National Cancer Institute
CARCINOGENESIS
Technical Report Series
No.147
1978

BIOASSAY OF MEXACARBATE FOR POSSIBLE CARCINOGENICITY

CAS No.315-18-4

NCI-CG-TR-147

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

BIOASSAY OF

MEXACARBATE

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) 78-1703

REPORT ON THE BIOASSAY OF MEXACARBATE 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 mexacarbate 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 chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly 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 mexacarbate 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. W. A. Kelly and Dr. L. M. Nelson (consultants for Hazleton Laboratories) 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 (6,9) and Mr.

R. M. Helfand (6), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (10).

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), task leader Dr. M. R. Kornreich (6,11), senior biologist Ms. P. Walker (6), biochemist Dr. B. Fuller (6), and the technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

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 (1,11), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,12), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (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. Now with the Solar Energy Research Institute, Cole Boulevard, Golden, Colorado.

10. 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.

11. Now with Clement Associates, Inc., 1010 Wisconsin Avenue, N.W., Washington, D.C.

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

SUMMARY

A bioassay of technical-grade mexacarbate for possible carcinogenicity was conducted using Osborne-Mendel rats and B6C3F1 mice. Mexacarbate was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The time-weighted average high and low dietary concentrations of mexacarbate were 418 and 209 ppm for male rats, 678 and 339 ppm for female rats, 654 and 327 ppm for male mice and 135 and 68 ppm for female mice. After a 78-week period of chemical administration, observation of rats continued for an additional 33 to 34 weeks and observation of mice continued for 14 to 15 additional weeks. For each species, 20 animals of each sex were placed on test as controls.

All groups except the male control mice survived sufficiently long to be at risk from late-appearing tumors. Because of poor survival of the male control mice, a pooled control group was used for statistical analysis of tumor incidence in male mice.

The possibility that female mice in this study did not receive maximum tolerated dosages of mexacarbate should be considered. Administration of mexacarbate had no significant effect on survival or body weights of female mice.

No neoplasms occurred in statistically significant increased incidences when dosed rats were compared to controls.

Among male mice surviving at least 56 weeks, significant associations with dietary concentration were indicated by the Cochran-Armitage test for hepatocellular carcinomas, for subcutaneous fibrosarcomas and for fibromas of the skin. In none of these cases, however, were these results supported by significant Fisher exact tests.

Under the conditions of this bioassay, sufficient evidence was not obtained for the carcinogenicity of mexacarbate for Osborne-Mendel rats or B6C3F1 mice.

TABLE OF CONTENTS

		Page
I.	INTRODUCTION	1
II.	MATERIALS AND METHODS	4
	A. Chemicals	4
	B. Dietary Preparation	4
	C. Animals	5
	D. Animal Maintenance	5
	E. Selection of Initial Concentrations	7
	F. Experimental Design	8
	G. Clinical and Histopathologic Examinations	12
	H. Data Recording and Statistical Analyses	13
III.	CHRONIC TESTING RESULTS: RATS	18
	A. Body Weights and Clinical Observations	18
	B. Survival	20
	C. Pathology	20
	D. Statistical Analyses of Results	22
IV.	CHRONIC TESTING RESULTS: MICE	30
	A. Body Weights and Clinical Observations	30
	B. Survival	30
	C. Pathology	33
	D. Statistical Analyses of Results	34
V.	DISCUSSION	45
VI.	BIBLIOGRAPHY	47
APPENDIX A	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH MEXACARBATE	A-1
APPENDIX B	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH MEXACARBATE	B-1
APPENDIX C	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH MEXACARBATE	C-1
APPENDIX D	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH MEXACARBATE	D-1

LIST OF ILLUSTRATIONS

Figure Number		Page
1	CHEMICAL STRUCTURE OF MEXACARBATE	2
2	GROWTH CURVES FOR MEXACARBATE CHRONIC STUDY RATS	19
3	SURVIVAL COMPARISONS OF MEXACARBATE CHRONIC STUDY RATS	21
4	GROWTH CURVES FOR MEXACARBATE CHRONIC STUDY MICE	31
5	SURVIVAL COMPARISONS OF MEXACARBATE CHRONIC STUDY MICE	32

LIST OF TABLES

Table Number		Page
1	DESIGN SUMMARY FOR OSBORNE-MENDEL RATS--MEXACARBATE FEEDING EXPERIMENT	9
2	DESIGN SUMMARY FOR B6C3F1 MICE--MEXACARBATE FEEDING EXPERIMENT	10
3	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH MEXACARBATE	23
4	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH MEXACARBATE	26
5	TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH MEXACARBATE	35
6	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH MEXACARBATE	40
A1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH MEXACARBATE	A-3

LIST OF TABLES (Concluded)

Table Number		Page
A2	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH MEXACARBATE	A-6
B1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH MEXACARBATE	B-3
B2	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH MEXACARBATE	B-6
C1	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH MEXACARBATE	C-3
C2	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH MEXACARBATE	C-8
D1	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH MEXACARBATE	D-3
D2	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH MEXACARBATE	D-7

I. INTRODUCTION

Mexacarbate (Figure 1) (NCI No. C00544) is one of a group of agricultural pesticides that scientists at the National Cancer Institute noted, in the late 1960s, had not been adequately tested for carcinogenicity. In 1969, the Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health (U.S. Department of Health, Education, and Welfare, 1969) recommended first-priority testing for mexacarbate. This recommendation was partially based upon the inconclusive results of a study by Bionetics Research Laboratories (1968) in which an elevated incidence of tumors was observed in mexacarbate-treated mice.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 4-(dimethylamino)-3,5-dimethylphenyl methylcarbamate.* It is also called 4-dimethylamino-3,5-xylyl methylcarbamate. Mexacarbate is a phenylcarbamate insecticide (Matsumura, 1975).

Production of mexacarbate has been suspended since 1974 by Dow Chemical Company, the sole producer, as a result of high production costs and an inadequate market (Gray, 1977). Prior to that, high toxicity to animals resulted in the recommendation that mexacarbate not be used by homeowners (Virginia Polytechnic Institute, 1968). Mexacarbate has been used as an insecticide and as a molluscicide for

*The CAS registry number is 315-18-4.

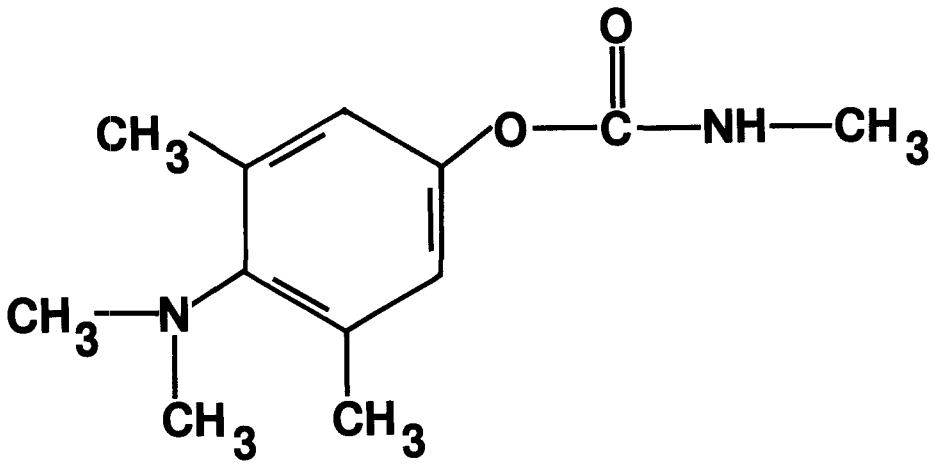


FIGURE 1
CHEMICAL STRUCTURE OF MEXACARBATE

the control of pests on lawns, turf, and flowers (U.S. Environmental Protection Agency, 1974).

II. MATERIALS AND METHODS

A. Chemicals

Technical-grade mexacarbate (Zectran®) was purchased from Dow Chemical Company, Midland, Michigan. Chemical analysis was performed by Hazleton Laboratories America, Inc., Vienna, Virginia. The experimentally determined melting point (61° to 78°C) had a 17° spread and differed from the literature value of 85°C (Windholz, 1976); this suggested the presence of impurities. Gas-liquid chromatography (GLC), which indicated the presence of five minor peaks, confirmed the presence of impurities.

The same material, retested a year later, had a melting point range of 60° to 85°C. GLC using the same methodology as the first year, showed the presence of three peaks of major prominence and twelve minor peaks; the three major peaks accounted for approximately 78, 12, and 8 percent of the total area. The 78 percent peak was assumed to be mexacarbate.

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

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinois) plus 2 percent Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) by weight. Fresh mixtures of mexacarbate in corn oil were

prepared each week and stored in the dark. These mixtures of mexacarbate in corn oil were incorporated into the appropriate amount of laboratory diet in a twin-shell blender fitted with an accelerator bar.

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 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 to 15 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 and sipper tubes were provided three times a week. Food and water were available ad libitum.

Dosed rats and their controls were housed in the same room with other rats receiving diets containing* dioxathion (78-34-2); dicofol (115-32-2); nitrofen (1836-75-5); endosulfan (115-29-7); and trifluralin (1582-09-8).

All mice, including controls, were housed in the same room as other mice receiving diets containing chlorobenzilate (510-15-6); dioxathion (78-34-2); DDT (50-29-3); methoxychlor (72-43-5); DDE (72-55-9); TDE (72-54-8); dicofol (115-32-2); pentachloronitrobenzene (82-68-8); clonitralid (1420-04-8); nitrofen (1836-75-5); endosulfan (115-29-7); trifluralin (1582-0908); amitrole (61-82-5); acetylaminofluorene (53-96-3); safrole (94-59-7); and sulfallate (95-06-7).

---

*CAS registry numbers are given in parentheses.

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of mexacarbate for addition to the diets of dosed 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. Mexacarbate was premixed with a small amount of corn oil. This mixture was then incorporated into the laboratory diet and fed *ad libitum* to five of the six rat groups and five of the six mouse groups in concentrations of 100, 178, 316, 562, and 1000 ppm. The sixth group of each species served as a control group, receiving only the basal diet of corn oil and laboratory chow. The dosed dietary preparations were administered for a period of 6 weeks, followed by a 2-week observation period during which all animals were fed the basal diet.

A concentration inducing no mortality and resulting in a depression in mean group body weight of approximately 20 percent relative to controls was selected as the initial high concentration for the chronic study.

In rats, depressions in mean body weight at 316, 562, and 1000 ppm were 4, 35, and 35 percent, respectively, in the males and 12, 14 and 24 percent, in the females. No deaths occurred at any level. The high doses selected for administration to rats in the chronic study were 375 and 600 ppm for males and females, respectively.

In male mice, depressions in mean body weight at 316 and 562 ppm were 20 and 15 percent, respectively. In the female mice, depressions in mean body weight at 100, 178, and 316 ppm were 13, 45, and 35 percent, respectively. No deaths occurred among male or female mice at any level. The high concentrations selected for administration to mice in the chronic study were 450 and 74 ppm for males and females, respectively.

F. Experimental Design

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

All rats shared the same median date of birth and were approximately 6 weeks old when the bioassay began. The concentrations of mexacarbate initially utilized for male rats were 375 and 188 ppm. Throughout this report those males initially receiving the former concentration are referred to as the high dose group and those initially receiving the latter concentration are referred to as the low dose group. In week 18 of the study, the high and low concentrations administered to the male rats were increased to 430 and 215 ppm, respectively, as the animals appeared to be tolerating the initial concentrations administered. For female rats, the initial dietary concentrations administered were 600 and 300 ppm. Throughout this report those female rats initially receiving the former concentration are referred to as the high dose group and those initially

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
MEXACARBATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	MEXACARBATE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		110	0
LOW DOSE	50	188	17		209
		215	61		
		0		33	
HIGH DOSE	50	375	17		418
		430	61		
		0		33	
FEMALE					
CONTROL	20	0		110	0
LOW DOSE	50	300	17		339
		350	61		
		0		33	
HIGH DOSE	50	600	17		678
		700	61		
		0		34	

[a]Concentrations given in parts per million.

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

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
MEXACARBATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	MEXACARBATE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		91	0
LOW DOSE	50	225	6		327
		275	14		
		350	58		
		0		14	
HIGH DOSE	50	450	6		654
		550	14		
		700	58		
		0		15	
FEMALE					
CONTROL	20	0		91	0
LOW DOSE	50	37	6		68
		50	14		
		75	58		
		0		14	
HIGH DOSE	50	74	6		135
		100	14		
		150	58		
		0		14	

[a]Concentrations given in parts per million.

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

receiving the latter concentration are referred to as the low dose group. During week 18, the high and low concentrations administered to female rats were increased to 700 and 350 ppm, respectively, and these concentrations were maintained until termination of chemical administration (week 78). Final observations of all rats were made 32 weeks after chemical administration was discontinued.

All mice shared the same median date of birth and were approximately 6 weeks old on the first day of the bioassay. The initial concentrations administered to the male mice were 450 and 225 ppm. Throughout this report those male mice initially receiving the former concentration are referred to as the high dose group and those initially receiving the latter concentration are referred to as the low dose group. Initial concentrations administered to the female mice were 74 and 37 ppm. Throughout this report those female mice initially receiving the former concentration are referred to as the high dose group and those initially receiving the latter concentration are referred to as the low dose group. During week 7, the high and low concentrations were increased to 550 and 275 ppm for the males, and to 100 and 50 ppm for the females. In week 21 the high and low concentrations were again increased, to 700 and 350 ppm for the male mice, and to 150 and 75 ppm for the females. The concentration increases were made in response to apparent toleration of the chemical by the animals. The levels administered during week 21 were maintained throughout the remainder of the dosing period. Final

observations of mice were made 12 weeks after chemical administration was discontinued.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. 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. From the first day, all animals were inspected daily for mortality. The presence of tissue masses was determined by observation and palpation of each animal.

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

Tissues 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.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph

nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, uterus, mammary gland, and ovary.

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.

H. 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) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when 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 when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early

tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

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

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

and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

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

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

A slight dose-related mean body weight depression was observed in male and female rats throughout most of the dosing period (Figure 2), but was not clearly apparent during the observation period following chemical administration. In female rats dose-related mean body weight depression was extremely slight and body weight curves for the three female groups tended to converge as the study progressed. 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.

No clinical signs were observed during the first 20 weeks of the study except for occasional hunched appearance, reddened or squinted eyes, and abdominal urine stains in a few dosed rats. From week 22 to cessation of compound administration (week 78) a hunched appearance was observed in an increasing number of dosed rats. During the same period, abdominal urine stains were observed in approximately 30 to 80 percent of the high dose females and in 10 to 40 percent of the low dose females. Abdominal urine stains were observed at comparable rates in the controls (males and females) and the dosed male rats. Respiratory signs characterized by labored respiration, wheezing, and/or nasal discharge were present at a low incidence in all groups. Other signs often associated with aging in laboratory rats were observed at similar frequencies in the control and dosed animals during

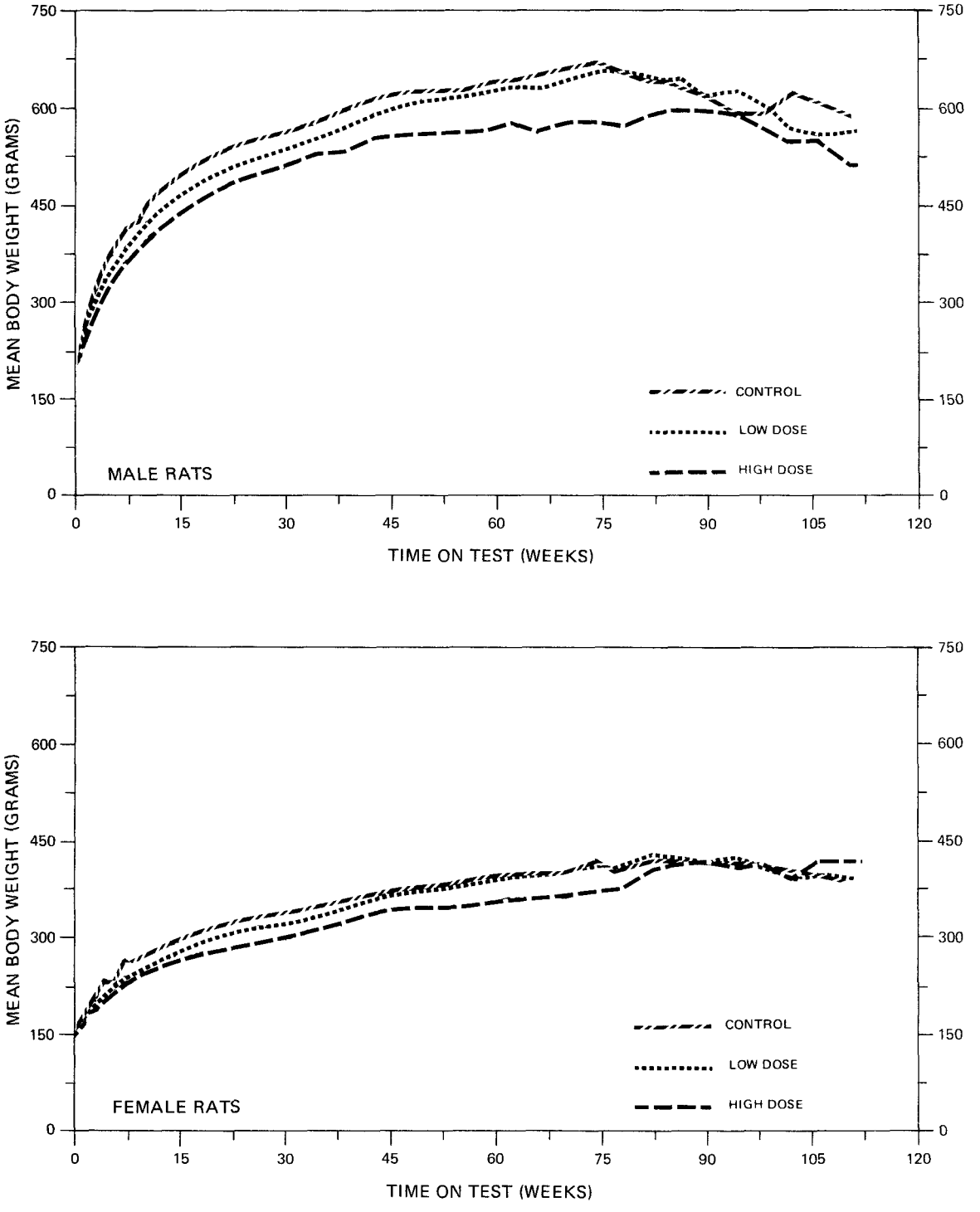


FIGURE 2
GROWTH CURVES FOR MEXACARBATE CHRONIC STUDY RATS

the second year. These included sores on the body and/or extremities, localized alopecia, rough or stained fur, reddish discharge around body orifices, tissue masses, and palpable nodules.

B. Survival

The estimated probabilities of survival for male and female rats in the control and mexacarbate-dosed groups are shown in Figure 3. The Tarone tests for association between dosage and mortality were not significant for either male or female rats.

Among the male rats 64 percent (32/50) of the high dose and 48 percent (24/50) of the low dose groups survived on test over 105 weeks. Fifty percent (10/20) of the control rats survived on test over 98 weeks. Among the female rats 68 percent (34/50) of the high dose, 68 percent (34/50) of the low dose, and 65 percent (13/20) of the control group survived on test at least 110 weeks. Thus, adequate numbers of rats were at risk from late-developing tumors.

C. Pathology

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

Malignant lymphoma, histiocytic type, occurred in 2/49 (4 percent) low dose males, 2/48 (4 percent) high dose males, 6/50 (12 percent) low dose females, and 1/50 (2 percent) high dose females. No histiocytic malignant lymphomas were observed in male or female

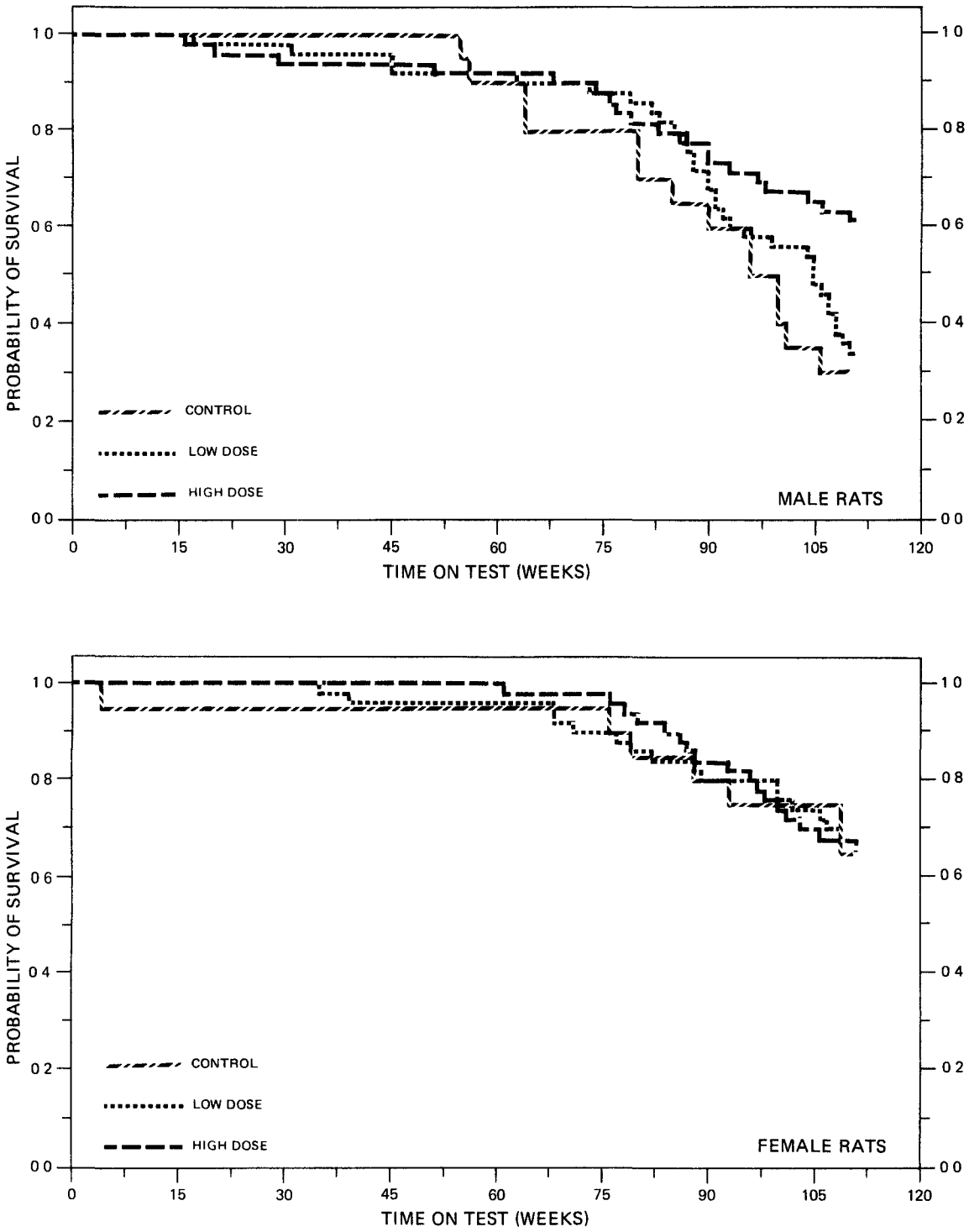


FIGURE 3
SURVIVAL COMPARISONS OF MEXACARBATE CHRONIC STUDY RATS

control rats. Leukemia, granulocytic type, occurred in one low dose male, one low dose female, and one high dose female. Leukemia was not observed in high dose males or in control rats of either sex. However, since granulocytic leukemia and multiple malignant lymphoma can occur spontaneously in the Osborne-Mendel rat at incidences similar to those observed in this study these neoplasms were not considered to be related to compound administration.

Other neoplasms occurred in rats in this study with essentially comparable frequency in the control and dosed animals. Inflammatory, degenerative, and proliferative lesions as seen in the control and dosed animals were similar in number and type to lesions that occur naturally in aged Osborne-Mendel rats. The nonneoplastic lesions that occurred most frequently were chronic murine pneumonia and chronic inflammation of the kidneys.

This pathologic examination provided no evidence for the carcinogenicity of mexacarbate in Osborne-Mendel rats under the conditions of this bioassay.

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 mexacarbate-dosed groups of either sex is included.

For females the Cochran-Armitage test indicated a significant ($P = 0.031$) negative association between dosage and the incidence

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	1/20(0.05)	2/49(0.04)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.816	0.417
Lower Limit	---	0.046	0.006
Upper Limit	---	47.195	32.057
Weeks to First Observed Tumor	55	110	111
Subcutaneous Tissue: Fibrosarcoma[b]	2/20(0.10)	1/49(0.02)	0/48(0.00)
P Values[c]	P = 0.037(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.204	0.000
Lower Limit	---	0.004	0.000
Upper Limit	---	3.754	1.400
Weeks to First Observed Tumor	85	109	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	0/20(0.00)	3/49(0.06)	2/48(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.256	0.128
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	79	106

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	3/20(0.15)	11/49(0.22)	7/47(0.15)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.497	0.993
Lower Limit	---	0.460	0.261
Upper Limit	---	7.741	5.533
Weeks to First Observed Tumor	96	104	90
Pancreatic Islets: Islet-Cell Adenoma[b]	0/20(0.00)	0/49(0.00)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.267
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	77
Salivary Gland: Mixed Tumor, Benign[b]	0/14(0.00)	2/40(0.05)	0/40(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.153	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	90	---

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	1/20(0.05)	2/48(0.04)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.833	0.426
Lower Limit	---	0.047	0.006
Upper Limit	---	48.155	32.720
Weeks to First Observed Tumor	110	104	111

[a]Treated groups received time-weighted average doses of 209 or 418 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.

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	0/20(0.00)	6/50(0.12)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Departure From Linear Trend[e]	P = 0.016	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.666	0.022
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	102	88
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	0/20(0.00)	7/50(0.14)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Departure From Linear Trend[e]	P = 0.019	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.809	0.123
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	79	88
Pituitary: Chromophobe Adenoma[b]	9/20(0.45)	14/49(0.29)	10/49(0.20)
P Values[c]	P = 0.031(N)	N.S.	P = 0.040(N)
Relative Risk (Control)[d]	---	0.635	0.454
Lower Limit	---	0.324	0.208
Upper Limit	---	1.427	1.092
Weeks to First Observed Tumor	79	79	87

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenoma NOS[b]	0/20(0.00)	2/50(0.04)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.123	0.250
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	84
Mammary Gland: Adenocarcinoma NOS[b]	0/20(0.00)	3/50(0.06)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure From Linear Trend[e]	P = 0.047	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.250	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	39	---
Mammary Gland: Fibroadenoma[b]	5/20(0.25)	12/50(0.24)	12/50(0.24)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.960	0.960
Lower Limit	---	0.377	0.377
Upper Limit	---	3.140	3.140
Weeks to First Observed Tumor	109	68	93

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenoma NOS, Adenocarcinoma NOS or Fibroadenoma[b]	5/20(0.25)	17/50(0.34)	15/50(0.30)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.360	1.200
Lower Limit	---	0.580	0.499
Upper Limit	---	4.184	3.784
Weeks to First Observed Tumor	109	39	84
Uterus: Endometrial Stromal Polyp[b]	1/20(0.05)	0/49(0.00)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.400
Lower Limit	---	0.000	0.005
Upper Limit	---	7.624	30.802
Weeks to First Observed Tumor	110	---	112

[a]Treated groups received time-weighted average doses of 339 or 678 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 $P < 0.05$.

of pituitary chromophobe adenomas. The Fisher exact tests, however, were not significant under the Bonferroni criterion. Similarly, for males the Cochran-Armitage test indicated a significant negative association between dosage and the incidence of fibrosarcomas of the subcutaneous tissue. The Fisher exact tests, however, were not significant.

Based upon these statistical results, there was no evidence of the carcinogenicity of mexacarbate in rats.

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

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

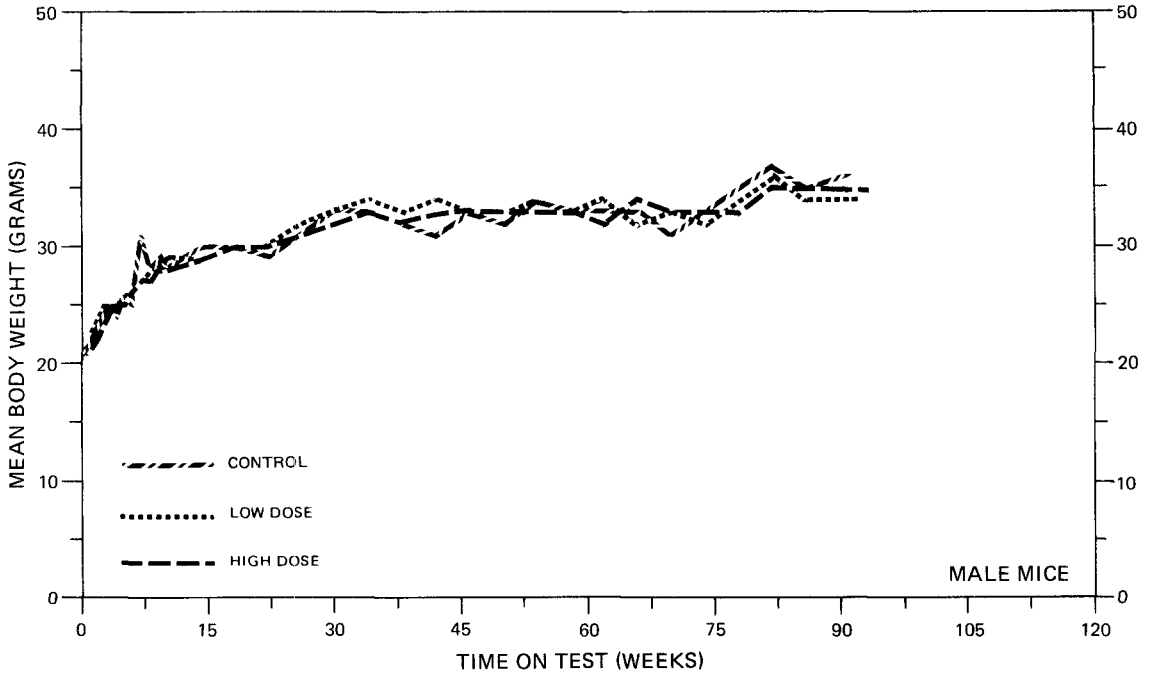
No readily apparent dose-related trend in mean body weight patterns was observed in male or female mice (Figure 4). All three groups of male mice maintained similar group mean body weights throughout the bioassay.

There was no evidence that the administration of mexacarbate at the levels used in this study produced any effect upon the physical appearance or behavior of the dosed mice. Signs commonly observed in laboratory mice were observed at a comparable rate for all groups during the first year, increasing gradually as the animals aged. These common signs included a hunched appearance, sores and/or desquamation on the tail and other parts of the body, localized alopecia, stains on the fur, a bloated appearance, and penile, vulvar, and/or anal irritation. Palpable nodules, tissue masses, and/or swollen areas on the body were observed with a slightly greater frequency in the dosed mice, particularly among the males.

B. Survival

The estimated probabilities of survival for male and female mice in the control and mexacarbate-dosed groups are shown in Figure 5. For both male and female mice the Tarone test did not indicate a significant positive association between dosage and mortality.

In male mice, 66 percent (33/50) of the high dose group and 68 percent (34/50) of the low dose group, but only 10 percent (2/20) of



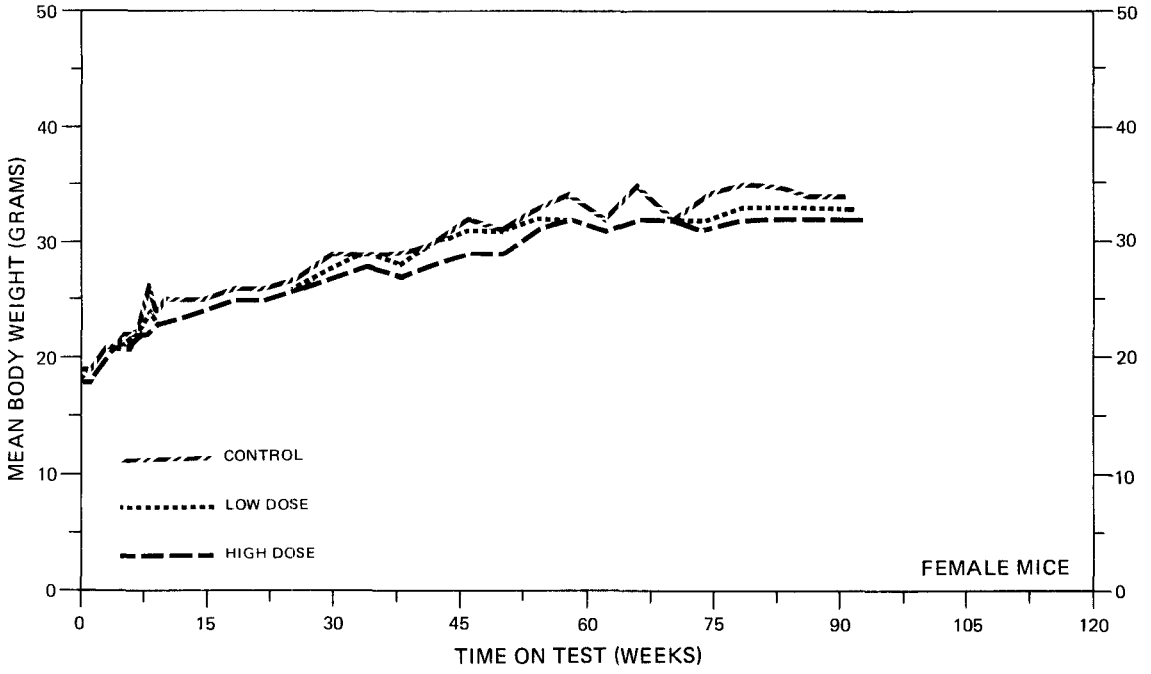
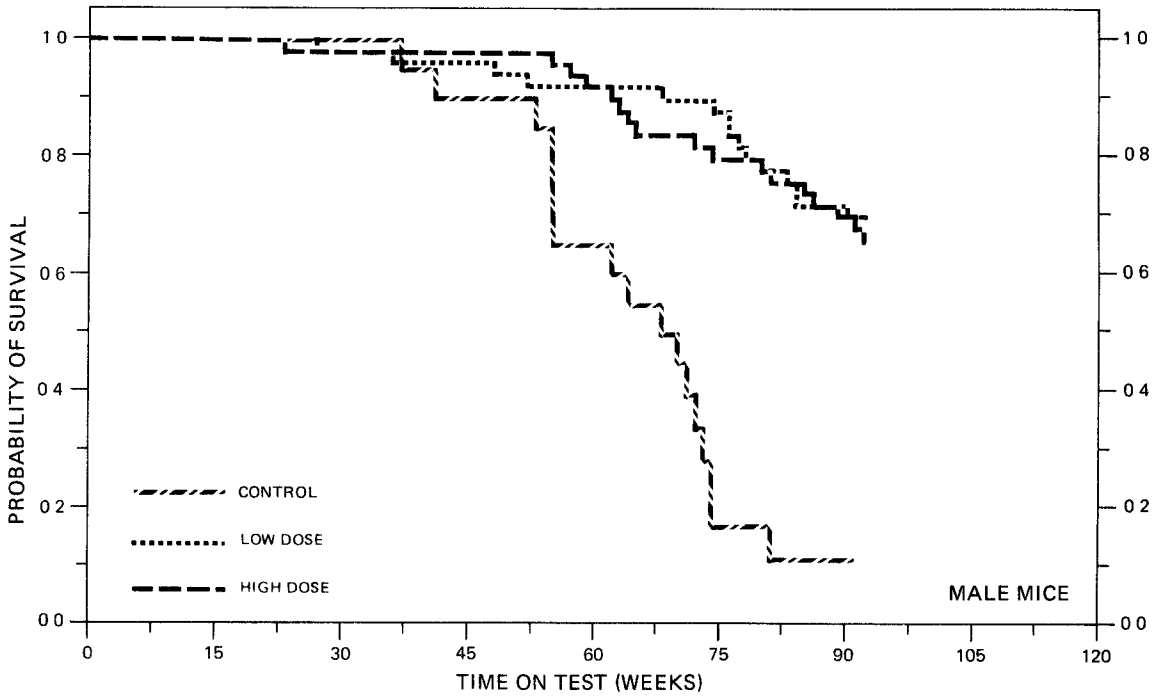


FIGURE 4
GROWTH CURVES FOR MEXACARBATE CHRONIC STUDY MICE



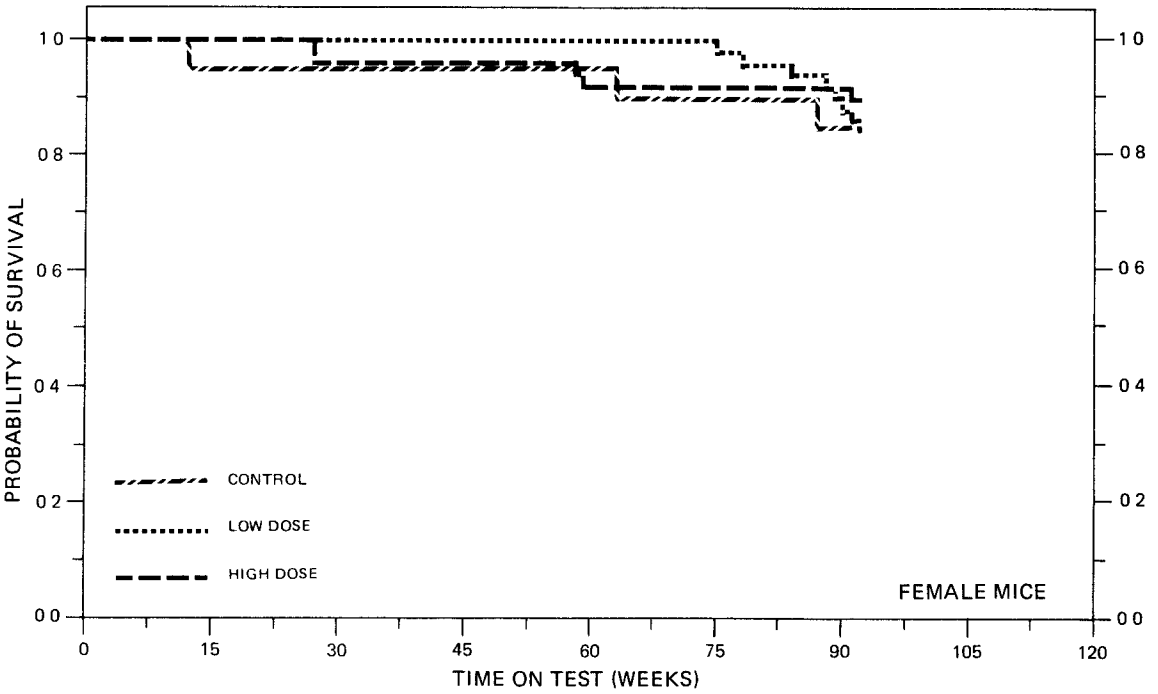


FIGURE 5
SURVIVAL COMPARISONS OF MEXACARBATE CHRONIC STUDY MICE

the control group, survived on test until the end of the study. Of the 18 control mice that did not survive, 12 had chronic inflammation of the kidney and also had amyloidosis at one or more sites; 5 were autolyzed or missing. The early deaths in the controls were not tumor-related since no tumors were observed in this group. Because of the poor survival of these controls, it was necessary to use a pooled control group for statistical analysis of tumor incidence.

In female mice, 90 percent (45/50) of the high dose group, 84 percent (42/50) of the low dose group, and 85 percent (17/20) of the control group survived on test until the termination of the study. Thus, adequate numbers of female mice were at risk from late-developing tumors.

C. Pathology

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

Fibrosarcomas of the subcutaneous tissues occurred in 6/46 (13 percent) low dose males and 7/47 (15 percent) high dose males. Cutaneous fibromas occurred in 1/46 (2 percent) low dose males and 6/47 (13 percent) high dose males. Fibromas and fibrosarcomas of the skin and subcutaneous tissue are not uncommonly observed in the B6C3F1 mouse and in the absence of suitable matched control mice, these lesions were not considered to be related to the administration of mexacarbate.

Hepatocellular carcinomas occurred in 0/15 control males, 4/46 (9 percent) low dose males, 15/47 (32 percent) high dose males, 1/20 (5 percent) control females, 1/48 (2 percent) low dose females and 2/48 (4 percent) high dose females. Hepatocellular adenomas occurred in 2/46 (4 percent) low dose males, and 1/48 (2 percent) high dose females.

Malignant lymphoma was observed in 8/46 (17 percent) low dose and 3/47 (6 percent) high dose male mice, and leukemia occurred in 2/46 (4 percent) low dose and 2/47 (4 percent) high dose male mice. These neoplasms were not observed in matched control animals. Other neoplasms that occurred in mice in this study showed no appreciable difference in frequency between control and dosed animals.

Other inflammatory, degenerative, and proliferative lesions seen in the dosed and control animals were lesions that occur naturally in aged B6C3F1 mice.

This pathologic examination provided suggestive evidence for the association of hepatocellular carcinomas with administration of mexacarbate in male B6C3F1 mice.

D. Statistical Analyses of Results

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

TABLE 5

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH MEXACARBATE[a,f]

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Skin: Fibroma[b]	0/26(0.00)	0/10(0.00)	1/43(0.02)	6/45(0.13)
P Values[c]	P = 0.014	P = 0.037	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.033	0.949
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Matched Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.013	0.397
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	91	92
Subcutaneous Tissue: Fibrosarcoma[b]	0/26(0.00)	0/10(0.00)	6/43(0.14)	7/45(0.16)
P Values[c]	P = 0.049	N.S.	N.S.	P = 0.034*
Relative Risk (Pooled Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.993	1.151
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Matched Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.416	0.482
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	76	85

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	4/26(0.15)	0/10(0.00)	4/43(0.09)	15/45(0.33)
P Values[c]	P = 0.022	P = 0.002	N.S.	P = 0.029**
Relative Risk (Pooled Control)[d]	---	---	0.605	2.167
Lower Limit	---	---	0.124	0.794
Upper Limit	---	---	3.008	8.144
Relative Risk (Matched Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.240	1.171
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	84	---	91	63
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	4/26(0.15)	0/10(0.00)	6/43(0.14)	15/45(0.33)
P Values[c]	P = 0.032	P = 0.005	N.S.	P = 0.029**
Relative Risk (Pooled Control)[d]	---	---	0.907	2.167
Lower Limit	---	---	0.241	0.794
Upper Limit	---	---	4.029	8.144
Relative Risk (Matched Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.416	1.171
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	84	---	91	63

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	1/26(0.04)	0/10(0.00)	8/43(0.19)	3/45(0.07)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.026	P = 0.037	---	---
Relative Risk (Pooled Control)[d]	---	---	4.837	1.733
Lower Limit	---	---	0.714	0.150
Upper Limit	---	---	208.686	88.917
Relative Risk (Matched Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.594	0.149
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	90	---	76	57
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/26(0.04)	0/10(0.00)	10/43(0.23)	5/45(0.11)
P Values[c]	N.S.	N.S.	P = 0.030*	N.S.
Departure from Linear Trend[e]	P = 0.021	P = 0.034	---	---
Relative Risk (Pooled Control)[d]	---	---	6.047	2.889
Lower Limit	---	---	0.951	0.352
Upper Limit	---	---	254.726	133.354
Relative Risk (Matched Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.774	0.313
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	90	---	76	57

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	1/30(0.03)	0/13(0.00)	3/43(0.07)	4/45(0.09)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	2.093	2.667
Lower Limit	---	---	0.179	0.283
Upper Limit	---	---	107.238	128.260
Relative Risk (Matched Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.196	0.289
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	50	---	91	85
Adrenal: Pheochromocytoma[b]	0/26(0.00)	0/10(0.00)	3/43(0.07)	0/44(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.027	---	---	---
Relative Risk (Pooled Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.373	---
Upper Limit	---	---	Infinite	---
Relative Risk (Matched Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.155	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	91	---

TABLE 5 (CONCLUDED)

---

[a]Treated groups received time-weighted average doses of 327 or 654 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 control group (*) or the matched 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 $P < 0.05$.

[f]These analyses were based solely upon animals surviving at least 56 weeks, except for sites where the first tumor of interest was observed earlier than 56 weeks in any group of this sex and species, where the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

TABLE 6

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	1/20(0.05)	2/48(0.04)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.833	0.417
Lower Limit	---	0.047	0.006
Upper Limit	---	48.155	32.057
Weeks to First Cbserved Tumor	87	92	92
Hematopoietic System: Malignant Lymphoma[b]	4/20(0.20)	9/48(0.19)	5/48(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.938	0.521
Lower Limit	---	0.307	0.128
Upper Limit	---	3.804	2.415
Weeks to First Observed Tumor	91	75	58
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/20(0.25)	10/48(0.21)	6/48(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.833	0.500
Lower Limit	---	0.308	0.149
Upper Limit	---	2.794	1.878
Weeks to First Observed Tumor	87	75	58

TABLE 6 (CONCLUDED)

---

[a]Treated groups received time-weighted average doses of 68 or 135 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.

Due to the poor survival of the mexacarbate control the analyses for the males are based solely on those mice surviving at least 56 weeks. Also due to the poor survival of the mexacarbate control, two groups of controls were used for analyses of the male mouse data: the control group for the mexacarbate bioassay (designated in this section as the "matched" control) and a pooled control group that combined the untreated matched controls from the studies of chlorobenzilate and mexacarbate. These control males were of the same strain, were tested concurrently by the same laboratory in the same room for at least a year, and were examined by the same pathologists.

For male mice the Cochran-Armitage test indicated a significant positive association between dosage and the incidence of hepatocellular carcinomas when the dosed groups were compared to either the matched control ($P = 0.002$) or the pooled control ($P = 0.022$). The Fisher exact test comparing high dose to pooled control had a probability level of $P = 0.029$, a marginal result which was not significant under the Bonferroni criterion. In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, 74/482 (15 percent) of the untreated B6C3F1 male mice had this tumor, compared to the 15/45 (33 percent) in the high dose group. It should also be noted that one of the 16 untreated control groups in the historical data had an incidence of hepatocellular carcinomas that was higher (35 percent) than that found in the high dose group of this bioassay.

In male mice the Cochran-Armitage test for a positive association between dosage and the incidence of fibroma of the skin was significant using both the matched control (P = 0.037) and the pooled control (P = 0.014). The Fisher exact tests, however, were not significant.

For fibrosarcoma of the subcutaneous tissue in males, the Cochran-Armitage test was significant (P = 0.049) when the dosed groups were compared to the pooled control group. The Fisher exact test comparing the pooled control group to the high dose group had a probability level of P = 0.034, a marginal result which was not significant under the Bonferroni criterion. In historical control data collected by this laboratory, 23/432 (5 percent) of the untreated male B6C3F1 mice had this tumor, compared to the incidences in this study of 0/26, 0/10, 6/43 (14 percent), and 7/45 (16 percent) observed in the pooled control, matched control, low dose, and high dose groups, respectively.

For both male and female mice there were no other tumors at any site for which, under the Bonferroni criterion, the statistical tests showed a significant association between the administration of mexacarbate and an elevated incidence of tumors.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the

absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by mexacarbate that could not be established under the conditions of this test.

V. DISCUSSION

In both species, adequate numbers of mexacarbate-dosed animals survived long enough to be at risk from late-developing tumors. Because of poor survival of the male control mice, a pooled control group was used for the statistical analyses of tumor incidences among male mice. While mean body weight depression, relative to controls, was observed in dosed rats, dietary administration of mexacarbate had no significant effect on survival, mean body weight, or clinical manifestations of abnormalities in male or female mice. This may indicate that the concentrations of mexacarbate administered to mice did not approximate the maximum tolerated concentrations.

No neoplasms occurred in statistically significant increased incidences when dosed rats were compared to controls.

Application of the Cochran-Armitage test to the incidence of hepatocellular carcinoma among male mice surviving at least 56 weeks indicated a significant positive association between the dietary concentration of mexacarbate and tumor incidence. Significant associations between dietary concentration and tumor incidence in male mice surviving at least 56 weeks were also indicated for fibromas of the skin and for subcutaneous fibrosarcomas. These results were not, however, supported by results of Fisher exact tests using the Bonferroni correction for any tumor in male mice. In addition, in historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, 74/482 (15 percent) of the untreated

male B6C3F1 mice had hepatocellular carcinomas, and 1 of the 16 untreated control groups included in this historical data had an incidence that was higher (35 percent) than the incidence observed among high dose male mice in this bioassay (34 percent).

Mexacarbate has been previously bioassayed for carcinogenicity (Bionetics Research Laboratories, 1968). Mexacarbate was administered to groups of 18 (C57BL/6 x C3H/Anf) F1 mice of each sex and 18 (C57BL/6 x AKR) F1 mice of each sex. Mice were gavaged daily with 4.64 mg/kg body weight mexacarbate from 7 days to 4 weeks of age and then fed 11 mg mexacarbate per kg of diet until the mice were 78 weeks of age. An increased incidence of lung adenomas was observed in (C57BL/6 x C3H/Anf) F1 mice of both sexes (i.e., 4/14 [29 percent] males and 3/17 [18 percent] females). Increased incidences of "hepatomas" were observed in male mice of both strains (i.e., 5/14 [36 percent] C57BL/6 x C3H/Anf F1 and 2/17 [12 percent] C57BL/6 x AKR F1), but no "hepatomas" were observed among female mice. The International Agency for Research on Cancer (1976) did not consider these data sufficient to allow an evaluation of the carcinogenicity of mexacarbate to be made.

It is concluded that under the conditions of this bioassay, there was no convincing evidence that dietary administration of mexacarbate was carcinogenic to Osborne-Mendel rats or B6C3F1 mice.

VI. BIBLIOGRAPHY

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

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

Bionetics Research Laboratories, Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Vol. I: Carcinogenic Study. U.S. Department of Health, Education, and Welfare, National Cancer Institute, Bethesda, Maryland, 1968.

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.

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.

Gray, H., Dow Chemical Company, U.S.A., Midland, Michigan. Personal communication, March 24, 1977.

International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risk. Vol. 12: Some Carbamates, Thiocarbamates and Carbazides. United Nations World Health Organization, Geneva, Switzerland, 1976.

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.

Matsumura, F., Toxicology of Insecticides. Plenum Press, New York, 1975.

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.

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.

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

U.S. Department of Health, Education, and Welfare, Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health. Parts I and II. E. M. Mrak. NTIS No. PB-251-630, 1969.

U.S. Environmental Protection Agency, EPA Compendium of Registered Pesticides. U.S. Government Printing Office, Washington, D.C., 1974.

Virginia Polytechnic Institute, Pesticide Information Manual. Miscellaneous Publication No. 8, Virginia Cooperative Extension Service, Blacksburg, Virginia, 1968.

Windholtz, M., editor, The Merck Index: An Encyclopedia of Chemicals and Drugs, 9th edition. Merck and Company, Inc., Rahway, New Jersey, 1976.

Review of the Bioassay of Mexacarbate* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

June 29, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Mexacarbate for carcinogenicity.

Although the report concluded that Mexacarbate was not carcinogenic under the conditions of test, the reviewer noted that the incidence of hepatocellular carcinomas in the high dose treated male mice was statistically significant if compared to matched controls. However, the incidence was not statistically significant when compared with historical controls. The reviewer questioned the use of the historical control data since they may sometimes provide fallacious comparisons for commonly occurring tumor types, especially for those that may be influenced by dietary contaminants. After some discussion regarding alternative motions, the reviewer moved that the report on the bioassay of Mexacarbate be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

---

* 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.

☆U.S. GOVERNMENT PRINTING OFFICE: 1978-260-899/3183

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH MEXACARBATE

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

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	48
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(48)
FIBROMA	1 (5%)	2 (4%)	1 (2%)
FIBROSARCOMA	2 (10%)	1 (2%)	
LIPOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(20)	(49)	(48)
OSTEOSARCOMA		1 (2%)	
#LUNG	(20)	(49)	(48)
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	2 (4%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(20)	(49)	(47)
HEMANGIOMA		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(14)	(40)	(40)
MIXED TUMOR, BENIGN		2 (5%)	

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

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
#STOMACH	(20)	(49)	(47)
SQUAMOUS CELL PAPILLOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(47)
TUBULAR-CELL ADENOMA			1 (2%)
HAMARTOMA +		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(47)
CHROMOPHOBE ADENOMA	3 (15%)	11 (22%)	7 (15%)
#ADRENAL	(20)	(49)	(47)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(20)	(48)	(47)
FOLLICULAR-CELL ADENOMA	1 (5%)	1 (2%)	1 (2%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(20)	(49)	(47)
ISLET-CELL ADENOMA			3 (6%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(47)
ASTROCYTOMA			1 (2%)
OLIGODENDROGLIOMA		2 (4%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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 (CONCLUDED)

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	14	31	19
MORIBUND SACRIFICE		2	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	6	17	30
ANIMAL MISSING			1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	21	16
TOTAL PRIMARY TUMORS	7	28	19
TOTAL ANIMALS WITH BENIGN TUMORS	4	15	13
TOTAL BENIGN TUMORS	5	19	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	8	3
TOTAL MALIGNANT TUMORS	2	9	3
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	
TOTAL SECONDARY TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA	1 (5%)		
FIBROSARCOMA, METASTATIC			1 (2%)
LIPOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		2 (4%)	
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
FIBROSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		6 (12%)	1 (2%)
GRANULOCYTIC LEUKEMIA		1 (2%)	1 (2%)
#SPLEEN	(20)	(50)	(50)
HEMANGIOMA		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HEPATOCELLULAR CARCINOMA			1 (2%)
FIBROSARCOMA, METASTATIC			1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
#PANCREAS	(20)	(50)	(50)
GRANULOSA-CELL CARCINOMA, METAST		1 (2%)	
FIBROSARCOMA, METASTATIC			2 (4%)
#STOMACH	(20)	(50)	(50)
FIBROSARCOMA			2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(49)
ADENOMA,NOS		1 (2%)	
CHROMOPHOBE ADENOMA	9 (45%)	14 (29%)	10 (20%)
#ADRENAL	(20)	(50)	(50)
CORTICAL CARCINOMA		1 (2%)	
NEUROFIBROMA		1 (2%)	
#THYROID	(20)	(49)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)	2 (4%)
C-CELL ADENOMA	1 (5%)		
#PANCREATIC ISLETS	(20)	(50)	(50)
ISLET-CELL ADENOMA			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA,NOS		2 (4%)	3 (6%)
ADENOCARCINOMA, NOS		3 (6%)	
FIBROADENOMA	5 (25%)	12 (24%)	12 (24%)
#UTERUS	(20)	(49)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (5%)		1 (2%)
#OVARY	(20)	(49)	(50)
GRANULOSA-CELL TUMOR			1 (2%)
GRANULOSA-CELL CARCINOMA		1 (2%)	

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

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-P070	LOW DOSE 01-P073	HIGH DOSE 01-P074
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(50)
MENINGIOMA	1 (5%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
**MESENTERY	(20)	(50)	(50)
GRANULOSA-CELL CARCINOMA, METAST		1 (2%)	
FIBROSARCOMA, METASTATIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	15	16
MORIBUND SACRIFICE	1	1	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	34	33
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	33	28
TOTAL PRIMARY TUMORS	18	46	36
TOTAL ANIMALS WITH BENIGN TUMORS	11	29	24
TOTAL BENIGN TUMORS	17	33	30
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	11	5
TOTAL MALIGNANT TUMORS	1	13	5
TOTAL ANIMALS WITH SECONDARY TUMORS#		4	3
TOTAL SECONDARY TUMORS		5	7
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH MEXACARBATE

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

	CONTROL (VEH) 02-M077	LOW DOSE 02-M078	HIGH DOSE 02-M079
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	1	1
ANIMALS NECROPSIED	15	46	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	15	46	47
INTEGUMENTARY SYSTEM			
*SKIN	(15)	(46)	(47)
ADNEXAL ADENOMA			1 (2%)
FIBROMA		1 (2%)	6 (13%)
*SUBCUT TISSUE	(15)	(46)	(47)
FIBROSARCOMA		6 (13%)	7 (15%)
RESPIRATORY SYSTEM			
#LUNG	(15)	(46)	(46)
HEPATOCELLULAR CARCINOMA, METAST			2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (7%)	4 (9%)
FIBROSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
#BRAIN	(14)	(46)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
**MULTIPLE ORGANS	(15)	(46)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		5 (11%)	
GRANULOCYTIC LEUKEMIA		2 (4%)	2 (4%)
#CERVICAL LYMPH NODE	(13)	(45)	(45)
FIBROSARCOMA, METASTATIC		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#MESENTERIC L. NODE	(13)	(45)	(45)
HEMANGIOMA			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
#AXILLARY LYMPH NODE	(13)	(45)	(45)
FIBROSARCOMA, METASTATIC			1 (2%)

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

TABLE B1 (CONTINUED)

	CONTROL(VEH) 02-M077	LOW DOSE 02-M078	HIGH DOSE 02-M079
#SMALL INTESTINE	(14)	(43)	(43)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(15)	(46)	(47)
HEPATOCELLULAR ADENOMA		2 (4%)	
HEPATOCELLULAR CARCINOMA		4 (9%)	15 (32%)
HEMANGIOSARCOMA			1 (2%)
#LARGE INTESTINE	(13)	(45)	(46)
FIBROSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(15)	(46)	(47)
FIBROSARCOMA, METASTATIC		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(15)	(46)	(46)
PHEOCHROMOCYTOMA		3 (7%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(15)	(46)	(47)
ADENOMA, NOS			1 (2%)

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

TABLE B1 (CONCLUDED)

	CONTROL (VEH) 02-M077	LOW DOSE 02-M078	HIGH DOSE 02-M079
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	17	14	17
MORIBUND SACRIFICE		1	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	2	34	32
ANIMAL MISSING	1	1	1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*		24	28
TOTAL PRIMARY TUMORS		30	41
TOTAL ANIMALS WITH BENIGN TUMORS		9	11
TOTAL BENIGN TUMORS		9	13
TOTAL ANIMALS WITH MALIGNANT TUMORS		18	24
TOTAL MALIGNANT TUMORS		21	28
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	3
TOTAL SECONDARY TUMORS		2	4
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 MEXACARBATE

	CONTROL(VEH) 02-F077	LOW DOSE 02-F080	HIGH DOSE 02-F081
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	48	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(48)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (15%)	8 (17%)	2 (4%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	1 (2%)
GRANULOCYTIC LEUKEMIA	1 (5%)		
#SPLEEN	(20)	(48)	(47)
HEMANGIOSARCOMA		1 (2%)	
#MESENTERIC L. NODE	(19)	(47)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
#SMALL INTESTINE	(20)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#THYMUS	(19)	(47)	(46)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL (VEH) 02-P077	LOW DOSE 02-P080	HIGH DOSE 02-P081
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(48)
HEPATOCELLULAR ADENOMA			1 (2%)
HEPATOCELLULAR CARCINOMA	1 (5%)	1 (2%)	2 (4%)
#SMALL INTESTINE	(20)	(48)	(48)
ADENOMA, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(14)	(29)	(35)
CHROMOPHOBE ADENOMA			1 (3%)
REPRODUCTIVE SYSTEM			
*VAGINA	(20)	(48)	(48)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#UTERUS	(20)	(48)	(48)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#OVARY	(20)	(48)	(47)
ADENOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B2 (CONCLUDED)

	CONTROL (VEH) 02-F077	LOW DOSE 02-F080	HIGH DOSE 02-F081
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	8	5
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	42	45
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	16	13
TOTAL PRIMARY TUMORS	7	16	13
TOTAL ANIMALS WITH BENIGN TUMORS	1	3	5
TOTAL BENIGN TUMORS	1	3	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	13	8
TOTAL MALIGNANT TUMORS	6	13	8
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

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

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

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(48)
EPIDERMAL INCLUSION CYST	1 (5%)	1 (2%)	
INFLAMMATICN, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(20)	(49)	(48)
INFLAMMATICN, NOS	1 (5%)	6 (12%)	2 (4%)
INFLAMMATION, ACUTE			1 (2%)
#LUNG	(20)	(49)	(48)
INFLAMMATICN, NOS		1 (2%)	
INFLAMMATICN, ACUTE	1 (5%)	5 (10%)	7 (15%)
ABSCESS, NOS		9 (18%)	2 (4%)
PNEUMONIA, CHRONIC MURINE	9 (45%)	14 (29%)	25 (52%)
CALCIFICATION, NOS	1 (5%)	1 (2%)	3 (6%)
CALCIFICATION, FOCAL	1 (5%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(49)	(47)
HEMORRHAGE			1 (2%)
ABSCESS, NOS			1 (2%)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HEMATOPOIESIS	6 (30%)	7 (14%)	6 (13%)
#LYMPH NODE	(20)	(49)	(45)
INFLAMMATICN, NOS		7 (14%)	4 (9%)
ANGIECTASIS			1 (2%)
#CERVICAL LYMPH NODE	(20)	(49)	(45)
INFLAMMATICN, NOS	1 (5%)		

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
#THYMUS	(14)	(40)	(42)
HEMORRHAGE		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(20)	(49)	(48)
PERIARTERITIS	2 (10%)		
ARTERIOSCLEROSIS, NOS			3 (6%)
CALCIFICATION, NOS	5 (25%)	2 (4%)	3 (6%)
#MYOCARDIUM	(20)	(49)	(48)
FIBROSIS		1 (2%)	
DEGENERATICN, NOS	12 (60%)	6 (12%)	16 (33%)
*AORTA	(20)	(49)	(48)
PERIARTERITIS		1 (2%)	1 (2%)
ARTERIOSCLEROSIS, NOS	6 (30%)	5 (10%)	4 (8%)
MEDIAL CALCIFICATION	1 (5%)	1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(48)
CYST, NOS		1 (2%)	1 (2%)
THROMBOSIS, NOS			1 (2%)
ABSCESS, NOS			1 (2%)
DEGENERATICN, NOS	1 (5%)	7 (14%)	5 (10%)
METAMORPHOSIS FATTY	9 (45%)	9 (18%)	5 (10%)
ANGIECTASIS		2 (4%)	1 (2%)
#LIVER/CENTRILOBULAR	(20)	(49)	(48)
NECROSIS, NOS		3 (6%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
*BILE DUCT	(20)	(49)	(48)
HYPERPLASIA, NOS	2 (10%)	5 (10%)	8 (17%)
#PANCREAS	(20)	(49)	(47)
PERIARTERITIS	3 (15%)	7 (14%)	6 (13%)
ARTERIOSCLEROSIS, NOS	1 (5%)	1 (2%)	2 (4%)
ATROPHY, NOS		1 (2%)	
#PANCREATIC DUCT	(20)	(49)	(47)
HYPERPLASIA, NOS		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
#ESOPHAGUS	(20)	(46)	(48)
DILATATION, NOS		2 (4%)	
#STOMACH	(20)	(49)	(47)
INFLAMMATICN, NOS	1 (5%)	1 (2%)	
ULCER FOCAL	3 (15%)	3 (6%)	
CALCIFICATION, NOS	6 (30%)	7 (14%)	8 (17%)
HYPERKERATOSIS		1 (2%)	
ACANTHOSIS		1 (2%)	
#SMALL INTESTINE	(20)	(49)	(47)
INFLAMMATICN, NOS		3 (6%)	2 (4%)
PERIARTERITIS			1 (2%)
#DUODENUM	(20)	(49)	(47)
CALCIFICATION, NOS	2 (10%)		
#LARGE INTESTINE	(20)	(49)	(47)
PARASITISM		2 (4%)	8 (17%)
#COLON	(20)	(49)	(47)
INFLAMMATICN, NOS		5 (10%)	1 (2%)
#CECUM	(20)	(49)	(47)
INFLAMMATICN, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(47)
CALCULUS, NOS	1 (5%)	1 (2%)	5 (11%)
CYST, NOS			1 (2%)
ABSCESS, NOS		2 (4%)	
INFLAMMATICN CHRONIC	19 (95%)	35 (71%)	37 (79%)
NEPHROPATHY, TOXIC		2 (4%)	1 (2%)
CALCIFICATION, NOS	5 (25%)	2 (4%)	5 (11%)
#KIDNEY/PELVIS	(20)	(49)	(47)
INFLAMMATICN, NOS	1 (5%)	3 (6%)	3 (6%)
#URINARY BLADDER	(20)	(49)	(45)
CALCULUS, NOS		1 (2%)	
INFLAMMATION, NOS	5 (25%)	7 (14%)	1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(47)
CYST, NOS	1 (5%)	1 (2%)	4 (9%)
HYPERPLASIA, NOS	1 (5%)	1 (2%)	2 (4%)
HYPERPLASIA, CHROMOPHOBE-CELL			1 (2%)
#ADRENAL	(20)	(49)	(47)
CALCIFICATION, NOS	1 (5%)		1 (2%)
HYPERPLASIA, NOS		1 (2%)	3 (6%)
#ADRENAL CORTEX	(20)	(49)	(47)
DEGENERATION, NOS	8 (40%)	10 (20%)	14 (30%)
#THYROID	(20)	(48)	(47)
CYSTIC FOLLICLES	4 (20%)	7 (15%)	6 (13%)
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)	1 (2%)	5 (11%)
#PARATHYROID	(20)	(49)	(47)
HYPERPLASIA, NOS	4 (20%)	1 (2%)	4 (9%)
#PANCREATIC ISLETS	(20)	(49)	(47)
HYPERPLASIA, NOS		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(20)	(45)	(44)
INFLAMMATION, NOS	3 (15%)	10 (22%)	6 (14%)
ATROPHY, NOS			2 (5%)
HYPERTROPHY, NOS		1 (2%)	1 (2%)
*SEMINAL VESICLE	(20)	(49)	(48)
ATROPHY, NOS			4 (8%)
HYPERTROPHY, NOS		1 (2%)	1 (2%)
*TESTIS	(20)	(48)	(46)
PERIARTERITIS	1 (5%)	3 (6%)	7 (15%)
ARTERIOSCLEROSIS, NOS	1 (5%)		
CALCIFICATION, NOS	1 (5%)		
ATROPHY, NOS	9 (45%)	17 (35%)	14 (30%)
*EPIDIDYMIS	(20)	(49)	(48)
NECROSIS, FAT		1 (2%)	

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

TABLE C1 (CONCLUDED)

	CONTROL (VEH) 01-M070	LOW DOSE 01-M071	HIGH DOSE 01-M072
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(49)	(47)
INFLAMMATION, NOS	2 (10%)	1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(20)	(49)	(48)
INFLAMMATION, NOS			1 (2%)
CATARACT		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(49)	(48)
FIBROUS OSTEODYSTROPHY	5 (25%)	3 (6%)	6 (13%)
*SKELETAL MUSCLE	(20)	(49)	(48)
INFLAMMATION, NOS		1 (2%)	
BODY CAVITIES			
*PLEURA	(20)	(49)	(48)
INFLAMMATION, NOS		2 (4%)	
*PERICARDIUM	(20)	(49)	(48)
INFLAMMATION, NOS	1 (5%)	4 (8%)	
*MESENTERY	(20)	(49)	(48)
PERIARTERITIS	1 (5%)	3 (6%)	5 (10%)
ARTERIOSCLEROSIS, NOS	4 (20%)	1 (2%)	5 (10%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY PERF			1
AUTOLYSIS/NO NECROPSY PERFORMED		1	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 MEXACARBATE

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	3 (6%)
RESPIRATORY SYSTEM			
#TRACHEA	(20)	(50)	(43)
INFLAMMATION, NOS	1 (5%)	2 (4%)	4 (9%)
#LUNG	(20)	(50)	(50)
INFLAMMATION, ACUTE	2 (10%)	3 (6%)	6 (12%)
ABSCESS, NOS	1 (5%)	2 (4%)	6 (12%)
PNEUMONIA, CHRONIC MURINE	11 (55%)	31 (62%)	19 (38%)
CALCIFICATION, NOS	2 (10%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(50)	(50)
ABSCESS, NOS		1 (2%)	
HEMATOPOIESIS	1 (5%)	14 (28%)	9 (18%)
#LYMPH NODE	(20)	(50)	(50)
INFLAMMATION, NOS		5 (10%)	4 (8%)
#CERVICAL LYMPH NODE	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
#MESENTERIC L. NODE	(20)	(50)	(50)
INFLAMMATION, NOS		2 (4%)	
#THYMUS	(17)	(42)	(46)
CYST, NOS			2 (4%)

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
ARTERIOSCLEROSIS, NOS		1 (2%)	2 (4%)
#MYOCARDIUM	(20)	(50)	(50)
DEGENERATION, NOS		3 (6%)	1 (2%)
#ENDOCARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*AORTA	(20)	(50)	(50)
ARTERIOSCLEROSIS, NOS	2 (10%)	2 (4%)	2 (4%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
CYST, NOS	1 (5%)		4 (8%)
DEGENERATION, NOS	2 (10%)	3 (6%)	2 (4%)
NECROSIS, FOCAL	2 (10%)	1 (2%)	
METAMORPHOSIS FATTY	3 (15%)	3 (6%)	6 (12%)
HYPERPLASIA, NOS	1 (5%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	1 (5%)		
#LIVER/CENTRILOBULAR	(20)	(50)	(50)
NECROSIS, NOS		2 (4%)	3 (6%)
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS	7 (35%)	8 (16%)	4 (8%)
#PANCREAS	(20)	(50)	(50)
PERIARTERITIS	2 (10%)	1 (2%)	
ARTERIOSCLEROSIS, NOS			2 (4%)
ATROPHY, NOS		1 (2%)	2 (4%)
#ESOPHAGUS	(20)	(50)	(50)
DILATATION, NOS	1 (5%)		1 (2%)
#STOMACH	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
ULCER, NOS		2 (4%)	2 (4%)
ULCER FOCAL		3 (6%)	1 (2%)
NECROSIS, FAT		1 (2%)	
CALCIFICATION, NOS	2 (10%)	1 (2%)	2 (4%)

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
#DUODENUM	(20)	(50)	(49)
INFLAMMATICN, NOS	2 (10%)		1 (2%)
#LARGE INTESTINE	(20)	(50)	(49)
PARASITISM	1 (5%)	2 (4%)	5 (10%)
#COLON	(20)	(50)	(49)
INFLAMMATICN, NOS			3 (6%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
CALCULUS, NOS	3 (15%)	11 (22%)	15 (30%)
PYELONEPHRITIS, NOS		1 (2%)	
INFLAMMATICN CHRONIC	12 (60%)	16 (32%)	14 (28%)
NEPHROPATHY, TOXIC		5 (10%)	1 (2%)
CALCIFICATION, NOS	3 (15%)	2 (4%)	2 (4%)
#KIDNEY/PELVIS	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)	2 (4%)	1 (2%)
#URINARY BLADDER	(20)	(50)	(50)
INFLAMMATICN, NOS	1 (5%)	5 (10%)	2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(49)
CYST, NOS	2 (10%)	3 (6%)	1 (2%)
NECROSIS, FOCAL		1 (2%)	
HYPERPLASIA, NOS		5 (10%)	5 (10%)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL CORTEX	(20)	(50)	(50)
DEGENERATICN, NOS	7 (35%)	20 (40%)	20 (40%)
#THYROID	(20)	(49)	(50)
CYSTIC FOLLICLES		1 (2%)	5 (10%)
#PARATHYROID	(20)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)		1 (2%)
#PANCREATIC ISLETS	(20)	(50)	(50)
HYPERPLASIA, NOS		2 (4%)	

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
*VAGINA	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)	5 (10%)	6 (12%)
#UTERUS	(20)	(49)	(50)
HYDROMETRA		5 (10%)	8 (16%)
HEMATOMETRA			1 (2%)
INFLAMMATION, NOS	2 (10%)	2 (4%)	2 (4%)
#UTERUS/ENDOMETRIUM	(20)	(49)	(50)
HYPERPLASIA, CYSTIC	3 (15%)	3 (6%)	1 (2%)
#OVARY	(20)	(49)	(50)
CYST, NOS		3 (6%)	
INFLAMMATION, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
CATARACT		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(50)	(50)
FIBROUS OSTEODYSTROPHY	3 (15%)	1 (2%)	2 (4%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
NECROSIS, FAT		1 (2%)	
*PLEURA	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		1 (2%)

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

TABLE C2 (CONCLUDED)

	CONTROL (VEH) 01-F070	LOW DOSE 01-F073	HIGH DOSE 01-F074
*PERICARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*MESENTERY	(20)	(50)	(50)
PERIARTERITIS		1 (2%)	
ARTERIOSCLEROSIS, NOS	2 (10%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

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

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

	CONTROL(VEH) 02-M077	LOW DOSE 02-M078	HIGH DOSE C2-M079
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	1	1
ANIMALS NECROPSIED	15	46	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	15	46	47
INTEGUMENTARY SYSTEM			
*SKIN	(15)	(46)	(47)
CYST, NOS	1 (7%)		
INFLAMMATICN, NOS	2 (13%)	5 (11%)	5 (11%)
*SUBCUT TISSUE	(15)	(46)	(47)
INFLAMMATION, ACUTE MEMBRANOUS		1 (2%)	
ABSCESS, NOS		4 (9%)	11 (23%)
RESPIRATCRY SYSTEM			
#LUNG	(15)	(46)	(46)
INFLAMMATICN, ACUTE		3 (7%)	3 (7%)
PNEUMONIA, CHRONIC MURINE		2 (4%)	
HYPERPLASIA, NOS		2 (4%)	3 (7%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(15)	(46)	(47)
ACCESSORY SPLEEN		1 (2%)	
AMYLOIDOSIS	9 (60%)	7 (15%)	6 (13%)
METAMORPHOSIS FATTY		1 (2%)	
CALCIUM DEPOSIT	1 (7%)		
HEMATOPOIESIS		3 (7%)	4 (9%)
#CERVICAL LYMPH NODE	(13)	(45)	(45)
INFLAMMATICN, NOS	1 (8%)	2 (4%)	1 (2%)
#LUMBAR LYMPH NODE	(13)	(45)	(45)
INFLAMMATION, NOS		1 (2%)	
#MESENTERIC L. NODE	(13)	(45)	(45)
INFLAMMATICN, NOS	2 (15%)	13 (29%)	6 (13%)
ANGIECTASIS		1 (2%)	2 (4%)

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M077	LOW DOSE 02-M078	HIGH DOSE 02-M079
CIRCULATORY SYSTEM			
#HEART	(15)	(46)	(47)
CALCIUM DEPOSIT	3 (20%)		
#MYOCARDIUM	(15)	(46)	(47)
DEGENERATION, NOS		2 (4%)	
#ENDOCARDIUM	(15)	(46)	(47)
INFLAMMATION, NOS	1 (7%)		
DIGESTIVE SYSTEM			
#LIVER	(15)	(46)	(47)
INFLAMMATION, NOS		1 (2%)	1 (2%)
DEGENERATION, NOS		2 (4%)	
INFARCT, NOS			2 (4%)
AMYLOIDOSIS	9 (60%)	4 (9%)	2 (4%)
CALCIUM DEPOSIT	1 (7%)		
HYPERPLASIA, NODULAR		5 (11%)	8 (17%)
#HEPATIC CAPSULE	(15)	(46)	(47)
INFARCT, NOS		1 (2%)	1 (2%)
#PANCREAS	(15)	(46)	(47)
AMYLOIDOSIS			1 (2%)
ATROPHY, NOS			1 (2%)
#ESOPHAGUS	(15)	(42)	(46)
INFLAMMATION, NOS		1 (2%)	
#STOMACH	(15)	(46)	(47)
CALCIUM DEPOSIT	1 (7%)	1 (2%)	2 (4%)
#LARGE INTESTINE	(13)	(45)	(46)
PARASITISM	1 (8%)	1 (2%)	3 (7%)
*RECTUM	(15)	(46)	(47)
PROLAPSE		7 (15%)	4 (9%)

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

TABLE D1 (CONTINUED)

	CONTROL(VEH) 02-M077	LOW DOSE 02-M078	HIGH DOSE 02-M079
URINARY SYSTEM			
#KIDNEY	(15)	(46)	(47)
HYDRONEPHROSIS			2 (4%)
THROMBOSIS, NOS		1 (2%)	
PYELONEPHRITIS, NOS	1 (7%)	3 (7%)	1 (2%)
ABSCESS, NOS	1 (7%)	1 (2%)	
INFLAMMATION CHRONIC	12 (80%)	16 (35%)	19 (40%)
AMYLOIDOSIS	9 (60%)	7 (15%)	8 (17%)
CALCIUM DEPOSIT			1 (2%)
#URINARY BLADDER	(14)	(46)	(46)
INFLAMMATION, NOS	3 (21%)	4 (9%)	2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(5)	(28)	(27)
CYST, NOS			2 (7%)
#ADRENAL	(15)	(46)	(46)
AMYLOIDOSIS	1 (7%)	1 (2%)	1 (2%)
HYPERTROPHY, NOS		1 (2%)	
#THYROID	(11)	(43)	(45)
AMYLOIDOSIS	3 (27%)	3 (7%)	4 (9%)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*PENIS	(15)	(46)	(47)
INFLAMMATION, NOS		1 (2%)	
#PROSTATE	(15)	(46)	(46)
INFLAMMATION, NOS	2 (13%)	3 (7%)	1 (2%)
*SEMINAL VESICLE	(15)	(46)	(47)
INFLAMMATION, NOS	1 (7%)	2 (4%)	1 (2%)
HYPERTROPHY, NOS	1 (7%)	2 (4%)	2 (4%)
#TESTIS	(15)	(46)	(47)
CALCIUM DEPOSIT	1 (7%)		
ATROPHY, NOS	1 (7%)	4 (9%)	3 (6%)
*SCROTUM	(15)	(46)	(47)
CYST, NOS		1 (2%)	

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

TABLE D1 (CONCLUDED)

	CONTROL (VEH) 02-M077	LOW DOSE 02-M078	HIGH DOSE 02-M079
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(15)	(46)	(47)
HYPERPLASIA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	5
ANIMAL MISSING/NO NECROPSY PERF	1	1	1
AUTOLYSIS/NO NECROPSY PERFORMED	4	3	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 MEXACARBATE

	CONTROL (VEH) 02-F077	LOW DOSE 02-F080	HIGH DOSE 02-F081
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	48	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(20)	(47)	(45)
INFLAMMATION, NOS		2 (4%)	
#LUNG	(20)	(48)	(48)
INFLAMMATION, ACUTE		3 (6%)	
PNEUMONIA, CHRONIC MURINE	2 (10%)	2 (4%)	2 (4%)
HYPERPLASIA, NOS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(48)	(47)
NECROSIS, NOS	1 (5%)		
AMYLOIDOSIS	1 (5%)	2 (4%)	
HYPERPLASIA, LYMPHOID			2 (4%)
HEMATOPOIESIS	3 (15%)	5 (10%)	8 (17%)
#CERVICAL LYMPH NODE	(19)	(47)	(47)
INFLAMMATION, NOS		3 (6%)	2 (4%)
#MESENTERIC L. NODE	(19)	(47)	(47)
INFLAMMATION, NOS		4 (9%)	2 (4%)
#RENAL LYMPH NODE	(19)	(47)	(47)
INFLAMMATION, NOS		4 (9%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(19)	(48)	(48)
PERIARTERITIS		1 (2%)	

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 02-F077	LOW DOSE 02-F080	HIGH DOSE 02-F081
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(48)
CYST, NOS		1 (2%)	1 (2%)
INFLAMMATION, NOS	1 (5%)		
DEGENERATION, NOS		1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (5%)	2 (4%)	
AMYLOIDOSIS		2 (4%)	
METAMORPHOSIS FATTY			1 (2%)
HYPERPLASIA, NODULAR		1 (2%)	4 (8%)
ANGIECTASIS			1 (2%)
HEMATOPOIESIS		3 (6%)	
#PANCREAS	(19)	(47)	(47)
CYST, NOS			1 (2%)
INFLAMMATION, NOS	1 (5%)		
ABSCESS, NOS			1 (2%)
ATROPHY, NOS		1 (2%)	
#LARGE INTESTINE	(20)	(48)	(48)
PARASITISM	1 (5%)		
URINARY SYSTEM			
#KIDNEY	(20)	(48)	(48)
INFLAMMATION CHRONIC		3 (6%)	2 (4%)
PERIARTERITIS		1 (2%)	
NEPHROPATHY, TOXIC		1 (2%)	
PIGMENTATION, NOS	1 (5%)		
#URINARY BLADDER	(19)	(48)	(46)
INFLAMMATION, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(14)	(29)	(35)
CYST, NOS	1 (7%)		
HYPERPLASIA, NOS		1 (3%)	2 (6%)
#ADRENAL	(20)	(47)	(45)
CYST, NOS		1 (2%)	
PERIARTERITIS		1 (2%)	
#THYROID	(18)	(45)	(45)
INFLAMMATION, NOS			1 (2%)

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

TABLE D2 (CONCLUDED)

	CONTROL (VEH) 02-F077	LOW DOSE 02-F080	HIGH DOSE 02-F081
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(48)	(48)
HYDROMETRA		5 (10%)	
INFLAMMATION, NOS	11 (55%)	29 (60%)	22 (46%)
#UTERUS/ENDOMETRIUM	(20)	(48)	(48)
CYST, NOS			1 (2%)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (5%)		
HYPERPLASIA, CYSTIC	13 (65%)	39 (81%)	44 (92%)
#OVARY	(20)	(48)	(47)
CYST, NOS	4 (20%)	12 (25%)	18 (38%)
INFLAMMATION, NOS	8 (40%)	21 (44%)	15 (32%)
NERVOUS SYSTEM			
#BRAIN	(20)	(47)	(48)
CYST, NOS	1 (5%)		
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(20)	(48)	(48)
HYPERPLASIA, NOS	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(20)	(48)	(48)
INFLAMMATION, NOS		2 (4%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
AUTOLYSIS/NO NECROPSY PERFORMED		2	2

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

DHEW Publication No. (NIH) 78-1703