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

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REPORT ON THE BIOASSAY OF METHOXYCHLOR
FOR POSSIBLE CARCINOGENICITY

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

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

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

Histopathologic examinations were performed by Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (6).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Dr. J. R. Joiner (6), and Mr. W. W. Belew (8), using methods selected for the Bioassay Program by Dr. J. J. Gart (9).

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

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

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SUMMARY

A bioassay for possible carcinogenicity of technical-grade methoxychlor was conducted using Osborne-Mendel rats and B6C3F1 mice. Methoxychlor was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. For each species, 20 animals of each sex were placed on test as controls. The time-weighted average high and low dietary concentrations of methoxychlor were, respectively, 845 and 448 ppm for male rats, 1385 and 750 ppm for female rats, 3491 and 1746 ppm for male mice, and 1994 and 997 ppm for female mice. After a treatment period of 78 weeks, the rat groups were observed for an additional 34 weeks and the mouse groups for an additional 15 weeks. A dose-related mean group body weight depression was observed in both rats and mice, but no effect on survival was detected.

Under the conditions of this study, methoxychlor was not found to be carcinogenic in Osborne-Mendel rats or B6C3F1 mice of either sex.

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I. INTRODUCTION

Methoxychlor (NCI No. C00497), a synthetic organochlorine insecticide and structural analog of DDT, was one of several widely used agricultural pesticides selected for bioassay by the National Cancer Institute because of a lack of adequate chronic toxicity data. The suspect state of all DDT-related chemicals was an important additional factor in its selection.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 1,1'-(2,2,2-trichloroethylidene)bis (4-methoxy)-benzene.* It is also known as 1,1,1-trichloro-2,2'-bis(p-methoxyphenyl)-ethane; dianisyl trichloroethane; dimethoxy DDT; and DMDT.

Methoxychlor is effective against a wide range of insects that attack fruits, vegetables, shade trees, home gardens, forage crops, and livestock. It is also used for the spray treatment of barns, grain storage bins, mushroom houses, dairies, and other agricultural buildings (Spencer, 1973; Brooks, 1974; Farm Chemicals Handbook, 1976). In 1971, the most recent year for which data are available, more than 3 million pounds of methoxychlor were used in the United States. Of this amount, approximately 2 million pounds were used to protect livestock and livestock buildings, with application to beef and dairy cattle accounting for 95 percent of livestock-related usage. The remaining 1 million pounds of methoxychlor were used to treat 725

*The CAS registry number is 72-43-5.

thousand acres of varied cropland. The major crop treated was alfalfa which accounted for 49 percent of crop-related methoxychlor usage and 66 percent of total treated acreage (Andrilenas, 1974). Although its activity range differs somewhat from that of DDT, methoxychlor is considered to be an excellent replacement for DDT for certain applications (Spencer, 1973; Farm Chemicals Handbook, 1976). It may also substitute in some cases for aldrin, dieldrin, chlordane and heptachlor, all of which have had their registrations cancelled (Ouellette and King, 1976).

According to the U.S. International Trade Commission (1977) 5.504×10^6 pounds of methoxychlor were produced in the United States in 1975, an almost 70 percent increase over 1974 production figures (3.248×10^6 pounds) (Fowler and Mahan, 1976).

The risk of exposure to methoxychlor is greatest for agricultural or farm workers engaged in pesticide application, although workers at pesticide formulating plants may also experience significant contact with the chemical. Since methoxychlor is relatively ineffective against soil organisms (Brooks, 1974), it is generally applied directly to crops via ground or aerial spraying. As a result, contamination of the atmosphere over treated lands and surrounding areas, with possible inhalational exposure of persons residing in those areas, may occur.

Methoxychlor possesses long residual insecticidal activity against many species (Farm Chemicals Handbook, 1976) probably as a

result of its low volatility and relative resistance to oxidation, heat, moisture and ultraviolet irradiation (Brooks, 1974). Consequently, residues may persist on treated crops for a length of time sufficient to permit low-level exposure among the general population. As an example, 5.3 ppm of methoxychlor were detected on alfalfa 33 days following treatment of the crop with 1 pound of insecticide per acre (Miles et al., 1964). A total diet study conducted in 1969-1970 revealed methoxychlor concentrations ranging from 0.008 to 0.05 ppm (Corneliussen, 1972) while total U.S. dietary intake in 1970 amounted to 0.02 μg/kg body weight/day (Duggan and Corneliussen, 1972).

Exposure of the general population through ingestion of contaminated beef or milk probably contributes minimally to total dietary intake since methoxychlor undergoes rapid biodegradation in mammals and shows little tendency to bioaccumulate in tissues (International Agency for Research on Cancer, 1974). An average level of 0.001 ppm methoxychlor was detected in dairy products in the 1960s (Duggan, 1967) while no residues were detected in the body fat of cattle fed 25 ppm methoxychlor in the diet for 16 weeks (Claborn, 1956).

Methoxychlor is generally considered a relatively safe pesticide with a low order of toxicity to humans and other warm blooded animals (Farm Chemicals Handbook, 1976). However, available chronic toxicity studies for assessing carcinogenic potential are either limited in scope or inconclusive. Evaluation of carcinogenicity following skin application or subcutaneous injection was performed only in the mouse.

No tumors were observed in C3H/Anf mice following weekly skin application of 0.1 or 10 mg of methoxychlor in acetone for a total of up to 980 mg or following a single subcutaneous injection of 10 mg of the pesticide in trioctanoin (Hodge et al., 1966).

II. MATERIALS AND METHODS

A. Chemicals

Technical-grade methoxychlor [1,1'-(2,2,2-trichloroethylidene)-bis(4-methoxy)-benzene] was purchased and analyzed by Hazleton Laboratories America, Inc., Vienna, Virginia. The observed melting point (86.5° to 87.5°C) suggested a compound of high purity. Gas-liquid chromatography suggested a purity greater than 95 percent but also indicated the presence of four minor contaminants. Analyses performed 1 and 2 years later showed no substantial change in the results and thus suggested that no decomposition had occurred.

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

B. Dietary Preparation

The basal laboratory diet for both control and treated animals consisted of 2 percent Duke's® corn oil (S.F. Sauer Company) by weight added to Wayne Lab-Blox® meal (Allied Mills, Inc.). Fresh mixtures of methoxychlor in corn oil were prepared weekly and stored in the dark. The mixtures of methoxychlor in corn oil were incorporated into the appropriate amount of basal laboratory diet in a twin-shell blender fitted with an accelerator bar.

C. Animals

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

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

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

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system 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 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 10 in solid-bottom polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Shurfire) were provided once each week for mice. Rats received sanitized cages with no

bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles were provided three times a week. Food and water were available ad libitum.

The methoxychlor-treated and control rats were housed in the same room with other rats receiving diets treated with* p,p'-DDE (72-55-9) and safrole (94-59-7). All mice used in the methoxychlor study, including controls, were housed in the same room as other mice receiving diets treated with trifluralin (1582-09-8), dioxathion (78-34-2), sulfallate (95-06-7), p,p'-DDT (50-29-3), chlorobenzilate (510-15-6), p,p'-DDE (72-55-9), p,p'-TDE (72-54-8), dicofol (115-32-2), pentachloronitrobenzene (82-68-8), amitrole (61-82-5), acetylaminofluorene (53-96-3), clonitralid (1420-04-8), nitrofen (1836-75-5), endosulfan (115-29-7), mexacarbate (315-18-4), and safrole (94-59-7).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of methoxychlor for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. Methoxychlor 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 at concentrations of 316, 562, 1000, 1780, and

*CAS registry numbers are given in parentheses.

3160 ppm and to five of the six mouse groups at concentrations of 1000, 1780, 3160, 5620, and 10,000 ppm. The sixth group of each species served as a control group, receiving only the basal laboratory diet. 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 of corn oil and laboratory chow.

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

The initial high concentrations selected for the chronic study for male and female rats were 720 and 1500 ppm, respectively. The initial high concentrations selected for the chronic study for mice were 2800 ppm for males and 1500 ppm for females.

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.

The high dose, low dose, and control rats were all approximately 6 weeks old at the time they were placed on test. The high and low concentrations of methoxychlor initially utilized for males were 720

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
METHOXYCHLOR FEEDING EXPERIMENT

	INITIAL GROUP SIZE	METHOXYCHLOR CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		111	0
LOW DOSE	50	360	29		448
		500	49		
		0		33	
HIGH DOSE	50	720	29		845
		1000	29		
		1000[c]	16	4	
		0		33	
FEMALE					
CONTROL	20	0		111	0
LOW DOSE	50	750	78		750
		0		33	
HIGH DOSE	50	1500	55		1385
		1500[c]	17	6	
		0		34	

[a] Concentrations given in parts per million.

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

[c] These concentrations were cyclically administered with a pattern of 1 dosage-free week followed by 4 weeks of treatment at the level indicated.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
METHOXYCHLOR FEEDING EXPERIMENT

	INITIAL GROUP SIZE	METHOXYCHLOR CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		92	
LOW DOSE	50	1400	1		1746
		1750	77		
		0		14	
HIGH DOSE	50	2800	1		3491
		3500	77		
		0		15	
FEMALE					
CONTROL	20	0		92	0
LOW DOSE	50	750	1		997
		1000	77		
		0		15	
HIGH DOSE	50	1500	1		1994
		2000	77		
		0		15	

[a] Concentrations given in parts per million.

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

and 360 ppm, respectively. At the end of week 30, the high concentration for males was increased to 1000 ppm and the low concentration was increased to 500 ppm. For females, the initial high and low concentrations of methoxychlor were 1500 and 750 ppm, respectively. In week 56 of the study, administration of methoxychlor to the high dose female rats ceased for 1 week and was then followed by 4 weeks of feeding at the previous concentration of 1500 ppm. This pattern of cyclic administration continued for the remainder of the treatment period. This same method of total intake reduction was employed for the high dose male rats beginning with week 59. Final observations on all rats were made 112 weeks after the experiment was initiated.

The high dose, low dose, and control mice were all approximately 6 weeks old at the time the experiment began. The high and low concentrations initially administered to male mice were 2800 and 1400 ppm, respectively. Female mice received initial high and low concentrations of 1500 and 750 ppm, respectively. At the end of week 2, the high and low concentrations of methoxychlor were increased, respectively, to 3500 and 1750 ppm for male mice and to 2000 and 1000 ppm for female mice. These dosages were maintained until the termination of treatment (week 78). Final observations on all mice were made 93 weeks after the experiment was initiated.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected daily

for mortality. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. The presence of tissue masses was determined by observation and palpation of each animal.

During the course of this bioassay several pathology protocols were in effect, each for different periods of time. The minimum protocol required that, if possible, certain tissues were to be taken and examined histopathologically from all control animals, from any animal in which a tumor was observed during gross examination, and from at least 10 grossly normal males and 10 grossly normal females from each treated group. In addition, any tissues showing gross abnormalities were to be taken and examined histopathologically. Under later protocols, some tissues were taken from additional dosed animals. The number of animals in each group from which a tissue was examined is indicated in Appendices A through D.

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

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

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

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

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) for testing two groups for equality and used Tarone's (1975) extensions of Cox's methods for testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined

histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

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

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship.

This method also provides a two-tailed test of departure from linear trend.

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

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

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

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

of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

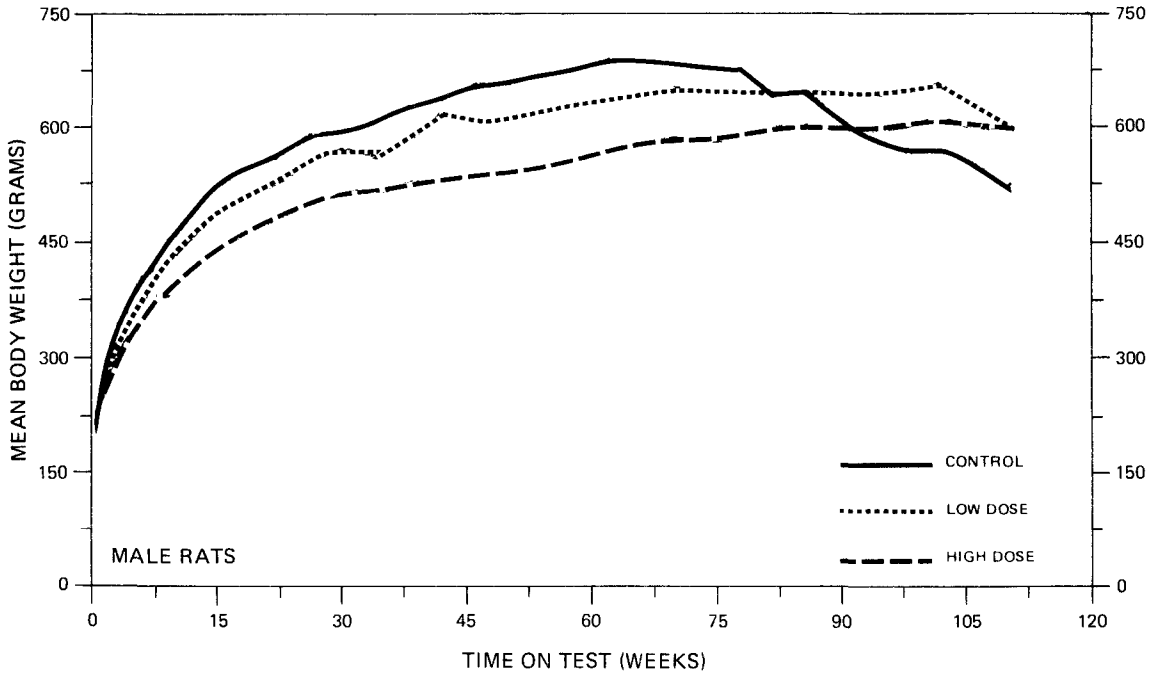
III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

Distinct, dose-related mean body weight depression was apparent throughout the treatment period in both males and females (Figure 1).

During the first 30 weeks of the study, the appearance and behavior of the treated rats were generally comparable with that of the controls, except that occasional hunched appearance, reddened eyes, and abdominal urine stains were noted in one to three treated rats as early as week 4.

From week 34 to cessation of treatment (week 78), some clinical signs were noted with slightly greater frequency in the treated groups than in the controls. During the post-treatment observation period these signs were observed at comparable rates in treated and control animals. These signs included hunched appearance; urine staining; body sores; rough fur; eyes that were cloudy, squinted, or reddened with discharge or crust; and palpable nodules or tissue masses. As the animals aged, the incidence of these signs in all groups gradually increased. Respiratory signs characterized by labored respiration, wheezing, and/or nasal discharge were observed at a low incidence in all groups throughout the study. Isolated, sporadic, and spontaneous observations in one to three rats included circling, small testes, head tilt, "stiff" gait, hind-limb paralysis, ataxia, and transient vaginal discharge.



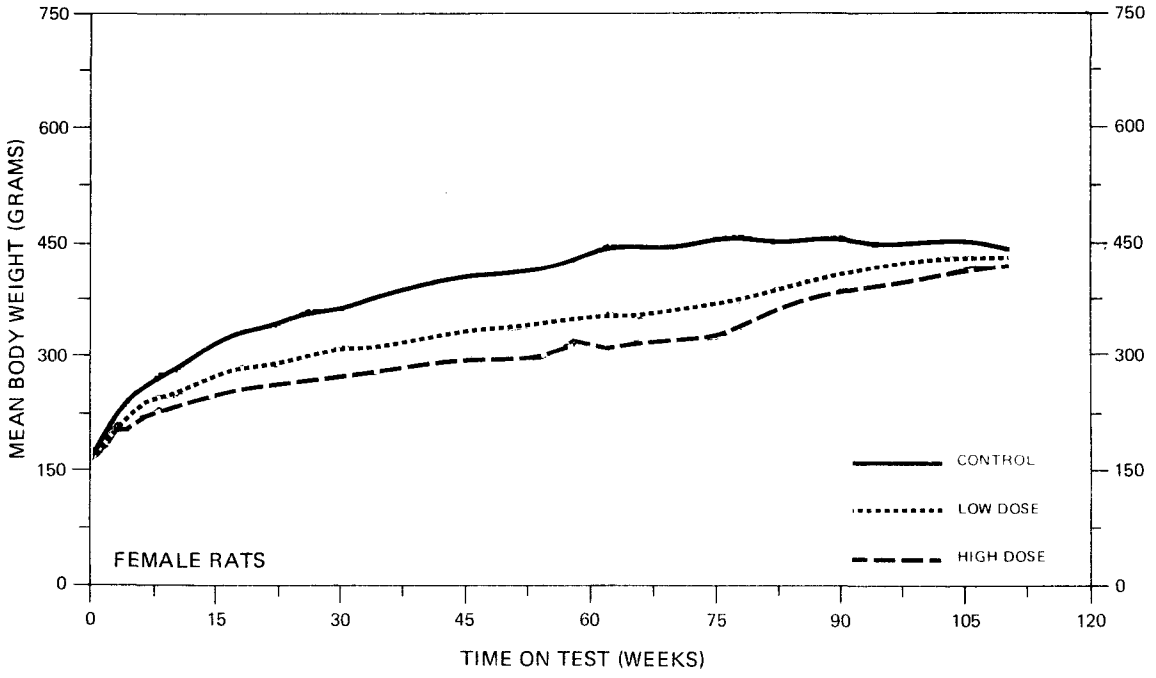


FIGURE 1
GROWTH CURVES FOR METHOXYCHLOR CHRONIC STUDY RATS

B. Survival

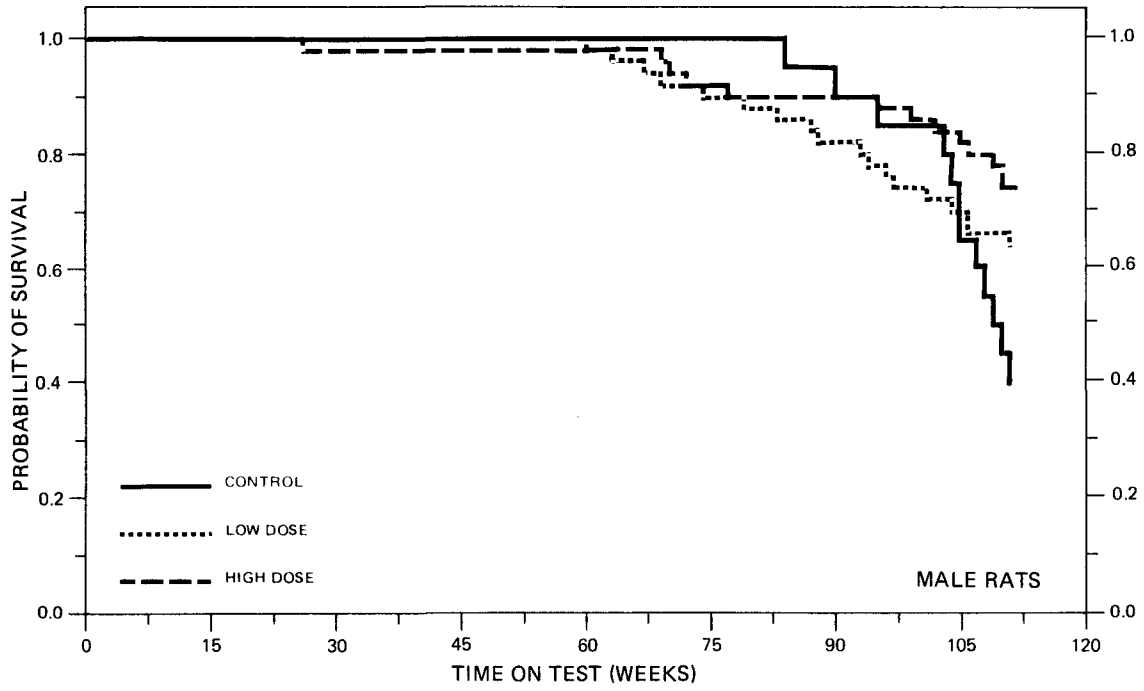
The estimated probabilities of survival for male and female rats in the control and methoxychlor-treated groups are shown in Figure 2. For both male and female rats the Tarone test did not detect a significant positive association between increased dosage and elevated mortality.

For males the actual survival was adequate as 86 percent of the high dose, 74 percent of the low dose and 85 percent of the control rats lived at least 100 weeks. For females the actual survival was also adequate as 94 percent of the high dose, 94 percent of the low dose, and 90 percent of the control rats lived at least 100 weeks.

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).

Hemangiosarcomas were the only tumors observed at unusually high incidences. The hemangiosarcomas occurred in the spleen of 1/20 control males, 6/44 low dose males, 2/42 high dose males, and 1/20 control females. Hemangiosarcomas also occurred as subcutaneous masses in 2/50 low dose males and as an abdominal tissue mass in 1/50 low dose male rats. Thus, there was an increased incidence of hemangiosarcomas at all sites in male rats receiving methoxychlor (9 low dose and 2 high dose) as compared to a single control male and a single control female with these tumors. The lack of a dose response in the



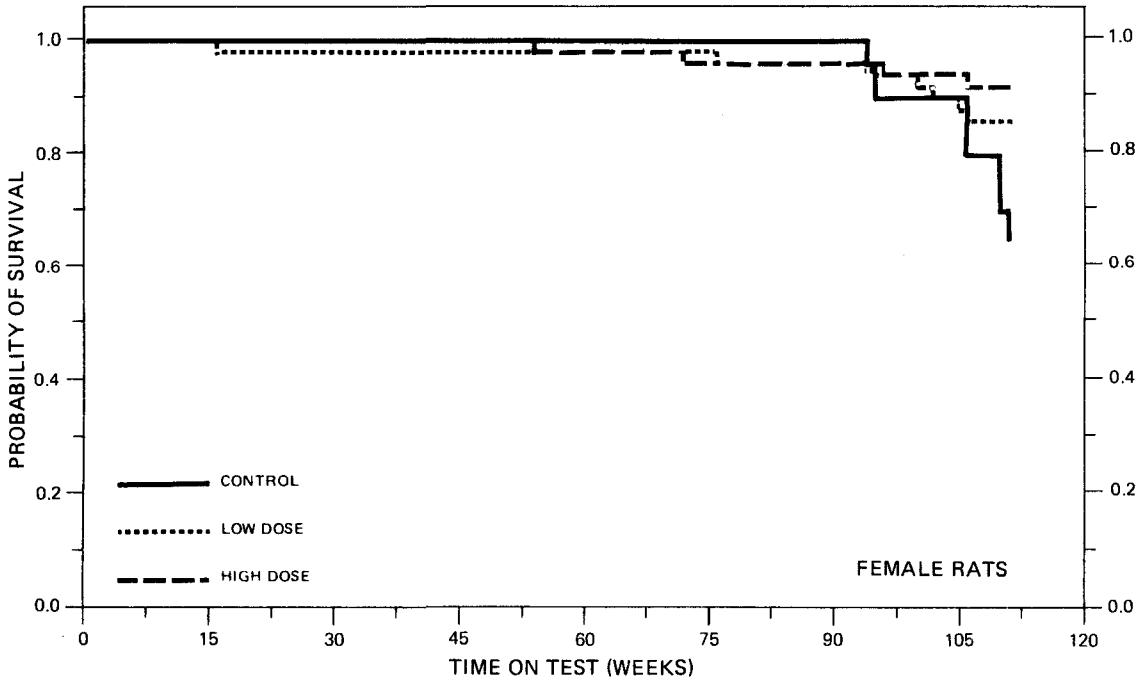


FIGURE 2
SURVIVAL COMPARISONS OF METHOXYCHLOR CHRONIC STUDY RATS

number of male rats with hemangiosarcomas makes this finding of questionable importance even though in our experience hemangiosarcomas occur relatively infrequently in the Osborne-Mendel rat. With the exception of a hemangiosarcoma in the spleen of one control female there were no unusual tumors or any unusual incidences of spontaneous tumors in the female rats.

Microscopically, the hemangiosarcomas consisted of the formation of capillaries and cavernous vascular spaces that often contained blood and were lined with hyperchromatic, plump anaplastic endothelial cells. There was piling up of these cells around the vascular spaces. These cells invaded and replaced the normal architecture of the spleen and involved tissues.

Other neoplasms observed during this examination were seen at incidences often found to occur naturally in untreated aged Osborne-Mendel rats.

Inflammatory, degenerative, and proliferative lesions as seen in the control and treated animals were similar in number and kind to those spontaneous lesions occurring in aged Osborne-Mendel rats.

There was no definitive evidence of the carcinogenicity of methoxychlor in Osborne-Mendel rats.

D. Statistical Analyses of Results

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

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma or Fibrosarcoma[b]	1/20(0.05)	2/50(0.04)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.800	1.200
Lower Limit	---	0.045	0.105
Upper Limit	---	46.273	61.724
Weeks to First Observed Tumor	111	101	26
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	0/19(0.00)	2/37(0.05)	0/37(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.157	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	96	---
Pancreas: Liposarcoma[b]	0/19(0.00)	1/20(0.05)	0/20(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.052	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	79	---

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Kidney: Transitional-Cell Carcinoma[b]	0/19(0.00)	1/21(0.05)	0/28(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.050	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	94	---
Kidney: Fibrous Histiocytoma, Malignant[b]	0/19(0.00)	1/21(0.05)	0/28(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.050	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	96	---
Kidney: Mixed Tumor, Malignant[b]	1/19(0.05)	2/21(0.10)	1/28(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.810	0.679
Lower Limit	---	0.103	0.009
Upper Limit	---	100.601	51.519
Weeks to First Observed Tumor	111	63	111

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Kidney: Hamartoma*[b]	0/19(0.00)	1/21(0.05)	0/28(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.050	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	111	---
Pituitary: Chromophobe Adenoma[b]	3/18(0.17)	8/21(0.38)	4/22(0.18)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.286	1.091
Lower Limit	---	0.662	0.216
Upper Limit	---	11.364	6.582
Weeks to First Observed Tumor	105	69	111
Adrenal: Pheochromocytoma[b]	0/20(0.00)	1/18(0.06)	1/19(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.061	0.058
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	111

*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 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma[b]	0/19(0.00)	4/27(0.15)	1/24(0.04)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.044	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.685	0.044
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	69	111
Thyroid: Follicular-Cell Adenoma[b]	1/19(0.05)	1/27(0.04)	2/24(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.704	1.583
Lower Limit	---	0.010	0.090
Upper Limit	---	53.206	89.314
Weeks to First Observed Tumor	105	111	111
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	1/19(0.05)	5/27(0.19)	3/24(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.519	2.375
Lower Limit	---	0.447	0.212
Upper Limit	---	159.091	118.982
Weeks to First Observed Tumor	105	69	111

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma[b]	2/19(0.11)	0/27(0.00)	2/24(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.792
Lower Limit	---	0.000	0.063
Upper Limit	---	2.319	10.089
Weeks to First Observed Tumor	109	---	110
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	2/19(0.11)	1/27(0.04)	3/24(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.352	1.188
Lower Limit	---	0.006	0.153
Upper Limit	---	6.315	13.079
Weeks to First Observed Tumor	109	111	110
Pancreatic Islets: Islet-Cell Adenoma[b]	0/19(0.00)	1/20(0.05)	1/20(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.052	0.052
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	101	111

TABLE 3 (Concluded)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	0/20(0.00)	0/19(0.00)	1/21(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.052
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	111
Circulatory System: Hemangiosarcoma[b]	1/20(0.05)	9/50(0.18)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.020	---	---
Relative Risk (Control)[d]	---	3.600	0.800
Lower Limit	---	0.562	0.045
Upper Limit	---	154.106	46.273
Weeks to First Observed Tumor	108	87	111

[a]Treated groups received time-weighted average doses of 448 or 845 ppm in feed.

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

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

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

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

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	1/20(0.05)	4/50(0.08)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.600	0.000
Lower Limit	---	0.175	0.000
Upper Limit	---	77.169	7.475
Weeks to First Observed Tumor	94	100	---
Subcutaneous Tissue: Fibroma or Fibrosarcoma[b]	1/20(0.05)	5/50(0.10)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.000	0.400
Lower Limit	---	0.249	0.005
Upper Limit	---	92.596	30.802
Weeks to First Observed Tumor	94	100	72
Pituitary: Chromophobe Adenoma[b]	8/20(0.40)	7/32(0.22)	10/36(0.28)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.547	0.694
Lower Limit	---	0.209	0.308
Upper Limit	---	1.474	1.722
Weeks to First Observed Tumor	106	95	106

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma[b]	0/20(0.00)	2/28(0.07)	0/31(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.220	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	111	---
Thyroid: C-Cell Adenoma[b]	0/20(0.00)	0/28(0.00)	3/31(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.404
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	112
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	0/20(0.00)	1/28(0.04)	3/31(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.039	0.404
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	112

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma NOS[b]	1/20(0.05)	1/50(0.02)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.400	1.200
Lower Limit	---	0.005	0.105
Upper Limit	---	30.802	61.724
Weeks to First Observed Tumor	111	16	106
Mammary Gland: Adenoma or Adenocarcinoma NOS[b]	1/20(0.05)	1/50(0.02)	5/50(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.400	2.000
Lower Limit	---	0.005	0.249
Upper Limit	---	30.802	92.596
Weeks to First Observed Tumor	111	16	106
Uterus: Endometrial Stromal Polyp[b]	0/19(0.00)	1/34(0.03)	4/35(0.11)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.031	0.526
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	111

TABLE 4 (Concluded)

[a]Treated groups received time-weighted average doses of 750 or 1385 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.

None of the statistical tests for rats of either sex indicated a significant positive association between the administration of methoxychlor and an elevated tumor incidence. Thus, at the dose levels used in this experiment there was no statistical evidence that methoxychlor was a carcinogen in Osborne-Mendel rats.

To provide additional insight, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of a significantly increased rate of tumor incidence induced in rats by methoxychlor that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

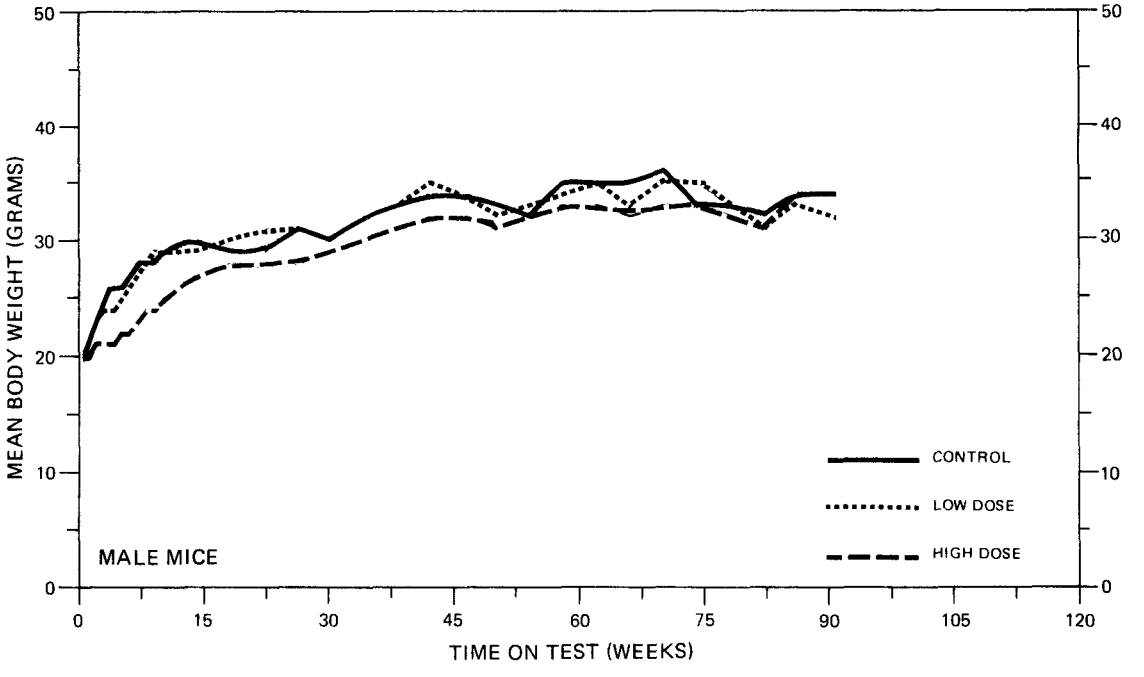
A. Body Weights and Clinical Observations

Distinct, dose-related mean body weight depression was apparent in treated females during the entire bioassay. There were no distinct differences in weight gain patterns of low dose and control male mice; high dose male mice gained slightly less weight than these groups during the treatment period (Figure 3).

Throughout the study there was no definitive evidence of compound effects with regard to physical appearance and behavior of the treated mice. Signs often observed in group-housed laboratory mice, particularly in males, were observed at a comparable rate in treated and control animals. These common signs included sores on the body and/or extremities (more prevalent in the males); a hunched appearance; localized alopecia; penile, vulvar, or anal irritation with apparent sores and abscesses around the inguinal area (more prevalent in male mice); rough or stained fur; bloating; and palpable nodules or tissue masses. Isolated observations in one or two mice from all groups included reddened or squinted eyes and labored respiration.

B. Survival

The estimated probabilities of survival for male and female mice in the control and methoxychlor-treated groups are shown in Figure 4. For both male and female mice the Tarone test did not detect a significant positive association between increased dosage and elevated mortality.



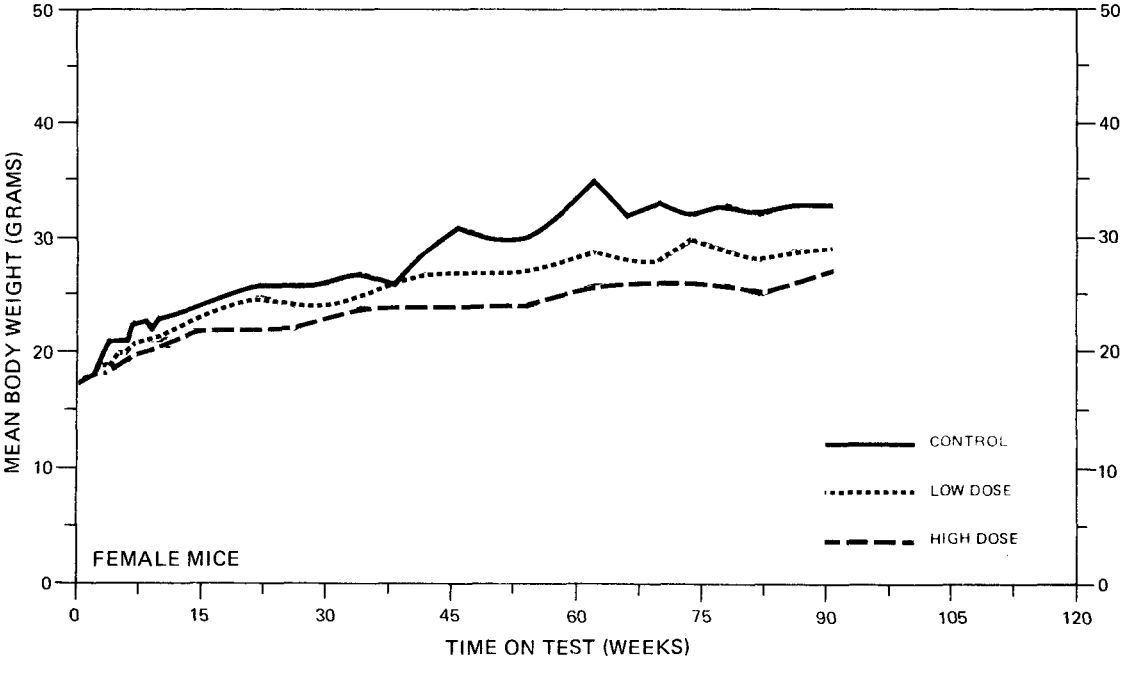


FIGURE 3
GROWTH CURVES FOR METHOXYCHLOR CHRONIC STUDY MICE

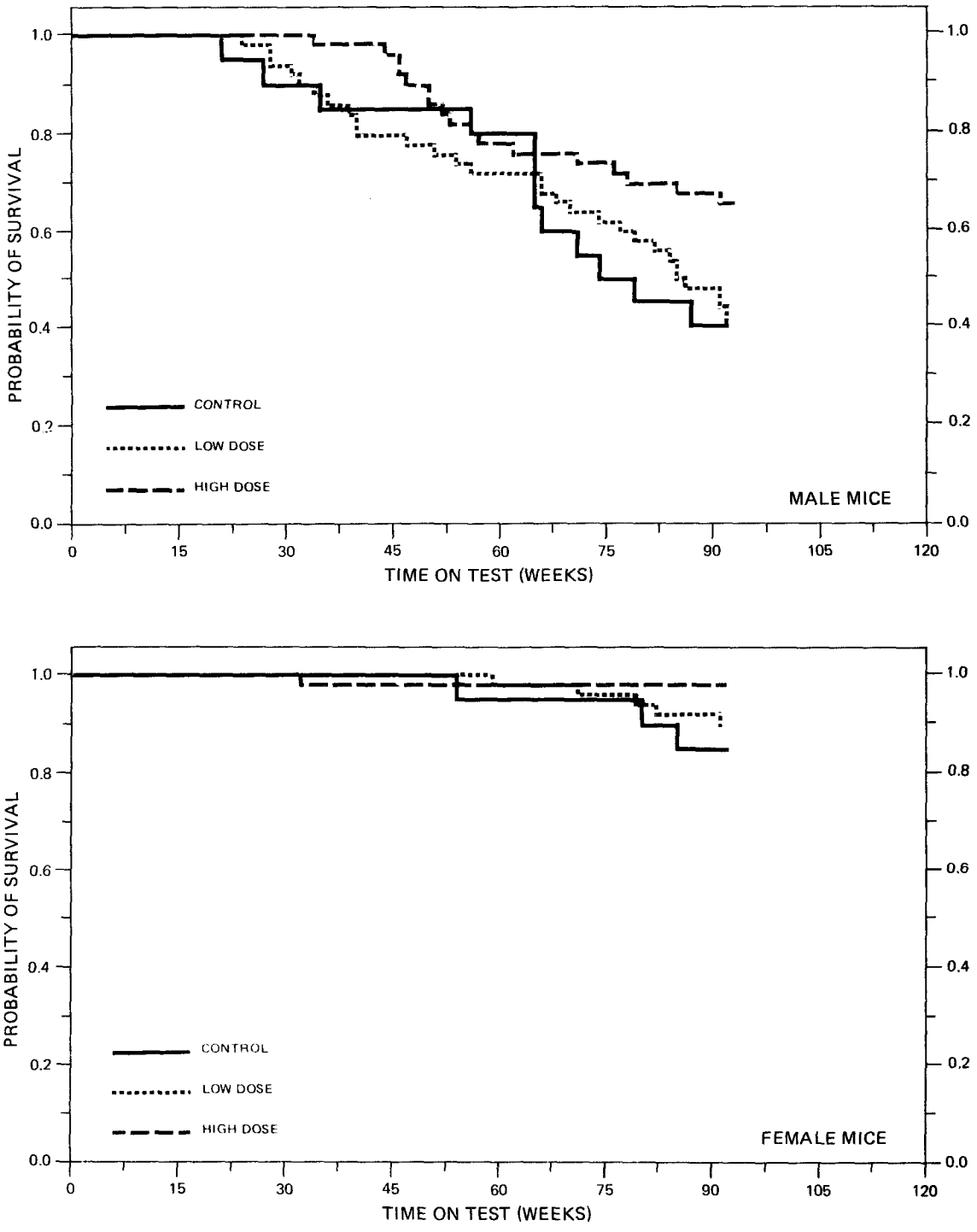


FIGURE 4
SURVIVAL COMPARISONS OF METHOXYCHLOR CHRONIC STUDY MICE

For males the actual survival was adequate as 69 percent of the high dose, 58 percent of the low dose, and 45 percent of the control mice survived over 81 weeks. For females the actual survival was high as 98 percent of the high dose, 90 percent of the low dose, and 85 percent of the control mice survived until the end of the test.

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).

A variety of neoplasms were observed among both treated and control mice. Each of the types of tumors represented has been encountered previously as a naturally occurring lesion in B6C3F1 mice, and is without apparent relationship to the administration of the chemical.

The inflammatory, degenerative, and proliferative lesions that occurred in the control and treated animals were also without appreciable differences in number and kind from those spontaneous lesions occurring in aged B6C3F1 mice.

No evidence for the carcinogenicity of methoxychlor in B6C3F1 mice was provided by this histopathologic examination.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis for every type

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	1/12(0.08)	2/44(0.05)	2/47(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.545	0.511
Lower Limit	---	0.032	0.031
Upper Limit	---	31.472	29.570
Weeks to First Observed Tumor	92	86	71
Liver: Hepatocellular Carcinoma[b]	3/13(0.23)	3/36(0.08)	6/32(0.19)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.361	0.813
Lower Limit	---	0.058	0.216
Upper Limit	---	2.452	4.490
Weeks to First Observed Tumor	91	85	92

[a]Treated groups received time-weighted average doses of 1746 or 3491 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 6

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	1/20(0.05)	5/46(0.11)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.174	0.400
Lower Limit	---	0.271	0.005
Upper Limit	---	100.415	30.802
Weeks to First Observed Tumor	92	79	93
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	1/17(0.06)	0/14(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.064	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	93	---
Uterus: Endometrial Stromal Polyp[b]	1/20(0.05)	0/17(0.00)	1/13(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	1.538
Lower Limit	---	0.000	0.021
Upper Limit	---	21.164	111.057
Weeks to First Observed Tumor	92	---	93

TABLE 6 (Concluded)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Ovary: Cystadenoma NOS[b]	0/20(0.00)	0/17(0.00)	1/14(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.079
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	93

[a]Treated groups received time-weighted average doses of 997 or 1994 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.

of tumor that was observed in more than 5 percent of any of the methoxychlor-dosed groups of either sex is included.

None of the statistical tests for mice of either sex indicated a significant positive association between the administration of methoxychlor and increased tumor incidence. Thus, at the dose levels used in this experiment, there was no statistical evidence that methoxychlor was a carcinogen in B6C3F1 mice.

To provide additional insight, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 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 a significantly increased rate of tumor incidence induced in mice by methoxychlor that could not be established under the conditions of this test.

V. DISCUSSION

Under the conditions of this bioassay, dietary administration of methoxychlor was not associated with an increased incidence of any type of neoplasm in rats or mice of either sex. No statistically significant positive association was demonstrated between dosage and mortality. In all treated groups there was dose-related mean body weight depression when compared to controls.

Although hemangiosarcomas occur relatively infrequently in Osborne-Mendel rats, the occurrence of these neoplasms in males (nine low dose and two high dose) in this bioassay is not considered to be compound-related, primarily due to the absence of a dose-related response. No significant statistical association was established between methoxychlor treatment and the incidence of any tumor in either male or female rats.

The pathologist detected no tumors of histopathologic significance in mice of either sex, and no tumors in dosed mice were observed at statistically significant incidences.

Methoxychlor has been previously assayed by the oral route in the rat. In two studies (Radomski et al., 1965; Deichmann et al., 1967), the incidence and distribution of both benign and malignant tumors were similar in treated and control groups; while in a third study (Hodge et al., 1952) the variety of tumors observed in the treated animals, but not observed in the controls (with the exception of one adenocarcinoma of the pancreas), was attributed to coincidence

since all these tumors commonly occurred in this particular colony of rats. None of these three studies presented evidence of the carcinogenicity of methoxychlor in rats.

Under the conditions of the present bioassay, methoxychlor was not found to be carcinogenic in Osborne-Mendel rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH METHOXYCHLOR

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

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	44	41
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
FIBROSARCOMA			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA	1 (5%)	2 (4%)	2 (4%)
FIBROSARCOMA			1 (2%)
LIPOSARCOMA	1 (5%)		
HEMANGIOSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(20)	(23)
HEPATOCELLULAR CARCINOMA, METAST		1 (5%)	
FIBROSARCOMA, METASTATIC			1 (4%)
MIXED TUMOR, METASTATIC		1 (5%)	
OSTEOSARCOMA, METASTATIC	1 (5%)		1 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
*SUBCUT TISSUE/BACK	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#SPLEEN	(20)	(44)	(42)
HEMANGIOSARCOMA	1 (5%)	6 (14%)	2 (5%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
DIGESTIVE SYSTEM			
#LIVER	(19)	(37)	(37)
NEOPLASTIC NODULE		1 (3%)	
HEPATOCELLULAR CARCINOMA		1 (3%)	
#PANCREAS	(19)	(20)	(20)
LIPOSARCOMA		1 (5%)	
URINARY SYSTEM			
#KIDNEY	(19)	(21)	(28)
TRANSITIONAL-CELL CARCINOMA		1 (5%)	
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (5%)	
MIXED TUMOR, MALIGNANT	1 (5%)	2 (10%)	1 (4%)
OSTEOSARCOMA, METASTATIC	1 (5%)		
HAMARTOMA+		1 (5%)	
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(21)	(22)
CHROMOPHOBE ADENOMA	3 (17%)	8 (38%)	4 (18%)
#ADRENAL	(20)	(18)	(19)
CORTICAL CARCINOMA	1 (5%)		
PHEOCHROMOCYTOMA		1 (6%)	1 (5%)
#THYROID	(19)	(27)	(24)
FOLLICULAR-CELL ADENOMA	1 (5%)	1 (4%)	2 (8%)
FOLLICULAR-CELL CARCINOMA		4 (15%)	1 (4%)
C-CELL ADENOMA	2 (11%)		2 (8%)
C-CELL CARCINOMA		1 (4%)	1 (4%)
#PANCREATIC ISLETS	(19)	(20)	(20)
ISLET-CELL ADENOMA		1 (5%)	1 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS		1 (2%)	1 (2%)
#TESTIS	(20)	(19)	(21)
INTERSTITIAL-CELL TUMOR			1 (5%)

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

TABLE A 1 (CONTINUED)

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
*EPIDIDYMIS	(20)	(50)	(50)
FIBROSARCOMA			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*VERTEBRAL COLUMN	(20)	(50)	(50)
OSTEOSARCOMA	2 (10%)		
*BONE/UPPER EXTREMITY	(20)	(50)	(50)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
FIBROSARCOMA			1 (2%)
HEMANGIOSARCOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	11	17	13
MORIBUND SACRIFICE	1	1	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	8	32	37
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	23	21
TOTAL PRIMARY TUMORS	13	37	26
TOTAL ANIMALS WITH BENIGN TUMORS	7	13	11
TOTAL BENIGN TUMORS	7	15	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	17	11
TOTAL MALIGNANT TUMORS	6	21	12
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	2
TOTAL SECONDARY TUMORS	2	2	2
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

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

	CONTROL (VEH) 01-F023	LOW DOSE 01-F026	HIGH DOSE 01-F027
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	47	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
FIBROMA	1 (5%)	4 (8%)	
FIBROSARCOMA		1 (2%)	1 (2%)
LIPOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(33)	(33)
SQUAMOUS CELL CARCINOMA, METASTA		1 (3%)	
HEPATOCELLULAR CARCINOMA, METAST	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
#SPLEEN	(20)	(46)	(48)
HEMANGIOSARCOMA	1 (5%)		
CIRCULATORY SYSTEM			
#ENDOCARDIUM	(20)	(32)	(30)
SARCOMA, NOS		1 (3%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(46)	(47)
NEOPLASTIC NODULE		1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	1 (5%)		1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F023	LOW DOSE 01-F026	HIGH DOSE 01-F027
*BILE DUCT	(20)	(50)	(50)
BILE DUCT ADENOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(32)	(30)
HAMARTOMA+	1 (5%)		
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(32)	(36)
CHROMOPHOBE ADENOMA	8 (40%)	7 (22%)	10 (28%)
#THYROID	(20)	(28)	(31)
FOLLICULAR-CELL ADENOMA		2 (7%)	
C-CELL ADENOMA			3 (10%)
C-CELL CARCINOMA		1 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS			2 (4%)
ADENOCARCINOMA, NOS	1 (5%)	1 (2%)	3 (6%)
FIBROADENOMA	8 (40%)	16 (32%)	9 (18%)
*VAGINA	(20)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
#UTERUS	(19)	(34)	(35)
ENDOMETRIAL STROMAL POLYP		1 (3%)	4 (11%)
#OVARY	(19)	(30)	(30)
CYSTADENOMA, NOS			1 (3%)
FIBROSARCOMA		1 (3%)	
NERVOUS SYSTEM			
#CEREBRUM	(20)	(32)	(30)
ASTROCYTOMA			1 (3%)
SPECIAL SENSE ORGANS			
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 A2 (CONTINUED)

	CONTROL (VEH) 01-F023	LOW DOSE 01-F026	HIGH DOSE 01-F027
MUSCULOSKELETAL SYSTEM			
*VERTEBRAL COLUMN	(20)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
FIBROMA		1 (2%)	
OSTEOSARCOMA, METASTATIC		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	3	4
MORIBUND SACRIFICE	1	4	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	43	46
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (VEH) 01-F023	LOW DOSE 01-F026	HIGH DOSE 01-F027
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	30	30
TOTAL PRIMARY TUMORS	22	41	37
TOTAL ANIMALS WITH BENIGN TUMORS	12	24	26
TOTAL BENIGN TUMORS	18	32	30
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	8	6
TOTAL MALIGNANT TUMORS	4	8	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	
TOTAL SECONDARY TUMORS	1	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH METHOXYCHLOR

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

	CONTROL (VEH) 02-M024	LOW DOSE 02-M025	HIGH DOSE 02-M026
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	12	44	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	12	35	31
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(12)	(44)	(47)
FIBROSARCOMA	1 (8%)	2 (5%)	2 (4%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(12)	(44)	(47)
GRANULOCYTIC LEUKEMIA			2 (4%)
#CERVICAL LYMPH NODE	(13)	(36)	(31)
FIBROSARCOMA, METASTATIC			1 (3%)
#MESENTERIC L. NODE	(13)	(36)	(31)
FIBROSARCOMA, METASTATIC			1 (3%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(13)	(36)	(32)
HEPATOCELLULAR CARCINOMA	3 (23%)	3 (8%)	6 (19%)
URINARY SYSTEM			
NONE			

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

TABLE B1 (CONTINUED)

	CONTROL (VEH) 02-M024	LOW DOSE 02-M025	HIGH DOSE 02-M026
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	12	28	17
MORIBUND SACRIFICE		2	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	8	20	32
ANIMAL MISSING			1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	CONTROL (VEH) 02-M024	LOW DOSE 02-M025	HIGH DOSE 02-M026
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	5	9
TOTAL PRIMARY TUMORS	4	5	10
TOTAL ANIMALS WITH BENIGN TUMORS			
TOTAL BENIGN TUMORS			
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	5	9
TOTAL MALIGNANT TUMORS	4	5	10
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
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 B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH METHOXYCHLOR

	CONTROL(VEH) 02-F024	LOW DOSE 02-F027	HIGH DOSE 02-F028
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	46	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	16	14
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(46)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		4 (9%)	1 (2%)
#COLON	(20)	(17)	(14)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (6%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(17)	(14)
HEPATOCELLULAR CARCINOMA		1 (6%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(17)	(13)
CORTICAL ADENOMA	1 (5%)		

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

TABLE B2 (CONTINUED)

	CONTROL (VEH) 02-F024	LOW DOSE 02-F027	HIGH DOSE 02-F028
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(17)	(13)
ENDOMETRIAL STROMAL POLYP	1 (5%)		1 (8%)
#OVARY	(20)	(17)	(14)
CYSTADENOMA, NOS			1 (7%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	5	1
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	44	49
ANIMAL MISSING		1	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL (VEH) 02-F024	LOW DOSE 02-F027	HIGH DOSE 02-F028
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	6	3
TOTAL PRIMARY TUMORS	3	6	3
TOTAL ANIMALS WITH BENIGN TUMORS	2		2
TOTAL BENIGN TUMORS	2		2
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	6	1
TOTAL MALIGNANT TUMORS	1	6	1
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 METHOXYCHLOR

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

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	44	41
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST		2 (4%)	1 (2%)
INFLAMMATION, NOS	4 (20%)		
ABSCESS, NOS	1 (5%)		
*SUBCUT TISSUE	(20)	(50)	(50)
ABSCESS, NOS	2 (10%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(20)	(23)
PNEUMONIA, CHRONIC MURINE	3 (15%)	3 (15%)	1 (4%)
#ALVEOLAR WALL	(20)	(20)	(23)
MINERALIZATION	1 (5%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(18)	(20)
METAMORPHOSIS FATTY	1 (5%)		
#SPLEEN	(20)	(44)	(42)
HYPERTROPHY, NOS			1 (2%)
HEMATOPOIESIS	1 (5%)	3 (7%)	2 (5%)
CIRCULATORY SYSTEM			
#HEART	(20)	(21)	(20)
ARTERIOSCLEROSIS, NOS	1 (5%)		
CALCIUM DEPOSIT	1 (5%)		
#MYOCARDIUM	(20)	(21)	(20)
INFLAMMATION, NOS		2 (10%)	
DEGENERATION, NOS	8 (40%)	6 (29%)	6 (30%)

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
#ENDOCARDIUM	(20)	(21)	(20)
INFLAMMATION, NOS		2 (10%)	
HYPERPLASIA, NOS	1 (5%)		1 (5%)
*AORTA	(20)	(50)	(50)
ARTERIOSCLEROSIS, NOS	1 (5%)	1 (2%)	
MEDIAL CALCIFICATION	2 (10%)		
CALCIUM DEPOSIT		1 (2%)	
*MESENTERIC ARTERY	(20)	(50)	(50)
ARTERIOSCLEROSIS, NOS	2 (10%)		
DIGESTIVE SYSTEM			
#LIVER	(19)	(37)	(37)
CYST, NOS	1 (5%)		1 (3%)
THROMBOSIS, NOS		1 (3%)	
INFLAMMATION, NOS		3 (8%)	
INFLAMMATION, GRANULOMATOUS			1 (3%)
METAMORPHOSIS FATTY	4 (21%)	4 (11%)	3 (8%)
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)		1 (2%)
#PANCREAS	(19)	(20)	(20)
PERIARTERITIS	1 (5%)		
#STOMACH	(20)	(20)	(21)
INFLAMMATION, NOS		1 (5%)	
ULCER, FOCAL	1 (5%)	2 (10%)	1 (5%)
CALCIUM DEPOSIT	3 (15%)		
URINARY SYSTEM			
#KIDNEY	(19)	(21)	(28)
INFLAMMATION, SUPPURATIVE		2 (10%)	
INFLAMMATION, CHRONIC	12 (63%)	3 (14%)	9 (32%)
NEPHROPATHY, TOXIC		1 (5%)	1 (4%)
ENDOCRINE SYSTEM			
#ADRENAL	(20)	(18)	(19)
ANGIECTASIS	1 (5%)		

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
#THYROID	(19)	(27)	(24)
CYSTIC FOLLICLES			1 (4%)
HYPERPLASIA, C-CELL		1 (4%)	
#PARATHYROID	(19)	(27)	(23)
HYPERPLASIA, NOS	2 (11%)	3 (11%)	2 (9%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
GALACTOCELE	1 (5%)	1 (2%)	
#TESTIS	(20)	(19)	(21)
INFLAMMATION, NOS			1 (5%)
CALCIUM DEPOSIT	1 (5%)		
ATROPHY, NOS	6 (30%)	2 (11%)	8 (38%)
*EPIDIDYMIS	(20)	(50)	(50)
ATROPHY, NOS	3 (15%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
CATARACT		1 (2%)	
*EYE/CORNEA	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*EYE/CILIARY BODY	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*EYE/IRIS	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*EYE/RETINA	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*EYE/CONJUNCTIVA	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	

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

TABLE C1 (CONCLUDED)

	CONTROL (VEH) 01-M023	LOW DOSE 01-M024	HIGH DOSE 01-M025
MUSCULOSKELETAL SYSTEM			
*MUSCLE HIP/THIGH	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
DEGENERATION, NOS			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
NECROSIS, FAT	1 (5%)	3 (6%)	1 (2%)
*PERICARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)	1 (2%)	
*MESENTERY	(20)	(50)	(50)
PERIARTERITIS	1 (5%)		1 (2%)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	12	10
NECROPSY PERF/NO HISTO PERFORMED		6	6
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO			3

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 METHOXYCHLOR

	CONTROL (VEH) 01-F023	LOW DOSE 01-F026	HIGH DOSE 01-F027
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	47	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(33)	(33)
INFLAMMATION, SUPPURATIVE			1 (3%)
PNEUMONIA, CHRONIC MURINE	3 (15%)	1 (3%)	2 (6%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(46)	(48)
HEMATOPOIESIS	3 (15%)	1 (2%)	2 (4%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(32)	(30)
DEGENERATION, NOS	2 (10%)	4 (13%)	4 (13%)
#ENDOCARDIUM	(20)	(32)	(30)
HYPERPLASIA, NOS		1 (3%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(46)	(47)
INFLAMMATION, CHRONIC		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
FOCAL CELLULAR CHANGE			1 (2%)
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F023	LOW DOSE 01-F026	HIGH DOSE 01-F027
#STOMACH	(20)	(31)	(31)
ULCER, FOCAL	2 (10%)		
URINARY SYSTEM			
#KIDNEY	(20)	(32)	(30)
HYDRONEPHROSIS		1 (3%)	
INFLAMMATION, SUPPURATIVE	1 (5%)		
INFLAMMATION, CHRONIC	3 (15%)	1 (3%)	5 (17%)
CALCIUM DEPOSIT			1 (3%)
ENDOCRINE SYSTEM			
#ADRENAL	(20)	(30)	(31)
ANGIECTASIS		1 (3%)	1 (3%)
#PARATHYROID	(19)	(28)	(31)
HYPERPLASIA, NOS	1 (5%)		
REPRODUCTIVE SYSTEM			
*VAGINA	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)		
POLYP			1 (2%)
#UTERUS	(19)	(34)	(35)
HYDROMETRA	2 (11%)	3 (9%)	4 (11%)
CYST, NOS			1 (3%)
INFLAMMATION, NOS	1 (5%)	3 (9%)	
#CERVIX UTERI	(19)	(34)	(35)
EPIDERMAL INCLUSION CYST			1 (3%)
INFLAMMATION, NOS		1 (3%)	
#UTERUS/ENDOMETRIUM	(19)	(34)	(35)
HYPERPLASIA, CYSTIC		5 (15%)	2 (6%)
NERVOUS SYSTEM			
NONE			

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

TABLE C2 (CONCLUDED)

	CONTROL (VEH) 01-F023	LOW DOSE 01-F026	HIGH DOSE 01-F027
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
SYNECHIA, POSTERIOR			1 (2%)
CATARACT		2 (4%)	2 (4%)
CALCIUM DEPOSIT			1 (2%)
*EYE/RETINA	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
NECROSIS, FAT		1 (2%)	
*MESENTERY	(20)	(50)	(50)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	12	12
NECROPSY PERF/NO HISTO PERFORMED		3	1

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

APPENDIX D

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

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

	CONTROL (VEH) 02-M024	LOW DOSE 02-M025	HIGH DOSE 02-M026
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	12	44	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	12	35	31
INTEGUMENTARY SYSTEM			
*SKIN	(12)	(44)	(47)
INFLAMMATION, NOS		2 (5%)	
*SUBCUT TISSUE	(12)	(44)	(47)
ABSCESS, NOS			3 (6%)
RESPIRATORY SYSTEM			
#LUNG	(13)	(36)	(33)
PNEUMONIA, CHRONIC MURINE		2 (6%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(12)	(36)	(33)
AMYLOIDOSIS	4 (33%)	9 (25%)	2 (6%)
HEMATOPOIESIS		1 (3%)	1 (3%)
#MESENTERIC L. NODE	(13)	(36)	(31)
CONGESTION, NOS	1 (8%)		
EDEMA, NOS	1 (8%)		
CIRCULATORY SYSTEM			
#HEART	(13)	(36)	(33)
THROMBOSIS, NOS		2 (6%)	
#MYOCARDIUM	(13)	(36)	(33)
INFLAMMATION, NOS		1 (3%)	
DEGENERATION, NOS		1 (3%)	
*AORTA	(12)	(44)	(47)
THROMBUS, ORGANIZED		1 (2%)	

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M024	LOW DOSE 02-M025	HIGH DOSE 02-M026
DIGESTIVE SYSTEM			
#LIVER	(13)	(36)	(32)
INFLAMMATION, NOS		1 (3%)	
METAMORPHOSIS FATTY	1 (8%)		
URINARY SYSTEM			
#KIDNEY	(12)	(36)	(33)
HYDRONEPHROSIS	1 (8%)	1 (3%)	
CYST, NOS			1 (3%)
PYELONEPHRITIS, NOS	1 (8%)	2 (6%)	1 (3%)
INFLAMMATION, CHRONIC	3 (25%)	8 (22%)	1 (3%)
AMYLOIDOSIS	1 (8%)	4 (11%)	
CALCIUM DEPOSIT		2 (6%)	
#URINARY BLADDER	(11)	(35)	(33)
INFLAMMATION, NOS		1 (3%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(12)	(44)	(47)
INFLAMMATION, NOS	1 (8%)		
*SEMINAL VESICLE	(12)	(44)	(47)
INFLAMMATION, NOS		1 (2%)	
ATROPHY, NOS		1 (2%)	
#TESTIS	(11)	(35)	(32)
CALCIUM DEPOSIT		1 (3%)	
ATROPHY, NOS		3 (9%)	
*EPIDIDYMIS	(12)	(44)	(47)
INFLAMMATION, NOS			1 (2%)
GRANULOMA, SPERMATIC			5 (11%)
*SCROTUM	(12)	(44)	(47)
INFLAMMATION, NOS		2 (5%)	
NERVOUS SYSTEM			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL (VEH) 02-M024	LOW DOSE 02-M025	HIGH DOSE 02-M026
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	11	13
ANIMAL MISSING/NO NECROPSY			1
NECROPSY PERF/NO HISTO PERFORMED		9	16
AUTO/NECROPSY/HISTO PERF		4	
AUTOLYSIS/NO NECROPSY	8	6	2

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH METHOXYCHLOR

	CONTROL (VEH) 02-F024	LOW DOSE 02-F027	HIGH DOSE 02-F028
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	46	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	16	14
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#STOMACH	(20)	(17)	(14)
INFLAMMATION, NOS			1 (7%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(17)	(13)
HYDROMETRA	4 (20%)	1 (6%)	
INFLAMMATION, NOS		1 (6%)	

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

TABLE D2 (CONCLUDED)

	CONTROL (VEH) 02-F024	LOW DOSE 02-F027	HIGH DOSE 02-F028
#UTERUS/ENDOMETRIUM	(20)	(17)	(13)
HYPERPLASIA, CYSTIC	3 (15%)	4 (24%)	
#OVARY	(20)	(17)	(14)
CYST, NOS	5 (25%)	2 (12%)	
INFLAMMATION, NOS		1 (6%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(20)	(46)	(50)
INFLAMMATION, NOS	1 (5%)		
CATARACT	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	6	6	10
ANIMAL MISSING/NO NECROPSY		1	
NECROPSY PERF/NO HISTO PERFORMED		30	36
AUTOLYSIS/NO NECROPSY		3	

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

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

November 28, 1977

The Clearinghouse on Environmental Carcinogens was established in May, 1976 under the authority of the National Cancer Act of 1971 (P.L. 92-218). The purpose of the Clearinghouse is to advise on the National Cancer Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in organic chemistry, 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 NCI bioassay reports on chemicals studied for carcinogenicity. In this context, below is the edited excerpt from the minutes of the Subgroup's meeting at which Methoxychlor was reviewed.

The primary reviewer agreed with the conclusion stated in the report, i.e., that Methoxychlor was not carcinogenic in either the rats or mice under the conditions of test. An experimental shortcoming, mentioned by the reviewer, was that other chemicals were tested at the same time and in the same room as Methoxychlor. He also noted that the treated animals were stressed as a result of the high dosages tested and that the number of matched control animals were inadequate. In conclusion, he opined that Methoxychlor is a safe pesticide with respect to human risk.

A motion was made that the report on the bioassay of Methoxychlor be accepted. The motion was seconded and approved unanimously.

Members present were:

Gerald N. Wogan (Chairman), Massachusetts Institute of Technology
Lawrence Garfinkel, American Cancer Society
Henry C. Pitot, University of Wisconsin Medical Center
George Roush, Jr., Monsanto Company
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
John H. Weisburger, American Health Foundation

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

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