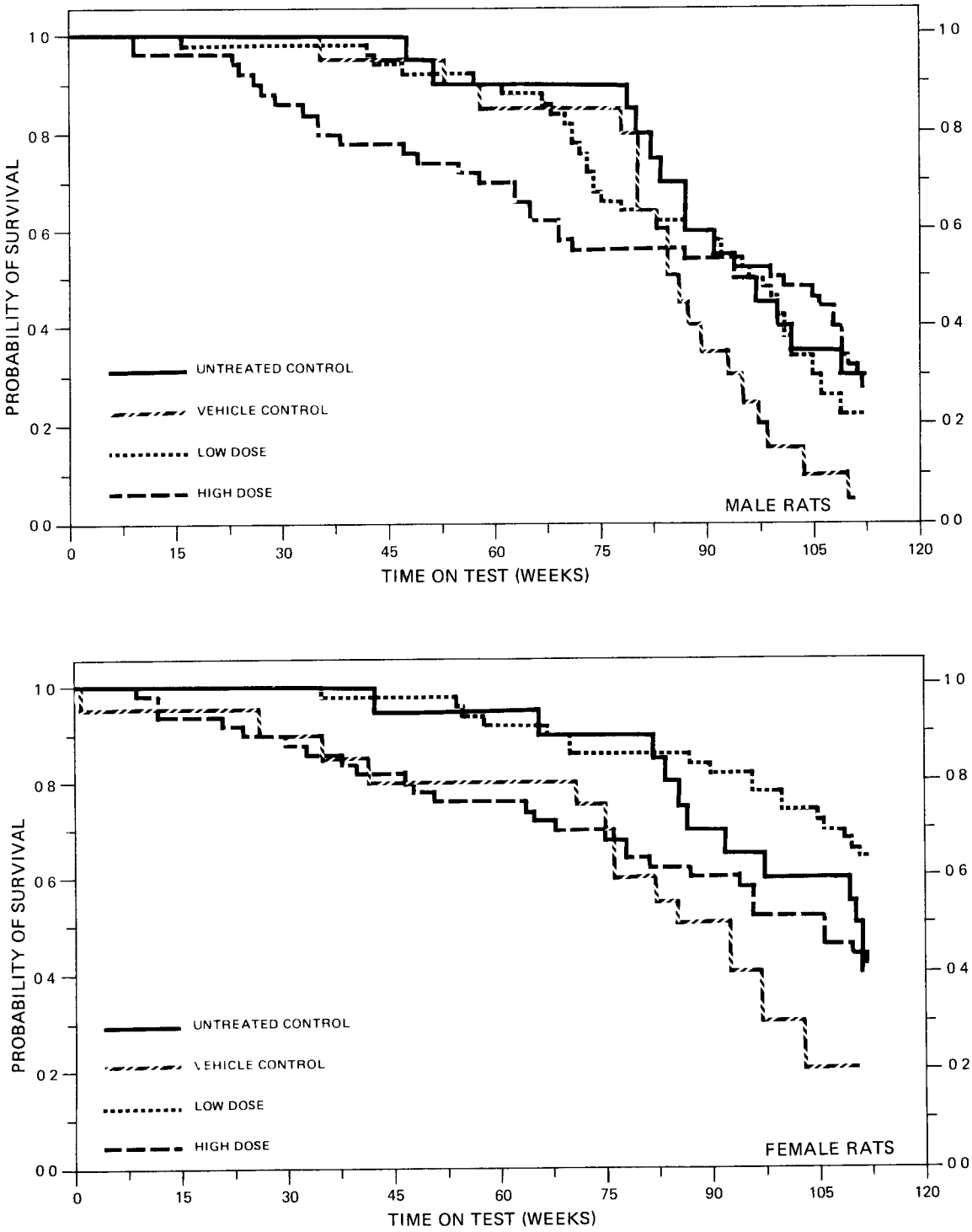


FIGURE 2
SURVIVAL COMPARISONS OF 1,1,2-TRICHLOROETHANE CHRONIC STUDY RATS

control groups survived more than 105 weeks. Thus adequate numbers of rats were at risk from late-developing 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).

Adrenal cortical carcinomas occurred in 1/50 (2 percent) high dose males, 2/50 (4 percent) low dose females and 1/50 (2 percent) high dose females. Lesions of this type were not present in any untreated or vehicle control rats. Microscopically, the adrenal cortical carcinomas had nests and sheets of large anaplastic cells, with nuclear atypia, large nucleoli, and some multinucleated cells. The cells were acidophilic, supported by dense bands of fibrous connective tissue. Mitotic figures and metastases were often seen. This neoplasm metastasized to the lung, liver, and spleen in one high dose female. A cortical-cell adenoma occurred in one low dose female. The histologic structure of the adrenal adenoma closely simulated the normal adrenal cortex. The tumor cells were enlarged and vacuolated and surrounded by a fibrous capsule.

Transitional-cell carcinoma of the kidney occurred in 1/50 (2 percent) low dose males. Renal tubular adenomas were present in 1/50 (2 percent) low dose and 1/50 (2 percent) high dose males. Hemangiosarcomas of the spleen occurred in 3/49 (6 percent) low dose males, in the pancreas in 1/49 (2 percent) low dose males, and as a

tissue mass in the abdomen in 1/50 (2 percent) low dose males. Hemangiosarcoma occurred as a subcutaneous tissue mass in one high dose male and one low dose female. Some of the above hemangiosarcomas metastasized to nearby organs.

Other neoplasms observed in treated and control animals in this study were observed at incidences known to occur spontaneoulsy in Osborne-Mendel rats. The nonneoplastic lesions that occurred most frequently were chronic murine pneumonia and chronic nephritis. Other inflammatory, degenerative, and proliferative lesions seen in the control and treated animals were similar in number and kind to those lesions often found in aged rats.

This study did not provide histopathologic evidence for the carcinogenicity of 1,1,2-trichloroethane 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. In these analyses no statistical comparisons of the dosed groups to the vehicle control groups were made because of the atypically poor survival noted in both male and female vehicle control groups. The analysis for every type of tumor that was observed in more than 5 percent of any of the 1,1,2-trichloroethane-dosed groups of either sex is included.

Only those comparisons between the dosed groups and the untreated control groups are presented here since the survival was poor for the vehicle control groups and since the vehicle control groups were

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	0/19(0.00)	5/47(0.11)	1/46(0.02)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.033	---	---
Relative Risk (Untreated Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.533	0.023
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	98	112
Hematopoietic System: Malignant Lymphoma[b]	1/20(0.05)	1/50(0.02)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	0.400	1.200
Lower Limit	---	0.005	0.106
Upper Limit	---	30.802	61.724
Weeks to First Observed Tumor	80	42	94

[a]Treated groups received time-weighted average doses of 46 or 92 mg/kg by gavage.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	2/20(0.10)	0/50(0.00)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.047	---	---
Relative Risk (Untreated Control)[d]	---	0.000	0.200
Lower Limit	---	0.000	0.004
Upper Limit	---	1.345	3.682
Weeks to First Observed Tumor	111	---	106
Pituitary: Chromophobe Adenoma[b]	2/20(0.10)	9/48(0.19)	5/48(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	1.875	1.042
Lower Limit	---	0.444	0.192
Upper Limit	---	16.902	10.410
Weeks to First Observed Tumor	111	55	112
Kidney: Hamartoma*[b]	0/20(0.00)	4/50(0.08)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.386	0.022
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	112	112

*This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of proliferative lipocytes, tubular structures, fibroblasts, and vascular spaces in varying proportions.

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	0/20(0.00)	3/50(0.06)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.250	0.022
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	113
Mammary Gland: Adenocarcinoma NOS[b]	1/20(0.05)	0/50(0.00)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	0.000	1.600
Lower Limit	---	0.000	0.175
Upper Limit	---	7.475	77.169
Weeks to First Observed Tumor	110	---	51
Mammary Gland: Fibroadenoma[b]	6/20(0.30)	16/50(0.32)	9/50(0.18)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	1.067	0.600
Lower Limit	---	0.482	0.229
Upper Limit	---	2.931	1.828
Weeks to First Observed Tumor	82	70	87

TABLE 4 (Concluded)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma NOS or Fibroadenoma[b]	7/20(0.35)	16/50(0.32)	13/50(0.26)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	0.914	0.743
Lower Limit	---	0.439	0.338
Upper Limit	---	2.288	1.928
Weeks to First Observed Tumor	82	70	51
Uterus: Endometrial Stromal Polyp[b]	0/20(0.00)	5/50(0.10)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure From Linear Trend[e]	P = 0.010	---	---
Relative Risk (Untreated Control)[d]	---	Infinite	---
Lower Limit	---	0.525	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	90	---

[a]Treated groups received time-weighted average doses of 46 or 92 mg/kg by gavage.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

maintained in another room. Additionally, the vehicle controls were put on test at the age of 8 weeks (compared to 6 weeks for the other groups) and at a time 4 weeks before the other groups were started. No statistically significant differences were found when comparing the specific tumor incidences in the untreated control group to those in the vehicle control group or to the corresponding spontaneous tumor rates observed in the historical vehicle control record for Osborne-Mendel rats compiled by this laboratory for the NCI Bioassay Program.

For both male and female rats neither the Cochran-Armitage tests nor the Fisher exact tests were significant for any type of tumor.

On the basis of these results there was no statistical evidence for the carcinogenicity of 1,1,2-trichloroethane in rats at the dose levels used in this experiment.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative ris have been estimated and entered in the tables based upon the observed tumor incidence rates. In all 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 all 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-trichloroethane that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

There was no appreciable difference between body weight gain in the treated and untreated mice (Figure 3).

During the first year of the experiment the appearance and behavior of treated mice was generally similar to that of controls. Sores on the body and/or extremities, and generalized or localized alopecia were observed throughout this study, particularly in male mice. Other clinical signs frequently associated with group-housed or aging laboratory mice were observed at comparable rates among control and treated mice. These signs included a hunched appearance, anal prolapse, penile or vulvar redness, rough or stained fur, palpable nodules, and reddish discharge or crust around the eyes.

After 46 weeks of compound administration, abdominal distension was evident in a few high dose males and females and thereafter was observed in gradually increasing numbers in these groups. By week 74, approximately 70 percent of the high dose animals had distended abdomens which persisted until they either died, were sacrificed *in extremis*, or were sacrificed at termination of the bioassay. Abdominal distension was also seen in two untreated control females, six low dose females, and one low dose male. Subsequent necropsy of these mice indicated that liver tumors were the cause of this abdominal distension.

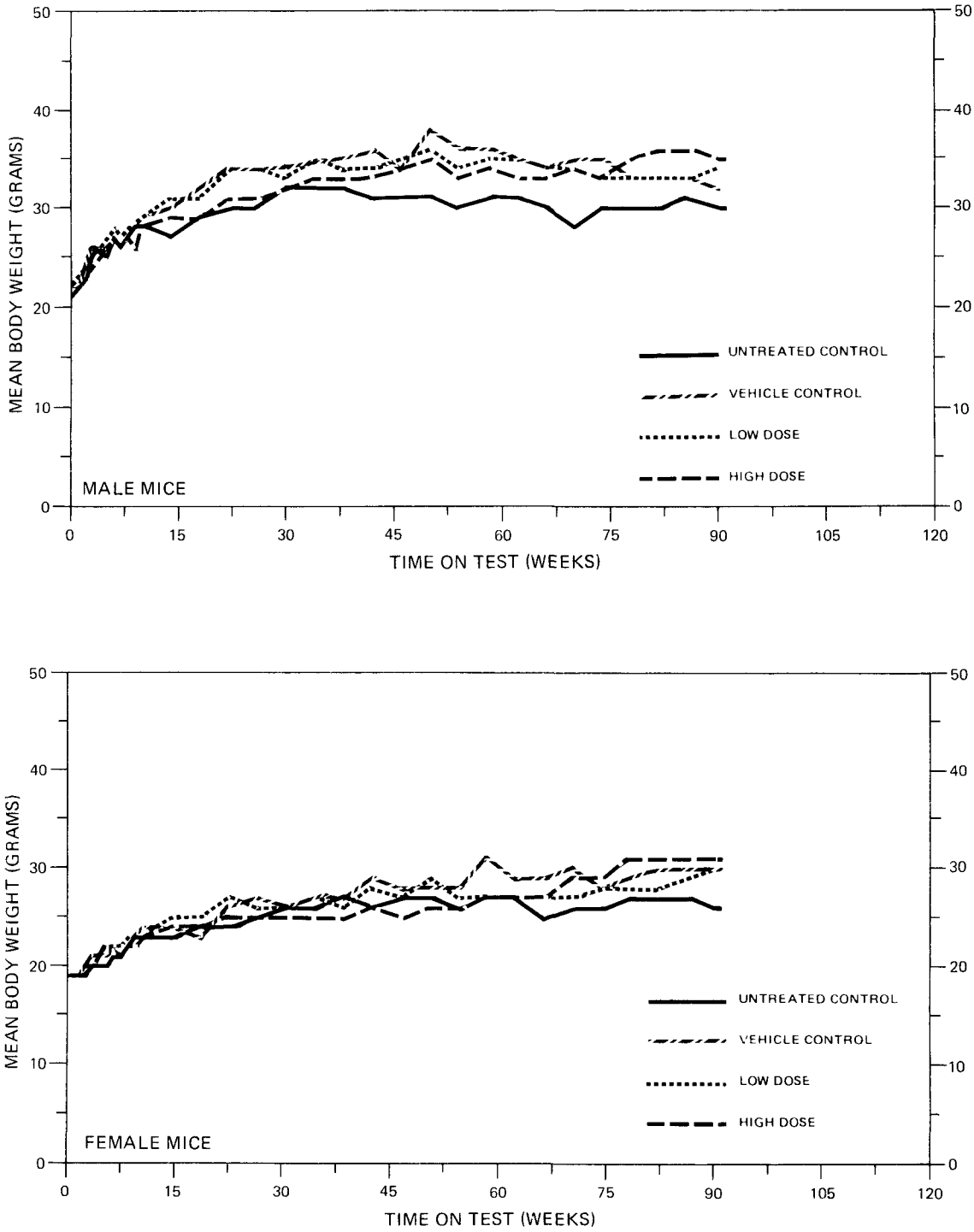


FIGURE 3
GROWTH CURVE FOR 1,1,2-TRICHLOROETHANE CHRONIC STUDY MICE

B. Survival

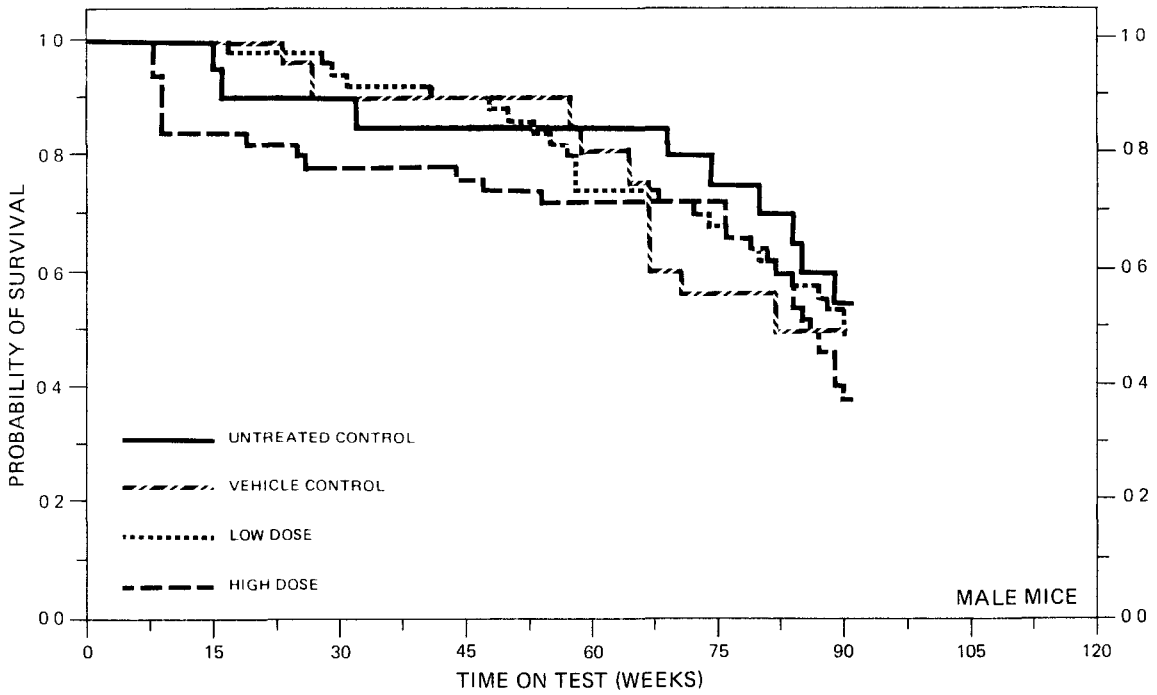
The estimated probabilities of survival for male and female mice in the control and 1,1,2-trichloroethane-dosed groups are shown in Figure 4.

In male mice the Tarone test for association between increased dosage and accelerated mortality was not significant. At least 50 percent of the male mice in each group were alive after week 86. Thus adequate numbers of male mice were at risk from late-developing tumors.

In female mice the Tarone test indicated a significant ($P < 0.001$) association between increased dosage and accelerated mortality. Although the low dose group exhibited the greatest mortality, largely due to the early deaths of 8 mice in week 36 and 11 mice in week 55, the departure from linear trend was not considered significant ($P = 0.058$). There was no indication that these low dose mice died from any common cause. The early deaths in the low dose females were not associated with tumors: in 23 of the 24 deaths prior to week 58 (not counting the 1 animal that was missing) no tumor at any site was observed. Fifty percent of the mice were still alive after 81, 58, 89, and 90 weeks for the high dose, low dose, vehicle control, and untreated control groups, respectively.

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).



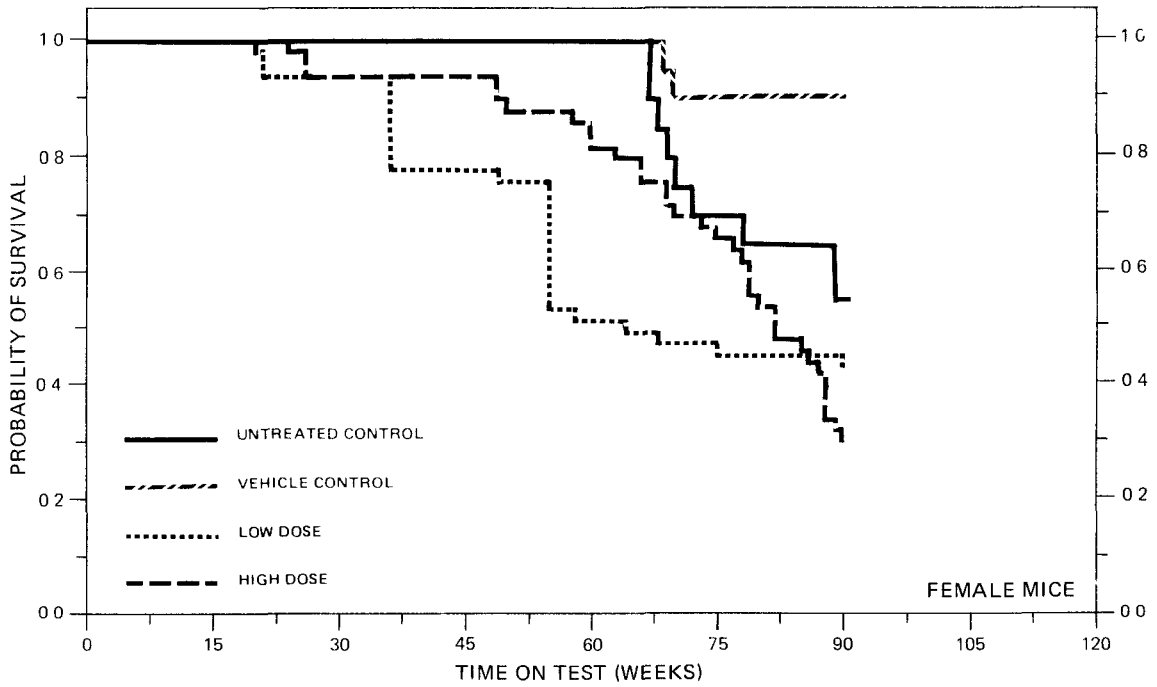


FIGURE 4
SURVIVAL COMPARISONS OF 1,1,2-TRICHLOROETHANE CHRONIC STUDY MICE

Hepatocellular carcinomas were observed in 2/17 (12 percent) untreated control males, 2/20 (10 percent) vehicle control males, 18/49 (37 percent) low dose males, and 37/49 (76 percent) high dose males. Hepatocellular carcinomas were also seen in 2/20 (10 percent) untreated control female, 0/20 vehicle control female, 16/48 (33 percent) low dose female, and 40/45 (89 percent) high dose female mice.

Microscopically, the hepatocellular carcinomas varied greatly in appearance. Some lesions contained well-differentiated hepatic cells that had a relatively uniform arrangement of the cords, and others had very anaplastic liver cells with large hyperchromatic nuclei, often with inclusion bodies and with vacuolated, pale cytoplasm. Arrangement of the neoplastic liver cells varied from short stubby cords to nests of cells and occasionally acinar formation. Mitotic figures were often present. Some of the tumors were characterized by discrete areas of highly anaplastic cells. Metastasis to the lung occurred in one low dose male, one high dose male, and two high dose female mice. The hepatic neoplasms that occurred in the control mice were not different in appearance from those noted in the chemically treated mice.

Adrenal pheochromocytomas were present in 8/48 (17 percent) high dose males and in 12/43 (28 percent) high dose females but not in any other mouse groups. The neoplastic cells occurred in nests of large irregular or polyhedral cells with central nuclei and abundant cytoplasm, and were surrounded by a thin vascular connective tissue

stroma. An adrenal cortical carcinoma occurred in one high dose male with metastasis to the lung, cervical lymph nodes, pancreas, prostate, and epididymis.

Squamous-cell carcinomas of the forestomach occurred in one low dose and one high dose male and one high dose female. A squamous-cell papilloma occurred in one low dose male.

Other neoplasms occurred in mice with no appreciable difference in frequency between control and treated animals. A relatively low incidence of degenerative and inflammatory lesions occurred in the treated and control mice.

The increased incidence of hepatocellular carcinomas and adrenal pheochromocytomas in male and female mice provided histopathologic evidence for the carcinogenicity of 1,1,2-trichloroethane in B6C3F1 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 1,1,2-trichloroethane-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 incidence of specific tumors in these control groups was compared to the corresponding spontaneous tumor rates for the historical controls

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	2/18(0.11)	0/20(0.00)	3/49(0.06)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.551	0.180
Lower Limit	---	---	0.071	0.003
Upper Limit	---	---	6.284	3.307
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.255	0.012
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	84	---	90	91
Liver: Hepatocellular Carcinoma[b]	2/17(0.12)	2/20(0.10)	18/49(0.37)	37/49(0.76)
P Values[c]	P < 0.001	P < 0.001	P = 0.047* P = 0.022**	P < 0.001* P < 0.001**
Relative Risk (Untreated Control)[d]	---	---	3.122	6.418
Lower Limit	---	---	0.885	2.025
Upper Limit	---	---	25.955	47.713
Relative Risk (Vehicle Control)[d]	---	---	3.673	7.551
Lower Limit	---	---	1.020	2.337
Upper Limit	---	---	30.643	56.311
Weeks to First Observed Tumor	91	90	55	19

TABLE 5 (Continued)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma[b]	0/18(0.00)	0/20(0.00)	0/49(0.00)	8/48(0.17)
P Values[c]	P = 0.003	P = 0.003	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.900
Upper Limit	---	---	---	Infinite
Relative Risk (Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.992
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	76
Hematopoietic System: Malignant Lymphoma[b]	1/18(0.06)	2/20(0.10)	7/49(0.14)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.046	---	---	---
Relative Risk (Untreated Control)[d]	---	---	2.571	0.360
Lower Limit	---	---	0.374	0.005
Upper Limit	---	---	113.260	27.724
Relative Risk (Vehicle Control)[d]	---	---	1.429	0.200
Lower Limit	---	---	0.309	0.004
Upper Limit	---	---	13.396	3.681
Weeks to First Observed Tumor	91	66	76	90

TABLE 5 (Concluded)

[a]Treated groups received time-weighted average doses of 195 or 390 mg/kg by gavage.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 6

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

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	1/20(0.05)	0/20(0.00)	3/48(0.06)	2/39(0.05)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	1.250	1.026
Lower Limit	---	---	0.110	0.058
Upper Limit	---	---	64.251	58.952
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.260	0.157
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	91	---	55	79
Liver: Hepatocellular Carcinoma[b]	2/20(0.10)	0/20(0.00)	16/48(0.33)	40/45(0.89)
P Values[c]	P < 0.001	P < 0.001	P = 0.041* P = 0.002**	P < 0.001* P < 0.001**
Relative Risk (Untreated Control)[d]	---	---	3.333	8.889
Lower Limit	---	---	0.907	2.898
Upper Limit	---	---	28.087	54.670
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	2.200	6.515
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	91	---	64	49

TABLE 6 (Continued)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma[b]	0/20(0.00)	0/20(0.00)	0/48(0.00)	12/43(0.28)
P Values[c]	P < 0.001	P < 0.001	N.S.	P = 0.006* P = 0.006**
Departure from Linear Trend[e]	P = 0.021	P = 0.021	---	---
Relative Risk (Untreated Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	1.782
Upper Limit	---	---	---	Infinite
Relative Risk (Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	1.782
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	85
Hematopoietic System: Malignant Lymphoma[b]	0/20(0.00)	4/20(0.20)	4/48(0.08)	2/46(0.04)
P Values[c]	N.S.	P = 0.043(N)	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.402	0.133
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	0.417	0.217
Lower Limit	---	---	0.088	0.022
Upper Limit	---	---	2.063	1.406
Weeks to First Observed Tumor	---	69	91	70

TABLE 6 (Concluded)

[a]Treated groups received time-weighted average doses of 195 or 390 mg/kg by gavage.

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

[c]The probability level for the Cochrar-Armitage test is given beneath the incidence of tumors in the corresponding control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

for this laboratory compiled to date on B6C3F1 mice for the NCI Bioassay Program; no significant differences were observed.

In dosed male mice, hepatocellular carcinomas were found in large numbers and were detected as early as week 19. The Cochran-Armitage tests for positive dose-related trend were highly significant ($P < 0.001$) using either the untreated controls or the vehicle controls. Additionally, the Fisher exact test comparing tumor incidences of the dosed to the control groups confirmed these positive findings: vehicle control-high dose ($P < 0.001$); untreated control-high dose ($P < 0.001$); and vehicle control-low dose ($P = 0.022$). The comparison between the low dose and the untreated control was $P = 0.047$, a marginal result which was not significant when the Bonferroni criterion was applied. These statistical results indicate that the occurrence of hepatocellular carcinomas in male mice was associated with the administration of 1,1,2-trichloroethane at the dose levels of this experiment.

The incidence of hepatocellular carcinomas was also highly significant in female mice. The Cochran-Armitage tests for positive dose-related trend in proportions were found to be significant ($P < 0.001$) compared to either the untreated control or the vehicle control. The results of the Fisher exact tests confirmed these positive findings: high dose animals demonstrated significant ($P < 0.001$) tumor increases when compared to either the untreated or the vehicle controls. The low dose group was significantly different from the

vehicle control (P = 0.002); the comparison of low dose to untreated control had a probability level of P = 0.041, a marginal result which was not significant under the Bonferroni criterion. These statistical tests indicate that the occurrence of hepatocellular carcinomas in female mice was associated with the administration of 1,1,2-trichloroethane at the dose levels of this experiment.

For high dose groups, both male and female mice exhibited an unusually high incidence of pheochromocytomas of the adrenal gland. In the males the Cochran-Armitage tests indicated a significant (P = 0.003) positive association between dose and tumor incidence compared to both the untreated and vehicle control groups. Fisher exact tests, however, were not significant. For female mice not only did the Cochran-Armitage tests prove significant ($P < 0.001$), but the Fisher exact tests confirmed these results for comparisons between the high dose group and both the untreated (P = 0.006) and the vehicle (P = 0.006) control groups. In historical data collected by this laboratory for the NCI Bioassay Program on B6C3F1 mice used as vehicle controls, 0/180 males and 0/180 females had pheochromocytomas. Assuming a binomial distribution and a spontaneous tumor rate of 1/181, both the probability of observing 8 pheochromocytomas out of 48 males and the probability of observing 12 pheochromocytomas out of 43 females are less than 0.00001. Based upon these results the administration of 1,1,2-trichloroethane was associated with an increased incidence of pheochromocytomas in male and female mice.

There were no other tumors for which statistical tests indicated a positive association between dosage and tumor incidence. The possibility of a negative association between dosage and the incidence of malignant lymphoma was noted for female mice.

V. DISCUSSION

There were no significant associations between administration of 1,1,2-trichloroethane and mortality in rats of either sex or in male mice. Although there was a significant association between increased dosage and accelerated mortality among female mice, adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

The possibility that the rats in this bioassay did not receive dosages approximating the maximum tolerated dosage must be considered because compound administration had no significant effect upon survival or body weight gain in either sex. The premature deaths observed in rats receiving the second and third lowest dosages in the preliminary study may have caused difficulty in selecting the appropriate dosages for the chronic study.

Adrenal cortical carcinoma, transitional-cell carcinoma of the kidney, renal tubular adenoma, and hemangiosarcomas of the spleen, pancreas, abdomen, and subcutaneous tissue were some of the neoplastic lesions observed in treated but not control rats. In all these cases, however, no statistically significant difference could be found between the dosed groups and the untreated control groups.

In treated mice of both sexes, the incidence of hepatocellular carcinomas was highly significant ($P < 0.001$) when compared to the respective untreated or vehicle control groups, as well as to combined controls (of 1,1,2-trichloroethane and those of four other studies).

Hepatocellular carcinomas metastasized to the lung in one low dose male, one high dose male, and two high dose female mice. Administration of 1,1,2-trichloroethane also apparently shortened the latency period for development of hepatocellular carcinomas. The first and second hepatocellular carcinomas observed in each group of treated mice were, respectively, in weeks 55 and 74 in low dose males, in weeks 19 and 47 in high dose males, in weeks 64 and 75 in low dose females, and both in week 49 in high dose females. No hepatocellular carcinomas were observed in male or female control mice before week 90. Pheochromocytomas were observed in the high dose mouse groups of both sexes (8/48 or 17 percent in the male and 12/43 or 28 percent in the female mice) but not in the low dose or in either control group. The historical incidences of this tumor in male and female B6C3F1 vehicle controls used at this laboratory for the NCI Bioassay Program are 0/180 and 0/180, respectively. Assuming a binomial distribution and a spontaneous tumor rate of 1/181 for both sexes, the probability of observing this tumor in the incidences that were revealed by this bioassay is less than 0.00001 for both sexes.

The results of this study do not provide convincing evidence for the carcinogenicity of 1,1,2-trichloroethane in Osborne-Mendel rats. Under the conditions of this bioassay the compound is carcinogenic in B6C3F1 mice of both sexes, causing hepatocellular carcinomas and adrenal pheochromocytomas.

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APPENDIX A

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

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

	CONTROL(UNTR) 01-131M	CONTROL(VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
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			2 (4%)	1 (2%)
FIBROSARCOMA				1 (2%)
HEMANGIOSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)			2 (4%)
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#SPLEEN	(20)	(20)	(49)	(50)
HEMANGIOSARCOMA			3 (6%)	
#CERVICAL LYMPH NODE	(20)	(20)	(47)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)		
CIRCULATORY SYSTEM				
#ENDOCARDIUM	(20)	(20)	(50)	(50)
SARCOMA, NOS			1 (2%)	
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 A1 (CONTINUED)

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
#PANCREAS	(20)	(20)	(49)	(50)
HEMANGIOSARCOMA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA			1 (2%)	
TUBULAR-CELL ADENOMA			1 (2%)	1 (2%)
LIPOSARCOMA		1 (5%)		
MIXED TUMOR, MALIGNANT			1 (2%)	
HEMANGIOSARCOMA, METASTATIC			1 (2%)	
HAMARTOMA +	1 (5%)	1 (5%)	1 (2%)	
#RIGHT KIDNEY	(20)	(20)	(50)	(50)
MIXED TUMOR, MALIGNANT	1 (5%)			
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(47)	(46)
CHROMOPHOBE ADENOMA		1 (5%)	5 (11%)	1 (2%)
#ADRENAL	(20)	(20)	(50)	(50)
CORTICAL CARCINOMA				1 (2%)
MIXED TUMOR, METASTATIC	1 (5%)			
#THYROID	(20)	(19)	(48)	(50)
FOLLICULAR-CELL ADENOMA			1 (2%)	
FOLLICULAR-CELL CARCINOMA	1 (5%)	1 (5%)		
C-CELL CARCINOMA			1 (2%)	
#PANCREATIC ISLETS	(20)	(20)	(49)	(50)
ISLET-CELL ADENOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS		1 (5%)	1 (2%)	1 (2%)
FIBROADENOMA				1 (2%)
#TESTIS	(20)	(19)	(47)	(48)
INTERSTITIAL-CELL TUMOR		1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A1 (CONTINUED)

	CONTROL(UNTR) 01-131M	CONTROL(VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
NERVOUS SYSTEM				
#BRAIN	(20)	(20)	(50)	(49)
ASTROCYTOMA		1 (5%)		
#MEDULLA OBLONGATA	(20)	(20)	(50)	(49)
ASTROCYTOMA			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*VERTEBRAL COLUMN	(20)	(20)	(50)	(50)
OSTEOSARCOMA				1 (2%)
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	
*TUNICA VAGINALIS	(20)	(20)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)	2 (4%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	14	19	39	35
MORIBUND SACRIFICE				1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	6	1	11	14
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	21	11
TOTAL PRIMARY TUMORS	4	9	26	14
TOTAL ANIMALS WITH BENIGN TUMORS	1	3	11	4
TOTAL BENIGN TUMORS	1	3	13	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	5	12	8
TOTAL MALIGNANT TUMORS	3	6	12	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	
TOTAL SECONDARY TUMORS	1		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	2
TOTAL UNCERTAIN TUMORS			1	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-TRICHLOROETHANE

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	19	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(19)	(50)	(50)
FIBROMA	2 (10%)			1 (2%)
FIBROSARCOMA				1 (2%)
HEMANGIOSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(19)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(19)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		1 (2%)	
#SPLEEN	(20)	(19)	(49)	(50)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#LYMPH NODE	(20)	(19)	(47)	(45)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (2%)
#CERVICAL LYMPH NODE	(20)	(19)	(47)	(45)
SQUAMOUS CELL CARCINOMA				1 (2%)
#MESENTERIC L. NODE	(20)	(19)	(47)	(45)
FIBROSARCOMA			1 (2%)	
#THYMUS	(19)	(15)	(41)	(35)
SQUAMOUS CELL CARCINOMA			1 (2%)	

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

TABLE A2 (CONTINUED)

	CONTROL(UNTR) 01-131F	CONTROL(VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
CIRCULATORY SYSTEM				
#ENDOCARDIUM	(20)	(19)	(50)	(50)
SARCOMA, NOS	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(50)	(50)
NEOPLASTIC NODULE	1 (5%)		1 (2%)	1 (2%)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
#SMALL INTESTINE	(20)	(19)	(50)	(46)
FIBROSARCOMA			1 (2%)	
#LARGE INTESTINE	(20)	(19)	(50)	(50)
FIBROSARCOMA				1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(19)	(50)	(50)
HAMARTOMA+			4 (8%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(19)	(48)	(48)
CHROMOPHOBE ADENOMA	2 (10%)	2 (11%)	9 (19%)	5 (10%)
#ADRENAL	(20)	(19)	(50)	(50)
CORTICAL ADENOMA			1 (2%)	
CORTICAL CARCINOMA			2 (4%)	1 (2%)
LIPOSARCOMA	1 (5%)			
#THYROID	(20)	(18)	(50)	(50)
FOLLICULAR-CELL ADENOMA			2 (4%)	1 (2%)
FOLLICULAR-CELL CARCINOMA			1 (2%)	
#PANCREATIC ISLETS	(20)	(19)	(47)	(48)
ISLET-CELL ADENOMA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

	CONTROL(UNTR) 01-131F	CONTROL(VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(19)	(50)	(50)
ADENOMA, NOS			2 (4%)	
ADENOCARCINOMA, NOS	1 (5%)			4 (8%)
FIBROADENOMA	6 (30%)	2 (11%)	16 (32%)	9 (18%)
#UTERUS	(20)	(19)	(50)	(50)
ENDOMETRIAL STROMAL POLYP			5 (10%)	
NERVOUS SYSTEM				
NONE				
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@	12	15	17	29
MORIBUND SACRIFICE		1	1	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	8	4	32	21
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	4	34	22
TOTAL PRIMARY TUMORS	15	4	50	28
TOTAL ANIMALS WITH BENIGN TUMORS	9	4	29	15
TOTAL BENIGN TUMORS	10	4	40	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	3		6	9
TOTAL MALIGNANT TUMORS	4		9	10
TOTAL ANIMALS WITH SECONDARY TUMORS#				2
TOTAL SECONDARY TUMORS				4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		1	1
TOTAL UNCERTAIN TUMORS	1		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-TRICHLOROETHANE

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

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M132	HIGH DOSE 02-M133
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	18	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	20	49	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(18)	(20)	(49)	(50)
FIBROSARCOMA			2 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(18)	(20)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (11%)		2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	1 (2%)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(18)	(20)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (6%)	1 (5%)	4 (8%)	1 (2%)
#SPLEEN	(18)	(20)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#CERVICAL LYMPH NODE	(18)	(20)	(48)	(49)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
#MESENTERIC L. NODE	(18)	(20)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
#LIVER	(17)	(20)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)		
CIRCULATORY SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M132	HIGH DOSE 02-M133
DIGESTIVE SYSTEM				
#LIVER	(17)	(20)	(49)	(49)
HEPATOCELLULAR CARCINOMA	2 (12%)	2 (10%)	18 (37%)	37 (76%)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
#PANCREAS	(18)	(20)	(49)	(48)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
#STOMACH	(18)	(20)	(49)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (2%)	1 (2%)
#SMALL INTESTINE	(18)	(20)	(49)	(50)
ADENOCARCINOMA, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(18)	(20)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (6%)			
TUBULAR-CELL ADENOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(18)	(19)	(49)	(46)
CHROMOPHOBE ADENOMA			2 (4%)	
#ADRENAL	(18)	(20)	(49)	(48)
CORTICAL CARCINOMA				1 (2%)
PHEOCHROMOCYTOMA				8 (17%)
#THYROID	(18)	(20)	(49)	(46)
FOLLICULAR-CELL ADENOMA		1 (5%)		
FOLLICULAR-CELL CARCINOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
#PROSTATE	(18)	(19)	(48)	(46)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
*EPIDIDYMIS	(18)	(20)	(49)	(50)
CORTICAL CARCINOMA, METASTATIC				1 (2%)

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M132	HIGH DOSE 02-M133
NERVOUS SYSTEM				
#CEREBRUM	(18)	(19)	(49)	(49)
EPENDYMOMA		1 (5%)		
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(18)	(20)	(49)	(50)
ADENOMA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	9	10	23	30
MORIBUND SACRIFICE			2	1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	11	10	24	19
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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-M132	HIGH DOSE 02-M133
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	28	38
TOTAL PRIMARY TUMORS	5	6	36	51
TOTAL ANIMALS WITH BENIGN TUMORS	2	1	6	9
TOTAL BENIGN TUMORS	2	1	6	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	5	27	38
TOTAL MALIGNANT TUMORS	3	5	30	42
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	2
TOTAL SECONDARY TUMORS	1		1	7
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-TRICHLOROETHANE

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F134	HIGH DOSE 02-F135
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	20	20	48	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	48	45
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(48)	(46)
SQUAMOUS CELL CARCINOMA	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(48)	(39)
HEPATOCELLULAR CARCINOMA, METAST				2 (5%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)		3 (6%)	1 (3%)
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (3%)
SARCOMA, NOS, METASTATIC				1 (3%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(48)	(46)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (5%)	3 (6%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (10%)	1 (2%)	1 (2%)
#CERVICAL LYMPH NODE	(20)	(20)	(48)	(45)
SARCOMA, NOS, METASTATIC				1 (2%)
#LUMBAR LYMPH NODE	(20)	(20)	(48)	(45)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (5%)		
#KIDNEY	(20)	(20)	(48)	(45)
MALIGNANT LYMPHOMA, NOS				1 (2%)
CIRCULATORY SYSTEM				
#ENDOCARDIUM	(20)	(20)	(48)	(38)
SARCOMA, NOS				1 (3%)

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-F134	HIGH DOSE 02-F135
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(48)	(45)
HEPATOCELLULAR CARCINOMA	2 (10%)		16 (33%)	40 (89%)
*BILE DUCT	(20)	(20)	(48)	(46)
BILE DUCT CARCINOMA				1 (2%)
#STOMACH	(20)	(20)	(48)	(45)
SQUAMOUS CELL CARCINOMA				1 (2%)
#SMALL INTESTINE	(20)	(20)	(48)	(44)
ADENOCARCINOMA, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(48)	(45)
SARCOMA, NOS, METASTATIC				1 (2%)
ENDOCRINE SYSTEM				
#ADRENAL	(20)	(20)	(48)	(43)
PHEOCHROMOCYTOMA				12 (28%)
#THYROID	(20)	(20)	(48)	(35)
FOLLICULAR-CELL ADENOMA				1 (3%)
REPRODUCTIVE SYSTEM				
#OVARY	(20)	(20)	(46)	(38)
GRANULOSA-CELL TUMOR		1 (5%)		
NERVOUS SYSTEM				
*CRANIAL NERVE	(20)	(20)	(48)	(46)
NEUROFIBROMA			1 (2%)	2 (4%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
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-F134	HIGH DOSE 02-F135
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	9	2	28	33
MORIBUND SACRIFICE				2
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	11	18	21	15
ANIMAL MISSING			1	
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	5	20	41
TOTAL PRIMARY TUMORS	4	5	24	63
TOTAL ANIMALS WITH BENIGN TUMORS	1		4	16
TOTAL BENIGN TUMORS	1		4	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	4	18	40
TOTAL MALIGNANT TUMORS	3	4	20	47
TOTAL ANIMALS WITH SECONDARY TUMORS#				3
TOTAL SECONDARY TUMORS				5
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-TRICHLOROETHANE

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

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
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)
EPIDERMAL INCLUSION CYST		1 (5%)		1 (2%)
INFLAMMATION, NOS			1 (2%)	
ABSCESS, NOS			1 (2%)	
HYPERKERATOSIS				1 (2%)
ACANTHOSIS				1 (2%)
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
ABSCESS, NOS	1 (5%)			
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(20)	(48)	(50)
INFLAMMATION, NOS	1 (5%)			
#LUNG	(20)	(20)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	14 (70%)	19 (95%)	45 (90%)	34 (68%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(49)	(50)
HEMATOPOIESIS	1 (5%)	1 (5%)	1 (2%)	2 (4%)
#CERVICAL LYMPH NODE	(20)	(20)	(47)	(46)
INFLAMMATION, NOS			1 (2%)	
#TRACHEAL LYMPH NODE	(20)	(20)	(47)	(46)
ANGIECTASIS	1 (5%)			
#THYMUS	(16)	(16)	(37)	(27)
INFLAMMATION, NOS				1 (4%)

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 01-131M	CONTROL(VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(50)
THROMBOSIS, NOS				1 (2%)
CALCIUM DEPOSIT				1 (2%)
#MYOCARDIUM	(20)	(20)	(50)	(50)
FIBROSIS	3 (15%)		2 (4%)	3 (6%)
DEGENERATION, NOS				1 (2%)
#ENDOCARDIUM	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS		1 (5%)		4 (8%)
*AORTA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)			
MEDIAL CALCIFICATION	2 (10%)		2 (4%)	
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)		2 (4%)	4 (8%)
PELIOSIS HEPATIS	1 (5%)			
METAMORPHOSIS FATTY	1 (5%)		1 (2%)	6 (12%)
FOCAL CELLULAR CHANGE				1 (2%)
ANGIECTASIS	1 (5%)		2 (4%)	
#LIVER/CENTRILOBULAR	(20)	(20)	(50)	(50)
DEGENERATION, NOS	1 (5%)		1 (2%)	
*BILE DUCT	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS	2 (10%)	1 (5%)	3 (6%)	5 (10%)
#PANCREAS	(20)	(20)	(49)	(50)
PERIARTERITIS	1 (5%)	1 (5%)		
#STOMACH	(20)	(20)	(50)	(50)
ULCER, FOCAL			1 (2%)	
CALCIUM DEPOSIT	2 (10%)		2 (4%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
HYDRONEPHROSIS				3 (6%)
THROMBUS, ORGANIZED			1 (2%)	
PYELONEPHRITIS, NOS		4 (20%)	3 (6%)	1 (2%)
INFLAMMATION, CHRONIC	13 (65%)	12 (60%)	22 (44%)	15 (30%)
CALCIUM DEPOSIT	1 (5%)		2 (4%)	

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

TABLE C 1 (CONTINUED)

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
#LEFT KIDNEY	(20)	(20)	(50)	(50)
INFLAMMATION, CHRONIC	1 (5%)			
#URINARY BLADDER	(17)	(20)	(48)	(47)
INFLAMMATION, NOS			1 (2%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(47)	(46)
ANGIECTASIS	1 (5%)			
#ADRENAL CORTEX	(20)	(20)	(50)	(50)
ANGIECTASIS	1 (5%)		3 (6%)	3 (6%)
#THYROID	(20)	(19)	(48)	(50)
FOLLICULAR CYST, NOS	1 (5%)			
#PARATHYROID	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS	4 (20%)		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM				
*PENIS	(20)	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)	
ABSCESS, NOS			1 (2%)	
#PROSTATE	(17)	(17)	(40)	(30)
INFLAMMATION, NOS		2 (12%)	4 (10%)	2 (7%)
*SEMINAL VESICLE	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			2 (4%)	2 (4%)
#TESTIS	(20)	(19)	(47)	(48)
CALCIUM DEPOSIT				2 (4%)
CALCIFICATION, NOS			1 (2%)	
ATROPHY, NOS	5 (25%)	7 (37%)	14 (30%)	7 (15%)
*EPIDIDYMIS	(20)	(20)	(50)	(50)
NECROSIS, FAT				1 (2%)
NERVOUS SYSTEM				
NONE				

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

TABLE C1 (CONCLUDED)

	CONTROL(UNTR) 01-131M	CONTROL(VEH) 01-081M	LOW DOSE 01-132M	HIGH DOSE 01-133M
SPECIAL SENSE ORGANS				
*EYE	(20)	(20)	(50)	(50)
SYNECHIA, ANTERIOR	1 (5%)			
CATARACT				1 (2%)
*EYE/CORNEA	(20)	(20)	(50)	(50)
VASCULARIZATION	1 (5%)			
*EYE/RETINA	(20)	(20)	(50)	(50)
ATROPHY, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
*PERICARDIUM	(20)	(20)	(50)	(50)
FIBROSIS			1 (2%)	
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS	1 (5%)	1 (5%)	1 (2%)	2 (4%)
NECROSIS, FAT		1 (5%)		
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	1	1	9

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-TRICHLOROETHANE

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	19	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(19)	(50)	(50)
ABSCESS, NOS		1 (5%)		
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(20)	(19)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	17 (85%)	17 (89%)	43 (86%)	32 (64%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(19)	(49)	(50)
ANGIECTASIS				1 (2%)
HEMATOPOIESIS	1 (5%)	1 (5%)	5 (10%)	4 (8%)
#SPLENIC CAPSULE	(20)	(19)	(49)	(50)
INFLAMMATION, NOS	1 (5%)			
#CERVICAL LYMPH NODE	(20)	(19)	(47)	(45)
INFLAMMATION, NOS			1 (2%)	1 (2%)
HYPERPLASIA, NOS				1 (2%)
#MESENTERIC L. NODE	(20)	(19)	(47)	(45)
INFLAMMATION, NOS	1 (5%)			1 (2%)
ANGIECTASIS				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(20)	(19)	(50)	(50)
THROMBUS, ORGANIZED	1 (5%)		1 (2%)	1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
#MYOCARDIUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
FIBROSIS			1 (2%)	2 (4%)
#ENDOCARDIUM	(20)	(19)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)	1 (2%)
*AORTA	(20)	(19)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(50)	(50)
INFLAMMATION, NOS			2 (4%)	1 (2%)
PELIOSIS HEPATIS			1 (2%)	
METAMORPHOSIS FATTY	1 (5%)		2 (4%)	
FOCAL CELLULAR CHANGE			2 (4%)	1 (2%)
*BILE DUCT	(20)	(19)	(50)	(50)
HYPERPLASIA, NOS			6 (12%)	6 (12%)
#PANCREAS	(20)	(19)	(47)	(48)
INFLAMMATION, NOS	1 (5%)			
PERIARTERITIS	1 (5%)		1 (2%)	
ATROPHY, NOS				1 (2%)
#ESOPHAGUS	(19)	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	1 (2%)
#STOMACH	(20)	(19)	(49)	(49)
ULCER, FOCAL		1 (5%)	1 (2%)	1 (2%)
CALCIUM DEPOSIT	1 (5%)			
HYPERKERATOSIS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(19)	(50)	(50)
MINERALIZATION		1 (5%)		
HYDRONEPHROSIS				2 (4%)
PYELONEPHRITIS, NOS			1 (2%)	
INFLAMMATION, CHRONIC	8 (40%)	2 (11%)	14 (28%)	2 (4%)
CALCIUM DEPOSIT	1 (5%)			
#KIDNEY/CAPSULE	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(19)	(48)	(48)
ANGIECTASIS	1 (5%)		1 (2%)	
#ADRENAL CORTEX	(20)	(19)	(50)	(50)
ANGIECTASIS	4 (20%)	3 (16%)	4 (8%)	5 (10%)
#THYROID	(20)	(18)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
REPRODUCTIVE SYSTEM				
*VAGINA	(20)	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
POLYP			1 (2%)	
#UTERUS	(20)	(19)	(50)	(50)
HYDROMETRA			7 (14%)	4 (8%)
#CERVIX UTERI	(20)	(19)	(50)	(50)
POLYP, INFLAMMATORY			1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS		1 (5%)	2 (4%)	1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)	
#OVARY	(20)	(19)	(50)	(50)
CYST, NOS	1 (5%)		2 (4%)	2 (4%)
INFLAMMATION, NOS		1 (5%)		
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) 01-131F	CONTROL(VEH) 01-081F	LOW DOSE 01-134F	HIGH DOSE 01-135F
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(19)	(50)	(50)
NECROSIS, FAT	1 (5%)		1 (2%)	
*PERITONEUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		1 (2%)	
*PERICARDIUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
*MESENTERY	(20)	(19)	(50)	(50)
PERIARTERITIS	2 (10%)			
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		2	1	11
AUTOLYSIS/NO NECROPSY		1		

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-TRICHLOROETHANE

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

	CONTROL (UNTR) 02-M141	CONTROL (VEH) 02-M131	LOW DOSE 02-M132	HIGH DOSE 02-M133
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	18	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	20	49	50
INTEGUMENTARY SYSTEM				
*SKIN	(18)	(20)	(49)	(50)
INFLAMMATION, NOS	1 (6%)			
ABSCESS, NOS			2 (4%)	
*SUBCUT TISSUE	(18)	(20)	(49)	(50)
EPIDERMAL INCLUSION CYST		2 (10%)		
ABSCESS, NOS		2 (10%)	1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(18)	(20)	(49)	(50)
PNEUMONIA, CHRONIC MURINE	5 (28%)		1 (2%)	
HYPERPLASIA, ADENOMATOUS				1 (2%)
LEUKEMOID REACTION		1 (5%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(18)	(19)	(48)	(48)
LEUKEMOID REACTION		1 (5%)		
#SPLEEN	(18)	(20)	(49)	(49)
AMYLOIDOSIS		3 (15%)	6 (12%)	
HEMATOPOIESIS				2 (4%)
#LYMPH NODE	(18)	(20)	(48)	(49)
ANGIECTASIS				1 (2%)
#CERVICAL LYMPH NODE	(18)	(20)	(48)	(49)
INFLAMMATION, NOS	1 (6%)			
#MESENTERIC L. NODE	(18)	(20)	(48)	(49)
INFLAMMATION, NOS	9 (50%)	1 (5%)	2 (4%)	1 (2%)
ANGIECTASIS	2 (11%)	2 (10%)	3 (6%)	4 (8%)

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-M132	HIGH DOSE 02-M133
CIRCULATORY SYSTEM				
#HEART	(18)	(20)	(49)	(50)
CALCIUM DEPOSIT		2 (10%)	5 (10%)	1 (2%)
#MYOCARDIUM	(18)	(20)	(49)	(50)
DEGENERATION, NOS		1 (5%)		
*MESENTERIC ARTERY	(18)	(20)	(49)	(50)
PERIARTERITIS				1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(17)	(20)	(49)	(49)
THROMBUS, ORGANIZED			1 (2%)	3 (6%)
INFLAMMATION, NOS		2 (10%)	1 (2%)	
AMYLOIDOSIS		1 (5%)		
FOCAL CELLULAR CHANGE				1 (2%)
HYPERPLASIA, NODULAR			1 (2%)	
ANGIECTASIS			1 (2%)	
#PANCREAS	(18)	(20)	(49)	(48)
THROMBUS, ORGANIZED				2 (4%)
INFLAMMATION, NOS			1 (2%)	1 (2%)
CALCIUM DEPOSIT				2 (4%)
#STOMACH	(18)	(20)	(49)	(50)
THROMBUS, ORGANIZED				1 (2%)
HYPERKERATOSIS			1 (2%)	
ACANTHOSIS			1 (2%)	
#COLON	(18)	(20)	(49)	(49)
NEMATODIASIS	1 (6%)			
URINARY SYSTEM				
#KIDNEY	(18)	(20)	(49)	(50)
HYDRONEPHROSIS	3 (17%)			
PYELONEPHRITIS, NOS	1 (6%)	1 (5%)	1 (2%)	
INFLAMMATION, CHRONIC		6 (30%)	16 (33%)	2 (4%)
AMYLOIDOSIS		4 (20%)	2 (4%)	
CALCIUM DEPOSIT		1 (5%)	1 (2%)	1 (2%)
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-M132	HIGH DOSE 02-M133
#URINARY BLADDER	(18)	(19)	(49)	(46)
INFLAMMATION, NOS			1 (2%)	
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(18)	(20)	(49)	(48)
ANGIECTASIS				2 (4%)
#ADRENAL MEDULLA	(18)	(20)	(49)	(48)
DEGENERATION, NOS				1 (2%)
REPRODUCTIVE SYSTEM				
*TESTIS	(17)	(19)	(49)	(48)
GRANULOMA, SPERMATIC		1 (5%)	1 (2%)	
CALCIUM DEPOSIT		1 (5%)		
ATROPHY, NOS	1 (6%)	3 (16%)	3 (6%)	2 (4%)
*EPIDIDYMIS	(18)	(20)	(49)	(50)
GRANULOMA, SPERMATIC		1 (5%)	1 (2%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(18)	(19)	(49)	(49)
INFLAMMATION, NOS				1 (2%)
SPECIAL SENSE ORGANS				
*EYE	(18)	(20)	(49)	(50)
CATARACT			1 (2%)	
ATROPHY, NOS			1 (2%)	
*HARDERIAN GLAND	(18)	(20)	(49)	(50)
INFLAMMATION, NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
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-M132	HIGH DOSE 02-M133
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	6	7	8
AUTOLYSIS/NO NECROPSY	2		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-TRICHLOROETHANE

	CONTROL (UNTR) 02-F141	CONTROL (VEH) 02-F131	LOW DOSE 02-F134	HIGH DOSE 02-F135
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	20	20	48	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	48	45
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(48)	(46)
ABSCESS, NOS		1 (5%)		2 (4%)
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(19)	(48)	(37)
INFLAMMATION, NOS				1 (3%)
#LUNG	(20)	(20)	(48)	(39)
PNEUMONIA, CHRONIC MURINE	7 (35%)			4 (10%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(48)	(45)
INFLAMMATION, NOS		1 (5%)		
ANGIECTASIS			1 (2%)	
HEMATOPOIESIS	1 (5%)			3 (7%)
#LYMPH NODE	(20)	(20)	(48)	(45)
INFLAMMATION, NOS				1 (2%)
#MESENTERIC L. NODE	(20)	(20)	(48)	(45)
INFLAMMATION, NOS	6 (30%)	3 (15%)		
ANGIECTASIS	2 (10%)		1 (2%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(20)	(19)	(48)	(35)
CYST, NOS				1 (3%)
INFLAMMATION, NOS				1 (3%)

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-F134	HIGH DOSE 02-F135
#LIVER	(20)	(20)	(48)	(45)
THROMBUS, ORGANIZED		1 (5%)	1 (2%)	3 (7%)
INFLAMMATION, NOS			1 (2%)	
PELIOSIS HEPATIS	1 (5%)			
HYPERPLASTIC NODULE			1 (2%)	
#PANCREAS	(20)	(20)	(47)	(42)
INFLAMMATION, NOS	1 (5%)			
#STOMACH	(20)	(20)	(48)	(45)
ULCER, FOCAL			1 (2%)	
HYPERKERATOSIS	1 (5%)			1 (2%)
ACANTHOSIS	1 (5%)	1 (5%)		1 (2%)
#SMALL INTESTINE	(20)	(20)	(48)	(44)
THROMBUS, ORGANIZED				1 (2%)
#COLON	(20)	(20)	(48)	(44)
NEMATODIASIS	4 (20%)			
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(48)	(45)
HYDRONEPHROSIS	1 (5%)			3 (7%)
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(20)	(20)	(48)	(43)
DEGENERATION, NOS			1 (2%)	
#THYROID	(20)	(20)	(48)	(35)
FOLLICULAR CYST, NOS	1 (5%)	2 (10%)		1 (3%)
REPRODUCTIVE SYSTEM				
#UTERUS	(20)	(20)	(46)	(37)
HYDROMETRA	4 (20%)	4 (20%)	6 (13%)	
CYST, NOS			1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(20)	(46)	(37)
CYST, NOS			1 (2%)	
INFLAMMATION, NOS		1 (5%)	1 (2%)	
HYPERPLASIA, CYSTIC	3 (15%)	11 (55%)	11 (24%)	

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

TABLE D2 (CONTINUED)

	CONTROL(UNTR) 02-F141	CONTROL(VEH) 02-F131	LOW DOSE 02-F134	HIGH DOSE 02-F135
*OVARY	(20)	(20)	(46)	(38)
CYST, NOS	11 (55%)	6 (30%)	4 (9%)	3 (8%)
THROMBUS, ORGANIZED				1 (3%)
INFLAMMATION, NOS	1 (5%)			
#LEFT OVARY	(20)	(20)	(46)	(38)
CYST, NOS			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(20)	(20)	(48)	(46)
PHTHISIS BULBI				1 (2%)
*EYE/LACRIMAL GLAND	(20)	(20)	(48)	(46)
INFLAMMATION, NOS	1 (5%)			
*HARDERIAN GLAND	(20)	(20)	(48)	(46)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, CYSTIC				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(48)	(46)
INFLAMMATION, NOS		1 (5%)		
ALL OTHER SYSTEMS				
NONE				

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-F134	HIGH DOSE 02-F135
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		1	20	3
ANIMAL MISSING/NO NECROPSY			1	
NECROPSY PERF/NO HISTO PERFORMED				1
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY			1	4

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

Review of the Bioassay of 1,1,2-Trichloroethane* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

January 18, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976 under the authority of the National Cancer Act of 1971 (P.L. 92-218). The purpose of the Clearinghouse is to advise on the National Cancer Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in organic chemistry, biostatistics, biochemistry, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of NCI bioassay reports on chemicals studied for carcinogenicity. In this context, below is the edited excerpt from the minutes of the Subgroup's meeting at which 1,1,2-Trichloroethane was reviewed.

The primary reviewer said that he agreed with the staff's conclusion that the evidence was not convincing that 1,1,2-Trichloroethane was carcinogenic in the treated rats, under the conditions of test. In the mice, however, it induced hepatocellular carcinomas and adrenal pheochromocytomas. He added that the malignant nature of the hepatocellular carcinomas was evident based on their cellular characteristics and lung metastases. He felt that the maximum tolerated dose probably was not reached in the treated rats. Based on the results from the mouse portion of the study, the primary reviewer concluded that 1,1,2-Trichloroethane may pose a carcinogenic risk to humans.

The secondary reviewer was critical of the study in that a number of other compounds, some of which are carcinogenic, were tested at the same time and in the same room as 1,1,2-Trichloroethane. However, he agreed that the results in the treated mice were sufficiently significant to conclude that the carcinogenic effect was induced by 1,1,2-Trichloroethane.

It was moved that the report be accepted as written and that 1,1,2-Trichloroethane be considered as posing a potential carcinogenic risk to humans. The motion was seconded and approved by all the Subgroup members except Dr. Rowe, who abstained.

Members Present Were:

Arnold Brown (Acting Chairman), Mayo Clinic
Lawrence Garfinkel, American Cancer Society
Joseph Highland, Environmental Defense Fund
Charles Kensler, Arthur D. Little Company
Verald K. Rowe, Dow Chemical, U.S.A.
Sheldon Samuels, Industrial Union Department, AFL-CIO
Louise Strong, University of Texas Health Sciences Center
Sidney Wolfe, Health Research Group

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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