National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 68
1978

BIOASSAY OF HEXACHLOROETHANE FOR POSSIBLE CARCINOGENICITY

CAS No. 67-72-1

NCI-CG-TR-68

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

BIOASSAY OF

HEXACHLOROETHANE

FOR POSSIBLE CARCINOGENICITY

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

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

DHEW Publication No. (NIH) 78-1318

REPORT ON THE BIOASSAY OF HEXACHLOROETHANE
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 hexachloroethane 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 in animals. Negative results, in which the test animals do not have a 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 hexachloroethane 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.

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 Dr. D. R. Patterson (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).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), the task leader, Dr. M. R. Kornreich (6), the senior biologist, Ms. P. Walker (6), and the technical editor, Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

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).

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), and Dr. J. M. Ward (1).

---

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

2. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

3. Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia.

4. Now with the Center for Regulatory Services, 2347 Paddock Lane, Reston, Virginia.

5. Now with Rhodia, Inc., 23 Belmont Drive, Somerset, New Jersey.

6. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

7. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

8. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

9. Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

10. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay for possible carcinogenicity of technical-grade hexachloroethane was conducted using Osborne-Mendel rats and B6C3F1 mice. Hexachloroethane in corn oil was administered by gavage, at either of two dosages, to groups of 50 male and 50 female animals of each species. The chemical was administered 5 days a week, cyclically for 44 of 78 weeks in rats and continuously for 78 weeks in mice, followed by an observation period of 33 or 34 weeks for rats and 12 or 13 weeks for mice. The high and low time-weighted average dosages of hexachloroethane were, respectively, 423 and 212 mg/kg/day for male and female rats and 1179 and 590 mg/kg/day for male and female mice. For each species, 20 animals of each sex were placed on test as vehicle controls. These animals were gavaged with pure 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.

A statistically significant association between increased dosage and accelerated mortality was observed in male and female rats but not in mice of either sex.

Toxic tubular nephropathy was observed in all groups of treated animals.

Statistical evaluation of the incidences of hepatocellular carcinomas revealed a significant positive association between hexachloroethane administration and tumor incidence in both male and female mice. No statistical significance was attributed to the incidence of any neoplasm in rats of either sex.

No evidence was provided for the carcinogenicity of the compound in Osborne-Mendel rats. It is concluded that under the conditions of this bioassay, hexachloroethane was carcinogenic in B6C3F1 mice, inducing hepatocellular carcinomas in both sexes.

TABLE OF CONTENTS

		Page
I.	INTRODUCTION	1
II.	MATERIALS AND METHODS	3
	A. Chemicals	3
	B. Dosage Preparation	4
	C. Animals	4
	D. Animal Maintenance	5
	E. Gastric Intubation	6
	F. Selection of Initial Dose Levels	6
	G. Experimental Design	8
	H. Clinical and Histopathologic Examinations	11
	I. Data Recording and Statistical Analyses	13
III.	CHRONIC TESTING RESULTS: RATS	18
	A. Body Weights and Clinical Observations	18
	B. Survival	20
	C. Pathology	22
	D. Statistical Analyses of Results	23
IV.	CHRONIC TESTING RESULTS: MICE	29
	A. Body Weights and Clinical Observations	29
	B. Survival	29
	C. Pathology	32
	D. Statistical Analyses of Results	33
V.	DISCUSSION	41
VI.	BIBLIOGRAPHY	43
APPENDIX A	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH HEXACHLOROETHANE	A-1
APPENDIX B	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH HEXACHLOROETHANE	B-1
APPENDIX C	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH HEXACHLOROETHANE	C-1
APPENDIX D	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH HEXACHLOROETHANE	D-1

LIST OF ILLUSTRATIONS

Figure Number		Page
1	GROWTH CURVES FOR HEXACHLOROETHANE CHRONIC STUDY RATS	19
2	SURVIVAL COMPARISONS OF HEXACHLOROETHANE CHRONIC STUDY RATS	21
3	GROWTH CURVES FOR HEXACHLOROETHANE CHRONIC STUDY MICE	30
4	SURVIVAL COMPARISONS OF HEXACHLOROETHANE CHRONIC STUDY MICE	31

LIST OF TABLES

Table Number		Page
1	DESIGN SUMMARY FOR OSBORNE-MENDEL RATS--HEXACHLOROETHANE GAVAGE EXPERIMENT	9
2	DESIGN SUMMARY FOR B6C3F1 MICE--HEXACHLOROETHANE GAVAGE EXPERIMENT	10
3	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH HEXACHLOROETHANE WHICH SURVIVED AT LEAST 52 WEEKS	24
4	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH HEXACHLOROETHANE	26
5	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH HEXACHLOROETHANE	34
6	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH HEXACHLOROETHANE	36
7	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH HEXACHLOROETHANE WHICH SURVIVED AT LEAST 41 WEEKS	39

LIST OF TABLES (Concluded)

Table Number		Page
A1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH HEXACHLOROETHANE	A-3
A2	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH HEXACHLOROETHANE	A-7
B1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH HEXACHLOROETHANE	B-3
B2	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH HEXACHLOROETHANE	B-6
C1	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH HEXA-CHLOROETHANE	C-3
C2	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH HEXA-CHLOROETHANE	C-10
D1	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH HEXA-CHLOROETHANE	D-3
D2	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH HEXA-CHLOROETHANE	D-7

I. INTRODUCTION

Hexachloroethane (NCI No. C04604), a chlorinated alkane with a wide variety of uses, was selected for bioassay by the National Cancer Institute because of its structural similarity to chloroform, a compound which has been found to induce hepatomas in NLC mice (Rudali, 1967).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is hexachloro-ethane.* It is also known as carbon hexachloride, perchloroethane, ethylene hexachloride, and Avlothane®.

Hexachloroethane is used as a veterinary anthelmintic for control of liver and stomach flukes in domestic animals (Farm Chemicals Handbook, 1976). It is also used as a solvent, a camphor substitute in the preparation of Celluloid®, a rubber vulcanizing accelerator, a retarding agent in fermentation, and in explosives, pyrotechnics, and smoke devices (Hawley, 1971; Windholz, 1976).

Specific production figures for hexachloroethane are not available; however, the inclusion of the compound in the 1977 Directory of Chemical Producers, U.S.A. (Stanford Research Institute, 1977) implies an annual production in excess of 1000 pounds or $1000 in value.

The risk of exposure to hexachloroethane is greatest for workers in the chemical, rubber, plastics, pharmaceutical and explosives

---

*The CAS registry number is 67-72-1.

industries, and for those persons using the compound for veterinary purposes. The risk of inhaling hexachloroethane vapor in industrial settings is minimal because the compound is a solid with a relatively low vapor pressure (Irish, 1967); consequently, exposure would occur primarily through dermal contact or ingestion.

The major physiological effect of hexachloroethane is depression of the central nervous system. Ingestion of the compound results in severe injury to the mucous membranes and often in liver necrosis (Gosselin et al., 1976).

II. MATERIALS AND METHODS

A. Chemicals

One batch of technical-grade hexachloroethane was purchased from Aldrich Chemical Company by Hazleton Laboratories America, Inc., Vienna, Virginia. The purity of the compound was determined at Hazleton Laboratories, using gas-liquid chromatography (GLC) total-area analysis and melting point tests. The initial GLC analysis showed five peaks; one, hexachloroethane, accounted for almost 99 percent of the total area while the other four accounted for approximately 1 percent of the total area. Additional analyses were performed one and two years after the initiaal analyses. In the second analysis by GLC, hexachloroethane accounted for over 98 percent of the total area and in the third GLC analysis, the hexachloroethane peak accounted for almost 100 percent of the total area. It was concluded that these determinations of hexachloroethane purity by GLC agreed favorably with the vendor's stated purity of 98 percent and that the chemical was stable under the laboratory storage conditions.

In the literature it is indicated that hexachloroethane sublimes at 187°C. In an open capillary the test material began to melt at 183.5°C and all the material sublimed at 188.0°C. In a sealed capillary, a melting point of 184.7° to 185.3°C was obtained. The narrow melting point range indicated a material of high purity.

Throughout this report the term hexachloroethane is used to represent this technical-grade material.

B. Dosage Preparation

Fresh solutions of hexachloroethane in Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) were prepared weekly, sealed, and stored in dark bottles at 24°C. These hexachloroethane solutions were considered generally stable for 10 days under the indicated storage conditions. The concentration of hexachloroethane in the corn oil was 10 percent for the rat bioassay and 10 to 12 percent for the mouse bioassay.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts with the Division of Cancer Treatment, National Cancer Institute. The Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various 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 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 12 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle. The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors. 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. 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 hexachloroethane and both the vehicle and untreated controls were housed in the same room with rats intubated with* 3-sulfolene (77-79-2) and iodoform (75-47-8).

The hexachloroethane-dosed and all control mice were housed in the same room as mice intubated with allyl chloride (107-05-1),

*CAS registry numbers are given in parentheses.

chloroform (67-66-3), chloropicrin (76-06-2), dibromochloropropane (96-12-8), 1,2-dibromoethane (106-93-4), 1,2-dichloroethane (107-06-2), 1,1-dichloroethane (75-34-3), 3-sulfolene (77-79-2), trichloroethylene (79-01-6),iodoform (75-47-8), methylchloroform (71-55-6), 1,1,2-trichloroethane (79-00-5), tetrachloroethylene (127-18-4), 1,1,2,2-tetrachloroethane (79-34-5), carbon disulfide (75-15-0), trichlorofluoromethane (75-69-4), and carbon tetrachloride (56-23-5).

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a mg/kg of body weight basis, utilizing the most recently observed group mean body weight as a guide for determining the dose. Mean 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. Animals were gavaged with hexachloroethane solutions under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

F. Selection of Initial Dose Levels

In order to establish the estimated maximum tolerated dosages of hexachloroethane 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. Hexachloroethane mixed with corn oil was introduced by gavage to five of the six rat

groups at dosages of 178, 316, 562, 1000, and 1780 mg/kg/day and five of the six mouse groups at dosages of 316, 562, 1000, 1780, and 3160 mg/kg/day. The sixth group of each species served as a control group, receiving only the corn oil by gavage. Intubation was performed 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity.

A dosage inducing no mortality and resulting in a depression in mean group body weight of approximately 20 percent relative to controls was to be selected as the initial high dose. When weight gain criteria were not applicable, mortality data alone were utilized.

At a level of 562 mg/kg/day all the male and female rats survived to the end of the 8-week period. Some rats survived dosages of 1000 mg/kg/day, but all rats receiving dosages of 1780 mg/kg/day died before the 8 weeks were over. Mean body weight gain of male and female rats receiving dosages of 316 mg/kg/day or less was similar to that of controls. At 1000 mg/kg/day mean body weight depression was 38 percent for male rats and 18 percent for female rats. The initial dosage used in the chronic bioassay for both high dose males and females was 500 mg/kg/day.

All male mice survived dosages of 1000 mg/kg/day or less and all female mice survived dosages of 1780 mg/kg/day or less. However, at doses of 3160 mg/kg/day four out of five male mice and three out of five female mice died. Mean body weight gain in mice receiving

dosages of 1000 mg/kg/day or less (except in the group of female mice receiving 562 mg/kg/day) was similar to that of controls. Mean body weight gain was substantially depressed in mice receiving dosages of 3160 mg/kg/day. The initial high dose selected for the chronic bioassay was 1000 mg/kg/day for both male and female mice.

G. Experimental Design

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

The untreated control and all treated rats were approximately 6 weeks old at the time the experiment began. The vehicle control rats were approximately 8 weeks older than the other rat groups and were started on test 6 weeks before the others. The vehicle control animals were approximately 8 weeks old when they received their first intubation. The doses utilized throughout the 78-week intubation period for both male and female rats were 250 and 500 mg/kg/day. Throughout this report rats receiving the former dosage are referred to as the low dose groups while those receiving the latter dosage are referred to as the high dose groups. In week 23 intubation ceased for all treated animals for 1 week, followed by 4 weeks of dose administration. This pattern of cyclic administration was maintained for the remainder of the dosing period. After the period of compound

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
HEXACHLOROETHANE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	HEXACHLORO-ETHANE 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		112	0
VEHICLE CONTROL	20	0	78	33	0
LOW DOSE	50	250	22		212
		250[c]	44	12	
		0		34	
HIGH DOSE	50	500	22		423
		500[c]	44	12	
		0		34	
FEMALE					
UNTREATED CONTROL	20	0		112	0
VEHICLE CONTROL	20	0	78	33	0
LOW DOSE	50	250	22		212
		250[c]	44	12	
		0		34	
HIGH DOSE	50	500	22		423
		500[c]	44	12	
		0		34	

[a] Doses, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

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

[c] These dosages were cyclically administered with a pattern of 1 dose-free week followed by 4 weeks of dosing at the indicated levels.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
HEXACHLOROETHANE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	HEXACHLORO-ETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0	0	90	0
VEHICLE CONTROL	20	0	78	12	0
LOW DOSE	50	500	8		590
		600	70		
		0		13	
HIGH DOSE	50	1000	8		1179
		1200	70		
		0		13	
FEMALE					
UNTREATED CONTROL	20	0		90	0
VEHICLE CONTROL	20	0	78	13	0
LOW DOSE	50	500	8		590
		600	70		
		0		13	
HIGH DOSE	50	1000	8		1179
		1200	70		
		0		13	

[a]Doses, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

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

administration the animals were observed for an additional 33 or 34 weeks.

The vehicle control and treated mice were approximately 5 weeks old at the time they were started on test while the untreated control mice were approximately 6 weeks old. The vehicle control and treated mice shared the same median date of birth while the untreated control mice were approximately 7 weeks older. Therefore, the untreated controls were placed on test approximately 6 weeks earlier than the other groups. The doses initially administered to male and female mice were 500 and 1000 mg/kg/day. Throughout this report those mice initially receiving the former dosage are referred to as the low dose groups while those receiving the latter dosage are referred to as the high dose groups. In week 9 the low and high doses were increased to 600 and 1200 mg/kg/day and these doses were utilized for the remainder of the dosing period. After the dosing period the animals were observed for 12 or 13 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 histopatologic 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: 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, muscle, 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.

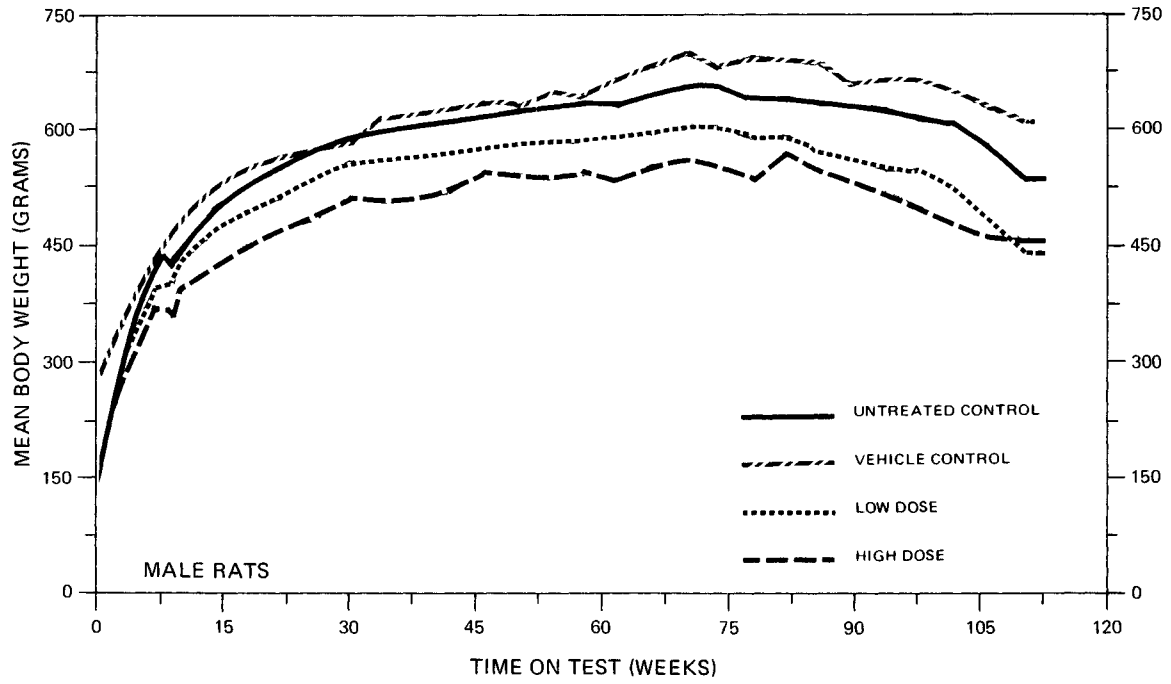
III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

Distinct dose-related depression in mean body weight was evident in male rat groups (Figure 1). For female rats, low dose and control groups exhibited similar growth patterns, but mean body weight of high dose rats was slightly depressed relative to the other female rat 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 year of the study the incidence of observed clinical signs was slightly increased in the treated rats when compared to the untreated controls. The signs observed with the most frequency were hunched appearance; reddened, squinted or lacrimating eyes; and abdominal urine stains. The incidences of these signs were comparable between low and high dose animals; however, the high dose females showed a higher frequency of abdominal urine staining from week 4 until termination of the bioassay. During the second year of the study, behavior and appearance were comparable between treated and control animals.

Respiratory abnormalities were observed in all groups during the latter part of the first year. The incidence of respiratory symptoms increased at gradual and comparable rates for all groups during the last six months of the study. Clinical observations associated with aging in laboratory rats were noted in comparable numbers of treated



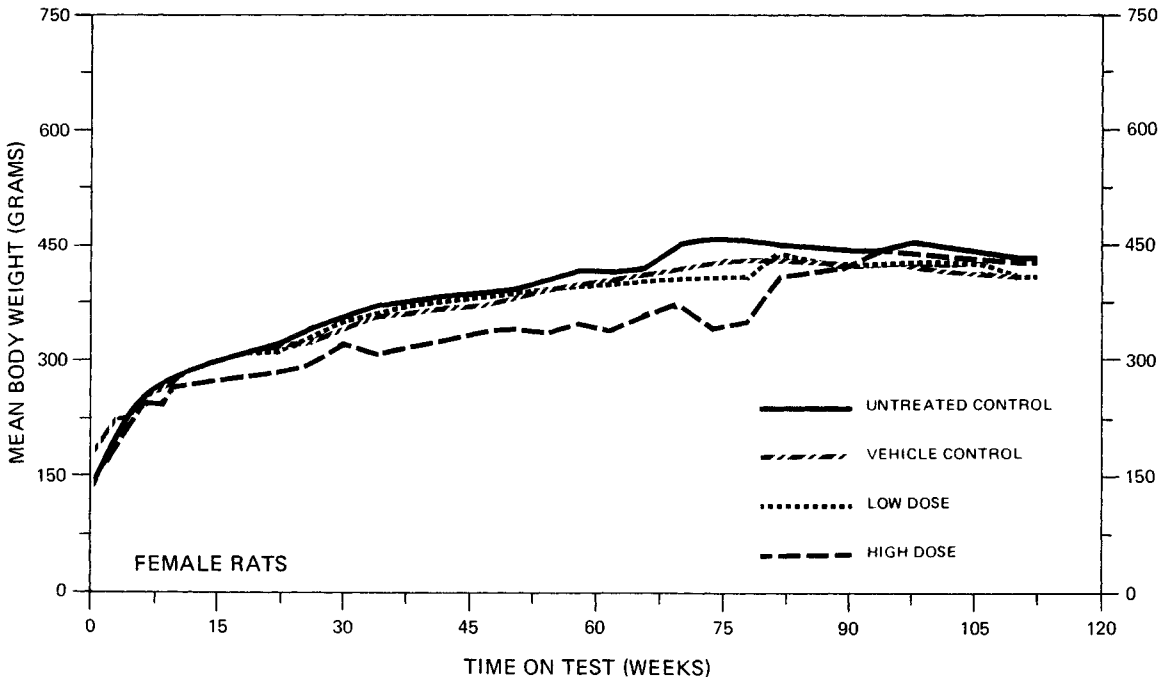


FIGURE 1
GROWTH CURVES FOR HEXACHLOROETHANE CHRONIC STUDY RATS

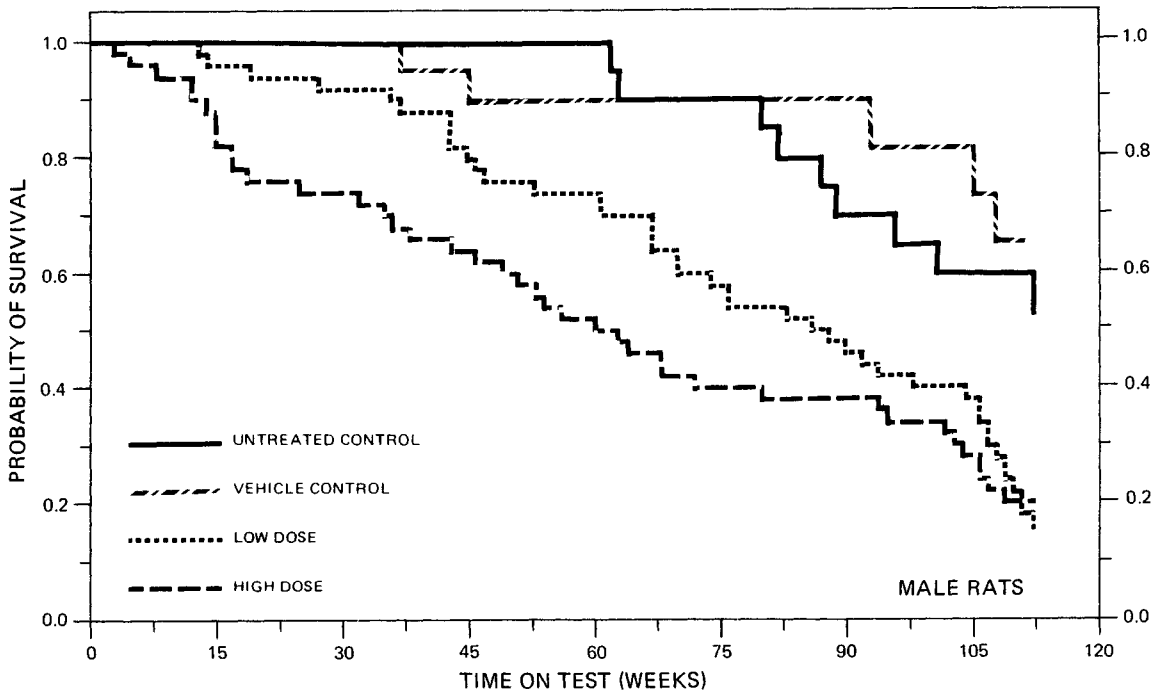
and untreated controls during the second year. These signs included: sores on the tail or other parts of the body, alopecia, discolored or rough fur, eye discharge or red crust around the eyes and palpable nodules and/or tissue masses. Isolated, apparently spontaneous observations noted in several treated rats included transient tremors, vaginal discharge and ataxia.

B. Survival

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

For male rats the Tarone test indicated a significant ($P < 0.001$) association between increased dosage and accelerated mortality. Thirty-eight percent (19/50) of the high dose and 48 percent (24/50) of the low dose males survived at least 90 weeks, compared to 70 percent (14/20) of the untreated controls, and, despite the sacrifice of seven rats in week 60, 55 percent (11/20) of the vehicle controls.

For female rats mortality was significantly increased in the dosed groups compared to the untreated groups. The actual survival, however, was adequate for statistical analysis of late-developing tumors as 48 percent (24/50) of the high dose, 54 percent (27/50) of the low dose, 70 percent (14/20) of the vehicle control, and 70 percent (14/20) of the untreated control rats survived until the end of the test.



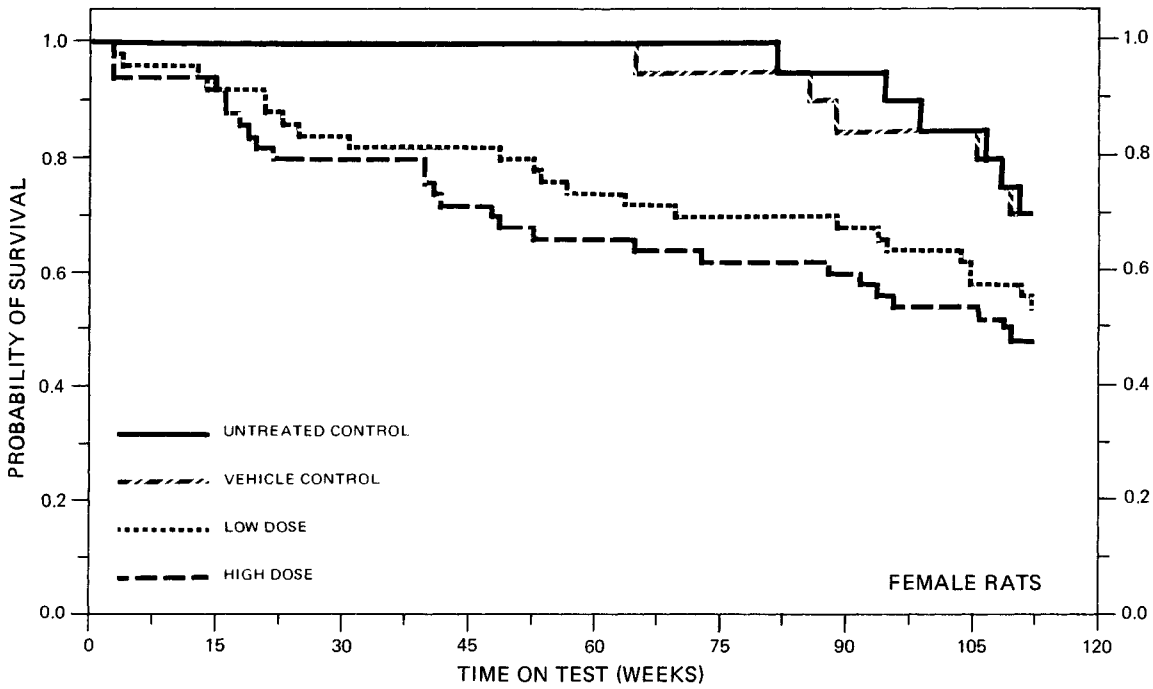


FIGURE 2
SURVIVAL COMPARISONS OF HEXACHLOROETHANE CHRONIC STUDY RATS

C. Pathology

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

Each of the tumor types detected has been encountered previously as a spontaneous lesion in Osborne-Mendel rats and no appreciable difference in frequency was noted between the control and treated rats.

With the exception of certain renal lesions, inflammatory, degenerative, and proliferative lesions seen in control and treated rats were similar in number and kind to those naturally occurring lesions found in aged rats. In addition to the chronic inflammatory lesions of the kidney seen in control and treated animals, toxic tubular nephropathy was associated with compound exposure. The lesion occurred in 22/49 (45 percent) low dose males, 33/50 (66 percent) high dose males, 9/50 (18 percent) low dose females, and 29/49 (59 percent) high dose females and was characterized by degeneration, necrosis, and the presence of large hyperchromatic regenerative epithelial cells. Overlying the tubular lesions were chronic interstitial nephritis and fibrosis, focal pyonephritis, tubular ectasia, cast formation, and focal glomerulosclerosis. Renal tubular-cell adenomas were found in four low dose male rats.

In conclusion, there is no histopathologic evidence that hexachloroethane is carcinogenic in Osborne-Mendel rats under the

conditions of this experiment. Toxic tubular nephropathy was present in rats of both sexes at both dose levels, but not in the control rats.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis for every type of tumor that was observed in more than 5 percent of any of the hexachloroethane-dosed groups of either sex is included. Because of the high early mortality in the high dose males, the statistical analyses for males (Table 3) are based exclusively upon rats which survived at least 52 weeks.

For male rats the Cochran-Armitage test indicated a significant ($P = 0.048$) positive association between dosage and the incidence of interstitial-cell tumors of the testis. The Fisher exact tests, however, were not significant. Renal tubular-cell adenomas, found in four low dose male rats, were not statistically significant.

For female rats a significant negative association between dosage and the incidence of pituitary chromophobe adenomas was indicated by the Cochran-Armitage test. The Fisher exact tests, however, were not significant under the Bonferroni criterion.

Based upon these results there was no conclusive statistical evidence that hexachloroethane was a carcinogen in Osborne-Mendel rats.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH HEXACHLOROETHANE WHICH SURVIVED AT LEAST 52 WEEKS[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Kidney: Tubular-Cell Adenoma[b]	0/18(0.00)	4/37(0.11)	0/29(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.023	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	---
Lower Limit	---	0.473	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	86	---
Pituitary: Chromophobe Adenoma[b]	2/18(0.11)	4/32(0.13)	0/24(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.125	0.000
Lower Limit	---	0.184	0.000
Upper Limit	---	11.543	3.735
Weeks to First Observed Tumor	105	104	---
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	2/18(0.11)	3/36(0.08)	5/28(0.18)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.750	1.607
Lower Limit	---	0.097	0.305
Upper Limit	---	8.370	15.499
Weeks to First Observed Tumor	111	92	60

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	0/18(0.00)	0/36(0.00)	3/29(0.10)
P Values[c]	P = 0.048	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	0.391
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	109

[a]Treated groups received time-weighted average doses of 212 or 423 ppm in feed.

[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 $P < 0.05$.

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Kidney: Hamartoma*[b]	0/20(0.00)	0/50(0.00)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	0.255
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	112
Pituitary: Chromophobe Adenoma[b]	7/20(0.35)	15/50(0.30)	6/46(0.13)
P Values[c]	P = 0.021(N)	N.S.	P = 0.045(N)
Relative Risk (Vehicle Control)[d]	---	0.857	0.373
Lower Limit	---	0.405	0.124
Upper Limit	---	2.169	1.149
Weeks to First Observed Tumor	89	89	112
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	2/20(0.10)	3/47(0.06)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.638	0.638
Lower Limit	---	0.080	0.080
Upper Limit	---	7.284	7.284
Weeks to First Observed Tumor	111	112	109

*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 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	6/20(0.30)	13/50(0.26)	9/50(0.18)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.867	0.600
Lower Limit	---	0.371	0.229
Upper Limit	---	2.463	1.828
Weeks to First Observed Tumor	106	57	94
Ovary: Granulosa-Cell Tumor[b]	1/20(0.05)	4/48(0.08)	0/49(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.667	0.000
Lower Limit	---	0.182	0.000
Upper Limit	---	80.314	7.624
Weeks to First Observed Tumor	111	111	---

[a]Treated groups received time-weighted average doses of 212 or 423 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.

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 hexachloroethane that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

No distinct dose-related depression in mean body weight was evident in males or females (Figure 3). 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.

There was no evidence of compound effect with regard to physical appearance or behavior of the treated mice during the first 34 weeks of the study. Signs often observed in group-housed laboratory mice, particularly males, were observed at a comparable rate in all groups. These signs included sores on the body and/or extremities, a hunched appearance, localized alopecia, external genital irritation, and rough or stained fur.

A hunched or thin appearance was observed with greater frequency in the treated groups from week 38 until termination of the bioassay in week 91. The incidence of palpable nodules, tissue masses, or swollen areas was slightly greater in the treated mice than in the controls.

B. Survival

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

For both male and female mice there was no significant positive association between dose and mortality. For males the survival was

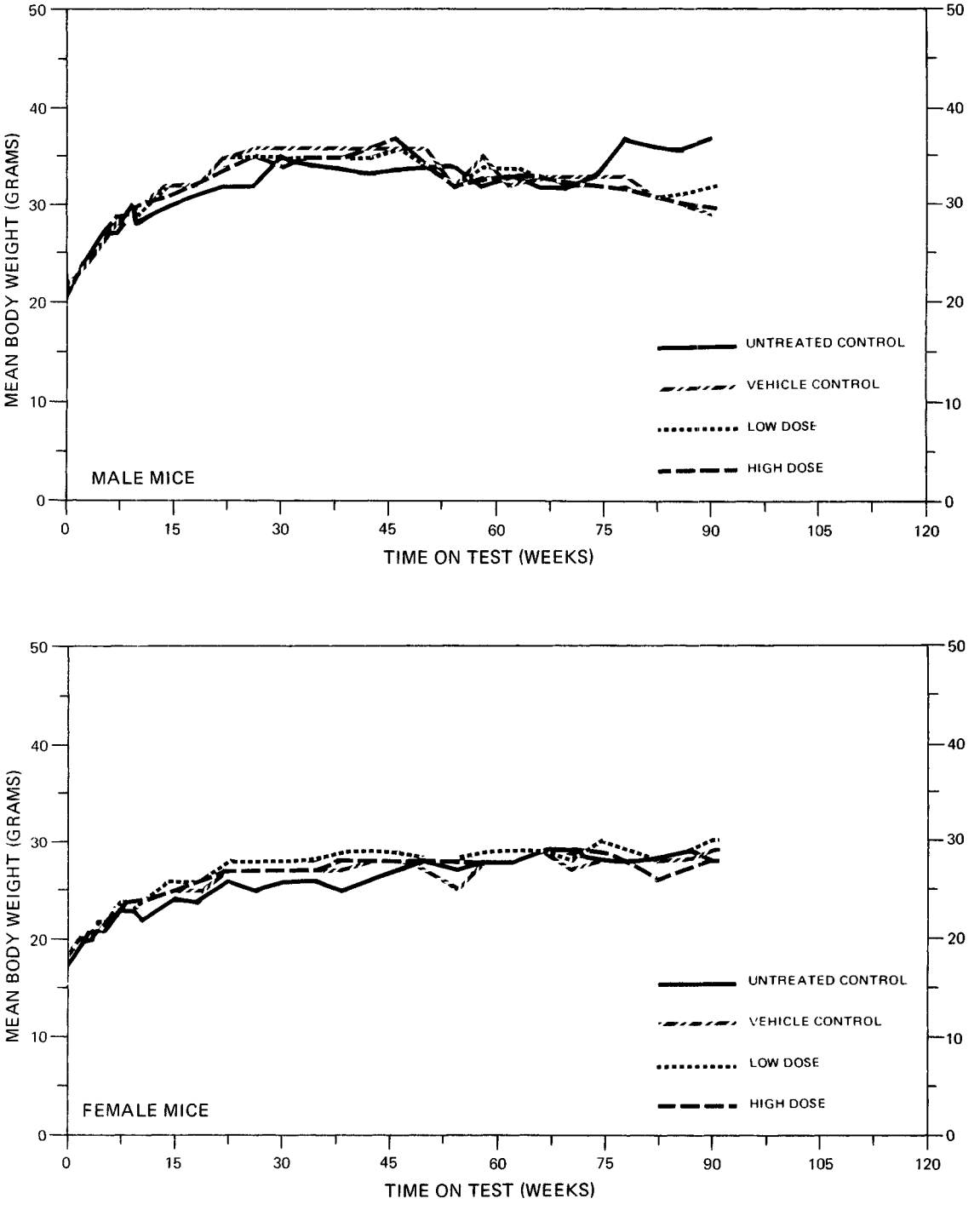
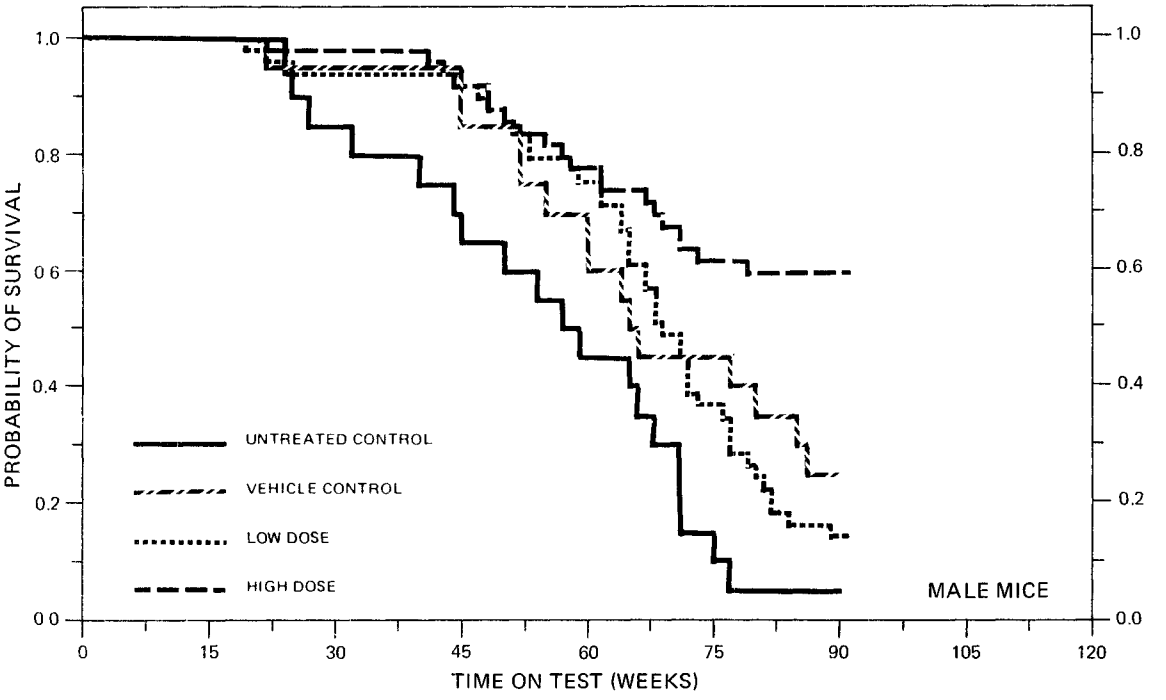


FIGURE 3
GROWTH CURVES FOR HEXACHLOROETHANE CHRONIC STUDY MICE



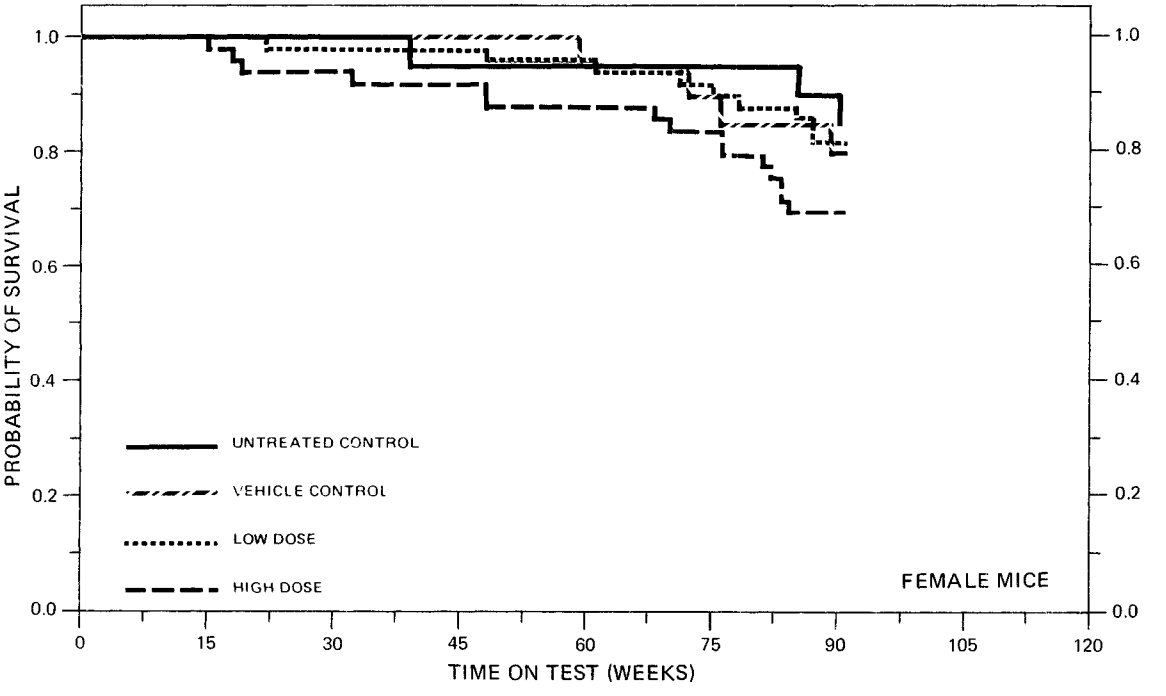


FIGURE 4
SURVIVAL COMPARISONS OF HEXACHLOROETHANE CHRONIC STUDY MICE

unexpectedly low in the control groups and the low dose group as only 25 percent (5/20) of the vehicle control, 5 percent (1/20) of the untreated control, and 14 percent (7/50) of the low dose mice survived until the end of the test, compared to 58 percent (29/50) of the high dose mice.

There were adequate numbers of females at risk from late-developing tumors as 68 percent (34/50) of the high dose, 80 percent (40/50) of the low dose, 80 percent (16/20) of the vehicle control, and 85 percent (17/20) of the untreated control mice survived until the end of the test.

C. Pathology

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

Hepatocellular carcinomas occurred in 1/18 (6 percent) male untreated controls, 3/20 (15 percent) male vehicle controls, 15/50 (30 percent) low dose males, 31/49 (63 percent) high dose males, 0/18 untreated control females, 2/20 (10 percent) vehicle control females, 20/50 (40 percent) low dose females, and 15/49 (31 percent) high dose females.

Microscopically, the hepatocellular carcinomas varied greatly in appearance. Some 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 hepatic cells and occasionally pseudo-acinar formation. Mitotic figures were often present. The hepatic neoplasms occurring in the control mice were not different in appearance from those seen in the hexachloroethane-dosed animals.

Toxic nephropathy occurred in 49/50 (98 percent) low dose males, 47/49 (96 percent) high dose males, 50/50 (100 percent) low dose females, and 45/49 (92 percent) high dose females. Microscopically, the nephropathy was characterized by degeneration of convoluted tubule epithelium at the junction of the cortex and medulla. Some affected tubules contained hyalin casts. Occasionally the damaged cells were replaced by enlarged dark staining regenerative tubular epithelium. At this stage, the kidney often showed infiltration of inflammatory cells, fibrosis, and calcium deposition.

Results of this histopathologic examination indicate that hexachloroethane was carcinogenic, causing an increased incidence of hepatocellular carcinomas in male and female mice. This chemical also caused toxic nephropathy in mice of both sexes.

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 hexachloroethane-dosed groups of either sex is included.

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/60(0.00)	0/20(0.00)	2/50(0.04)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.354	0.733
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Matched Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.123	0.255
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	91	91
Liver: Hepatocellular Carcinoma[b]	6/60(0.10)	3/20(0.15)	15/50(0.30)	31/49(0.63)
P Values[c]	P < 0.001	P < 0.001	P = 0.008*	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P = 0.023	---	---	---
Relative Risk (Pooled Vehicle Control)[d]	---	---	3.000	6.327
Lower Limit	---	---	1.197	2.931
Upper Limit	---	---	8.686	16.064
Relative Risk (Matched Vehicle Control)[d]	---	---	2.000	4.218
Lower Limit	---	---	0.662	1.577
Upper Limit	---	---	9.943	18.987
Weeks to First Observed Tumor	55	55	53	41

TABLE 5 (CONCLUDED)

---

[a]Treated groups received time-weighted average doses of 590 or 1179 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 6

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

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Brochiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	2/60(0.03)	1/20(0.05)	1/50(0.02)	4/49(0.08)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	0.600	2.449
Lower Limit	---	---	0.010	0.366
Upper Limit	---	---	11.160	26.112
Relative Risk (Matched Vehicle Control)[d]	---	---	0.400	1.633
Lower Limit	---	---	0.005	0.179
Upper Limit	---	---	30.802	78.704
Weeks to First Observed Tumor	90	91	91	91
Liver: Hepatocellular Carcinoma[b]	2/60(0.03)	2/20(0.10)	20/50(0.40)	15/49(0.31)
P Values[c]	P < 0.001	N.S.	P < 0.001* P = 0.012**	P < 0.001*
Departure from Linear Trend[e]	P = 0.002	P = 0.028	---	---
Relative Risk (Pooled Vehicle Control)[d]	---	---	12.000	9.184
Lower Limit	---	---	3.140	2.287
Upper Limit	---	---	100.443	78.968
Relative Risk (Matched Vehicle Control)[d]	---	---	4.000	3.061
Lower Limit	---	---	1.128	0.823
Upper Limit	---	---	33.077	26.000
Weeks to First Observed Tumor	90	90	85	91

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	8/60(0.13)	4/20(0.20)	12/50(0.24)	9/49(0.18)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)[d]	---	---	1.800	1.378
Lower Limit	---	---	0.737	0.509
Upper Limit	---	---	4.656	3.783
Relative Risk (Matched Vehicle Control)[d]	---	---	1.200	0.918
Lower Limit	---	---	0.430	0.300
Upper Limit	---	---	4.650	3.731
Weeks to First Observed Tumor	69	72	71	68

[a]Treated groups received time-weighted average doses of 590 or 1179 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 $P < 0.05$.

Because of the poor survival of several of the control groups, two control groups were used for statistical analyses: the vehicle control group (designated in this section as the "matched" vehicle control group) and a pooled vehicle control group, combining the vehicle controls from the studies of hexachloroethane, trichloroethylene, and 1,1,2-trichloroethane. The pooled vehicle controls were of the same strain, were housed in the same room, were all intubated with corn oil, were tested concurrently for at least a year, and were diagnosed by the same pathologists.

For both male and female mice the incidence of hepatocellular carcinomas was significant. For both sexes the Cochran-Armitage test showed a significant ($P < 0.001$) positive association between dosage and incidence when comparing the dosed groups to either control group. For females the departure from linear trend was significant, principally because the observed incidence was higher in the low dose group than in the high dose group. For both male and female mice the Fisher exact tests comparing either the low dose or the high dose to the pooled control group were significant ($P \leq 0.008$). Additionally, the comparisons of high dose males ($P < 0.001$) and low dose females ($P = 0.012$) to the matched controls were also significant.

Because of the unexpectedly high mortality observed among male mice in the low dose group and in both control groups, additional time-adjusted analyses were conducted. In Table 7 the analysis for the incidences of hepatocellular carcinomas is presented, an analysis

TABLE 7

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH HEXACHLOROETHANE WHICH SURVIVED AT LEAST 41 WEEKS[a]

TOPOGRAPHY:MORPHOLOGY	POOLED VEHICLE CONTROL	MATCHED VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	6/55(0.11)	3/19(0.16)	15/46(0.33)	31/48(0.65)
P Values[c]	P < 0.001	P < 0.001	P = 0.007*	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P = 0.020	---	---	---
Relative Risk (Pooled Vehicle Control)[d]	---	---	2.989	5.920
Lower Limit	---	---	1.203	2.761
Upper Limit	---	---	8.572	14.905
Relative Risk (Matched Vehicle Control)[d]	---	---	2.065	4.090
Lower Limit	---	---	0.690	1.542
Upper Limit	---	---	10.187	18.279
Weeks to First Observed Tumor	55	55	53	41

[a]Treated groups received time-weighted average doses of 590 or 1179 ppm in feed.

[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.

based exclusively upon males which survived at least 41 weeks. Both Cochran-Armitage tests, the Fisher exact comparisons of the high dose to both control groups, and the Fisher exact comparison of the low dose to the pooled control group were significant ($P \leq 0.007$).

Based upon these results the statistical conclusion is that the administration of hexachloroethane was associated with an increased incidence of hepatocellular carcinomas in B6C3F1 mice.

V. DISCUSSION

There was a significant association between increased dosage and accelerated mortality in rats of both sexes. The survival among the high dose male rats was not considered adequate for meaningful statistical analysis of the incidence of late-developing tumors. Doses administered to rats were high enough to cause growth retardation in the high dose female group and both dosed male groups. Adequate numbers of animals in all mouse groups survived long enough to be at risk from late-developing tumors.

Hepatocellular carcinomas were detected in 0/18, 2/20 (10 percent), 20/50 (40 percent), and 15/49 (31 percent) of the untreated control, vehicle control, low dose, and high dose female mouse groups, respectively. The Cochran-Armitage test indicated a significant positive association between dosage and the incidence of this neoplasm in female mice. This association was supported by the Fisher exact test using the pooled vehicle control group and by the comparison of the low dose females to the matched vehicle controls. Despite the relatively early appearance of tumors in the male matched vehicle control group and the fact that mortality of low dose mice was higher than that of high dose mice, results for male mice support those found for female mice. Hepatocellular carcinomas were detected in 1/18 (6 percent), 3/20 (15 percent), 15/50 (30 percent), and 31/49 (63 percent) of the untreated control, vehicle control, low dose, and high dose male mouse groups, respectively. The Cochran-Armitage test

indicated a significant positive association between dosage and tumor incidence. This was supported by Fisher exact tests comparing the high dose male mouse group to the pooled vehicle and to the matched vehicle control groups and comparing the low dose male mouse group to the pooled vehicle control group. No other neoplasms of significance were observed in rats or mice of either sex.

Toxic tubular nephropathy was observed in all groups of treated animals. In rats 22/49 (45 percent), 33/50 (66 percent), 9/50 (18 percent), and 29/49 (59 percent) of the low and high dose males and low and high dose females, respectively, exhibited this lesion. The incidences in mice were higher (i.e., 49/50 [98 percent], 47/49 [96 percent], 50/50 [100 percent], 45/49 [92 percent] of the low dose males, high dose males, low dose females, and high dose females, respectively).

No evidence was provided for the carcinogenicity of hexachloroethane in Osborne-Mendel rats. It is concluded that under the conditions of this bioassay, hexachloroethane was carcinogenic in male and female B6C3F1 mice, causing hepatocellular carcinomas.

VI. BIBLIOGRAPHY

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

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

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

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

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

Farm Chemicals Handbook. Meister Publishing Company, Willoughby, Ohio, 1976.

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

Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason, Clinical Toxicology of Commercial Products, 4th edition. The Williams and Wilkins Company, Baltimore, Maryland, 1976.

Hawley, G.G., editor. The Condensed Chemical Dictionary, 8th edition. Van Nostrand Reinhold Company, New York, 1971.

Irish, D.D., "Aliphatic Saturated Hydrocarbons." Industrial Hygiene and Toxicology, 2nd revised edition. F.A. Patty, editor. Interscience, New York, 1967.

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

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

Miller, R.G., Simultaneous Statistical Inference. McGraw-Hill Book Co., New York, 1966.

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

Rudali, G., "A Propos de l'Activite Oncogene de Quelques Hydrocarbures Halogenes Utilises en Therapeutique." UICC Monograph Series 7: 138-143, 1967. (French).

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

Stanford Research Institute, 1977 Directory of Chemical Producers, U.S.A. Menlo Park, California, 1977.

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

Windholz, M., editor, The Merck Index: An Encyclopedia of Chemicals and Drugs, Ninth edition. Merck and Co., Inc., Rahway, New Jersey, 1976.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH HEXACHLOROETHANE

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

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	49	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
PAPILLOMA, NOS			1 (2%)	
FIBROMA		1 (5%)		
FIBROSARCOMA	1 (5%)	2 (10%)	2 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(49)	(50)
FIBROSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)			
#SPLEEN	(20)	(20)	(49)	(49)
HEMANGIOMA		1 (5%)		
#MESENTERIC L. NODE	(20)	(18)	(46)	(44)
HEMANGIOMA	1 (5%)	1 (6%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(18)	(11)	(34)	(22)
FIBROUS HISTIOCYTOMA, METASTATIC		1 (9%)		
#LIVER	(20)	(20)	(49)	(50)
HEMANGIOSARCOMA			1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
#PANCREAS	(19)	(20)	(49)	(48)
FIBROUS HISTIOCYTOMA, METASTATIC		1 (5%)		
#STOMACH	(20)	(20)	(49)	(50)
LEIOMYOSARCOMA		1 (5%)		
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(49)	(50)
TUBULAR-CELL ADENOMA			4 (8%)	
FIBROUS HISTIOCYTOMA, METASTATIC		1 (5%)		
MIXED TUMOR, MALIGNANT			1 (2%)	
HAMARTOMA +			1 (2%)	
#URINARY BLADDER	(20)	(19)	(48)	(48)
TRANSITIONAL-CELL CARCINOMA	1 (5%)			
ENDOCRINE SYSTEM				
#PITUITARY	(18)	(19)	(42)	(44)
CHROMOPHOBE ADENOMA	4 (22%)	2 (11%)	4 (10%)	
#ADRENAL	(19)	(20)	(49)	(50)
PHEOCHROMOCYTOMA	2 (11%)	1 (5%)	2 (4%)	
MIXED TUMOR, METASTATIC			1 (2%)	
#THYROID	(20)	(20)	(48)	(48)
FOLLICULAR-CELL ADENOMA	2 (10%)	1 (5%)	2 (4%)	5 (10%)
FOLLICULAR-CELL CARCINOMA	1 (5%)	1 (5%)	1 (2%)	
C-CELL ADENOMA				1 (2%)
#PANCREATIC ISLETS	(19)	(20)	(49)	(48)
ISLET-CELL CARCINOMA	1 (5%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
MEDULLARY CARCINOMA		1 (5%)		
FIBROADENOMA	1 (5%)			
#TESTIS	(20)	(20)	(48)	(50)
INTERSTITIAL-CELL TUMOR				3 (6%)

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) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
*EPIDIDYMIS	(20)	(20)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)	
MIXED TUMOR, METASTATIC			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(20)	(20)	(49)	(50)
ASTROCYTOMA				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(20)	(50)	(50)
FIBROUS HISTIOCYTOMA, METASTATIC		1 (5%)		
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (5%)		
*TUNICA VAGINALIS	(20)	(20)	(50)	(50)
MESOTHELIOMA, NOS			2 (4%)	2 (4%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	9	5	42	39
MORIBUND SACRIFICE				1
SCHEDULED SACRIFICE		7		
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	11	8	8	10
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	9	17	11
TOTAL PRIMARY TUMORS	15	13	22	12
TOTAL ANIMALS WITH BENIGN TUMORS	6	7	12	8
TOTAL BENIGN TUMORS	10	7	14	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	4	6	1
TOTAL MALIGNANT TUMORS	5	6	6	1
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	2	
TOTAL SECONDARY TUMORS		4	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			2	2
TOTAL UNCERTAIN TUMORS			2	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 HEXACHLOROETHANE

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
FIBROMA			1 (2%)	
FIBROSARCOMA	1 (5%)			
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)	
RESPIRATORY SYSTEM				
*NASAL CAVITY	(20)	(20)	(50)	(50)
NEUROBLASTOMA			1 (2%)	
#LUNG	(20)	(20)	(50)	(49)
CORTICAL CARCINOMA, METASTATIC				1 (2%)
FIBROSARCOMA, METASTATIC	1 (5%)			
MIXED TUMOR, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(19)	(20)	(49)	(49)
FIBROSARCOMA, METASTATIC	1 (5%)			
HEMANGIOSARCOMA	1 (5%)			
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(49)
NEOPLASTIC NODULE	1 (5%)			
#PANCREAS	(20)	(20)	(50)	(49)
FIBROSARCOMA, METASTATIC	1 (5%)			

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
#STOMACH	(20)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(49)
FIBROSARCOMA, METASTATIC	1 (5%)			
MIXED TUMOR, MALIGNANT			1 (2%)	
HAMARTOMA +	1 (5%)			3 (6%)
ENDOCRINE SYSTEM				
#PITUITARY	(18)	(20)	(50)	(46)
CHROMOPHOBE ADENOMA	8 (44%)	7 (35%)	15 (30%)	6 (13%)
#ADRENAL	(20)	(20)	(50)	(49)
CORTICAL CARCINOMA		1 (5%)		1 (2%)
PHEOCHROMOCYTOMA		1 (5%)	1 (2%)	
#THYROID	(20)	(20)	(47)	(47)
FOLLICULAR-CELL ADENOMA	1 (5%)	1 (5%)	3 (6%)	3 (6%)
FOLLICULAR-CELL CARCINOMA	2 (10%)	1 (5%)		
C-CELL ADENOMA			2 (4%)	1 (2%)
#PANCREATIC ISLETS	(20)	(20)	(50)	(49)
ISLET-CELL ADENOMA			2 (4%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOMA, NOS	1 (5%)	1 (5%)		1 (2%)
ADENOCARCINOMA, NOS	2 (10%)		2 (4%)	1 (2%)
PAPILLARY ADENOCARCINOMA			1 (2%)	
FIBROADENOMA	4 (20%)	6 (30%)	13 (26%)	9 (18%)
*VAGINA	(20)	(20)	(50)	(50)
ENDOMETRIAL STROMAL SARCOMA, MET		1 (5%)		
*UTERUS	(20)	(20)	(49)	(49)
ADENOCARCINOMA, NOS		1 (5%)		
ENDOMETRIAL STROMAL POLYP		1 (5%)	3 (6%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA		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 A2 (CONTINUED)

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
#OVARY	(19)	(20)	(48)	(49)
GRANULOSA-CELL TUMOR		1 (5%)	4 (8%)	
NERVOUS SYSTEM				
#BRAIN	(20)	(20)	(50)	(49)
OLIGODENDROGLIOMA				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MESENTERY	(20)	(20)	(50)	(50)
FIBROSARCOMA, METASTATIC	1 (5%)			
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (5%)			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	5	6	21	26
MORIBUND SACRIFICE	1		2	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	14	14	27	24
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	14	33	20
TOTAL PRIMARY TUMORS	24	22	50	27
TOTAL ANIMALS WITH BENIGN TUMORS	11	11	29	18
TOTAL BENIGN TUMORS	15	17	40	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	4	6	3
TOTAL MALIGNANT TUMORS	8	4	6	3
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1	1
TOTAL SECONDARY TUMORS	5	1	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	4	
TOTAL UNCERTAIN TUMORS	1	1	4	
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 HEXACHLOROETHANE

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

	CONTROL (UNTR) 02-M161	CONTROL (VEH) 02-M151	LOW DOSE 02-M152	HIGH DOSE 02-M153
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	18	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	17	20	50	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(18)	(20)	(50)	(49)
FIBROSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
*LUNG	(18)	(20)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*LIVER	(18)	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (6%)			
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*LIVER	(18)	(20)	(50)	(49)
HEPATOCELLULAR CARCINOMA	1 (6%)	3 (15%)	15 (30%)	31 (63%)
HEMANGIOSARCOMA	1 (6%)			1 (2%)
*PANCREAS	(18)	(20)	(50)	(49)
HEMANGIOSARCOMA, METASTATIC	1 (6%)			
*STOMACH	(18)	(20)	(50)	(49)
SQUAMOUS CELL PAPILLOMA				1 (2%)
URINARY SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M161	CONTROL (VEH) 02-M151	LOW DOSE 02-M152	HIGH DOSE 02-M153
ENDOCRINE SYSTEM				
#PANCREATIC ISLETS	(18)	(20)	(50)	(49)
ISLET-CELL ADENOMA		1 (5%)		
REPRODUCTIVE SYSTEM				
*TESTIS	(18)	(20)	(49)	(48)
INTERSTITIAL-CELL TUMOR				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(18)	(20)	(50)	(49)
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@	19	15	41	17
MORIBUND SACRIFICE			1	3
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	1	5	7	29
ANIMAL MISSING				1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 02-M161	CONTROL (VEH) 02-M151	LOW DOSE 02-M152	HIGH DOSE 02-M153
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	4	17	34
TOTAL PRIMARY TUMORS	3	4	17	39
TOTAL ANIMALS WITH BENIGN TUMORS		1	1	5
TOTAL BENIGN TUMORS		1	1	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	3	16	33
TOTAL MALIGNANT TUMORS	3	3	16	34
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	
TOTAL SECONDARY TUMORS	1		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 HEXACHLOROETHANE

	CONTROL (UNTR) 02-F161	CONTROL (VEH) 02-F151	LOW DOSE 02-F154	HIGH DOSE 02-F155
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	19	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	18	20	50	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(19)	(20)	(50)	(49)
OSTEOSARCOMA	1 (5%)			
NEUROFIBROSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(18)	(20)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (6%)		1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (5%)		1 (2%)
OSTEOSARCOMA, METASTATIC	1 (6%)			
NEUROFIBROSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(19)	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)	2 (10%)	6 (12%)	5 (10%)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)	1 (2%)
#SPLEEN	(18)	(20)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#CERVICAL LYMPH NODE	(18)	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#MESENTERIC L. NODE	(18)	(20)	(50)	(49)
HEMANGIOSARCOMA				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#LUNG	(18)	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)		
#LIVER	(18)	(20)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)	

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F161	CONTROL (VEH) 02-F151	LOW DOSE 02-F154	HIGH DOSE 02-F155
#STOMACH	(18)	(20)	(50)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)		
#OVARY	(18)	(19)	(49)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(18)	(20)	(50)	(49)
HEPATOCELLULAR CARCINOMA		2 (10%)	20 (40%)	15 (31%)
HEMANGIOSARCOMA			1 (2%)	1 (2%)
#DUODENUM	(18)	(20)	(50)	(48)
ADENOMATOUS POLYP, NOS	1 (6%)			
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#THYROID	(17)	(20)	(47)	(45)
FOLLICULAR-CELL ADENOMA	2 (12%)	2 (10%)		
C-CELL ADENOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(19)	(20)	(50)	(49)
ADENOCARCINOMA, NOS			2 (4%)	1 (2%)
#UTERUS	(18)	(20)	(49)	(49)
ADENOCARCINOMA, NOS			1 (2%)	
ENDOMETRIAL STROMAL POLYP				1 (2%)
#OVARY	(18)	(19)	(49)	(49)
PAPILLARY CYSTADENOMA, NOS			1 (2%)	

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F161	CONTROL (VEH) 02-F151	LOW DOSE 02-F154	HIGH DOSE 02-F155
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@	3	4	10	13
MORIBUND SACRIFICE				2
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				1
TERMINAL SACRIFICE	17	16	40	34
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 02-F161	CONTROL (VEH) 02-F151	LOW DOSE 02-F154	HIGH DOSE 02-F155
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	8	32	26
TOTAL PRIMARY TUMORS	6	9	40	32
TOTAL ANIMALS WITH BENIGN TUMORS	3	2	3	4
TOTAL BENIGN TUMORS	4	2	3	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	6	31	24
TOTAL MALIGNANT TUMORS	2	7	37	28
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	
TOTAL SECONDARY TUMORS	1		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

APPENDIX C

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

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

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	49	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(20)	(48)	(49)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, CHRONIC	1 (5%)	2 (10%)	4 (8%)	1 (2%)
#LUNG	(20)	(20)	(49)	(50)
MINERALIZATION			5 (10%)	1 (2%)
INFLAMMATION, NOS	1 (5%)			
PNEUMONIA, ASPIRATION			1 (2%)	
INFLAMMATION, ACUTE				1 (2%)
PNEUMONIA, CHRONIC MURINE	13 (65%)	15 (75%)	24 (49%)	25 (50%)
INFLAMMATION, GRANULOMATOUS		1 (5%)		
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)	
PERIARTERITIS	1 (5%)			
CALCIFICATION, METASTATIC		1 (5%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(20)	(20)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC		1 (5%)		
#SPLEEN	(20)	(20)	(49)	(49)
HEMOSIDEROSIS	1 (5%)		1 (2%)	2 (4%)
HEMATOPOIESIS	1 (5%)	1 (5%)	3 (6%)	
#LYMPH NODE	(20)	(18)	(46)	(44)
HYPERPLASIA, NOS		1 (6%)		
#SUBMANDIBULAR L.NODE	(20)	(18)	(46)	(44)
INFLAMMATION, NOS				1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
*CERVICAL LYMPH NODE	(20)	(18)	(46)	(44)
LYMPHANGIECTASIS			1 (2%)	
INFLAMMATION, NOS	1 (5%)			
INFLAMMATION, ACUTE	1 (5%)			
HYPERPLASIA, LYMPHOID	2 (10%)		5 (11%)	
*THYMUS	(12)	(11)	(38)	(25)
ATROPHY, NOS	1 (8%)	1 (9%)		
CIRCULATORY SYSTEM				
*HEART	(20)	(20)	(49)	(49)
INFLAMMATION, CHRONIC				1 (2%)
CALCIFICATION, METASTATIC		1 (5%)		
*MYOCARDIUM	(20)	(20)	(49)	(49)
MINERALIZATION			3 (6%)	
INFLAMMATION, NOS	1 (5%)			
INFLAMMATION, FOCAL	1 (5%)			
FIBROSIS	7 (35%)		10 (20%)	1 (2%)
FIBROSIS, FOCAL	2 (10%)		1 (2%)	2 (4%)
DEGENERATION, NOS	1 (5%)		1 (2%)	
*ARTERY	(20)	(20)	(50)	(50)
MINERALIZATION		1 (5%)		
INFLAMMATION, NOS		1 (5%)		
NECROSIS, NOS		1 (5%)		
HYPERPLASIA, HEMATOPOIETIC		1 (5%)		
*AORTA	(20)	(20)	(50)	(50)
MINERALIZATION			8 (16%)	1 (2%)
MEDIAL CALCIFICATION		1 (5%)		
*CORONARY ARTERY	(20)	(20)	(50)	(50)
MINERALIZATION			1 (2%)	
*PULMONARY ARTERY	(20)	(20)	(50)	(50)
MINERALIZATION			7 (14%)	1 (2%)
*MESENTERIC ARTERY	(20)	(20)	(50)	(50)
MINERALIZATION			5 (10%)	1 (2%)
PERIARTERITIS			1 (2%)	
MEDIAL CALCIFICATION		1 (5%)		
*RENAL ARTERY	(20)	(20)	(50)	(50)
MINERALIZATION			1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(49)	(50)
HEMORRHAGE	1 (5%)			
GRANULOMA, NOS	1 (5%)			
PERIARTERITIS			1 (2%)	
PELIOSIS HEPATIS	4 (20%)	3 (15%)	3 (6%)	
METAMORPHOSIS FATTY		1 (5%)		
FOCAL CELLULAR CHANGE				2 (4%)
#HEPATIC LOBULE	(20)	(20)	(49)	(50)
METAMORPHOSIS FATTY				1 (2%)
#LIVER/CENTRILOBULAR	(20)	(20)	(49)	(50)
NECROSIS, NOS	1 (5%)		1 (2%)	
METAMORPHOSIS FATTY	2 (10%)		3 (6%)	2 (4%)
#LIVER/PERIPORTAL	(20)	(20)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (5%)		
FIBROSIS		1 (5%)		
#LIVER/HEPATOCYTES	(20)	(20)	(49)	(50)
FOCAL CELLULAR CHANGE			3 (6%)	
#BILE DUCT	(20)	(20)	(50)	(50)
DILATATION, NOS				1 (2%)
INFLAMMATION, NOS	3 (15%)		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
HYPERPLASIA, NOS	5 (25%)	5 (25%)	5 (10%)	
#PANCREAS	(19)	(20)	(49)	(48)
INFLAMMATION, ACUTE/CHRONIC		1 (5%)		
PERIARTERITIS	1 (5%)	1 (5%)	3 (6%)	2 (4%)
PERIVASCULITIS			1 (2%)	
#PANCREATIC DUCT	(19)	(20)	(49)	(48)
DISTENTION	1 (5%)			
#PANCREATIC ACINUS	(19)	(20)	(49)	(48)
ATROPHY, NOS	1 (5%)			
#ESOPHAGUS	(19)	(20)	(47)	(47)
PERFORATION, INFLAMMATORY				1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
#STOMACH	(20)	(20)	(49)	(50)
MINERALIZATION	1 (5%)		7 (14%)	1 (2%)
ULCER, FOCAL	1 (5%)		2 (4%)	2 (4%)
ULCER, ACUTE			1 (2%)	
PERIARTERITIS			1 (2%)	1 (2%)
CALCIFICATION, METASTATIC		1 (5%)		
HYPERKERATOSIS			1 (2%)	1 (2%)
ACANTHOSIS			1 (2%)	1 (2%)
#LARGE INTESTINE	(20)	(18)	(49)	(48)
MINERALIZATION			1 (2%)	
PARASITISM		2 (11%)	2 (4%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(49)	(50)
MINERALIZATION	5 (25%)		4 (8%)	1 (2%)
PYELONEPHRITIS, NOS			1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE	1 (5%)			
INFLAMMATION, CHRONIC	15 (75%)	14 (70%)	32 (65%)	25 (50%)
NEPHROPATHY, TOXIC			22 (45%)	33 (66%)
CALCIFICATION, NOS		3 (15%)		
CALCIFICATION, METASTATIC		1 (5%)		
FOCAL CELLULAR CHANGE				1 (2%)
#KIDNEY/PELVIS	(20)	(20)	(49)	(50)
INFLAMMATION, NOS				3 (6%)
INFLAMMATION, ACUTE				1 (2%)
#URINARY BLADDER	(20)	(19)	(48)	(48)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, HEMORRHAGIC			1 (2%)	
INFLAMMATION, ACUTE	1 (5%)			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (5%)			
INFLAMMATION, CHRONIC			1 (2%)	2 (4%)
HYPERPLASIA, EPITHELIAL	1 (5%)			1 (2%)
METAPLASIA, SQUAMOUS				1 (2%)
*URETHRA	(20)	(20)	(50)	(50)
INFLAMMATION, ACUTE	2 (10%)			
ENDOCRINE SYSTEM				
#PITUITARY	(18)	(19)	(42)	(44)
HYPERPLASIA, CHROMOPHOBE-CELL		1 (5%)	3 (7%)	3 (7%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
#ADRENAL CORTEX	(19)	(20)	(49)	(50)
HEMORRHAGE			1 (2%)	
DEGENERATION, NOS	12 (63%)	7 (35%)	12 (24%)	12 (24%)
ANGIECTASIS	2 (11%)	1 (5%)	3 (6%)	
#ADRENAL MEDULLA	(19)	(20)	(49)	(50)
HYPERPLASIA, FOCAL	1 (5%)			1 (2%)
#THYROID	(20)	(20)	(48)	(48)
CYSTIC FOLLICLES			4 (8%)	
FOLLICULAR CYST, NOS	1 (5%)			
INFLAMMATION, NOS	1 (5%)			
HYPERPLASIA, C-CELL			2 (4%)	1 (2%)
#PARATHYROID	(10)	(17)	(29)	(20)
HYPERPLASIA, NOS	9 (90%)	2 (12%)	14 (48%)	5 (25%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(20)	(16)	(40)	(33)
MINERALIZATION	1 (5%)		1 (3%)	
INFLAMMATION, FOCAL			1 (3%)	
INFLAMMATION, ACUTE	6 (30%)		5 (13%)	2 (6%)
INFLAMMATION, ACUTE FOCAL	1 (5%)		1 (3%)	1 (3%)
INFLAMMATION, ACUTE/CHRONIC			1 (3%)	
INFLAMMATION, CHRONIC		1 (6%)	1 (3%)	2 (6%)
#SEMINAL VESICLE	(20)	(20)	(50)	(50)
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
#TESTIS	(20)	(20)	(48)	(50)
MINERALIZATION	4 (20%)		5 (10%)	4 (8%)
HEMORRHAGE			1 (2%)	
PERIARTERITIS	1 (5%)	1 (5%)		3 (6%)
CALCIFICATION, NOS				1 (2%)
ATROPHY, NOS	5 (25%)	1 (5%)	2 (4%)	7 (14%)
HYPOSPERMATOGENESIS	7 (35%)	4 (20%)	15 (31%)	6 (12%)
#EPIDIDYMIS	(20)	(20)	(50)	(50)
MINERALIZATION			1 (2%)	
PERIARTERITIS		1 (5%)		
NECROSIS, FAT		1 (5%)		

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
NERVOUS SYSTEM				
#BRAIN	(20)	(20)	(49)	(50)
HYDROCEPHALUS, NOS				1 (2%)
HEMORRHAGE				1 (2%)
NECROSIS, FOCAL				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(20)	(20)	(50)	(50)
FIBROUS OSTEODYSTROPHY		1 (5%)		
*STERNUM	(20)	(20)	(50)	(50)
PERIARTERITIS			1 (2%)	
BODY CAVITIES				
*MEDIASTINUM	(20)	(20)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)	
ABSCESS, NOS				1 (2%)
PERIARTERITIS			1 (2%)	
*PLEURA	(20)	(20)	(50)	(50)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, ACUTE				3 (6%)
INFLAMMATION, PYOGRANULOMATOUS				1 (2%)
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, ACUTE				2 (4%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
*EPICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, ACUTE				1 (2%)
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS	1 (5%)	3 (15%)	3 (6%)	2 (4%)

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-151M	CONTROL (VEH) 01-101M	LOW DOSE 01-152M	HIGH DOSE 01-153M
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MINERALIZATION	3 (15%)			
THORAX				
PERIARTERITIS	1			
PLEURAL CAVITY				
HEMORRHAGE				1
INFLAMMATION, PYOGRANULOMATOUS				1
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			3	5
AUTO/NECROPSY/HISTO PERF				1
AUTO/NECROPSY/NO HISTO			1	

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

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

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
ULCER, NOS		1 (5%)		
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
HEMORRHAGIC CYST			1 (2%)	
RESPIRATORY SYSTEM				
#TRACHEA	(20)	(20)	(49)	(49)
INFLAMMATION, ACUTE	1 (5%)		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC	1 (5%)		2 (4%)	1 (2%)
*LUNG	(20)	(20)	(50)	(49)
ATELECTASIS			1 (2%)	
INFLAMMATION, ACUTE		1 (5%)	1 (2%)	
ABSCESS, NOS		1 (5%)		1 (2%)
PNEUMONIA, CHRONIC MURINE	18 (90%)	18 (90%)	32 (64%)	29 (59%)
CALCIFICATION, METASTATIC		1 (5%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(20)	(20)	(50)	(49)
HYPERPLASIA, HEMATOPOIETIC		4 (20%)		
#SPLEEN	(19)	(20)	(49)	(49)
INFLAMMATION, ACUTE			1 (2%)	
HEMOSIDEROSIS			1 (2%)	
HEMATOPOIESIS	3 (16%)	2 (10%)	3 (6%)	2 (4%)
#MANDIBULAR L. NODE	(19)	(20)	(47)	(49)
INFLAMMATION, NOS		1 (5%)		
INFLAMMATION, ACUTE		1 (5%)		

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
#CERVICAL LYMPH NODE	(19)	(20)	(47)	(49)
HYPERPLASIA, NOS	1 (5%)			
HYPERPLASIA, LYMPHOID	2 (11%)	1 (5%)	1 (2%)	1 (2%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(20)	(20)	(50)	(49)
FIBROSIS	1 (5%)	1 (5%)		
DEGENERATION, NOS	1 (5%)			
*ARTERY	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION		1 (5%)		
CALCIFICATION, METASTATIC		1 (5%)		
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(49)
PELIOSIS HEPATIS	1 (5%)		1 (2%)	
FOCAL CELLULAR CHANGE	1 (5%)	1 (5%)	5 (10%)	1 (2%)
ANGIECTASIS			1 (2%)	2 (4%)
#LIVER/CENTRILOBULAR	(20)	(20)	(50)	(49)
NECROSIS, FOCAL				1 (2%)
#LIVER/HEPATOCYTES	(20)	(20)	(50)	(49)
FOCAL CELLULAR CHANGE				1 (2%)
*BILE DUCT	(20)	(20)	(50)	(50)
DILATATION, NOS	3 (15%)			1 (2%)
INFLAMMATION, CHRONIC	1 (5%)			
HYPERPLASIA, NOS	5 (25%)	6 (30%)	2 (4%)	
ANGIECTASIS		1 (5%)		
#PANCREAS	(20)	(20)	(50)	(49)
INFLAMMATION, ACUTE HEMORRHAGIC			1 (2%)	
PERIARTERITIS	2 (10%)	1 (5%)		
ATROPHY, NOS	1 (5%)			
#ESOPHAGUS	(19)	(20)	(50)	(48)
PERFORATION, INFLAMMATORY			2 (4%)	4 (8%)
#STOMACH	(20)	(20)	(50)	(49)
ULCER, FOCAL	3 (15%)		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
PERIARTERITIS			1 (2%)	
CALCIFICATION, METASTATIC		1 (5%)		

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

TABLE C2 (CONTINUED)

CON

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
#SMALL INTESTINE	(20)	(20)	(48)	(48)
ULCER, NOS		1 (5%)		
#LARGE INTESTINE	(20)	(20)	(49)	(49)
NEMATODIASIS	1 (5%)			
PARASITISM		1 (5%)	2 (4%)	
#COLON	(20)	(20)	(49)	(49)
PARASITISM		1 (5%)		
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(49)
MINERALIZATION	7 (35%)	2 (10%)	2 (4%)	
HYDRONEPHROSIS		1 (5%)		
PYELONEPHRITIS, NOS		1 (5%)		
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC	8 (40%)	4 (20%)	18 (36%)	20 (41%)
NEPHROPATHY		1 (5%)		
NEPHROPATHY, TOXIC			9 (18%)	29 (59%)
INFARCT, FOCAL				1 (2%)
CALCIFICATION, NOS		7 (35%)		
#KIDNEY/PELVIS	(20)	(20)	(50)	(49)
INFLAMMATION, NOS				1 (2%)
#URINARY BLADDER	(18)	(20)	(49)	(48)
INFLAMMATION, CHRONIC			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(18)	(20)	(50)	(46)
CYST, NOS			2 (4%)	
HYPERPLASIA, CHROMOPHOBE-CELL	4 (22%)	2 (10%)	4 (8%)	2 (4%)
#ADRENAL CORTEX	(20)	(20)	(50)	(49)
DEGENERATION, NOS	5 (25%)	6 (30%)	10 (20%)	4 (8%)
ANGIECTASIS	10 (50%)	8 (40%)	10 (20%)	12 (24%)
#THYROID	(20)	(20)	(47)	(47)
CYSTIC FOLLICLES			4 (9%)	1 (2%)
FOLLICULAR CYST, NOS	1 (5%)			
HYPERPLASIA, C-CELL	1 (5%)		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
*PARATHYROID	(12)	(18)	(19)	(21)
HYPERPLASIA, NOS	8 (67%)		3 (16%)	2 (10%)
REPRODUCTIVE SYSTEM				
*VAGINA	(20)	(20)	(50)	(50)
PROLAPSE			1 (2%)	
*UTERUS	(20)	(20)	(49)	(49)
HYDROMETRA			4 (8%)	4 (8%)
*UTERUS/ENDOMETRIUM	(20)	(20)	(49)	(49)
INFLAMMATION, NOS		1 (5%)	1 (2%)	
INFLAMMATION, ACUTE	2 (10%)		1 (2%)	
HYPERPLASIA, CYSTIC	1 (5%)			1 (2%)
*OVARY	(19)	(20)	(48)	(49)
CYST, NOS			1 (2%)	
FOLLICULAR CYST, NOS		1 (5%)		1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(20)	(50)	(50)
PERIARTERITIS		1 (5%)		
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (5%)			
*PLEURA	(20)	(20)	(50)	(50)
INFLAMMATION, ACUTE			3 (6%)	
INFLAMMATION, ACUTE FIBRINOUS			1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS			2 (4%)	5 (10%)

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 01-151F	CONTROL (VEH) 01-101F	LOW DOSE 01-154F	HIGH DOSE 01-155F
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, ACUTE			4 (8%)	
INFLAMMATION, CHRONIC				2 (4%)
*EPICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, ACUTE			2 (4%)	
INFLAMMATION, ACUTE FIBRINOUS			1 (2%)	
INFLAMMATION, CHRONIC				2 (4%)
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS	2 (10%)		1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
MINERALIZATION	1 (5%)			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			3	8
AUTO/NECROPSY/NO HISTO				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 HEXACHLOROETHANE

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

	CONTROL (UNTR) 02-M161	CONTROL (VEH) 02-M151	LOW DOSE 02-M152	HIGH DOSE 02-M153
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	18	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	17	20	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(18)	(20)	(50)	(49)
EPIDERMAL INCLUSION CYST	1 (6%)		2 (4%)	
INFLAMMATION, NOS		1 (5%)		1 (2%)
*SUBCUT TISSUE	(18)	(20)	(50)	(49)
ABSCESS, NOS	1 (6%)	1 (5%)	6 (12%)	1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(17)	(19)	(49)	(49)
INFLAMMATION, NOS			1 (2%)	1 (2%)
#LUNG	(18)	(20)	(50)	(49)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)	1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (5%)	12 (24%)	2 (4%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(18)	(19)	(50)	(49)
AMYLOIDOSIS	10 (56%)	6 (32%)	8 (16%)	
HEMATOPOIESIS			1 (2%)	1 (2%)
#MESENTERIC L. NODE	(16)	(19)	(47)	(49)
INFLAMMATION, NOS	3 (19%)	3 (16%)	14 (30%)	3 (6%)
#THYMUS	(10)	(5)	(26)	(36)
INFLAMMATION, NOS				1 (3%)
CIRCULATORY SYSTEM				
#HEART	(18)	(20)	(50)	(49)
CALCIUM DEPOSIT		1 (5%)	1 (2%)	

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M161	CONTROL (VEH) 02-M151	LOW DOSE 02-M152	HIGH DOSE 02-M153
#HEART/ATRIUM	(18)	(20)	(50)	(49)
THROMBUS, ORGANIZED			1 (2%)	
#MYOCARDIUM	(18)	(20)	(50)	(49)
FIBROSIS			2 (4%)	
DEGENERATION, NOS			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(15)	(19)	(49)	(48)
CYST, NOS				1 (2%)
ATROPHY, NOS				1 (2%)
#LIVER	(18)	(20)	(50)	(49)
THROMBUS, ORGANIZED			1 (2%)	1 (2%)
INFLAMMATION, NOS		1 (5%)	3 (6%)	
FIBROSIS		1 (5%)		
NECROSIS, NOS			1 (2%)	
INFARCT, NOS				1 (2%)
AMYLOIDOSIS	1 (6%)		1 (2%)	
#LIVER/CENTRILOBULAR	(18)	(20)	(50)	(49)
NECROSIS, NOS			1 (2%)	
*BILE DUCT	(18)	(20)	(50)	(49)
HYPERPLASIA, NOS		1 (5%)		
#PANCREAS	(18)	(20)	(50)	(49)
CYST, NOS				1 (2%)
INFLAMMATION, NOS		1 (5%)		
#STOMACH	(18)	(20)	(50)	(49)
ULCER, FOCAL				2 (4%)
#LARGE INTESTINE	(18)	(20)	(49)	(49)
NEMATODIASIS		1 (5%)		
#COLON	(18)	(20)	(49)	(49)
NEMATODIASIS			2 (4%)	

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M161	CONTROL (VEH) 02-M151	LOW DOSE 02-M152	HIGH DOSE 02-M153
URINARY SYSTEM				
#KIDNEY	(18)	(20)	(50)	(49)
HYDRONEPHROSIS		1 (5%)	4 (8%)	
CYST, NOS			6 (12%)	2 (4%)
PYELONEPHRITIS, NOS	4 (22%)	2 (10%)	2 (4%)	
INFLAMMATION, CHRONIC	12 (67%)	16 (80%)	33 (66%)	9 (18%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
NEPHROPATHY, TOXIC			49 (98%)	47 (96%)
AMYLOIDOSIS	9 (50%)	9 (45%)	7 (14%)	
CALCIUM DEPOSIT			2 (4%)	
#URINARY BLADDER	(18)	(20)	(49)	(48)
INFLAMMATION, NOS	4 (22%)	1 (5%)	1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(14)	(17)	(43)	(46)
INFLAMMATION, NOS				1 (2%)
#THYROID	(16)	(18)	(46)	(45)
FOLLICULAR CYST, NOS	1 (6%)			
REPRODUCTIVE SYSTEM				
*PREPUCE	(18)	(20)	(50)	(49)
INFLAMMATION, NOS		1 (5%)		
#PROSTATE	(18)	(20)	(49)	(48)
INFLAMMATION, NOS	3 (17%)			
*SEMINAL VESICLE	(18)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (6%)			
#TESTIS	(18)	(20)	(49)	(48)
CALCIUM DEPOSIT				1 (2%)
ATROPHY, NOS			2 (4%)	5 (10%)
*EPIDIDYMIS	(18)	(20)	(50)	(49)
GRANULOMA, SPERMATIC		1 (5%)	1 (2%)	
NERVOUS SYSTEM				
NONE				

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 02-M161	CONTROL (VEH) 02-M151	LOW DOSE 02-M152	HIGH DOSE 02-M153
SPECIAL SENSE ORGANS				
*EYE	(18)	(20)	(50)	(49)
SYNECHIA, ANTERIOR				1 (2%)
SYNECHIA, POSTERIOR				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(18)	(20)	(50)	(49)
AMYLOIDOSIS	4 (22%)	1 (5%)	3 (6%)	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		3	1	1
ANIMAL MISSING/NO NECROPSY				1
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY	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 HEXACHLOROETHANE

	CONTROL (UNTR) 02-F161	CONTROL (VEH) 02-F151	LOW DOSE 02-F154	HIGH DOSE 02-F155
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	19	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	20	50	49
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(18)	(20)	(50)	(49)
PNEUMONIA, CHRONIC MURINE	1 (6%)	1 (5%)	13 (26%)	5 (10%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(18)	(20)	(50)	(49)
HEMATOPOIESIS			2 (4%)	
#CERVICAL LYMPH NODE	(18)	(20)	(50)	(49)
INFLAMMATION, NOS			1 (2%)	
#MESENTERIC L. NODE	(18)	(20)	(50)	(49)
INFLAMMATION, NOS			1 (2%)	4 (8%)
ANGIECTASIS			1 (2%)	
CIRCULATORY SYSTEM				
#MYOCARDIUM	(18)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (6%)			
#ENDOCARDIUM	(18)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (6%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(18)	(19)	(49)	(48)
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-F161	CONTROL (VEH) 02-F151	LOW DOSE 02-F154	HIGH DOSE 02-F155
#LIVER	(18)	(20)	(50)	(49)
THROMBUS, ORGANIZED			1 (2%)	
PELIOSIS HEPATIS			1 (2%)	
AMYLOIDOSIS			1 (2%)	
METAMORPHOSIS FATTY		1 (5%)		
HYPERPLASIA, NODULAR				1 (2%)
#STOMACH	(18)	(20)	(50)	(48)
HYPERKERATOSIS			1 (2%)	1 (2%)
ACANTHOSIS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(18)	(20)	(50)	(49)
CYST, NOS		1 (5%)		
INFLAMMATION, CHRONIC		3 (15%)		1 (2%)
NEPHROPATHY, TOXIC			50 (100%)	45 (92%)
AMYLOIDOSIS			1 (2%)	
ENDOCRINE SYSTEM				
#THYROID	(17)	(20)	(47)	(45)
INFLAMMATION, NOS	1 (6%)			
HYPERPLASIA, C-CELL				1 (2%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)	
REPRODUCTIVE SYSTEM				
#UTERUS	(18)	(20)	(49)	(49)
HYDROMETRA	4 (22%)	5 (25%)	8 (16%)	9 (18%)
INFLAMMATION, NOS	1 (6%)	1 (5%)		1 (2%)
#UTERUS/ENDOMETRIUM	(18)	(20)	(49)	(49)
INFLAMMATION, NOS			1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	5 (28%)	9 (45%)	8 (16%)	6 (12%)
#OVARY	(18)	(19)	(49)	(49)
CYST, NOS	2 (11%)	6 (32%)	7 (14%)	5 (10%)
FOLLICULAR CYST, NOS			4 (8%)	2 (4%)
INFLAMMATION, NOS	1 (6%)	1 (5%)	2 (4%)	2 (4%)
NERVOUS SYSTEM				
NONE				

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 02-F161	CONTROL (VEH) 02-F151	LOW DOSE 02-F154	HIGH DOSE 02-F155
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(19)	(20)	(50)	(49)
AMYLOIDOSIS		1 (5%)		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	1		2
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY	1			1

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

Review of the Bioassay of Hexachloroethane* 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 Hexachloroethane was reviewed.

The primary reviewer agreed with the staff's conclusion that Hexachloroethane was carcinogenic in the treated mice, under the conditions of test, but there was no evidence for such an effect in the treated rats. He opined that the failure to see a carcinogenic effect in the rats may have been due to their early death, as evidenced by the association between increased dosage and accelerated mortality. Despite the overt toxicity produced by the treatment, the primary reviewer agreed with the conclusion that Hexachloroethane was carcinogenic in the treated mice. He added that Hexachloroethane may pose a carcinogenic risk to humans and that notification of the bioassay results should be given to the National Institute for Occupational Safety and Health, Occupational Safety and Health Administration, and exposed workers. (All bioassay reports are routinely sent to the relevant regulatory agencies.)

The secondary reviewer, also agreed with the conclusions given in the report. She noted the controversy regarding the implications to humans of mouse hepatocarcinogens.

A Subgroup member moved that the bioassay report on Hexachloroethane be accepted as written. The motion was seconded and approved unanimously. (In reviewing the minutes, Dr. Rowe noted that he had abstained during the vote on the motion.)

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

---

* 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.

DHEW Publication No. (NIH) 78-1318