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BIOASSAY OF

1,1-DICHLOROETHANE

FOR POSSIBLE CARCINOGENICITY

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

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REPORT ON THE BIOASSAY OF 1,1-DICHLOROETHANE
FOR POSSIBLE CARCINOGENICITY

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

CONTRIBUTORS: This report presents the results of the bioassay of 1,1-dichloroethane conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This bioassay was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Bioassay Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3, 5) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathologic examinations were performed by Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

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. R. Joiner (7), using methods selected for the Bioassay Program by Dr. J. J. Gart (9).

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The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (9), Mr. J. Nam (9), Dr. H. M. Pettigrew (9), and Dr. R. E. Tarone (9).

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SUMMARY

A bioassay of technical-grade 1,1-dichloroethane for possible carcinogenicity was conducted using Osborne-Mendel rats and B6C3F1 mice. 1,1-Dichloroethane 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 33 weeks for rats and 13 weeks for mice.

A preliminary subchronic toxicity test, consisting of 6 weeks of 1,1-dichloroethane administration at five dosage levels followed by 2 weeks of observation, was performed for the purpose of selecting initial dosages. Subsequent dosage adjustments were made during the course of the study. The high and low time-weighted average dosages of 1,1-dichloroethane were, respectively, 764 and 382 mg/kg/day for male rats; 950 and 475 mg/kg/day for female rats; 2885 and 1442 mg/kg/day for male mice; and 3331 and 1665 mg/kg/day for 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 times that dosed animals were gavaged with 1,1-dichloroethane mixtures. Twenty animals of each sex were placed on test as untreated controls for each species. These animals were not intubated.

Survival was poor in all rat groups and several mouse groups. Survival at the end of the study in the untreated control, vehicle control, low dose, and high dose groups was, respectively, 30, 5, 4, and 8 percent in male rats; 40, 20, 16 and 18 percent in female rats; 35, 55, 62 and 32 percent in male mice; and 80, 80, 80 and 50 percent in female mice. Pneumonia was observed in 80 percent of the rats in this bioassay.

There were dose-related marginal increases in mammary adenocarcinomas and in hemangiosarcomas among female rats and there was a statistically significant increase in the incidence of endometrial stromal polyps among dosed female mice as compared to controls. These findings are indicative of the possible carcinogenic potential of the test compound. However, it must be recognized that under the conditions of this bioassay there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane in Osborne-Mendel rats or B6C3F1 mice.

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I. INTRODUCTION

1,1-Dichloroethane (NCI No. C04535) is one of a group of halogenated solvents selected for bioassay by the National Cancer Institute. The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 1,1-dichloroethane.* It is also called ethylidene chloride.

The major industrial uses of 1,1-dichloroethane are as a chemical intermediate and as a solvent for extraction and degreasing (International Technical Information Institute, 1975; Hardie, 1964; Mullin, 1964). Human exposure to 1,1-dichloroethane occurs principally by inhalation in those industries using or manufacturing the chemical.

*The CAS registry number is 75-34-3

II. MATERIALS AND METHODS

A. Chemicals

One batch of technical-grade 1,1-dichloroethane was purchased by Hazleton Laboratories America, Inc., Vienna, Virginia, from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. The purity of the compound was determined using gas-liquid chromatography (GLC) total area analysis and infrared spectroscopy. The GLC analysis revealed six peaks; the major peak accounted for over 99 percent of the total area. The infrared spectrum of the chemical tested was consistent with that expected from the structure of 1,1-dichloroethane, and no bands that might indicate impurities were observed.

Throughout this report the term 1,1-dichloroethane refers to this technical-grade material.

B. Dosage Preparation

Fresh solutions of 1,1-dichloroethane in Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) were prepared weekly, sealed, and stored at 1°C. Concentrations of 1,1-dichloroethane in corn oil of 15 to 36 percent and 30 to 90 percent were utilized for mice and rats, respectively. These 1,1-dichloroethane solutions were considered generally stable for 10 days under the indicated storage conditions.

C. Animals

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

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

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

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

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

*CAS registry numbers are given in parentheses.

mean body weight as a guide for determining the dosage. 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. 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 establish the maximum tolerated dosages of 1,1-dichloroethane 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. 1,1-Dichloroethane dissolved in corn oil was introduced by gavage to five of the six rat groups at dosages of 562, 1000, 1780, 3160, and 5620 mg/kg/day and five of the six mouse groups at dosages of 1000, 1780, 3160, 5620, and 10,000 mg/kg/day. The sixth group of each species received only corn oil. Intubation was performed 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity.

The mean body weight depression in the male rats at 562 and 1000 mg/kg/day was 16 and 29 percent, respectively. In the female rats a 20 percent mean body weight depression was observed at 1780 and 3160 mg/kg/day; however, two animals died at the latter level. The initial high dosages estimated for the chronic study were 700 and 1500 mg/kg/day for male and female rats, respectively.

No mean body weight depression was observed in mice; however, two male and three female mice died at 5620 mg/kg/day. The initial high dose estimated for the chronic study was 1800 mg/kg/day for mice of both sexes.

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.

Intubation was performed five consecutive days per week. The initial doses utilized for male rats were 700 and 350 mg/kg/day, respectively, while for female rats they were 1500 and 750 mg/kg/day, respectively. Throughout this report those rats receiving the higher of the two dosages administered to their sex are referred to as the high dose group and those receiving the lower of the two dosages are referred to as the low dose group. During week 9 of the experiment, due to apparent tolerance to the chemical, the high and low doses for male rats were increased to 900 and 450 mg/kg/day, and the high and low doses for the female rats were increased to 1800 and 900 mg/kg/day. In week 18, the dosages administered to the female groups were halved, to 900 and 450 mg/kg/day, respectively. Fourteen weeks after this dose decrease (week 32 of the experiment), intubation of all animals ceased for 1 week, followed by 4 weeks of 1,1-dichloroethane administration at the previous levels. This cyclic pattern of

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
1,1-DICHLOROETHANE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	1,1-DICHLOROETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE OVER A 78-WEEK PERIOD[b]
MALE					
UNTREATED CONTROL	20	0		109	0
VEHICLE CONTROL	20	0	78	33	0
LOW DOSE	50	350	8		382
		450	23		
		450[c]	37	10	
		0		33	
HIGH DOSE	50	700	8		764
		900	23		
		900[c]	37	10	
		0		33	
FEMALE					
UNTREATED CONTROL	20	0		105	0
VEHICLE CONTROL	20	0	78	33	0
LOW DOSE	50	750	8		475
		900	9		
		450	14		
		450[c]	37	10	
		0		33	
HIGH DOSE	50	1500	8		950
		1800	9		
		900	14		
		900[c]	37	10	
		0		33	

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

[b] Time-weighted average dosage = $\frac{\Sigma \text{ (dosage X number of weeks received)}}{78 \text{ weeks}}$

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

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
1,1-DICHLOROETHANE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	1,1-DICHLOROETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0		90	0
VEHICLE CONTROL	20	0	78	12	0
LOW DOSE	50	900	6		1442
		1200	3		
		1500	69		
		0		13	
HIGH DOSE	50	1800	6		2885
		2400	3		
		3000	69		
		0		13	
FEMALE					
UNTREATED CONTROL	20	0		91	0
VEHICLE CONTROL	20	0	78	12	0
LOW DOSE	50	900	6		1665
		1200	3		
		1500	11		
		1800	58		
		0		13	
HIGH DOSE	50	1800	6		3331
		2400	3		
		3000	11		
		3600	58		
		0		13	

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

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

chemical administration continued until dosage termination in week 78. These total dosage decreases were in response to the observed toxicity of the compound.

The vehicle control rats received corn oil in volumes equal to those administered to the high dose groups. The low dose, high dose, and vehicle control rats were all approximately 8 weeks old at the time the experiment began. The untreated controls, which were approximately 6 weeks younger than the other three rat groups, were included in the test approximately 4 weeks after intubation of the other rats had begun.

The untreated control, low dose, and high dose mice were all approximately 5 weeks old on the day the first dose was administered, while the vehicle control mice were approximately 2 weeks older. Therefore, administration of corn oil to the vehicle controls began correspondingly earlier than did 1,1-dichloroethane administration to the dosed mice. The male and female mice received initial dosages of 1800 and 900 mg/kg/day, respectively. Throughout this report those mice receiving the former dosage are referred to as the high dose groups, while those receiving the latter dosage are referred to as the low dose groups. The doses were increased in week 7 for both levels in both sexes, the high dose to 2400 mg/kg/day, and the low dose to 1200 mg/kg/day. In week 10, high and low doses were increased to 3000 and 1500 mg/kg/day for both males and females. In week 21 the high and low doses administered to the female mice were increased to

3600 and 1800 mg/kg/day, respectively, while the male groups continued to receive 3000 and 1500 mg/kg/day, respectively. The dosages were increased because the treated animals were exhibiting no apparent toxic effects. The vehicle control mice were the same used for the 1,2-dichloroethane carcinogenesis bioassay and received corn oil by gavage in amounts and frequencies corresponding to the high dose 1,2-dichlorethane-treated mice.

The untreated controls received no 1,1-dichloroethane or corn oil, while the vehicle controls were administered pure corn oil by gavage.

H. Clinical and Histopathologic Examinations

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

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

of major tissues, organs, or gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

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

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

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

I. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System

(Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

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

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

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which

that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

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

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the

one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

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

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

relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

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

the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

As indicated in Figure 1, comparison of the mean body weight patterns for vehicle control and treated rats revealed no apparent differences. The untreated controls did maintain a body weight consistently higher than the other groups. 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 20 weeks of the study the appearance and behavior of the treated rats were generally comparable to that of controls. From week 20 to cessation of intubation in week 78, a hunched appearance and abdominal urine stains were observed with a slightly greater frequency in the treated rats of both sexes than in their corresponding controls. These observations were, however, noted with comparable frequency in treated and control rats after cessation of treatment. Respiratory signs characterized by labored respiration, wheezing, nasal discharge, and/or a hunched appearance were observed at a low to moderate incidence in all groups during the latter part of the first year, increasing gradually for treated and control rats during the last 10 months of the study. In week 110, all surviving rats had a hunched appearance and showed labored respiration. Clinical signs commonly associated with aging in laboratory rats were noted for all rats during the second year of the study. These signs included sores on the tail, discolored or rough fur, soft feces, and

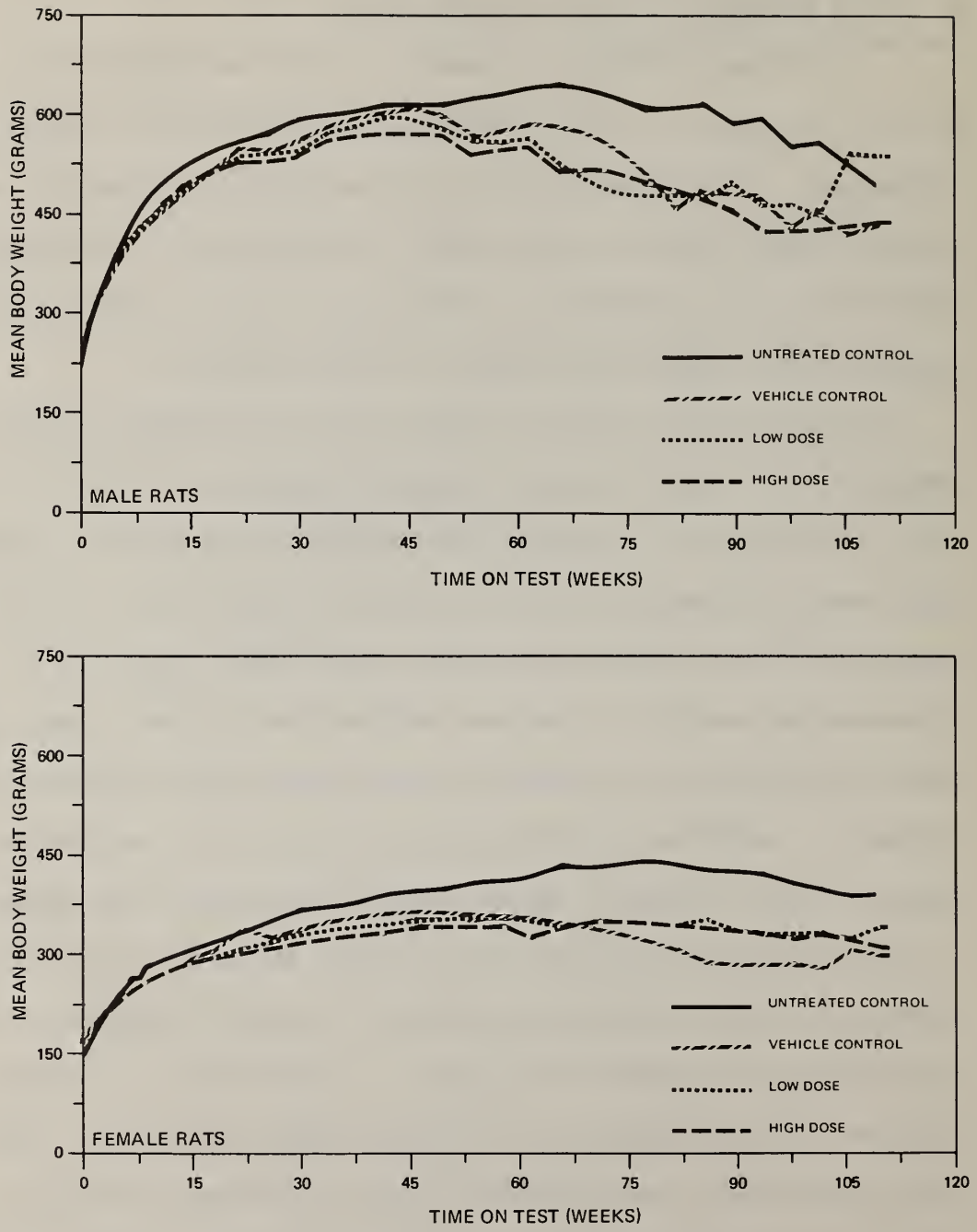


FIGURE 1
GROWTH CURVES FOR 1,1-DICHLOROETHANE CHRONIC STUDY RATS

eye discharge or reddish crust around the eyes. The incidence of palpable nodules and/or tissue masses in the treated rats was observed at a frequency similar to that in the control animals.

B. Survival

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

For male rats there was generally poor survival in all groups by the end of the study. The survival curve for the high dose male rats did not differ appreciably from the curve of the low dose male rats. Survival of both high and low dose male rats was, however, significantly ($P = 0.006$) lower than survival of either the vehicle control or the untreated control group. The median male survival was 62 weeks for both dosed groups. Although the early deaths among the dosed male rats were related to administration of 1,1-dichloroethane, the deaths were not caused by tumors; only one dosed rat died with a tumor during the first 62 weeks.

For female rats, survival was also poor. Although the survival curves for the dosed female rats indicated lower survival rates than those for the vehicle and untreated control animals from about week 15 to week 90, the Tarone test did not indicate a statistically significant association between dosage and mortality. No tumors were observed in any of the low dose females that died by 65 weeks on test, by which point 50 percent (25/50) of the group had died. Only

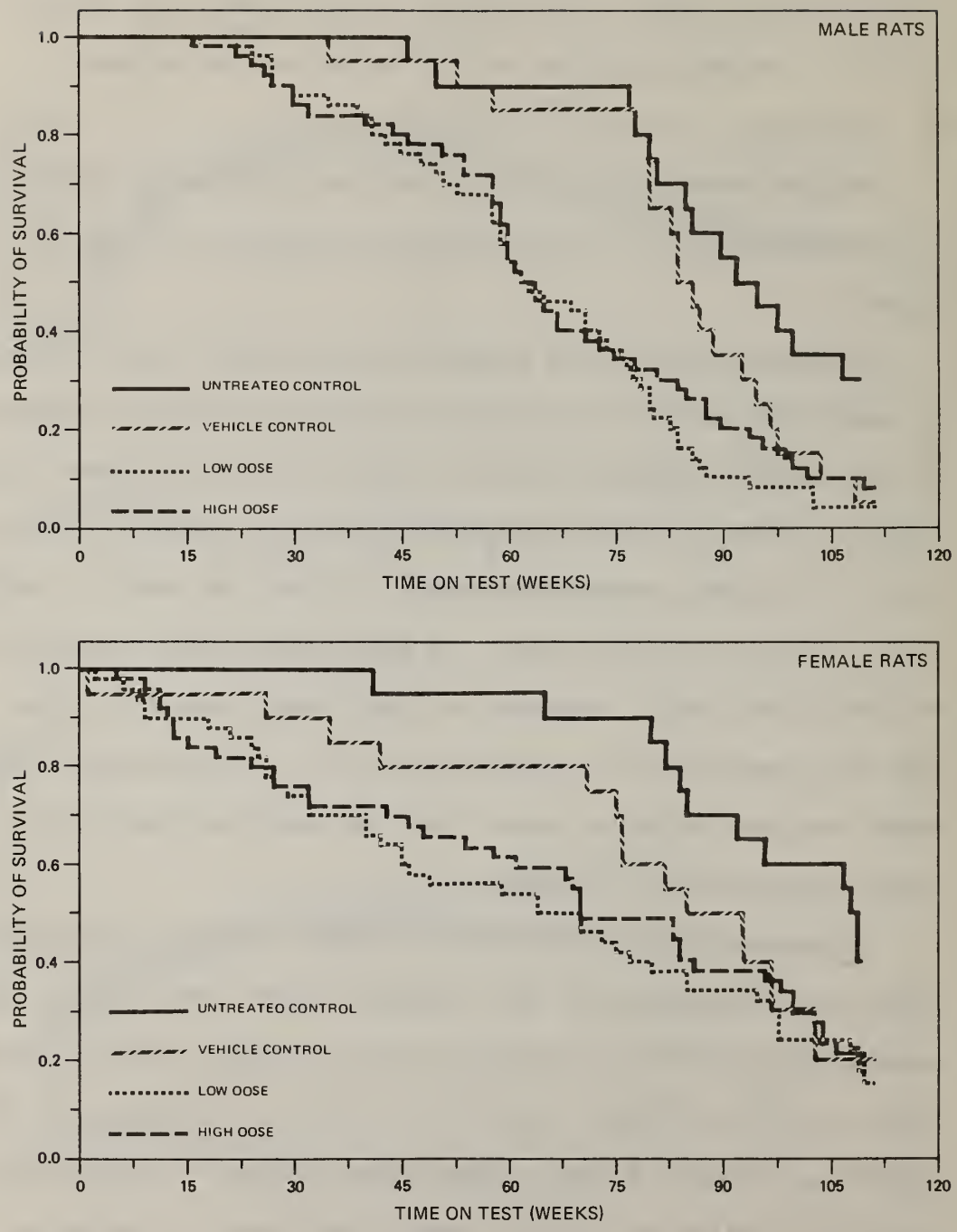


FIGURE 2
SURVIVAL COMPARISONS OF 1,1-DICHLOROETHANE CHRONIC STUDY RATS

one tumor was observed in the high dose group before the median survival for that group (week 70), and that tumor was detected during week 54. Thus tumors do not appear to have caused these deaths.

Due to the high early mortality observed in dosed rats of both sexes, the number of rats surviving long enough to be at risk from late-developing tumors was low.

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).

Histopathologic examination of the tissues and organs did not indicate a carcinogenic effect for 1,1-dichloroethane in Osborne-Mendel rats. An unusual tumor, an adenocarcinoma of the prostate, that metastasized to the lung, liver, cecum, and tissue around the prostate occurred in 1/33 low dose male rats. An adenocarcinoma of the small intestine that metastasized to the pancreas was present in 1/47 high dose females. Adenocarcinomas of the mammary gland occurred in 1/20 vehicle control males, 1/20 untreated control females, 1/50 low dose females, and 5/50 high dose females.

A variety of other neoplasms, which have been encountered previously as spontaneous lesions in Osborne-Mendel rats, were present in both treated and control rats. No appreciable difference in the incidence of neoplasia was noted in the control or the treated rats in this study.

Inflammatory, degenerative, and proliferative lesions as seen in the control and treated animals were similar in number and kind to those naturally occurring lesions found in aged Osborne-Mendel rats. The nonneoplastic lesions that were seen most frequently were chronic murine pneumonia and chronic inflammation of the kidney.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis for every type of tumor that was observed in more than 5 percent of any of the 1,1-dichloroethane-dosed groups of either sex is included.

The untreated control groups were not used for these statistical analyses because they were maintained in a different room from the dosed animals and because the comparison of vehicle control to treated groups was the comparison of choice. To gain more information on spontaneous rates of tumor incidence and to obtain a control group of increased sample size, a pooled vehicle control group was used in addition to the matched vehicle controls. This pooled vehicle control group was a combination of the vehicle controls used for chronic bioassays of 1,1-dichloroethane and trichloroethylene. The pooled control rats were of the same strain, were tested concurrently for at least one year, and were examined by the same pathologist.

In the female rats the Cochran-Armitage test indicated a significant positive association between dosage and the incidence of hemangiosarcoma when comparing both to the matched vehicle control

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	1/40(0.03)	1/20(0.05)	0/44(0.00)	2/46(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.000	1.739
Lower Limit	---	---	0.000	0.094
Upper Limit	---	---	16.921	100.348
Relative Risk (Matched Vehicle Control)[d]	---	---	0.000	0.870
Lower Limit	---	---	0.000	0.049
Upper Limit	---	---	8.471	50.196
Weeks to First Observed Tumor	84	84	---	67
Mammary Gland: Adenocarcinoma[b]	1/40(0.03)	1/20(0.05)	0/50(0.00)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	14.930	14.930
Relative Risk (Matched Vehicle Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	7.475	7.475
Weeks to First Observed Tumor	98	98	---	---

TABLE 3
(CONCLUDED)

[a]Treated groups received time-weighted average doses of 382 or 764 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 pooled vehicle control group (*) or the matched 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.

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	6/39(0.15)	2/19(0.11)	6/48(0.13)	4/48(0.08)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.813	0.542
Lower Limit	---	---	0.237	0.121
Upper Limit	---	---	2.811	2.123
Relative Risk (Matched Vehicle Control)[d]	---	---	1.188	0.792
Lower Limit	---	---	0.243	0.127
Upper Limit	---	---	11.426	8.329
Weeks to First Observed Tumor	68	103	108	104
Mammary Gland: Adenocarcinoma[b]	1/39(0.03)	0/19(0.00)	1/50(0.02)	5/50(0.10)
P Values[c]	N.S.	P = 0.043	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.780	3.900
Lower Limit	---	---	0.010	0.466
Upper Limit	---	---	60.033	180.520
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.021	0.503
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	102	---	111	54

TABLE 4
(CONTINUED)

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	5/39(0.13)	2/19(0.11)	6/50(0.12)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.936	0.936
Lower Limit	---	---	0.258	0.258
Upper Limit	---	---	3.615	3.615
Relative Risk (Matched Vehicle Control)[d]	---	---	1.140	1.140
Lower Limit	---	---	0.231	0.231
Upper Limit	---	---	10.985	10.985
Weeks to First Observed Tumor	97	97	97	84
Mammary Gland: Adenocarcinoma or Fibroadenoma[b]	6/39(0.15)	2/19(0.11)	6/50(0.12)	11/50(0.22)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.780	1.430
Lower Limit	---	---	0.227	0.537
Upper Limit	---	---	2.704	4.322
Relative Risk (Matched Vehicle Control)[d]	---	---	1.140	2.090
Lower Limit	---	---	0.232	0.526
Upper Limit	---	---	10.985	18.369
Weeks to First Observed Tumor	97	97	97	54

TABLE 4
(CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Circulatory System:Hemangiosarcoma[b]	0/39(0.00)	0/19(0.00)	0/50(0.00)	4/50(0.08)
P Values[c]	P = 0.021	P = 0.041	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.726
Upper Limit	---	---	---	Infinite
Relative Risk (Matched Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.726
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	86

[a]Treated groups received time-weighted average doses of 475 or 950 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 pooled vehicle control group (*) or the matched 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.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY MAMMARY TUMORS IN FEMALE RATS LIVING OVER 52 WEEKS TREATED WITH 1,1-DICHLOROETHANE[a]

TOPOGRAPHY:MORPHOLOGY	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma[b]	0/16(0.00)	1/28(0.04)	5/31(0.16)
P Values[c]	P = 0.034	N.S.	N.S.
Relative Risk (Matched Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.032	0.692
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	54
Mammary Gland: Fibroadenoma[b]	2/16(0.13)	6/28(0.21)	6/31(0.19)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Matched Vehicle Control)[d]	---	1.714	1.548
Lower Limit	---	0.362	0.326
Upper Limit	---	15.948	14.514
Weeks to First Observed Tumor	97	97	84
Mammary Gland: Adenocarcinoma or Fibroadenoma[b]	2/16(0.13)	6/28(0.21)	11/31(0.35)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Matched Vehicle Control)[d]	---	1.714	2.839
Lower Limit	---	0.362	0.743
Upper Limit	---	15.948	24.020
Weeks to First Observed Tumor	97	97	54

TABLE 5 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 475 or 950 mg/kg by gavage.

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

[c]Beneath the incidence of the control group is the probability level for the Cochran-Armitage test for dose-related trend in proportions when it is below 0.05; otherwise, not significant (N.S.) is indicated.

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

(P = 0.041) and to the pooled vehicle control (P = 0.021). The Fisher exact tests, however, did not detect any significant differences.

For females the Cochran-Armitage test also indicated a significant (P = 0.043) positive association between the incidence of mammary adenocarcinoma and dosage. Comparison with the pooled vehicle controls, however, was not significant and none of the Fisher exact tests indicated a significantly increased incidence of adenocarcinoma in dosed rats. All tests of either the incidence of fibroadenoma of the mammary gland or the combined incidence of fibroadenoma and adenocarcinoma failed to indicate significant differences.

Due to the high early mortality noted in the dosed rats, an additional analysis was performed based only upon those rats that survived at least 52 weeks. For this analysis, the only tumor for which a test was statistically significant was the adenocarcinoma of the mammary gland of female rats (Table 5): The Cochran-Armitage test showed a significant (P = 0.034) positive association between dosage and tumor incidence. The Fisher exact tests, however, were not significant.

All other statistical tests in male and female rats failed to establish significant differences.

Based upon these results the statistical conclusion is that there was insufficient evidence to indicate the carcinogenic effect of 1,1-dichloroethane.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative

risk 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 tumor induction in rats by 1,1-dichloroethane that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

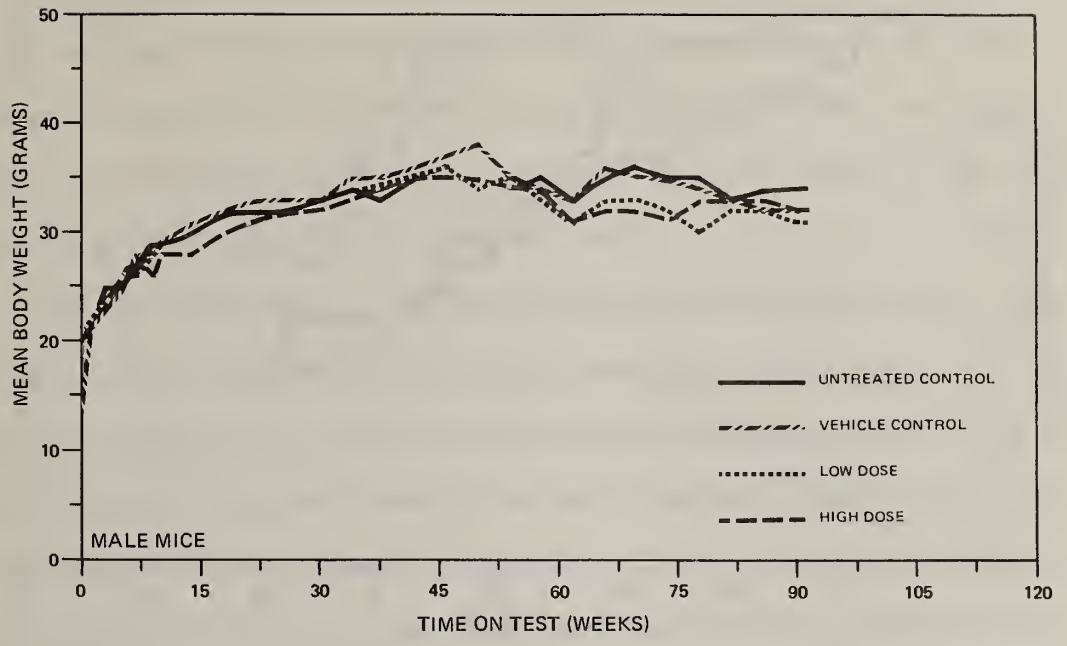
A. Body Weights and Clinical Observations

As indicated in Figure 3, comparison of the mean body weight patterns for control and treated mice indicates no significant difference. Therefore, it appears that 1,1-dichloroethane did not affect the growth of mice at the dosage levels used in this bioassay.

Throughout the study no definitive evidence of the effect of chemcal administration with regard to physical appearance and behavior was observed. During the first year, signs often observed in group-housed laboratory mice were noted among both control and treated animals. These included a hunched appearance, sores on the back and other parts of the body (more prevalent in male than female mice), localized alopecia, and rough or stained fur. The incidence of these abnormalities increased at a comparable rate in treated and control animals during the remainder of the study. Other signs observed sporadically among all the groups were penile or vulvar irritation (sometimes with red discharge), anal prolapse, reddened or squinted eyes, head tilt or circling, and bloating. Palpable subcutaneous nodules, masses, or seemingly swollen areas were observed with comparable frequency among the control and treated mice during the second year of the study.

B. Survival

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



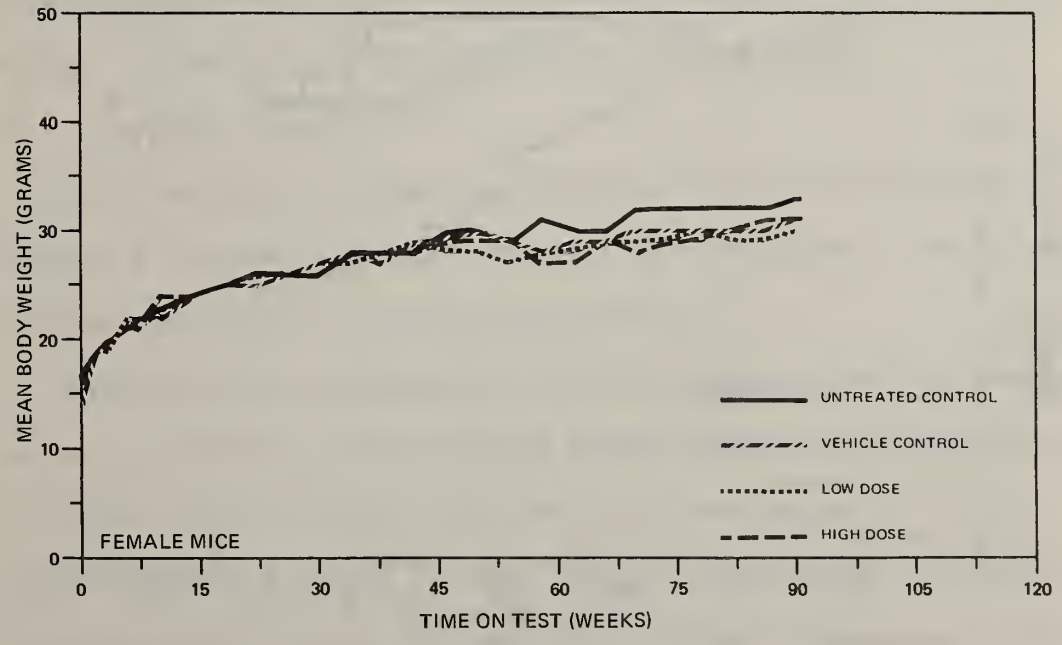
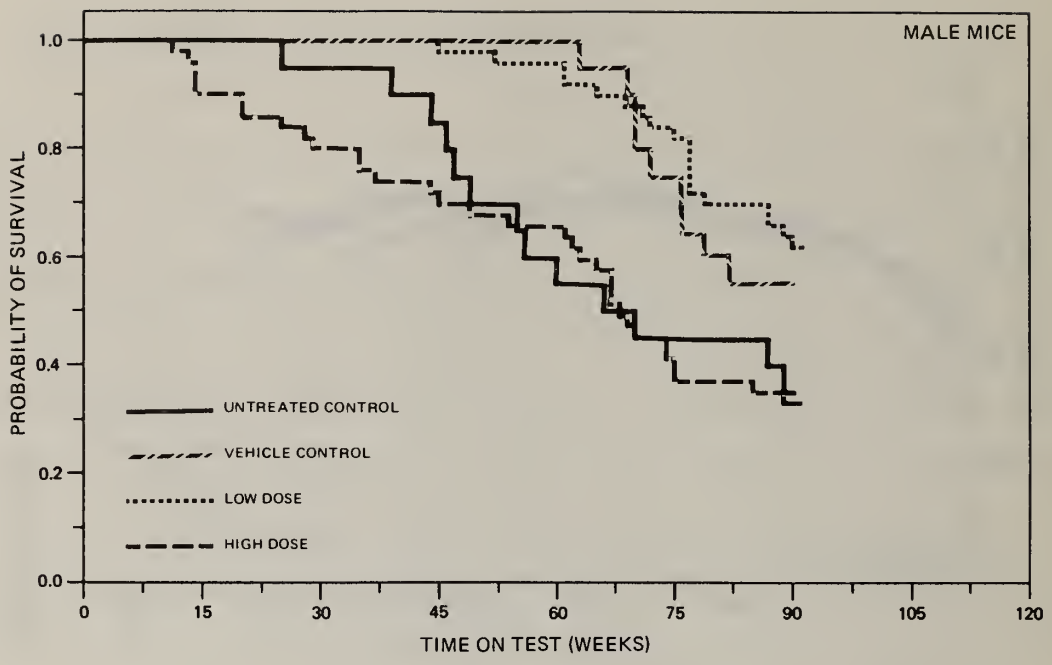


FIGURE 3
GROWTH CURVES FOR 1,1-DICHLOROETHANE CHRONIC STUDY MICE



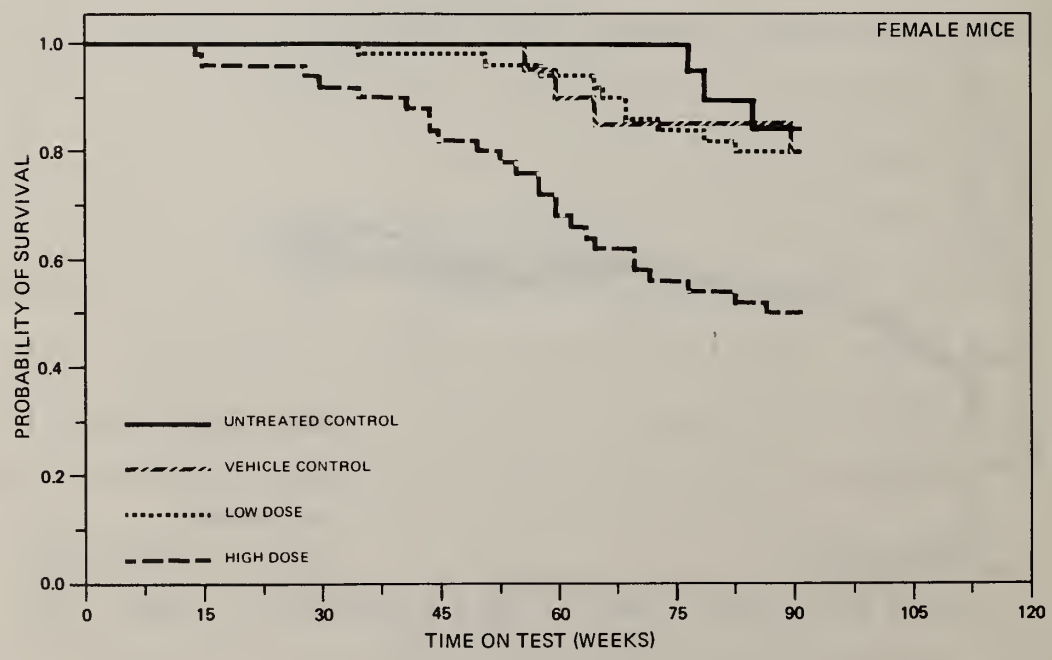


FIGURE 4
SURVIVAL COMPARISONS OF 1,1-DICHLOROETHANE CHRONIC STUDY MICE

For males the Tarone test indicated a significant positive association between dosage and mortality. The median survival in the high dose male mouse group was 67 weeks; only 32 percent of these animals survived until the end of the experiment. Since only two tumors were observed in the high dose males prior to week 89, the early deaths do not appear to be tumor-related.

In the female mice, the Tarone test for a positive dose-related trend in mortality was highly significant ($P < 0.001$). This was due mainly to mortality in the high dose group since the low dose and the control group survival curves were quite similar. There was no evidence that the early deaths were tumor-related. Despite the elevated mortality, 50 percent of the high dose female mice survived to the end of the experiment, providing adequate numbers of animals to make statistical analysis of late-appearing tumors possible.

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).

Hepatocellular carcinoma was the most commonly observed neoplasm and was diagnosed in 2/17 untreated control males, 1/19 vehicle control males, 8/49 low dose males, 8/47 high dose males, 1/20 vehicle control females, and 1/47 low dose females. The hepatic neoplasms occurring in the control mice were not different in appearance from those noted in the 1,1-dichloroethane-treated mice. No liver tumors

were seen in the 19 untreated control female or 46 high dose female mice.

Endometrial stromal polyps (benign endometrial neoplasms) were observed in 4/46 high dose females but were not found in any of the other groups.

The nonneoplastic lesions such as degeneration, inflammation, and proliferation occurring in the treated and control animals were similar and in relatively low incidences.

D. Statistical Analyses of Results

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

Since the comparison of vehicle control to treated groups was the comparison of choice, the untreated control groups were not used in these analyses. To gain more information on spontaneous rates of tumor incidence and to obtain a control group of increased sample size, pooled vehicle control groups were used in addition to the groups designated in the experimental design as the vehicle control groups for 1,1-dichloroethane (referred to in this section as the "matched" vehicle controls). The pooled vehicle control groups were a combination of the vehicle controls used for the chronic bioassays of 1,1-dichloroethane, 1,1,2-trichloroethane, trichloroethylene, and allyl chloride. These control mice were of the same strain, were

TABLE 6

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

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	6/79(0.08)	1/19(0.05)	8/49(0.16)	8/47(0.17)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	2.150	2.241
Lower Limit	---	---	0.697	0.726
Upper Limit	---	---	7.032	7.312
Relative Risk (Matched Vehicle Control)[d]	---	---	3.102	3.234
Lower Limit	---	---	0.469	0.491
Upper Limit	---	---	134.437	140.000
Weeks to First Observed Tumor	56	90	91	70
Hematopoietic System: Malignant Lymphoma[b]	5/79(0.06)	2/19(0.11)	4/49(0.08)	2/48(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	1.290	0.658
Lower Limit	---	---	0.267	0.064
Upper Limit	---	---	5.674	3.824
Relative Risk (Matched Vehicle Control)[d]	---	---	0.776	0.396
Lower Limit	---	---	0.125	0.031
Upper Limit	---	---	8.165	5.212
Weeks to First Observed Tumor	66	90	77	89

TABLE 6
(CONTINUED)

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	3/79(0.04)	0/19(0.00)	1/49(0.02)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.537	2.241
Lower Limit	---	---	0.010	0.397
Upper Limit	---	---	6.442	14.623
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.022	0.390
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	56	---	77	20
Kidney: Tubular-Cell Adenoma[b]	0/78(0.00)	0/18(0.00)	3/49(0.06)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.006	---	---	---
Relative Risk (Pooled Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.950	---
Upper Limit	---	---	Infinite	---
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.232	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	87	---

TABLE 6
(CONCLUDED)

[a]Treated groups received time-weighted average doses of 1442 or 2885 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 pooled vehicle control group (*) or the matched 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 7

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

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	1/79(0.01)	1/20(0.05)	1/47(0.02)	0/46(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	1.681	0.000
Lower Limit	---	---	0.022	0.000
Upper Limit	---	---	129.159	31.981
Relative Risk (Matched Vehicle Control)[d]	---	---	0.426	0.000
Lower Limit	---	---	0.006	0.000
Upper Limit	---	---	32.720	8.111
Weeks to First Observed Tumor	90	90	91	---
Hematopoietic System: Malignant Lymphoma[b]	9/79(0.11)	4/20(0.20)	3/47(0.06)	7/47(0.15)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.560	1.307
Lower Limit	---	---	0.101	0.439
Upper Limit	---	---	2.105	3.653
Relative Risk (Matched Vehicle Control)[d]	---	---	0.319	0.745
Lower Limit	---	---	0.052	0.220
Upper Limit	---	---	1.743	3.175
Weeks to First Observed Tumor	56	56	91	65

TABLE 7
(CONTINUED)

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	3/79(0.04)	1/20(0.05)	2/47(0.04)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	1.121	0.000
Lower Limit	---	---	0.095	0.000
Upper Limit	---	---	9.380	2.796
Relative Risk (Matched Vehicle Control)[d]	---	---	0.851	0.000
Lower Limit	---	---	0.048	0.000
Upper Limit	---	---	49.165	7.942
Weeks to First Observed Tumor	90	90	91	---
Uterus: Endometrial Stromal Polyp[b]	0/79(0.00)	0/20(0.00)	0/47(0.00)	4/46(0.09)
P Values[c]	P = 0.005	P = 0.036	N.S.	P = 0.017*
Relative Risk (Pooled Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	1.578
Upper Limit	---	---	---	Infinite
Relative Risk (Matched Vehicle Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.420
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	91

TABLE 7
(CONCLUDED)

[a]Treated groups received time-weighted average doses of 1665 or 3331 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 pooled vehicle control group (*) or the matched 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 $P < 0.05$.

tested by the same laboratory no more than 6 months apart, and were diagnosed by the same pathologist.

In female mice, the Cochran-Armitage tests indicated a positive association between dosage and the incidence of endometrial stromal polyps of the uterus for both the matched vehicle controls ($P = 0.036$), and the pooled vehicle controls ($P = 0.005$). The Fisher exact test showed a significantly higher incidence of these tumors in the high dose mice ($P = 0.017$) than in the pooled vehicle controls. In historical data collected by Hazleton Laboratories for the NCI Bioassay Program, none of the 180 female vehicle control B6C3F1 mice had an endometrial stromal polyp. Assuming a probability of spontaneous incidence of 1/200, the probability of observing 4 or more such tumors out of 46 females (as in the high dose group) was $P = 0.005$, a significant result. These statistical results indicated an association between 1,1-dichloroethane treatment and endometrial stromal polyps of the uterus. No other sites exhibited a significant incidence of tumors in female mice.

In male mice, neither the Cochran-Armitage tests for positive dose-related trend nor any of the Fisher exact tests for tumors of any site were significant.

Because the unusually high early death rate in the high dose males resulted in many of the mice dying before being at risk from late-developing tumors, the standard statistical analysis was repeated using only the data for male mice that survived at least 52 weeks.

As shown in Table 8, the incidence of hepatocellular carcinoma in male mice that survived at least 52 weeks was 1/19 (5 percent), 6/72 (8 percent), 8/48 (17 percent) and 8/32 (25 percent) for the matched vehicle control, pooled vehicle control, low dose, and high dose groups, respectively. Based upon these data, the Cochran-Armitage test indicated a significant ($P = 0.016$) positive association between dosage and tumor incidence when comparing to the pooled vehicle control. The Fisher exact test comparing the high dose to the pooled vehicle control had a probability level of $P = 0.027$, a marginal result which was not significant under the Bonferroni criterion.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 6, 7, and 8, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by 1,1-dichloroethane that could not be established under the conditions of this test.

TABLE 8

ANALYSES OF THE INCIDENCE OF HEPATOCELLULAR CARCINOMA IN MALE MICE LIVING OVER 52 WEEKS TREATED WITH 1,1-DICHLOROETHANE[a]

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	6/72(0.08)	1/19(0.05)	8/48(0.17)	8/32(0.25)
P Values[c]	P = 0.016	N.S.	N.S.	P = 0.027*
Relative Risk (Pooled Vehicle Control)[d]	---	---	2.000	3.000
Lower Limit	---	---	0.648	0.987
Upper Limit	---	---	6.526	9.453
Relative Risk (Matched Vehicle Control)[d]	---	---	3.167	4.750
Lower Limit	---	---	0.480	0.727
Upper Limit	---	---	137.162	202.296
Weeks to First Observed Tumor	56	90	91	70

[a]Treated groups received time-weighted average doses of 1442 or 2885 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 pooled vehicle control group (*) or the matched 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.

V. DISCUSSION

High mortality rates of rats and mice during the course of this study complicate interpretation of the results of this bioassay. The final survivorship in the untreated control, vehicle control, low dose, and high dose groups was, respectively, 30, 5, 4, and 8 percent in the male rats; 40, 20, 16, and 18 percent in the female rats; 35, 55, 62, and 32 percent in the male mice; and 80, 80, 80, and 50 percent in the female mice. The high early mortality in rats appeared to be related to a high incidence of pneumonia. Lesions of pneumonia were observed during the histopathologic examination in approximately 80 percent of the rats used for this bioassay. Incidence of pneumonia was similar in vehicle controls, untreated controls, high dose, and low dose rats of both sexes. Animals dying early may not have been at risk from types of tumors that characteristically appear late. When statistical analyses based exclusively on animals surviving at least 52 weeks were performed, the reduction in sample size increased the probability that a statistical test would fail to detect a real difference in tumor incidence.

Despite the fact that large numbers of rats of both sexes did not survive long enough to be at risk from late-developing tumors, there were suggestions of carcinogenicity to rats indicated by the results of this bioassay. There was a significant positive relationship between dosage and the incidence of mammary adenocarcinomas in female rats when compared to matched vehicle controls but not when

compared to pooled vehicle controls. Fisher exact tests did not, however, indicate that the incidence in either dosed group was significantly greater than in the matched or pooled vehicle control groups. Among female rats, a significant positive relationship between dosage and the incidence of hemangiosarcomas resulted when either the matched or pooled vehicle control groups was used, but none of the Fisher exact tests indicated statistical significance.

A statistically significant incidence of endometrial stromal polyps (a benign neoplasm) occurred in female mice, the only sex and species in which at least half of the high dose group survived for the duration of the chronic bioassay. A statistical analysis based on data for mice surviving at least 52 weeks indicated a significant positive relationship between dosage and the incidence of hepatocellular carcinoma in male mice compared to pooled vehicle controls; this result was not, however, supported by Fisher exact tests using the Bonferroni criterion.

There were dose-related increases in mammary adenocarcinomas and in hemangiosarcomas among female rats, and there was a statistically significant increase in the incidence of endometrial stromal polyps among dosed female mice as compared to controls. These findings are indicative of the possible carcinogenic potential of the test compound. However, it must be recognized that under the conditions of this bioassay there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane in Osborne-Mendel rats or B6C3F1 mice.

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APPENDIX A

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

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

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-082M	HIGH DOSE 01-083M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
FIBROMA				1 (2%)
LIPOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
FIBROSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)			
#SPLEEN	(20)	(20)	(49)	(49)
HEMANGIOSARCOMA				1 (2%)
#CERVICAL LYMPH NODE	(20)	(20)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
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 01-082M	HIGH DOSE 01-083M
#CECUM	(20)	(20)	(50)	(48)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
LIPOSARCOMA		1 (5%)		
MIXED TUMOR, MALIGNANT			1 (2%)	
HAMARTOMA +	1 (5%)	1 (5%)		
#RIGHT KIDNEY	(20)	(20)	(50)	(50)
MIXED TUMOR, MALIGNANT	1 (5%)			
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(44)	(46)
CHROMOPHOBE ADENOMA		1 (5%)		2 (4%)
#ADRENAL	(20)	(20)	(50)	(50)
PHEOCHROMOCYTOMA				2 (4%)
MIXED TUMOR, METASTATIC	1 (5%)			
#THYROID	(20)	(19)	(48)	(48)
FOLLICULAR-CELL ADENOMA			1 (2%)	
FOLLICULAR-CELL CARCINOMA	1 (5%)	1 (5%)		
C-CELL ADENOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS		1 (5%)		
#PROSTATE	(17)	(17)	(33)	(32)
ADENOCARCINOMA, NOS			1 (3%)	
#TESTIS	(20)	(19)	(50)	(50)
INTERSTITIAL-CELL TUMOR		1 (5%)		
NERVOUS SYSTEM				
#BRAIN	(20)	(20)	(50)	(50)
ASTROCYTOMA		1 (5%)		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 A1 (CONTINUED)

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-082M	HIGH DOSE 01-083M
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
FIBROSARCOMA			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	14	19	47	45
MORIBUND SACRIFICE			1	1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	6	1	2	4
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 01-082M	HIGH DOSE 01-083M
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	6	5
TOTAL PRIMARY TUMORS	4	9	6	7
TOTAL ANIMALS WITH BENIGN TUMORS	1	3	3	4
TOTAL BENIGN TUMORS	1	3	3	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	5	3	2
TOTAL MALIGNANT TUMORS	3	6	3	2
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		2	
TOTAL SECONDARY TUMORS	1		5	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 1,1-DICHLOROETHANE

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-084F	HIGH DOSE 01-085F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	19	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(19)	(50)	(50)
SQUAMOUS CELL PAPILLOMA				1 (2%)
*SUBCUT TISSUE	(20)	(19)	(50)	(50)
FIBROMA	2 (10%)		1 (2%)	
HEMANGIOSARCOMA				2 (4%)
RESPIRATORY SYSTEM				
#LUNG	(20)	(19)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
HEMANGIOSARCOMA				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(19)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)			
#SPLEEN	(20)	(19)	(50)	(49)
HEMANGIOSARCOMA				1 (2%)
CIRCULATORY SYSTEM				
#ENDOCARDIUM	(20)	(19)	(49)	(50)
SARCOMA, NOS	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(19)	(50)	(50)
NEOPLASTIC NODULE	1 (5%)			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 01-084F	HIGH DOSE 01-085F
#PANCREAS	(20)	(19)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
#SMALL INTESTINE	(20)	(19)	(49)	(47)
ADENOCARCINOMA, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(19)	(50)	(50)
MIXED TUMOR, MALIGNANT			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(19)	(48)	(48)
CHROMOPHOBE ADENOMA	2 (10%)	2 (11%)	6 (13%)	4 (8%)
#ADRENAL	(20)	(19)	(50)	(49)
LIPOSARCOMA	1 (5%)			
MIXED TUMOR, METASTATIC			1 (2%)	
#THYROID	(20)	(18)	(46)	(43)
C-CELL CARCINOMA			1 (2%)	
#PANCREATIC ISLETS	(20)	(19)	(50)	(50)
ISLET-CELL ADENOMA				2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(19)	(50)	(50)
ADENOMA, NOS				1 (2%)
ADENOCARCINOMA, NOS	1 (5%)		1 (2%)	5 (10%)
FIBROADENOMA	6 (30%)	2 (11%)	6 (12%)	6 (12%)
#OVARY	(20)	(19)	(50)	(49)
CYSTADENOMA, NOS				1 (2%)
LIPOMA			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-084F	HIGH DOSE 01-085F
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	40	39
MORIBUND SACRIFICE		1	2	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				2
TERMINAL SACRIFICE	8	4	8	9
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	4	12	18
TOTAL PRIMARY TUMORS	15	4	17	26
TOTAL ANIMALS WITH BENIGN TUMORS	9	4	11	10
TOTAL BENIGN TUMORS	10	4	14	15
TOTAL ANIMALS WITH MALIGNANT TUMORS	3		3	10
TOTAL MALIGNANT TUMORS	4		3	10
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	2
TOTAL SECONDARY TUMORS			1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1			1
TOTAL UNCERTAIN TUMORS	1			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS				
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN				

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 1,1-DICHLOROETHANE

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

	CONTROL (UNTR) 02-M081	CONTROL (VEH) 02-M071	LOW DOSE 02-M082	HIGH DOSE 02-M083
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	18	19	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	17	19	49	47
INTEGUMENTARY SYSTEM				
*SKIN	(18)	(19)	(49)	(48)
SQUAMOUS CELL CARCINOMA				1 (2%)
FIBROSARCOMA	1 (6%)			
*SUBCUT TISSUE	(18)	(19)	(49)	(48)
FIBRCSARCOMA			3 (6%)	
RESPIRATORY SYSTEM				
#LUNG	(17)	(19)	(49)	(47)
ALVEOLAR/BRCNCHIOLAR ADENOMA			1 (2%)	4 (9%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(18)	(19)	(49)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)	1 (2%)
*SUBCUT TISSUE/BACK	(18)	(19)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
*SUBCUT TISSUE/GROIN	(18)	(19)	(49)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
#SPLEEN	(17)	(18)	(49)	(47)
HEMANGIOSARCOMA			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#RENAL LYMPH NODE	(17)	(19)	(49)	(47)
SQUAMCUS CELL CARCINOMA, METASTA		1 (5%)		
#KIDNEY	(17)	(18)	(49)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (6%)		

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M081	CONTROL (VEH) 02-M071	LOW DOSE 02-M082	HIGH DOSE 02-M083
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(17)	(19)	(49)	(47)
SQUAMOUS CELL CARCINOMA				1 (2%)
#LIVER	(17)	(19)	(49)	(47)
HEPATOCELLULAR CARCINOMA	2 (12%)	1 (5%)	8 (16%)	8 (17%)
#STOMACH	(17)	(19)	(49)	(47)
SQUAMOUS CELL CARCINOMA		1 (5%)	1 (2%)	
URINARY SYSTEM				
#KIDNEY	(17)	(18)	(49)	(47)
TUBULAR-CELL ADENOMA			3 (6%)	
ENDOCRINE SYSTEM				
#THYROID	(17)	(17)	(49)	(47)
FOLLICULAR-CELL ADENOMA				1 (2%)
REPRODUCTIVE SYSTEM				
#TESTIS	(17)	(19)	(49)	(47)
INTERSTITIAL-CELL TUMOR			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 02-M081	CONTROL (VEH) 02-M071	LOW DOSE 02-M082	HIGH DOSE 02-M083
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	12	9	19	32
MORIBUND SACRIFICE	1			1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				1
TERMINAL SACRIFICE	7	11	31	16
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	4	19	15
TOTAL PRIMARY TUMORS	3	4	22	17
TOTAL ANIMALS WITH BENIGN TUMORS			5	5
TOTAL BENIGN TUMORS			5	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	4	16	11
TOTAL MALIGNANT TUMORS	3	4	17	12
TOTAL ANIMALS WITH SECONDARY TUMORS#		1		
TOTAL SECONDARY TUMORS		1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH 1,1-DICHLOROETHANE

	CONTROL (UNTR) 02-F081	CONTROL (VEH) 02-F071	LOW DOSE 02-F084	HIGH DOSE 02-F085
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	19	20	47	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	47	47
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(19)	(20)	(47)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	1 (5%)	2 (4%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(19)	(20)	(47)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (11%)	2 (10%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)	2 (10%)		4 (9%)
#SPLEEN	(19)	(20)	(47)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#CERVICAL LYMPH NODE	(19)	(20)	(47)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				2 (4%)
#LIVER	(19)	(20)	(47)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	1 (2%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(19)	(20)	(47)	(46)
HEPATOCELLULAR CARCINOMA		1 (5%)	1 (2%)	

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F081	CONTROL (VEH) 02-F071	LOW DOSE 02-F084	HIGH DOSE 02-F085
#STOMACH	(19)	(20)	(47)	(46)
SQUAMOUS CELL CARCINOMA		1 (5%)		
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*VAGINA	(19)	(20)	(47)	(47)
PAPILLOMA, NOS				1 (2%)
#UTERUS	(19)	(20)	(47)	(46)
ENDOMETRIAL STROMAL POLYP				4 (9%)
#OVARY	(19)	(20)	(47)	(47)
CYSTADENOMA, NOS			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 02-F081	CONTROL (VEH) 02-F071	LOW DOSE 02-F084	HIGH DOSE 02-F085
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	3	4	10	25
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED	1			
TERMINAL SACRIFICE	16	16	40	25
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	6	12
TOTAL PRIMARY TUMORS	4	7	7	12
TOTAL ANIMALS WITH BENIGN TUMORS	1	1	3	5
TOTAL BENIGN TUMORS	1	1	3	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	5	4	7
TOTAL MALIGNANT TUMORS	3	6	4	7
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 1,1-DICHLOROETHANE

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

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-082M	HIGH DOSE 01-083M
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%)		
INFLAMMATION, NOS				1 (2%)
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
ABSCESS, NOS	1 (5%)		1 (2%)	
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			1 (2%)
#LUNG	(20)	(20)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	14 (70%)	19 (95%)	40 (80%)	42 (84%)
CALCIUM DEPOSIT				1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(49)	(49)
HEMATOPOIESIS	1 (5%)	1 (5%)	3 (6%)	2 (4%)
#CERVICAL LYMPH NODE	(20)	(20)	(49)	(50)
INFLAMMATION, NOS				1 (2%)
#TRACHEAL LYMPH NODE	(20)	(20)	(49)	(50)
ANGIECTASIS	1 (5%)			
#MESENTERIC L. NODE	(20)	(20)	(49)	(50)
PERIARTERITIS				1 (2%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(20)	(20)	(50)	(50)
FIBROSIS	3 (15%)			

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 01-082M	HIGH DOSE 01-083M
DEGENERATION, NOS				1 (2%)
#ENDOCARDIUM	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS		1 (5%)		
*AORTA	(20)	(20)	(50)	(50)
THROMBUS, ORGANIZED			1 (2%)	
INFLAMMATION, NOS	2 (10%)			
MEDIAL CALCIFICATION	2 (10%)		1 (2%)	1 (2%)
*MESENTERIC ARTERY	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION			1 (2%)	1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)			
GRANULOMA, NOS				2 (4%)
PELIOSIS HEPATIS	1 (5%)			
METAMORPHOSIS FATTY	1 (5%)		3 (6%)	1 (2%)
ANGIECTASIS	1 (5%)			
#LIVER/CENTRILOBULAR	(20)	(20)	(50)	(50)
DEGENERATION, NOS	1 (5%)			
*BILE DUCT	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS	2 (10%)	1 (5%)	1 (2%)	1 (2%)
#PANCREAS	(20)	(20)	(50)	(50)
PERIARTERITIS	1 (5%)	1 (5%)	2 (4%)	5 (10%)
#STOMACH	(20)	(20)	(50)	(50)
CALCIUM DEPOSIT	2 (10%)		1 (2%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
PYELONEPHRITIS, NOS		4 (20%)		
INFLAMMATION, CHRONIC	13 (65%)	12 (60%)	14 (28%)	16 (32%)
CALCIUM DEPOSIT	1 (5%)			1 (2%)
#LEFT KIDNEY	(20)	(20)	(50)	(50)
INFLAMMATION, CHRONIC	1 (5%)			
#URINARY BLADDER	(17)	(20)	(50)	(47)
INFLAMMATION, NOS				1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-131M	CONTROL (VEH) 01-081M	LOW DOSE 01-082M	HIGH DOSE 01-083M
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(44)	(46)
ANGIECTASIS	1 (5%)			
#ADRENAL CORTEX	(20)	(20)	(50)	(50)
ANGIECTASIS	1 (5%)		2 (4%)	1 (2%)
#ADRENAL MEDULLA	(20)	(20)	(50)	(50)
CALCIUM DEPOSIT				1 (2%)
#THYROID	(20)	(19)	(48)	(48)
FOLLICULAR CYST, NOS	1 (5%)			
#PARATHYROID	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS	4 (20%)		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(17)	(17)	(33)	(32)
INFLAMMATION, NOS		2 (12%)	4 (12%)	1 (3%)
#TESTIS	(20)	(19)	(50)	(50)
ATROPHY, NOS	5 (25%)	7 (37%)	11 (22%)	16 (32%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(20)	(20)	(50)	(50)
SYNECHIA, ANTERIOR	1 (5%)			
*EYE/CORNEA	(20)	(20)	(50)	(50)
VASCULARIZATION	1 (5%)			
MUSCULOSKELETAL 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 01-082M	HIGH DOSE 01-083M
BODY CAVITIES				
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS	1 (5%)	1 (5%)		3 (6%)
NECROSIS, FAT		1 (5%)		
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	1	7	6

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-DICHLOROETHANE

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-084F	HIGH DOSE 01-085F
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%)		1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(19)	(49)	(50)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(20)	(19)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	17 (85%)	17 (89%)	34 (68%)	32 (64%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(19)	(50)	(49)
HEMATOPOIESIS	1 (5%)	1 (5%)	2 (4%)	4 (8%)
#SPLENIC CAPSULE	(20)	(19)	(50)	(49)
INFLAMMATION, NOS	1 (5%)			
#CERVICAL LYMPH NODE	(20)	(19)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
#TRACHEAL LYMPH NODE	(20)	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
#MESENTERIC L. NODE	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
CIRCULATORY SYSTEM				
#HEART	(20)	(19)	(49)	(50)
THROMBUS, ORGANIZED	1 (5%)			

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 01-084F	HIGH DOSE 01-085F
#MYOCARDIUM	(20)	(19)	(49)	(50)
INFLAMMATION, NOS			1 (2%)	
*AORTA	(20)	(19)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(18)	(15)	(19)	(25)
INFLAMMATION, NOS				1 (4%)
#LIVER	(20)	(19)	(50)	(50)
METAMORPHOSIS FATTY	1 (5%)		1 (2%)	
ANGIECTASIS			1 (2%)	
*BILE DUCT	(20)	(19)	(50)	(50)
HYPERPLASIA, NOS			3 (6%)	
#PANCREAS	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
FIBROSIS				1 (2%)
PERIARTERITIS	1 (5%)			1 (2%)
ATROPHY, NOS				1 (2%)
#STOMACH	(20)	(19)	(50)	(50)
ULCER, FOCAL		1 (5%)		2 (4%)
CALCIUM DEPOSIT	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(20)	(19)	(50)	(50)
MINERALIZATION		1 (5%)		
INFLAMMATION, CHRONIC	8 (40%)	2 (11%)	2 (4%)	7 (14%)
CALCIUM DEPOSIT	1 (5%)			
HYPERPLASIA, EPITHELIAL				1 (2%)
#KIDNEY/CAPSULE	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(19)	(48)	(48)
ANGIECTASIS	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 01-084F	HIGH DOSE 01-085F
#ADRENAL CORTEX	(20)	(19)	(50)	(49)
DEGENERATION, NOS				1 (2%)
ANGIECTASIS	4 (20%)	3 (16%)	2 (4%)	3 (6%)
#THYROID	(20)	(18)	(46)	(43)
HYPERPLASIA, FOLLICULAR-CELL				1 (2%)
REPRODUCTIVE SYSTEM				
*VAGINA	(20)	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
#UTERUS	(20)	(19)	(48)	(48)
HYDROMETRA			2 (4%)	2 (4%)
#UTERUS/ENDOMETRIUM	(20)	(19)	(48)	(48)
INFLAMMATION, NOS		1 (5%)	2 (4%)	
#OVARY	(20)	(19)	(50)	(49)
CYST, NOS	1 (5%)		1 (2%)	
INFLAMMATION, NOS		1 (5%)	1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(20)	(19)	(50)	(50)
HYPERPLASIA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(19)	(50)	(50)
NECROSIS, FAT	1 (5%)		1 (2%)	
*PERITONEUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 01-131F	CONTROL (VEH) 01-081F	LOW DOSE 01-084F	HIGH DOSE 01-085F
*PERICARDIUM	(20)	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	1 (2%)
*MESENTERY	(20)	(19)	(50)	(50)
PERIARTERITIS	2 (10%)			1 (2%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		2	14	13
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-DICHLOROETHANE

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

	CONTROL (UNTR) 02-M081	CONTROL (VEH) 02-M071	LOW DOSE 02-M082	HIGH DOSE 02-M083
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	18	19	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	17	19	49	47
INTEGUMENTARY SYSTEM				
*SKIN	(18)	(19)	(49)	(48)
EPIDERMAL INCLUSION CYST				1 (2%)
INFLAMMATION, NOS	1 (6%)	1 (5%)	3 (6%)	1 (2%)
*SUBCUT TISSUE	(18)	(19)	(49)	(48)
ABSCESS, NOS	1 (6%)	1 (5%)	3 (6%)	2 (4%)
RESPIRATORY SYSTEM				
#TRACHEA	(17)	(19)	(49)	(47)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(17)	(19)	(49)	(47)
PNEUMONIA, CHRONIC MURINE			3 (6%)	2 (4%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(17)	(18)	(49)	(47)
AMYLOIDOSIS	4 (24%)	7 (39%)	3 (6%)	3 (6%)
HEMATOPOIESIS		1 (6%)	3 (6%)	
#LYMPH NODE	(17)	(19)	(49)	(47)
INFLAMMATION, NOS			1 (2%)	
#MESENTERIC L. NODE	(17)	(19)	(49)	(47)
INFLAMMATION, NOS		2 (11%)	3 (6%)	
ANGIECTASIS		2 (11%)	1 (2%)	2 (4%)
CIRCULATORY SYSTEM				
#HEART	(17)	(19)	(49)	(47)
THROMBUS, ORGANIZED		1 (5%)		

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M081	CONTROL (VEH) 02-M071	LOW DOSE 02-M082	HIGH DOSE 02-M083
#MYOCARDIUM	(17)	(19)	(49)	(47)
INFLAMMATION, NOS		1 (5%)		
#ENDOCARDIUM	(17)	(19)	(49)	(47)
INFLAMMATION, NOS		1 (5%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(17)	(19)	(49)	(47)
CYST, NOS			2 (4%)	1 (2%)
#LIVER	(17)	(19)	(49)	(47)
INFLAMMATION, NOS			2 (4%)	
AMYLOIDOSIS		3 (16%)		
ANGIECTASIS			1 (2%)	
#PANCREAS	(17)	(18)	(49)	(47)
INFLAMMATION, NOS		1 (6%)	1 (2%)	
NECROSIS, FAT			1 (2%)	
#STOMACH	(17)	(19)	(49)	(47)
CALCIUM DEPOSIT			1 (2%)	1 (2%)
HYPERKERATOSIS		1 (5%)	1 (2%)	
ACANTHOSIS		1 (5%)	1 (2%)	
#COLON	(17)	(19)	(49)	(47)
NEMATODIASIS		3 (16%)	1 (2%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(17)	(18)	(49)	(47)
PYELONEPHRITIS, NOS	3 (18%)	1 (6%)	1 (2%)	
INFLAMMATION, CHRONIC	5 (29%)	12 (67%)	8 (16%)	4 (9%)
AMYLOIDOSIS	4 (24%)	6 (33%)	2 (4%)	2 (4%)
CALCIUM DEPOSIT				1 (2%)
ENDOCRINE SYSTEM				
#THYROID	(17)	(17)	(49)	(47)
FOLLICULAR CYST, NOS				1 (2%)
REPRODUCTIVE SYSTEM				
*PENIS	(18)	(19)	(49)	(48)
EPIDERMAL INCLUSION CYST		1 (5%)		

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 02-M081	CONTROL (VEH) 02-M071	LOW DOSE 02-M082	HIGH DOSE 02-M083
#PROSTATE	(17)	(19)	(49)	(47)
INFLAMMATION, NOS		1 (5%)		
#TESTIS	(17)	(19)	(49)	(47)
ATROPHY, NOS			2 (4%)	2 (4%)
*EPIDIDYMIS	(18)	(19)	(49)	(48)
GRANULOMA, SPERMATIC			1 (2%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(17)	(19)	(49)	(47)
INFLAMMATION, NOS		1 (5%)		
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	6	1	16	23
AUTO/NECROPSY/NO HISTO	1			1
AUTOLYSIS/NO NECROPSY	2	1	1	2

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-DICHLOROETHANE

	CONTROL (UNTR) 02-F081	CONTROL (VEH) 02-F071	LOW DOSE 02-F084	HIGH DOSE 02-F085
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	19	20	47	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	47	47
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(19)	(20)	(47)	(47)
PNEUMONIA, CHRONIC MURINE			3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(19)	(20)	(47)	(46)
HEMATOPOIESIS		1 (5%)		
#CERVICAL LYMPH NODE	(19)	(20)	(47)	(47)
INFLAMMATION, NOS				1 (2%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(19)	(19)	(46)	(47)
CYST, NOS				2 (4%)
ANGIECTASIS				1 (2%)
*BILE DUCT	(19)	(20)	(47)	(47)
HYPERPLASIA, NOS			1 (2%)	
#PANCREAS	(19)	(20)	(47)	(46)
CYST, NOS				1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-F081	CONTROL (VEH) 02-F071	LOW DOSE 02-F084	HIGH DOSE 02-F085
INFLAMMATION, NOS	1 (5%)			
ATROPHY, NOS				1 (2%)
#STOMACH	(19)	(20)	(47)	(46)
HYPERKERATOSIS		1 (5%)		1 (2%)
ACANTHOSIS		1 (5%)		1 (2%)
#COLON	(19)	(19)	(47)	(47)
NEMATODIASIS		1 (5%)		
URINARY SYSTEM				
#URINARY BLADDER	(19)	(19)	(47)	(47)
INFLAMMATION, NOS		1 (5%)		
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
#UTERUS	(19)	(20)	(47)	(46)
HYDROMETRA	3 (16%)	4 (20%)	8 (17%)	5 (11%)
#UTERUS/ENDOMETRIUM	(19)	(20)	(47)	(46)
INFLAMMATION, NOS	2 (11%)	2 (10%)	1 (2%)	
HYPERPLASIA, CYSTIC	7 (37%)	11 (55%)	21 (45%)	5 (11%)
#OVARY	(19)	(20)	(47)	(47)
CYST, NOS	10 (53%)	10 (50%)	5 (11%)	10 (21%)
INFLAMMATION, NOS	2 (11%)	3 (15%)		3 (6%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 02-P081	CONTROL (VEH) 02-P071	LOW DOSE 02-P084	HIGH DOSE 02-P085
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	3	1	11	18
ACCIDENTAL DEATH	1			
AUTO/NECROPSY/HISTO PERF			1	
AUTOLYSIS/NO NECROPSY			3	3

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

Review of the Bioassay of 1,1-Dichloroethane* 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, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to 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 laboratory animal sciences, chemistry, biochemistry, biostatistics, 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 reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 1,1-Dichloroethane for carcinogenicity.

The primary reviewer said that 1,1-Dichloroethane was not carcinogenic in the treated mice, under the conditions of test. In the rats, he said that survival was too inadequate among the animals to reach any conclusion. He noted that the study was conducted in the same room in which 17 other compounds were studied. He added that at the dose level administered, it is likely that a portion of the dose was expelled through the lungs back into the animal room. In conclusion, the primary reviewer said that he agreed with the staff's conclusion in regard to the negative mouse study but thought that the rat study was too inadequate to draw any conclusion.

The secondary reviewer concurred with the primary reviewer's critique. He was particularly critical of the rat study in which there were too few controls, survival was poor, the MTD was not adequately determined, and the chronic treatment period was not continuous. Despite the slight increases in mammary adenocarcinomas and hemangiosarcomas in the treated female rats, the secondary reviewer concluded that the study was too inadequate to draw any conclusion.

A discussion ensued as to whether the mouse bioassay was adequate enough to reach a conclusion. It was agreed that survival was sufficient and the dose level high enough as to be able to make a judgment on the carcinogenicity of 1,1-Dichloroethane.

It was moved that there was no conclusive evidence as to the carcinogenicity of 1,1-Dichloroethane in the treated mice and that the rat study was inadequate to drawn any conclusion. The motion was seconded and, subsequently an amendment proposed that 1,1-Dichloroethane be referred to the Chemical Selection Working Group to be considered for retest in rats. Votes on the amendment and motion were 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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