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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogen Bioassay and Program Resources Branch
Carcinogenesis Program
Division of Cancer Cause and Prevention
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CONTRIBUTORS: This report presents the results of the bioassays of aldrin and dieldrin for possible carcinogenicity, conducted for the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. This bioassay was conducted by the Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI carcinogenesis bioassay program.

The experimental design was determined by Drs. J. H. Weisburger[1,2] and R. R. Bates[1,3]. The doses were selected by Drs. T. E. Shellenberger[4,5], J. H. Weisburger, and R. R. Bates. Animal treatment and observation were supervised by Drs. T. E. Shellenberger and H. P. Burchfield[4], with the technical assistance of Ms. D. H. Monceaux[4] and Mr. D. Broussard[4].

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Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[8]. The statistical analyses were performed by Dr. J. R. Joiner[9], using methods selected for the bioassay program by Dr. J. J. Gart[10]. Chemicals used in these bioassays were analyzed under the direction of Dr. H. P. Burchfield, and the analytical results were reviewed by Dr. S. S. Olin[9].

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SUMMARY

Bioassays of technical-grade aldrin and dieldrin for possible carcinogenicity were conducted by administering the test materials in feed to Osborne-Mendel rats and B6C3F1 mice.

Aldrin

Groups of 50 rats of each sex were administered aldrin at one of two doses, either 30 or 60 ppm. Male rats were treated for 74 weeks, followed by 37-38 weeks of observation; female rats were treated for 80 weeks, followed by 32-33 weeks of observation. Matched controls consisted of groups of 10 untreated rats of each sex; pooled controls, used for statistical evaluation, consisted of the matched-control groups combined with 58 untreated males and 60 untreated females from similar bioassays of other chemicals. All surviving rats were killed at 111-113 weeks.

Groups of 50 mice of each sex were administered aldrin at one of two doses for 80 weeks, then observed for 10-13 weeks. Time-weighted average doses were 4 or 8 ppm for males and 3 or 6 ppm for females. Matched controls consisted of groups of 20 untreated male mice and 10 female mice; pooled controls, used for statistical evaluation, consisted of the matched-control groups combined with 92 untreated male and 79 untreated female mice from similar bioassays of other chemicals. All surviving mice were killed at 90-93 weeks.

Mean body weights attained by the rats and mice fed diets containing aldrin were similar to those of the controls during the first year of the study; however, mean body weights of the treated rats were lower than those of the controls during the second year of the study. Hyperexcitability was observed in all treated groups with increasing frequency and severity during the second year. Aldrin produced no significant effect on the mortality of rats or of male mice, but there was a dose-related trend in the mortality of female mice, primarily due to the early deaths in the high-dose groups.

There was an increased combined incidence of follicular-cell adenoma and carcinoma of the thyroid both in male rats fed aldrin (matched controls 3/7, pooled controls 4/48, low-dose 14/38, high-dose 8/38) and female rats fed aldrin (matched controls 1/9, pooled controls 3/52, low-dose 10/39, high-dose 7/46). These incidences were significant in the low-dose but not in the high-dose groups both of males ($P = 0.001$) and females ($P = 0.009$) when compared with the pooled controls. Comparisons with matched controls, however, were not significant.

Cortical adenoma of the adrenal gland was also observed in aldrin-treated rats in significant proportions ($P = 0.001$) in low-dose (8/45) but not in high-dose (1/48) females when compared with pooled controls (0/55). Because these increased incidences were not consistently significant when compared with matched rather than pooled control groups, it is questionable whether the incidences of any of these adrenal tumors were associated with treatment.

In male mice, there was a significant dose-related increase in the incidence of hepatocellular carcinomas (matched controls 3/20, pooled controls 17/92, low-dose 16/49, high-dose 25/45) when compared with either matched controls ($P = 0.001$), or pooled controls ($P < 0.001$). The incidence in the high-dose group was significant when compared with matched controls ($P = 0.002$) or pooled controls ($P < 0.001$).

Dieldrin

Groups of 50 rats and 50 mice of each sex were administered dieldrin at one of two doses. Low-dose rats and both low- and high-dose mice were treated for 80 weeks, followed by observation periods of 30-31 weeks for rats and 10-13 weeks for mice. Treatment of high-dose rats was terminated after 59 weeks and followed by 51-52 weeks of observation. Time-weighted average doses for rats were 29 or 65 ppm; doses for mice were 2.5 or 5 ppm. Matched controls consisted of groups of 10 untreated rats of each sex and 20 untreated male mice and 10 female mice; pooled controls, used for statistical evaluation, consisted of the matched-control groups combined with untreated animals from similar bioassays of other chemicals (58 male and 60 female rats,

92 male and 79 female mice). All surviving rats were killed at 110-111 weeks, and all surviving mice at 90-93 weeks.

Mean body weights attained by the rats and mice fed diets containing dieldrin showed little or no differences compared with those of the controls during the first year of the study; however, mean body weights of the treated rats were lower than those of the controls during the second year of the study. Hyperexcitability was observed in all treated groups with increasing frequency during the second year, especially in high-dose rats.

There was a marked increase in the mortality rate of rats during the first 90 weeks of the study. However, because of the high rates of mortality in the control groups during the remaining 20 weeks, survival could not be shown to be statistically dose responsive.

In rats, there was a significant ($P = 0.007$) difference between the combined incidence of adrenal cortical adenoma or carcinoma in the low-dose females (6/45) and that in the pooled controls (0/55). Although this tumor was also found in animals treated with aldrin, it is not clearly associated with treatment, because the incidence in the high-dose (2/40) was not significant, and the incidences were not significant when matched, rather than pooled, controls were used for comparison.

In male mice, there was a significant positive dose-related trend ($P = 0.020$) in the incidence of hepatocellular carcinomas using the pooled controls (pooled controls 17/92, low-dose 12/50, high-dose 16/45). When high-dose males were compared with the pooled controls, the results were also significant ($P = 0.025$).

It is concluded that under the conditions of these bioassays, none of the tumors occurring in Osborne-Mendel rats treated with aldrin or dieldrin could clearly be associated with treatment.

Aldrin was carcinogenic for the liver of male B6C3F1 mice producing hepatocellular carcinomas. With dieldrin, there was a significant increase in the incidence of hepatocellular carcinomas in the high-dose males which may be associated with treatment.

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I. INTRODUCTION

Aldrin (CAS 309-00-2; NCI C00044) and dieldrin (CAS 60-57-1; NCI C00124) are organochlorine insecticides of the cyclodiene group. These chemicals are neurotoxins, and their predominant effect is the stimulation of the nervous system. Both aldrin and dieldrin are lipophilic and accumulate in mammalian tissues. Aldrin undergoes metabolic conversion to the epoxide, dieldrin (Brooks, 1975), and because of this structural relationship, reports of the bioassays of both chemicals have been combined in this single report.

Two of the major uses of aldrin since its introduction in 1950 have been foliage application on cotton plants and soil application for corn fields. A small amount has also been used for soil application for vegetables and root crops. These applications have resulted in residues of the chemical in food products.

Dieldrin was first introduced in the 1950's by cotton growers, when the chemical was found to be more effective than aldrin. Dieldrin has also been used as an insecticide on crops other than cotton, for public health pest control, and for mothproofing woolen goods (Federal Register, 1974).

Based partly on the evidence of the hepatocarcinogenicity of

dieldrin in the mouse (Thorpe and Walker, 1973; Walker et al., 1972), the registration of products containing aldrin and dieldrin was canceled in 1974 (Federal Register, 1974).

Aldrin and dieldrin were selected for testing in 1969 because data regarding their carcinogenicity were controversial and often inadequate and because there was potential for long-term human exposure to residues, especially in foods.

II. MATERIALS AND METHODS

A. Chemicals

1. Aldrin

The material tested was technical-grade aldrin, obtained in one batch from the Shell Chemical Company, San Ramon, California, for use in the chronic study. According to the manufacturer's specifications, the product was > 85% pure.

Gas chromatography using electron capture detection showed three components, with the major component accounting for 95% of the total peak area. Elemental analyses (C, H, Cl) were correct for $C_{12}H_8Cl_6$, the molecular formula of aldrin. Infrared, nuclear magnetic resonance, and mass spectra compared well with those of the analytical-grade reference standard (Shell Chemical Co.). No attempt was made to identify or quantitate impurities.

The chemical was stored in its original container at 4°C for the duration of the study.

2. Dieldrin

The material tested was technical-grade dieldrin, obtained in one batch from the Shell Chemical Company, San Ramon, California, for

use in the chronic study. According to the manufacturer's specifications, the product was > 85% pure.

Gas chromatography using electron capture detection showed two components, with the major component accounting for > 96% of the total peak area. Elemental analyses (C, H, Cl) were correct for $C_{12}H_8Cl_6O$, the molecular formula of dieldrin. Infrared, nuclear magnetic resonance, and mass spectra compared well with those of the analytical-grade reference standard (Shell Chemical Co.). No attempt was made to identify or quantitate impurities.

The chemical was stored in its original container at 4°C for the duration of the study.

B. Dietary Preparation

All diets were formulated using Wayne® Lab Blox (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of aldrin or dieldrin for each dietary concentration. The respective test chemical was first dissolved in a small amount of acetone (Mallinckrodt, Inc., St. Louis, Mo.), which was then added to the feed. Corn oil (Louana®, Opelousas Refinery Co., Opelousas, La.) was also added to the feed, primarily as a dust suppressant, and the diets were mixed mechanically to assure homogeneity of the mixtures and evaporation of the acetone. Final diets, including those for the control groups of animals,

contained corn oil equal to 2% of the final weight of feed. The diets were stored at approximately 17°C until used, but no longer than 1 week.

The stability of the aldrin or dieldrin in feed was tested by determining the concentrations of the chemical in formulated diets at intervals over a 7-day period. Diets containing 4 or 30 ppm aldrin or 5 or 40 ppm dieldrin showed no change in concentration on standing at ambient temperature for this period.

As a quality control test on the accuracy of the preparation of the diets, the concentration of aldrin or dieldrin was determined in different batches of formulated diets during the chronic study. The results are summarized in Appendix M. At each dietary concentration, the mean of the analytical concentrations for the checked samples was within 3% of the theoretical concentration, and the coefficient of variation was never more than 5.4%. Thus, the evidence indicates that the formulated diets were prepared accurately.

Three batches of the basal feed (Wayne® Lab Blox Meal) used during this period were analyzed by Gulf South Research Institute for pesticide residues. No aldrin was found at a 0.5 ppb limit of detection; however, dieldrin was found in small amounts (2.5 - 4.4 ppb) in three samples at a 1 ppb limit of detection.

C. Animals

Rats and mice of both sexes, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these studies. The rats were of the Osborne-Mendel strain obtained from Battelle Memorial Institute, Columbus, Ohio, and the mice were B6C3F1 hybrids obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon arrival at the laboratory, all animals were quarantined for an acclimation period (rats 8-9 days, mice 14-15 days) and were then assigned to control and test groups.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 22-24°C, and the relative humidity was maintained at 40-70%. The air in each room was changed 10-12 times per hour. Fluorescent lighting provided illumination 10 hours per day. Food and water were supplied ad libitum.

The rats were housed individually in hanging galvanized steel mesh cages, and the mice were housed in plastic cages with filter bonnets, five per cage for females, and two or three per cage for males. Initially, rats were transferred weekly to clean cages; later in the study, cages were changed every 2 weeks. Mice were

transferred weekly to clean cages with filter bonnets; bedding used for the mice was Absorb-Dri® (Lab Products, Inc., Garfield, N.J.). For rats, absorbent sheets under the cages were changed three times per week. Feeder jars and water bottles were changed and sterilized three times per week.

Cages for control and treated mice were placed on separate racks in the same room. Animal racks for both species were rotated laterally at weekly intervals; at the same time each cage was changed to a different position in the row within the same column. Rats receiving aldrin or dieldrin, along with their respective matched controls, were housed in rooms by themselves. Mice receiving aldrin were maintained in a room housing mice administered captan (CAS 133-06-2) or photodieldrin (CAS 13366-73-9), together with their respective matched controls. Mice receiving dieldrin were maintained in a room housing mice administered malathion (CAS 121-75-5) or tetrachlorvinphos (CAS 961-11-5), together with their respective matched controls.

E. Subchronic Studies

Subchronic studies were conducted with rats and mice to estimate maximum tolerated doses of aldrin or dieldrin, on the basis of which low and high concentrations (hereinafter referred to as "low doses" and "high doses") were determined for administration

in the chronic studies. In these subchronic studies, aldrin or dieldrin was added to the animal feed in the doses below for 6 weeks, followed by an observation period of 2 weeks. Experimental and treatment groups each consisted of five male and five female animals.

1. Aldrin

In these subchronic studies, aldrin was added to the animal feed in twofold increasing concentrations ranging from 40 to 320 ppm for rats. At concentrations of 40 or 80 ppm, there were no adverse effects on mean body weights of either male or female rats; however, at 160 ppm, mean body weights of both males and females were depressed initially, and at 320 ppm, mean body weights of males were lower than those of controls. One male and one female fed 160 ppm died, and three males and five females fed 320 ppm died. On the basis of these results, the low and high doses for rats were set at 60 and 120 ppm for the chronic studies.

Aldrin was added to the animal feed in twofold increasing concentrations ranging from 2.5 to 80 ppm for mice. These doses had no apparent effect on the mean body weights of surviving treated animals. However, all males and females fed 40 or 80 ppm died,

and one male and one female fed 20 ppm died. The low and high doses for mice were set at 8 and 15 ppm for the chronic studies.

2. Dieldrin

Dieldrin was added to the animal feed in twofold increasing concentrations ranging from 40 to 320 ppm for rats. Mean body weights of male rats receiving 80, 160, and 320 ppm were initially depressed, and two male rats fed 320 ppm died. Mean body weights of female rats at 40, 80, and 160 ppm were also initially depressed; one female fed 160 ppm died, and all five females fed 320 ppm died. Based on these results, the low and high doses for rats were initially set at 80 and 160 ppm for males and 40 and 80 ppm for females for the chronic studies. Before the chronic study was initiated, doses for males were lowered to those of the females.

Dieldrin was added to the animal feed in twofold increasing concentrations ranging from 2.5 to 40 ppm for mice. The chemical had no apparent adverse effect on mean body weights of male or female mice at any of the dietary concentrations used in this study. Three male and four female mice fed 20 ppm died, as did all animals fed 40 ppm. The low and high doses for mice were set at 5 and 10 ppm for the chronic studies.

F. Designs of Chronic Studies

Designs of the chronic studies are shown in tables 1, 2, 3, and 4. Initially, higher doses of each test chemical than are shown in the tables were fed to rats and mice. These initial doses were found to be too toxic for the animals, and studies were restarted as indicated in the footnotes of each respective table.

Since the numbers of animals in the matched-control groups were small, pooled-control groups also were used for statistical comparisons. Matched controls from the current studies on aldrin and dieldrin were combined with matched controls from studies performed on chlordane (CAS 57-74-9), heptachlor (CAS 76-44-8), dichlorvos (CAS 62-73-7), and dimethoate (CAS 60-51-5). The pooled controls for statistical tests using rats consisted of 58 males and 60 females; using mice, 92 males and 79 females. The studies on chemicals other than aldrin and dieldrin were also conducted at Gulf South Research Institute and overlapped the aldrin and dieldrin studies by at least 1 year. The matched-control groups for the different test chemicals were of the same strain and from the same supplier, and they were examined by the same pathologists. Because additional matched controls were started simultaneously with restarted treatment groups for some of these chemicals, the number of animals in the pooled-control groups varied.

Table 1. Design of Aldrin Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[a]	Aldrin in Diet[b] (ppm)	Time on Study: Treated (weeks)	Time on Study: Untreated[c] (weeks)
MALE				
Matched-Control	10	0		111
Low-Dose	50	30	74	
		0		37-38
High-Dose	50	60	74	
		0		37-38
FEMALE				
Matched-Control	10	0		111-112
Low-Dose	50	30	80	
		0		32
High-Dose	50	60	80	
		0		32-33

[a]All animals were approximately 35 days of age when placed on study.

[b]Initially, concentrations of 60 or 120 ppm aldrin were fed to rats of each sex; these doses were too toxic and the studies in rats were terminated and restarted as shown in the table.

[c]When diets containing aldrin were discontinued, all rats were fed the control diet (2% corn oil added) for 30 or 36 weeks.

Table 2. Design of Aldrin Chronic Feeding Studies in Mice

Sex and Treatment Group	Initial No. of Animals[a]	Aldrin in Diet[b] (ppm)	Time on Study: Treated (weeks)	Time on Study: Untreated[c] (weeks)	Time-Weighted Average Dose[d] (ppm)
MALE					
Matched-Control	20[e]	0		90-92	
Low-Dose	50	8	7		4
		4	73		
		0		10	
High-Dose	50	8	80		8
		0		12-13	
FEMALE					
Matched-Control	10	0		90	
Low-Dose	50	8	7		
		4	12		3
		2	61		
		0		10	
High-Dose	50	15	7		
		8	12		6
		4	61		
		0		10-11	

[a]All animals were approximately 35 days of age when placed on study.

[b]Initially, a concentration of 15 ppm aldrin was fed to the high-dose group of male mice; this dose was too toxic and the group was terminated and a new high-dose group started at 8 ppm. At this time, the low-dose males were lowered from 8 to 4 ppm and the females from 8 or 15 ppm to 4 or 8 ppm, respectively.

[c]When diets containing aldrin were discontinued, all mice were fed the control diet (2% corn oil added) until termination of the study.

Table 2. Design of Aldrin Chronic Feeding Studies in Mice

[d]Time-weighted average dose = $\frac{\Sigma(\text{dose in ppm x no. of weeks at that dose})}{\Sigma(\text{no. of weeks receiving each dose})}$

[e]Initially, 10 animals of each sex were placed on study as matched controls; however, when the study was restarted, 10 additional male mice were placed on study as matched controls.

Table 3. Design of Dieldrin Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[a]	Dieldrin in Diet[b] (ppm)	Time on Study: Treated (weeks)	Time on Study: Untreated[c] (weeks)	Time-Weighted Average Dose[d] (ppm)
MALE					
Matched-Control	10	0		110	
Low-Dose	50	40	37		29
		20	43		
		0		30	
High-Dose	50	80	37		
		40	22		65
		0		52	
FEMALE					
Matched-Control	10	0		110	
Low-Dose	50	40	37		
		20	43		29
		0		30-31	
High-Dose	50	80	37		
		40	22		65
		0		51-52	

[a]All animals were approximately 35 days of age when placed on study.

[b]The initial doses of dieldrin were too toxic and the doses were lowered at 37 weeks on study because of toxic signs.

[c]When diets containing dieldrin were discontinued, all rats were fed the control diet without corn oil for 8 weeks, then the control diet (2% corn oil added) for an additional 27 weeks.

[d]Time-weighted average dose = $\frac{\Sigma \text{(dose in ppm x no. of weeks at that dose)}}{\Sigma \text{(no. of weeks receiving each dose)}}$

Table 4. Design of Dieldrin Chronic Feeding Studies in Mice

Sex and Treatment Group	Initial No. of Animals[a]	Dieldrin in Diet[b] (ppm)	Time on Study: Treated (weeks)	Time on Study: Untreated[c] (weeks)
MALE				
Matched-Control	20[d]	0		91-93
Low-Dose	50	2.5	80	
		0		11
High-Dose	50	5	80	
		0		13
FEMALE				
Matched-Control	10	0		91-93
Low-Dose	50	2.5	80	
		0		10-11
High-Dose	50	5	80	
		0		13

[a]All animals were approximately 35 days of age when placed on study.

[b]Initially, a concentration of 10 ppm dieldrin was fed to high-dose mice of each sex; this dose was too toxic and the groups were terminated at 10 weeks and a low-dose group of 10 males was started at 2.5 ppm. The original low-dose groups then became the high-dose groups.

[c]When diets containing dieldrin were discontinued, all mice were fed the control diet (2% corn oil added) until termination of the study.

[d]Initially, 10 animals of each sex were placed on study as matched controls; however, when the study was restarted, 10 additional male mice were placed on study as matched controls.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, weighed at regular intervals, and palpated for masses at each weighing. Those animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally additional tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of

autolysis as to preclude histopathologic evaluation. Thus, the number of animals for which particular organs or tissues 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 Tarone's (1975) extensions of Cox's methods for testing for 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 is 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) was used to compare the tumor incidence of

a control group with 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)' 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), was also used. Under the assumption of a linear trend, this test determines 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 is 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 treated 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% 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. RESULTS - ALDRIN

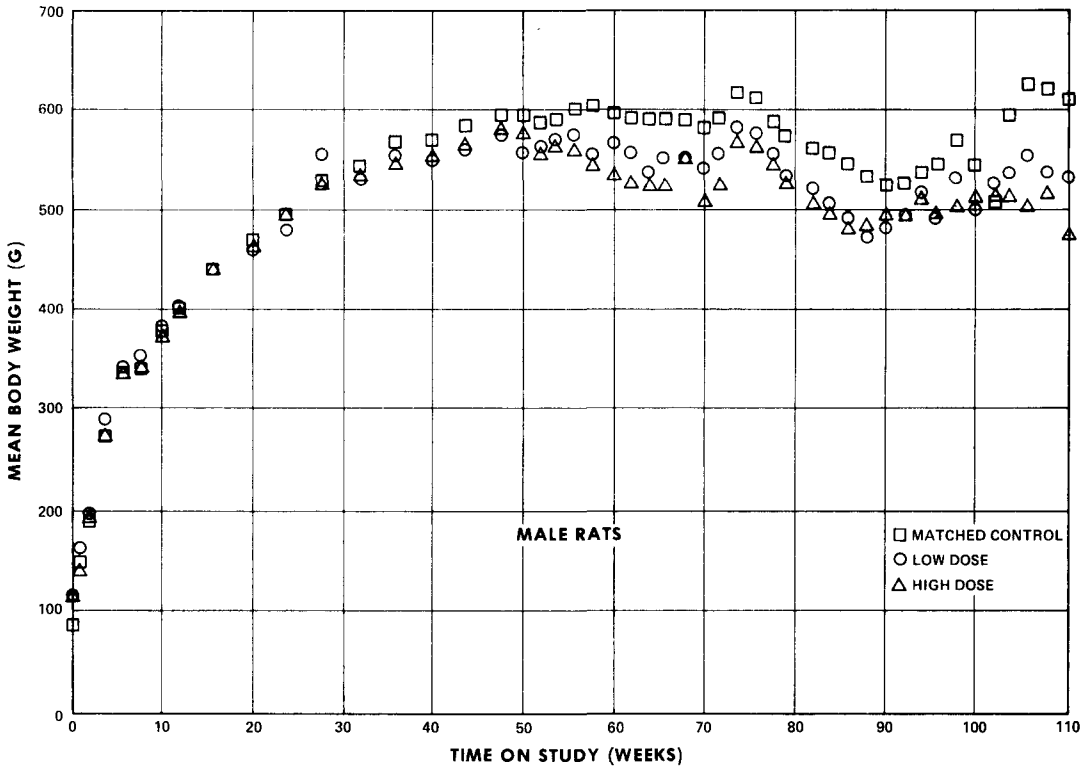
A. Rats

1. Body Weights and Clinical Signs (Rats) - Aldrin

Beginning at about the second year of the study, the mean body weights of the treated rats were consistently lower than those of the matched controls (figure 1).

During the first 6 months of the study, the treated animals were generally comparable to the controls in appearance and behavior, with the exception of seven treated animals that developed exophthalmus and corneal opacity, with occasional thickening of the palpebral conjunctival membranes. This condition was diagnosed as viral conjunctivitis by the pathologists at the laboratory. During the second 6 months of the study, beginning at week 32, convulsions were observed in several of the high-dose female rats.

At week 52, most high-dose male rats appeared to be nervous and excitable. Throughout the second year of the study, clinical signs including pale mucous membranes, rough hair coats, loss of weight, vaginal bleeding, hyperactivity, and convulsions were apparent in all treated groups. Several animals showed evidence



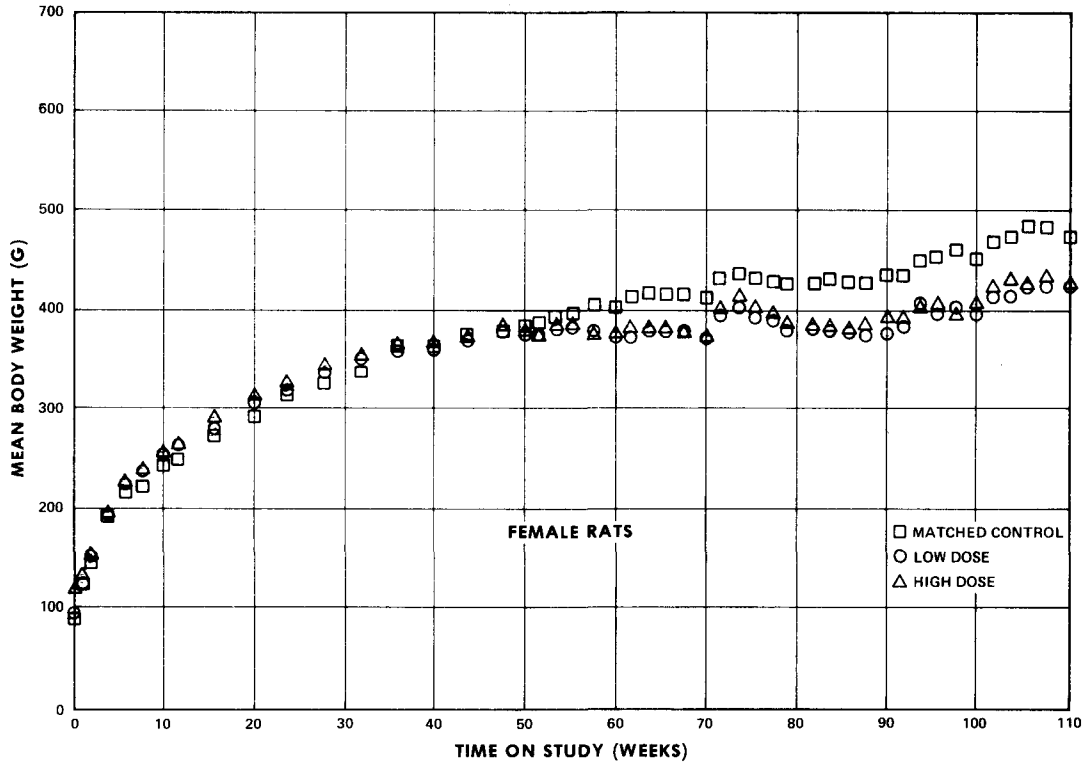


Figure 1. Growth Curves for Rats Fed Aldrin in the Diet

of discolored (dark) urine. Surviving rats were generally in poor physical condition at termination of the study.

2. Survival (Rats) - Aldrin

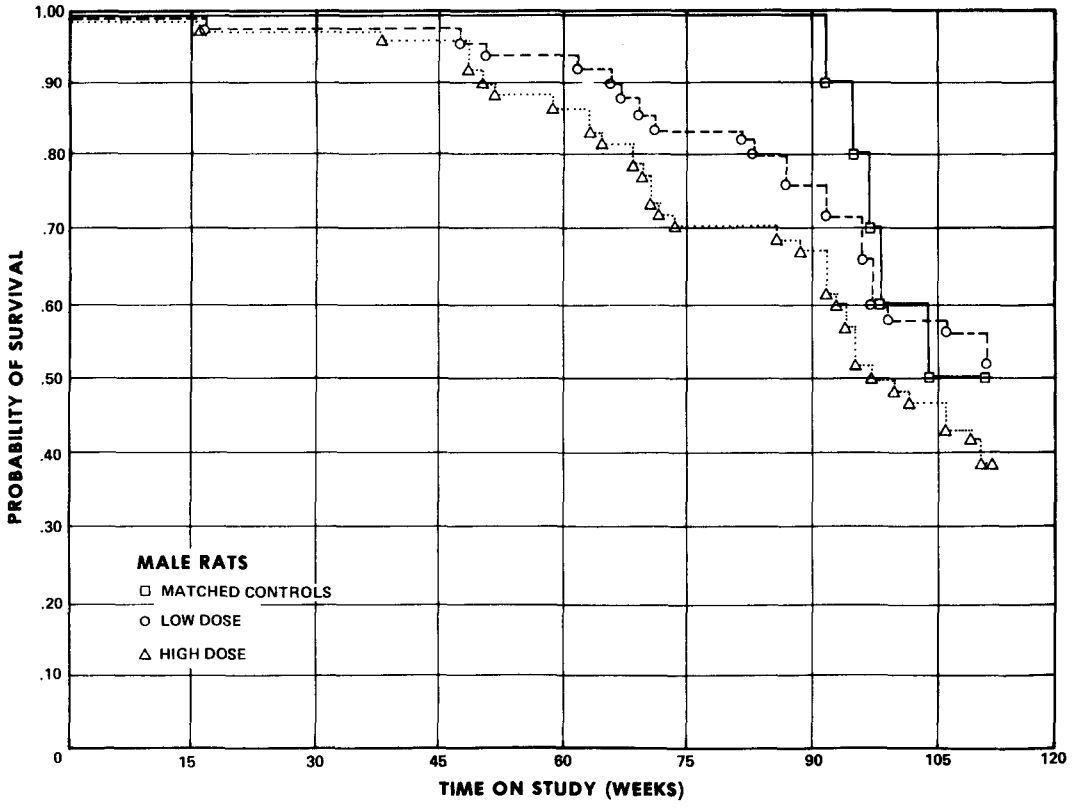
The male rats that received aldrin experienced a substantial decrease in survival over the period from weeks 45-90 (figure 2); however, the Tarone test result for life-table analyses over the entire period of the study was not significant ($P > 0.05$) indicating that the mortalities were not dose related. The median time on study at death was 97 weeks in the high-dose group and longer in the other male groups.

In female rats, there was no indication of a dose response, since there were more early deaths in the low-dose group, in which 68% of the rats lived to termination of the study, than in the high-dose group, in which 82% of the rats lived to termination of the study.

There were adequate numbers of both male and female treated rats for meaningful statistical analyses of the incidence of tumors.

3. Pathology (Rats) - Aldrin

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix E, tables E1 and E2.



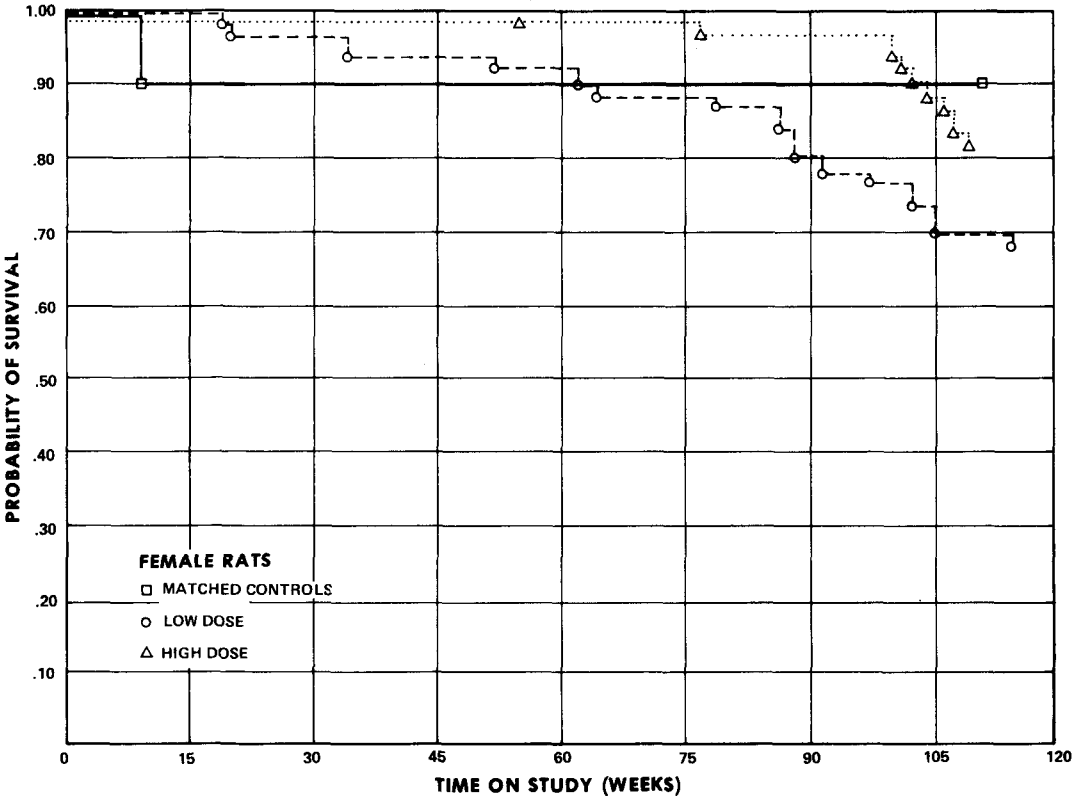


Figure 2. Survival Curves for Rats Fed Aldrin in the Diet

Numerous inflammatory, degenerative, and proliferative lesions commonly seen in aged rats occurred with approximately equal frequency in aldrin-treated and control animals. These included biliary hyperplasia; chronic nephritis with scarring, tubular dilatation and regeneration; C-cell hyperplasia of the thyroid; and testicular atrophy.

Both follicular-cell and C-cell neoplastic lesions of the thyroid were observed frequently, with no obvious difference in incidence between treated and control rats. Pituitary adenomas occurred frequently in all groups, and there was a low incidence of neoplasms of the adrenal cortex and medulla, parathyroid, and pancreatic islets.

A low incidence of hepatocellular carcinoma or neoplastic nodules, classified according to Squire and Levitt (1975), was observed in liver sections, with no apparent increased frequency for treated groups over controls.

Renal neoplasms occurred infrequently in both treated and control males. These renal lesions, classified as malignant mixed tumors, contained neoplastic tissue components having the appearance of renal mesenchymal stroma, adipose tissue, and primitive renal epithelium, in various proportions.

Primary vascular neoplasms occurred at several sites, including the spleen, subcutis, lung, and uterine cervix.

Endometrial stromal polyps were the most frequently occurring neoplasms of the reproductive tract. Numerous mammary fibroadenomas, some of which were multiple, were observed in both treated and control females.

There were instances where neoplasms occurred only in treated animals, or with increased frequency when compared with those in control groups. In the judgment of the pathologist, however, the nature, incidence, and severity of the lesions observed provided no clear evidence of a carcinogenic effect of aldrin on rats.

4. Statistical Analyses of Results (Rats) - Aldrin

Tables I1 and I2 of Appendix I contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

A significant positive linear trend (P = 0.002) in the incidence of follicular-cell adenoma or follicular-cell carcinoma of the thyroid was observed in the low-dose group of male rats when compared with that in the pooled controls; however, the proportion in the matched-control group of 3/7 (43%) was so high that a

negative trend (P = 0.075) was found. A time adjustment, eliminating all male rats dying before 1 year on study, resulted in incidences of 14/36 (39%) in the low-dose group and 8/36 (22%) in the high-dose group. There were no practical differences, however, between the statistical results of the tests made using the adjusted incidences and the results of the tests made without the adjustment. The occurrence of follicular-cell adenoma or follicular-cell carcinoma of the thyroid was also significant (P = 0.009) in low-dose female rats when compared with that in the pooled controls, but not when compared with that in the matched controls. Both male and female high-dose groups failed to confirm the significance seen in the low-dose group, even when survival was taken into account. The matched-control groups indicated a possible spontaneous rate of tumors of 11% in females and 43% in males, which is higher than that indicated by pooled controls (6% females, 8% males).

Cortical adenoma of the adrenal gland was not observed in significant proportions in the treated male rats (matched controls 2/10, low-dose 1/38, high-dose 2/43) but was observed in significant proportions (P = 0.002) in the low-dose females (8/45) when compared with those incidences in the pooled controls (0/55). The high-dose group, although having better survival, had only 1/48 (2%) of such tumors. The test for dose-related positive

linear trend in females was not significant, but there was a significant departure from linearity when either the pooled ($P < 0.001$) or matched ($P = 0.010$) controls were used. These departures resulted from the high incidence in the low-dose females compared with that in the high-dose group. The incidence of adrenal cortical adenoma or carcinoma in control groups of this strain of female rat so far reported in the laboratory is 3/240 (1.25%), which is somewhat, but not significantly, higher than 0/55 (0.0%) found in the pooled-control group.

In male rats, although the Cochran-Armitage tests of the proportions of islet-cell adenoma or carcinoma of the pancreatic islets are not significant, the Fisher exact tests show that the incidence in the low-dose group (5/37) is significantly higher than that in the pooled controls (1/52). However, one would not conclude that this incidence in the low-dose group is dose associated, since the simultaneous comparison criteria required a probability level of < 0.025 for significance. The incidence of this tumor in females was not significant.

In summary, significant statistical results are obtained for the combination of incidences of follicular-cell adenoma and follicular-cell carcinoma of the thyroid in both male and female rats and for cortical adenoma of the adrenal gland in female

rats, indicating a possible dose association of aldrin with these tumors.

B. Mice

1. Body Weights and Clinical Signs (Mice) - Aldrin

The administration of aldrin in the diet did not affect the mean body weights of mice (figures 3 and 4).

During the first 6 months of the study, the treated animals were generally comparable to the controls in appearance and behavior. During the second 6 months of the study, most of the treated animals, with the exception of the low-dose males, appeared to be hyperexcitable.

Clinical signs including rough hair coats, alopecia, and abdominal distention (noted in all treated groups, but predominantly in the high-dose males) appeared with increasing frequency during the second year of the study. Many of the treated males were observed fighting during the last half of the study.

2. Survival (Mice) - Aldrin

There was no significant dose-related trend in the mortality of the male mice (figure 5). In female mice, there was a

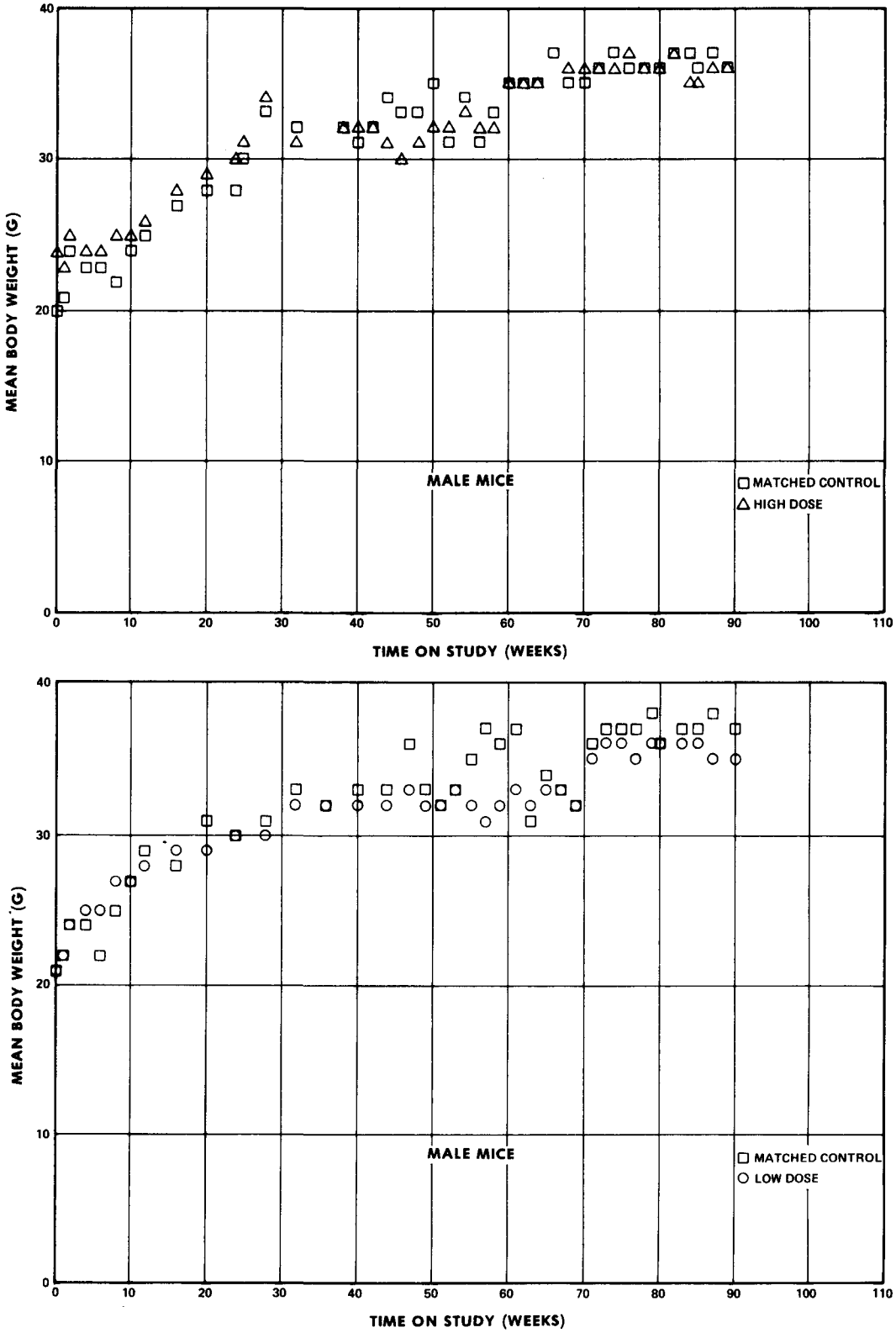


Figure 3. Growth Curves for Male Mice Fed Aldrin in the Diet

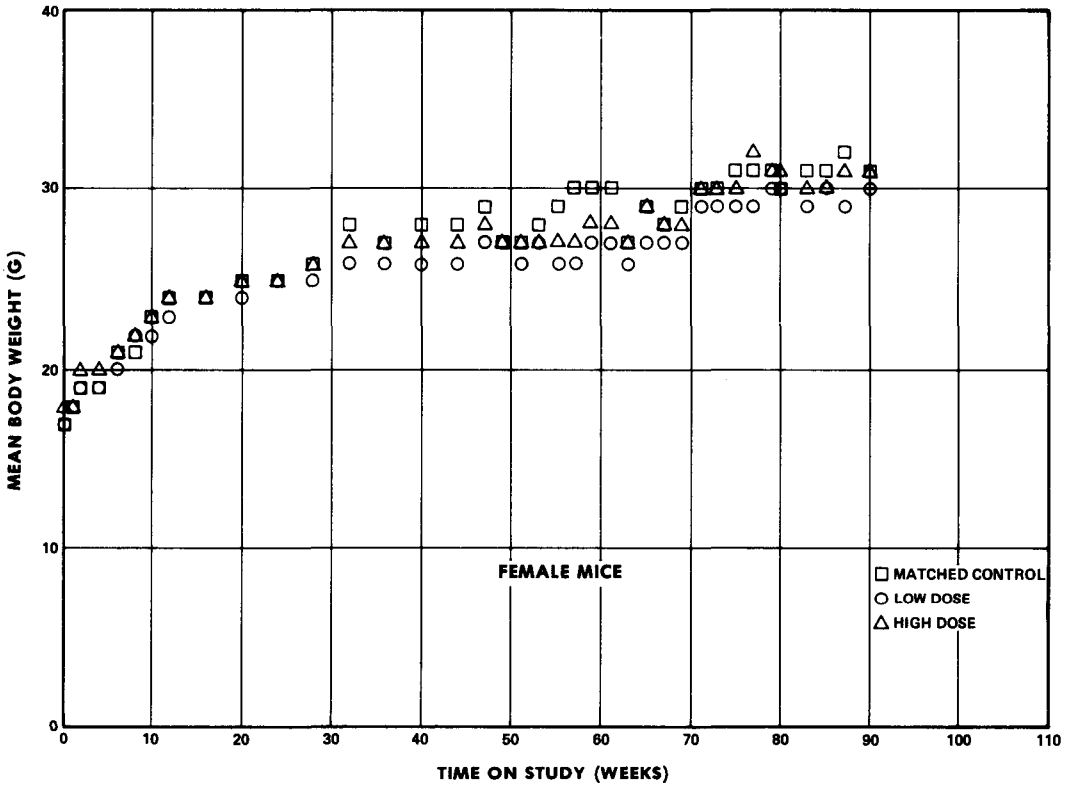


Figure 4. Growth Curves for Female Mice Fed Aldrin in the Diet

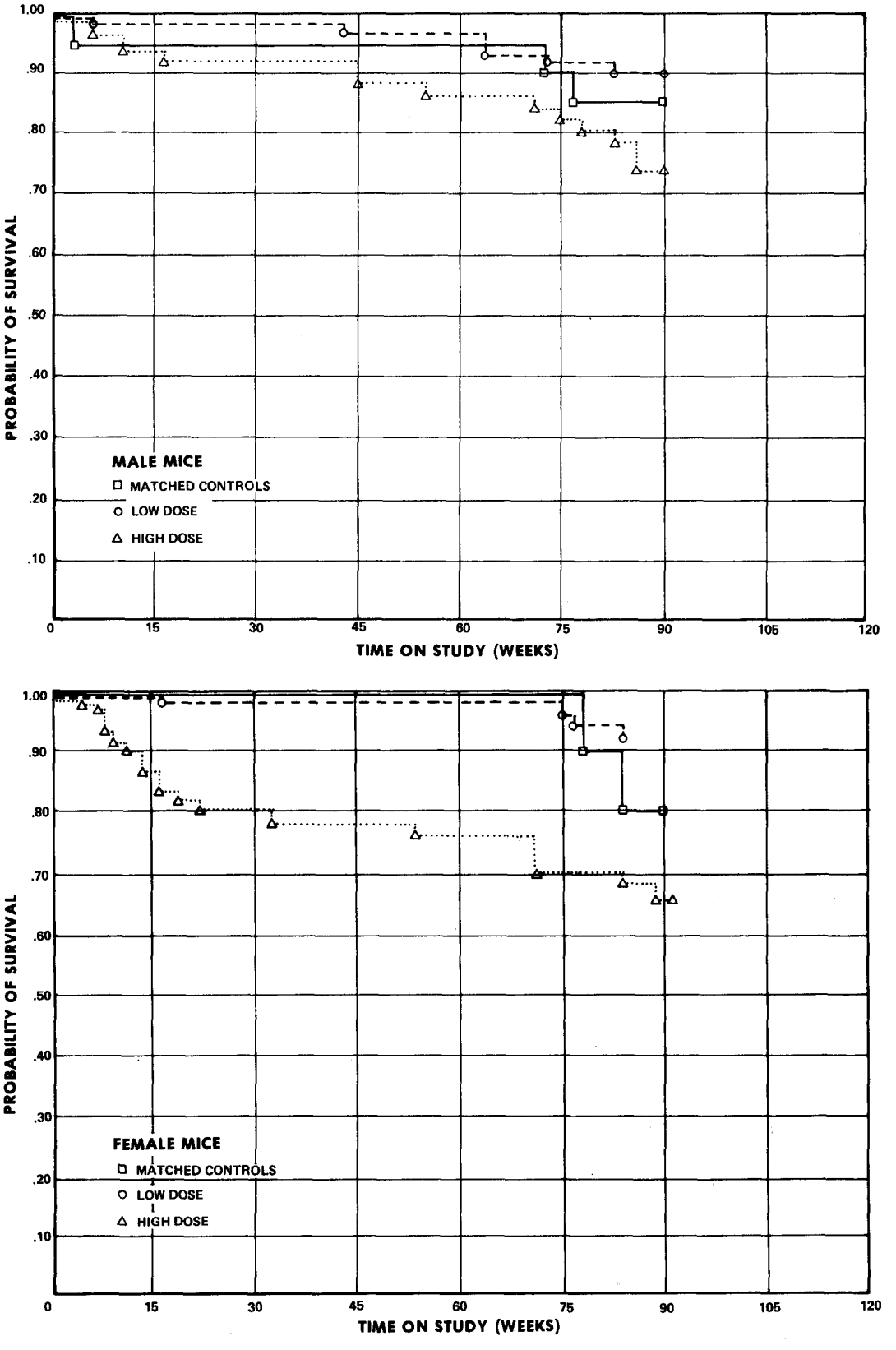


Figure 5. Survival Curves for Mice Fed Aldrin in the Diet

significant (P = 0.037) dose-related trend in mortality represented by the early deaths in the high-dose group shown in figure 5. These early deaths were not associated with tumors, since only 3/17 (18%) of the high-dose females that died before termination of the study were found to have tumors.

3. Pathology (Mice) - Aldrin

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix F, tables F1 and F2.

Several nonneoplastic lesions were observed in both treated and control mice. Peribronchial and/or perivascular lymphoid hyperplasia, generally mild in degree, was noted in sections of lung from many control and treated mice. Purulent oophoritis, endometritis, and cystic endometrial hyperplasia occurred frequently in both treated and control females. There was a low incidence of other inflammatory, degenerative, and nonneoplastic proliferative lesions in all groups.

Nodular proliferative lesions involving hepatocytes were classified as either hepatocellular carcinoma or nodular hyperplasia. The morphology of those lesions classified as hepatocellular carcinoma varied widely. Some were present as one or more small, discrete nodules containing solid cords and nests of well-differ-

entiated but hyperbasophilic hepatocytes with an increased nuclear : cytoplasmic ratio. These lesions appeared to have grown by expansion, with distinct compression but with no obvious invasion of adjacent normal hepatic parenchyma. Other hepatocellular carcinomas appeared as very large masses which had completely replaced one or more hepatic lobes, and which were composed of large anaplastic hepatocytes forming confluent sheets, papillae, and pseudoacini, with large foci of necrosis and complete loss of normal lobular architecture. The morphological appearances of the majority of hepatocellular carcinomas were somewhere between these two extremes. Those lesions classified as hepatocytomegaly were also considered to be proliferative in nature.

The data indicate an increased incidence of hepatocellular carcinomas in both the low- and high-dose male mice. The incidence of this neoplasm in treated females is much lower and is probably not biologically significant. Lesions classified as nodular hyperplasia were noted in a small number of treated animals, both male and female, but not in controls. Alterations classified as hepatocytomegaly were noted in several low- and high-dose males. The numbers in tables F1 and F2 indicate the incidence of hepatocytomegaly in animals which did not have hepatocellular carcinoma or nodular hyperplasia, although

hepatocytomegaly may also have been present to some degree in the animals with hyperplastic or neoplastic lesions in the liver.

There was a low incidence of other types of neoplasms involving various organs and tissues, with no obvious difference in incidence between treated and control groups.

4. Statistical Analyses of Results (Mice) - Aldrin

Tables J1 and J2 of Appendix J contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

There was a significant dose-related increase in hepatocellular carcinoma in the male mice when the treated groups were compared with the matched controls ($P = 0.001$) or with the pooled controls ($P < 0.001$). The results of the statistical analyses of the incidences of hepatocellular carcinoma in female mice were not significant. The laboratory historical controls showed hepatocellular carcinoma in 44/285 (16.8%) male mice, and in 6/259 (2.3%) female mice. These proportions were comparable to the observations in the matched controls of this experiment and to the pooled controls used in the analyses. There were no other tumors which appeared in statistically significant proportions when compared with the matched or the pooled controls.

IV. RESULTS - DIELDRIN

A. Rats

1. Body Weights and Clinical Signs (Rats) - Dieldrin

The mean body weights of the treated rats were consistently somewhat lower than those of the matched controls (figure 6).

During the first 6 months of the study, the treated animals were generally comparable to the controls in appearance and behavior, with the exception of the high-dose females. At week 8, convulsions were observed in two high-dose females. At week 19, five of the treated animals developed exophthalmus and corneal opacity, with occasional thickening of the palpebral conjunctival membranes. This condition was diagnosed as viral conjunctivitis by the pathologists at the laboratory. At week 21, approximately 28% of the high-dose males and high-dose females had convulsions. During the second 6 months of the study, clinical signs including diarrhea, alopecia, epistaxis, hematuria, discolored hair coats, tremors, and loss of weight were observed, predominantly in high-dose females.

These same clinical signs were observed with increasing frequency during the second year of study in both high- and low-dose groups, together with clinical signs including pale mucous

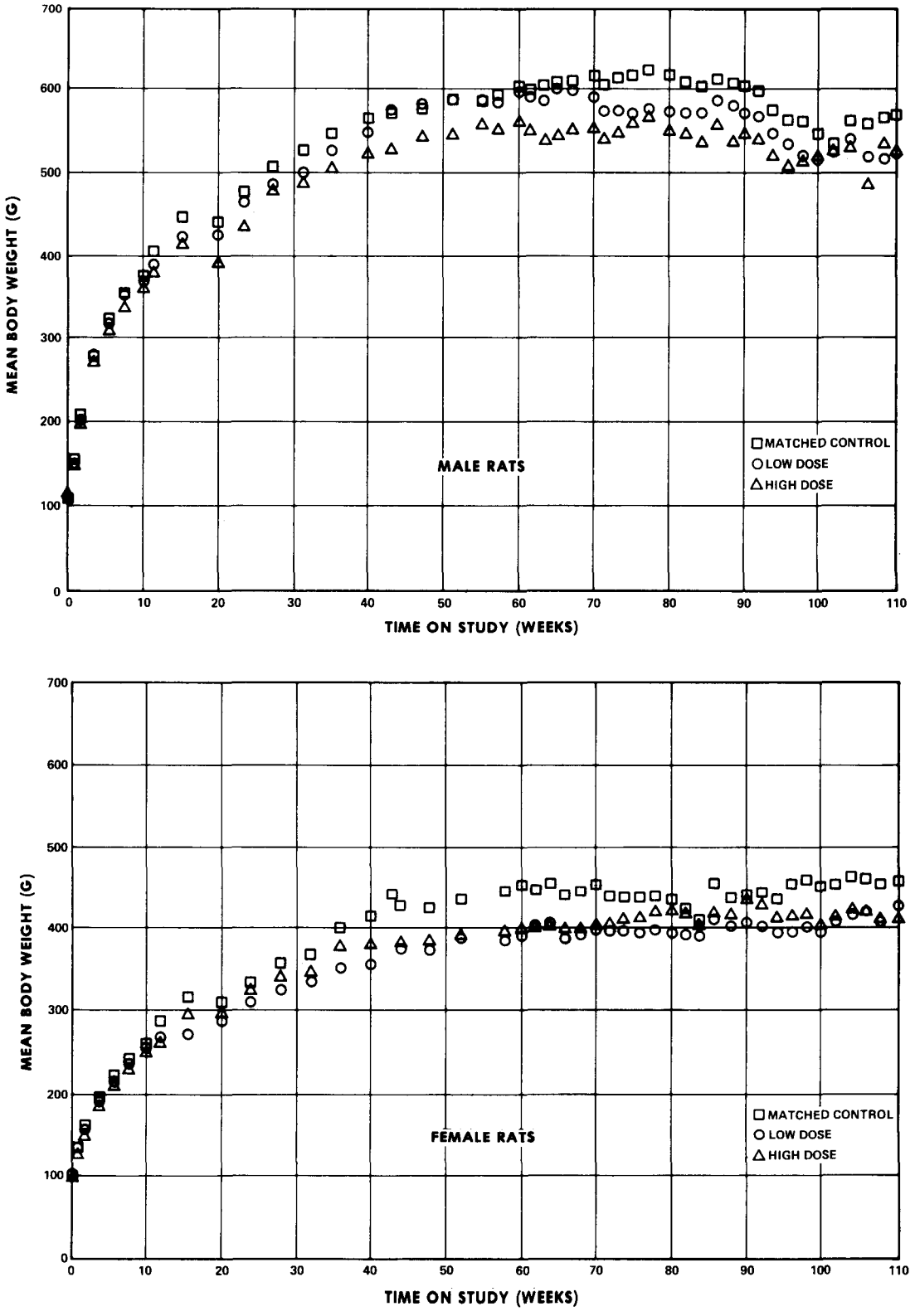


Figure 6. Growth Curves for Rats Fed Dieldrin in the Diet

membranes, vaginal bleeding, dermatitis, dyspnea, ataxia, tachypnea, abdominal distention, rough hair coats, and discolored (dark) urine. Surviving animals were generally in poor physical condition at termination of the study.

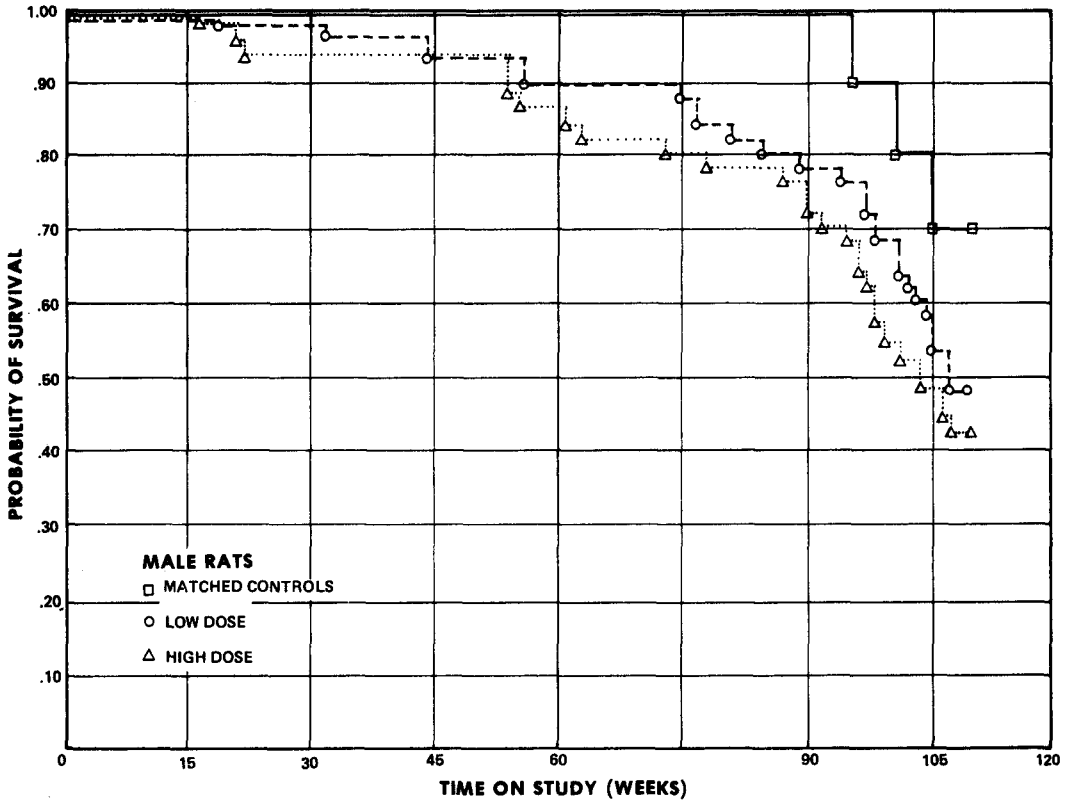
2. Survival (Rats) - Dieldrin

The survival curves of male and female rats (figure 7) indicate that the treated groups had higher mortality rates than the control groups during the first 90 weeks, but after that time, the increased number of deaths in the male and female matched controls prevented the Tarone test result for positive dose-related mortality from being significant over the study. Since over half of the treated male and female rats lived beyond 100 weeks, sufficient animals were available for meaningful statistical analyses of the incidences of late-developing tumors.

3. Pathology (Rats) - Dieldrin

Histopathologic findings on neoplasms in rats are summarized in Appendix C, tables C1 and C2; findings on nonneoplastic lesions are summarized in Appendix G, tables G1 and G2.

Numerous inflammatory, degenerative, and proliferative lesions commonly seen in aged rats occurred with approximately equal frequency in dieldrin-treated and control animals. These



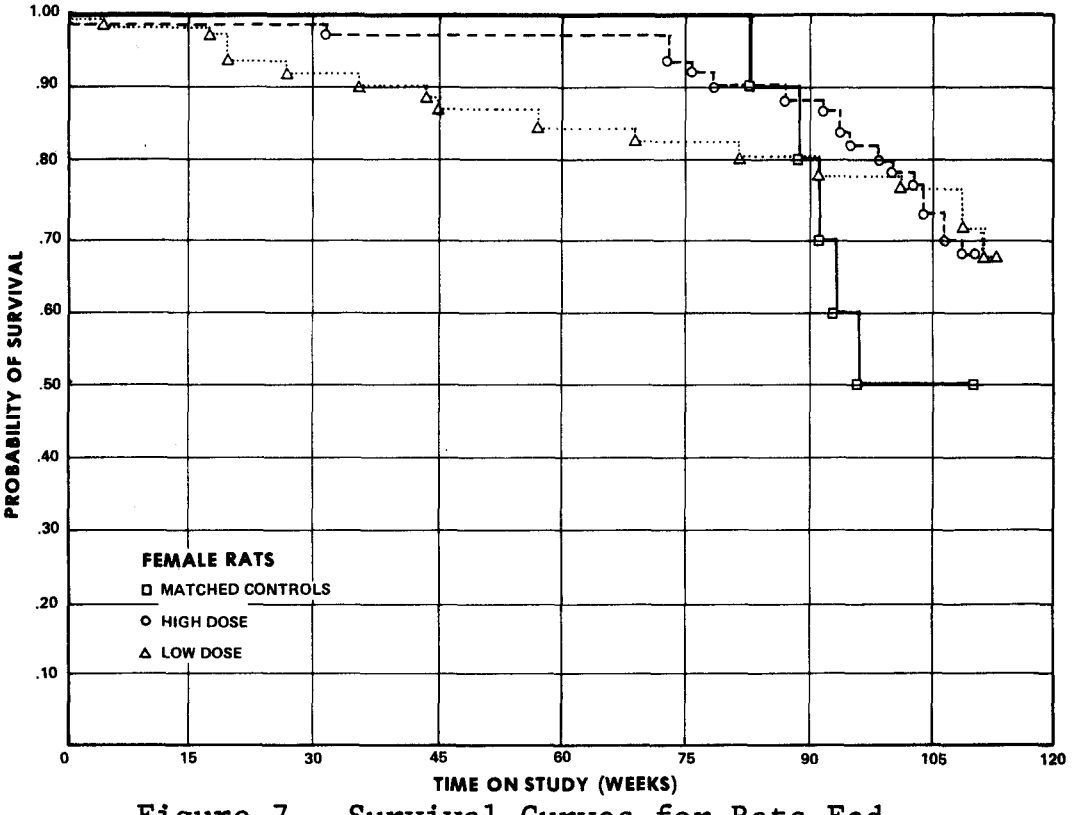


Figure 7. Survival Curves for Rats Fed Dieldrin in the Diet

included biliary hyperplasia, chronic nephritis with scarring, tubular dilatation and regeneration, C-cell hyperplasia of the thyroid, and testicular atrophy.

In the thyroid gland, both follicular-cell and C-cell neoplastic lesions were observed, with no obvious difference in incidence between treated and control rats. Pituitary adenomas occurred frequently in all groups, and there were infrequent incidences of neoplasms of the adrenal cortex and medulla, parathyroid, and pancreatic islets.

A low incidence of neoplastic nodules, classified according to Squire and Levitt (1975), was observed in liver sections, with no apparent increased frequency for treated groups over controls.

Three of the four hemangiosarcomas observed in treated animals were in the spleen, as were two of the hemangiomas. All three malignant lymphomas observed in treated rats involved multiple hematopoietic organs and abdominal viscera.

Endometrial stromal polyps in the uterus were the most frequently occurring neoplasms of the reproductive tract. Numerous mammary fibroadenomas, some of which were multiple, were observed in both treated and control females.

Renal neoplasms, classified as malignant mixed tumors, contained

neoplastic tissue components having the microscopic appearance of renal mesenchymal stroma, adipose tissue, and primitive renal epithelium, in various proportions.

There were instances where neoplasms occurred only in treated animals, or with increased frequency when compared with those in control groups. In the judgement of the pathologists, however, the nature, incidence, and severity of the lesions observed provide no clear evidence of a carcinogenic effect of dieldrin on rats.

4. Statistical Analyses of Results (Rats) - Dieldrin

Tables K1 and K2 of Appendix K contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

There was no statistically significant increase when the incidence of any tumor in the male or female treated groups was compared with that in the matched controls using the Fisher exact test. When the treated groups were compared with the pooled-control group, there was a significant ($P = 0.007$) difference between the proportions of combined adrenal cortical adenomas and carcinomas in the low-dose group of female rats and the pooled controls. However, the results obtained with the high-dose group

did not confirm this finding. An adjustment eliminating all animals that died in the first year on study did not change the results reported for the unadjusted groups of animals.

The results of the laboratory controls indicate an incidence of 3/240 (1.3%) cortical tumors of the adrenal gland in female rats, compared with 0/9 and 0/55 in the matched and pooled controls, respectively, as reported in table K2.

In high-dose female rats the comparison of the incidence of the combination of follicular-cell adenoma and carcinoma of the thyroid between the high-dose group and the pooled controls indicates P = 0.043 by the Fisher exact test, but this is above the 0.025 level required by the multiple comparison criterion. There were six adenomas and two carcinomas in the high-dose group. The Cochran-Armitage test result for positive linear trend is also significant (P = 0.030). The Fisher exact test result of the incidence of adenoma alone (pooled controls 2/52 [4%], high-dose 6/41 [15%]) was not significant at the 0.05 level, nor was the test of the incidence of carcinoma alone.

While a significant result is observed in fibroadenoma of the mammary gland in female rats, the probability level of 0.041 in the low-dose group is above the Bonferroni value of 0.025 neces-

sary for significance when the multiple comparison criterion is applied to the incidence in the low-dose group.

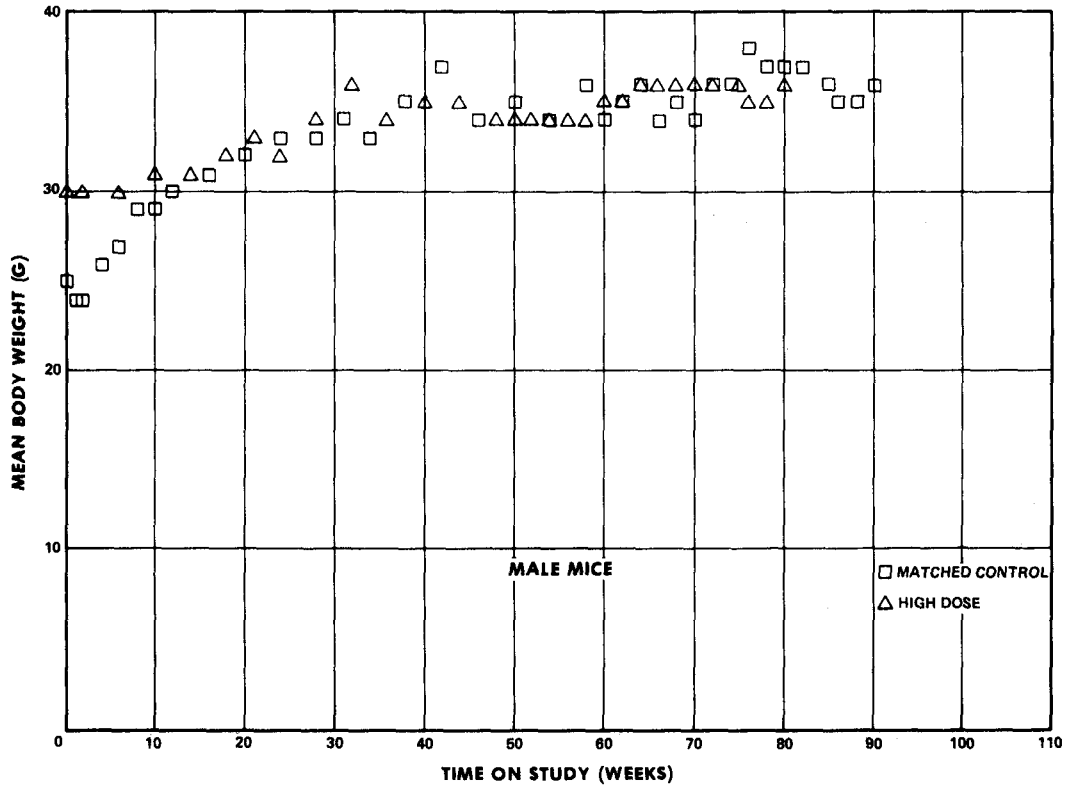
There were no other tumors appearing in statistically significant proportions. In each of the 95% confidence intervals shown in the tables, except those for adrenal cortical tumors in the low-dose females compared with the pooled-control group, the value of one is included, indicating the negative aspects of the results. It should also be noted that each of these intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by dieldrin, which could not be detected under the conditions of this test.

B. Mice

1. Body Weights and Clinical Signs (Mice) - Dieldrin

The administration of dieldrin produced essentially no effect on the mean body weights of mice (figures 8 and 9).

During the first 6 months of the study, the treated animals were generally comparable to the controls in appearance and behavior. During the second 6 months, clinical signs including tremors, abdominal distention, alopecia, tachypnea (noted predominantly in the low-dose males), and hyperexcitability (especially among male mice).



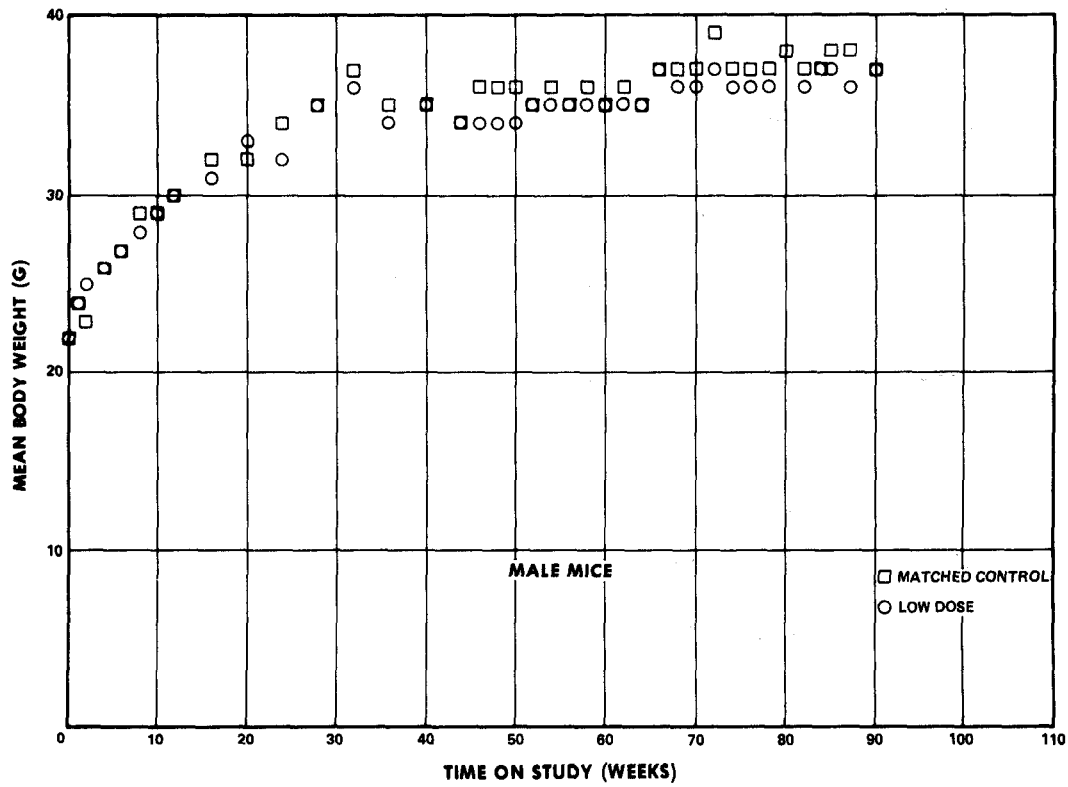
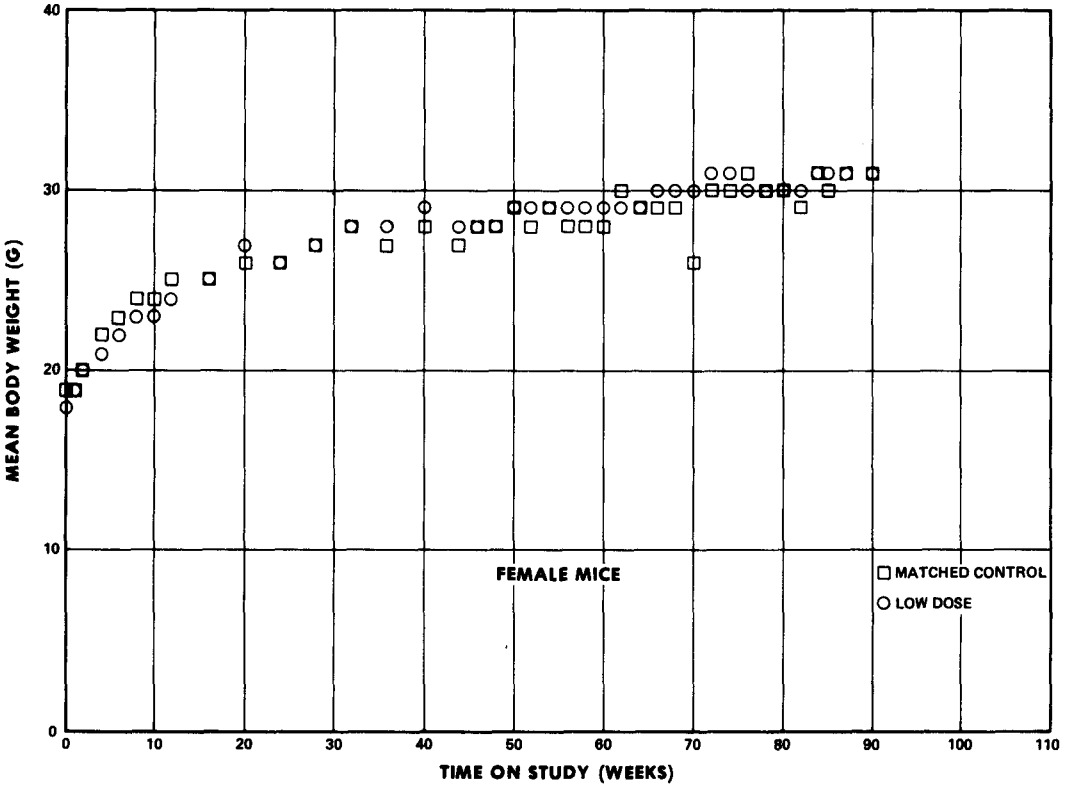


Figure 8. Growth Curves for Male Mice Fed Dieldrin in the Diet



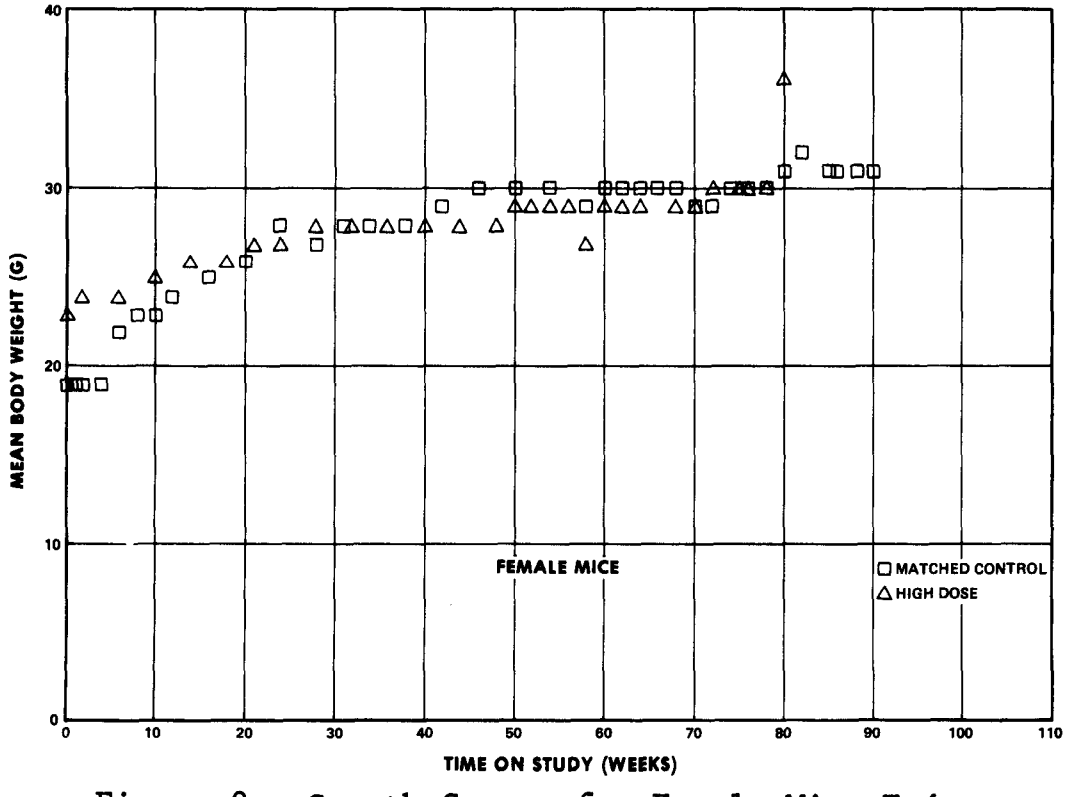


Figure 9. Growth Curves for Female Mice Fed Dieldrin in the Diet

Beginning at week 54, rough hair coats were observed in all treated male mice. At week 63, all of the low-dose females appeared hyperactive. During the second half of the study, all of the previously described clinical signs were noted, together with pale mucous membranes, dyspnea, and loss of weight. A majority of both low- and high-dose male mice were observed fighting.

2. Survival (Mice) - Dieldrin

The statistical tests for dose-related trend in mortality were not statistically significant for either sex (figure 10). In male mice, there was a greater rate of mortality in the high-dose group than in the low-dose group. Sufficient animals were available for meaningful statistical analyses of the incidence of tumors.

3. Pathology (Mice) - Dieldrin

Histopathologic findings on neoplasms in mice are summarized in Appendix D, tables D1 and D2; findings on nonneoplastic lesions are summarized in Appendix H, tables H1 and H2.

Several nonneoplastic lesions occurred frequently in both treated and control female mice. These included purulent oophoritis, endometritis, and cystic endometrial hyperplasia. There were

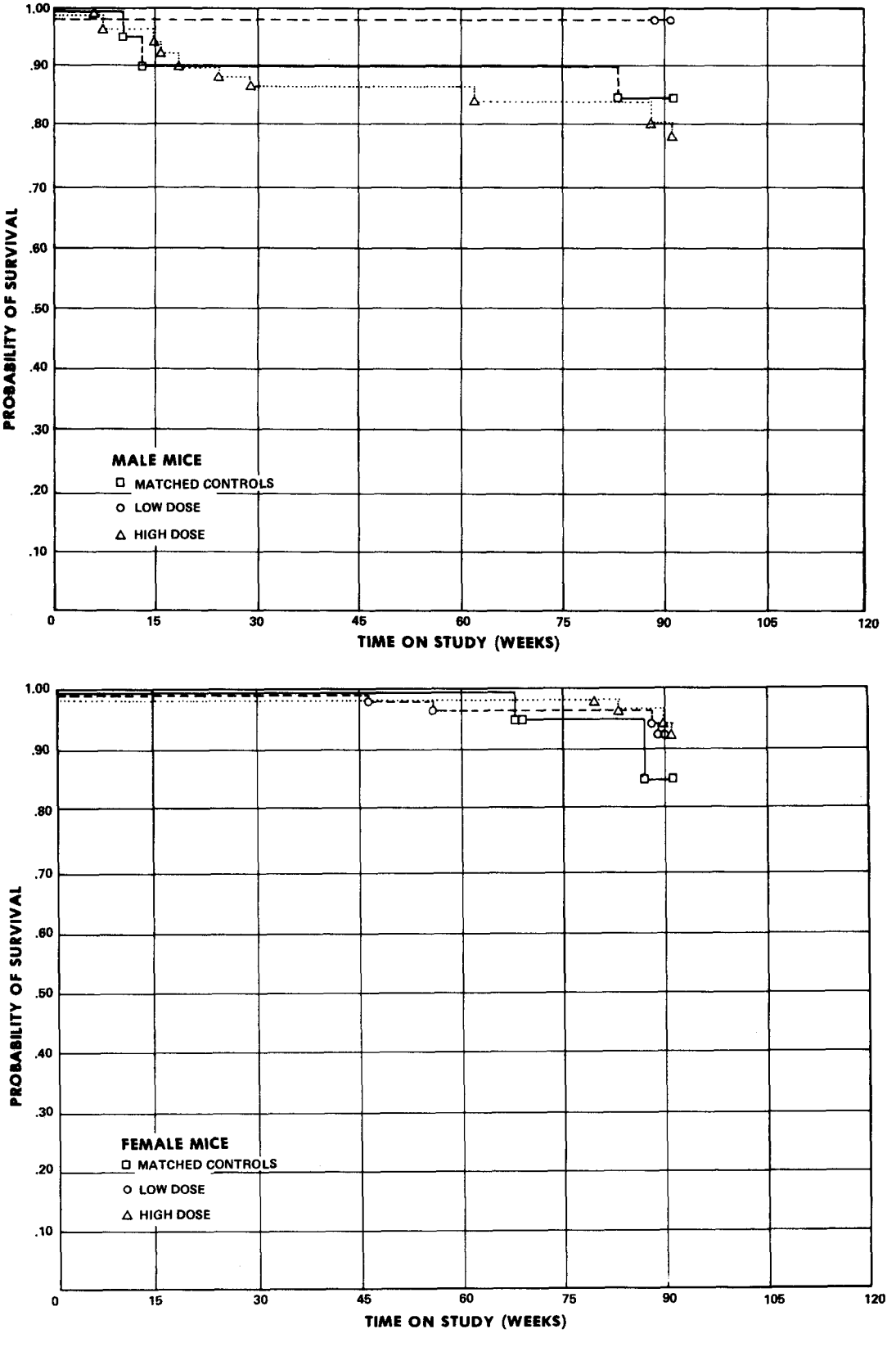


Figure 10. Survival Curves for Mice Fed Dieldrin in the Diet

infrequent incidences of other inflammatory, degenerative, and nonneoplastic proliferative lesions in all groups.

The most frequently occurring neoplasms were hepatocellular carcinomas. The morphology of these lesions varied widely. Some were present as one or more small, discrete nodules containing solid cords and nests of well-differentiated but hyperbasophilic hepatocytes with an increased nuclear : cytoplasmic ratio. These lesions appeared to have grown by expansion, with distinct compression but with no obvious invasion of adjacent normal hepatic parenchyma. Other hepatic neoplasms appeared as very large masses which had completely replaced one or more hepatic lobes, and which were composed of large anaplastic hepatocytes forming confluent sheets, papillae, and pseudoacini, with large foci of necrosis and complete loss of normal lobular architecture. The morphological appearances of the majority of hepatocellular carcinomas were between these two extremes. Metastasis was observed in two cases: multiple pulmonary metastases in a low-dose male; and metastases to heart, lung, kidney, diaphragm, and pleura in a high-dose male.

The overall incidence of hepatocellular carcinoma in both treated and control mice was much higher in males than in females. There was a definite increase in the incidence in treated male mice when compared with that in control males, and the amount of this

increase was greater in those males which received the higher dose of the test chemical (pooled control 17/92 [18.5%], low-dose 12/50 [24%], high-dose 16/45 [36%]). There was also a very slight increase in the incidence of this neoplasm in treated females (pooled controls 3/78 [3.8%], low-dose 6/50 [12%], high-dose 2/49 [4%]).

There was a low incidence of other types of neoplasms involving various organs and tissues, with no obvious difference in incidence between treated and control groups.

4. Statistical Analyses of Results (Mice) - Dieldrin

Tables L1 and L2 of Appendix L contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

With the exception of hepatocellular carcinoma, no tumors appeared in statistically significant proportions in the treated groups compared with those in either the matched or pooled controls. Using the pooled controls, the Cochran-Armitage test result for linear positive dose-related trend in the proportion of this liver tumor in male mice is significant ($P = 0.020$), with a statistically significant ($P = 0.025$) increase between the proportions in the high-dose and pooled-control groups. The test

for linear trend in the incidence of hepatocellular carcinoma in female mice indicated a significant departure from trend. This departure was due to the increased proportion of such tumors in the low-dose animals compared with that in either the control group or in the high-dose group; however, the probability level ($P = 0.08$) of the difference between the proportions observed in the low-dose animals and pooled controls was greater than $P = 0.05$. It may be concluded from the statistical analyses that the incidence of hepatocellular carcinoma in male mice increased as doses of dieldrin increased. The laboratory historical controls showed spontaneous incidences of hepatocellular carcinoma in 48/285 (16.8%) male mice and in 6/259 (2.3%) female mice.

There were no other tumors appearing in statistically significant proportions in these mice. In each of the 95% confidence intervals shown in the tables, with the exception of liver tumors in male mice, the value of one is included, indicating the negative aspects of the results. It should also be noted that each of the intervals, except for liver tumors in male mice, has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by dieldrin, which could not be detected under the conditions of this test.

V. DISCUSSION

Aldrin and dieldrin are organochlorine insecticides of the cyclodiene group whose predominant clinical signs of toxicity relate to effects on the central nervous system. Hyperexcitability, a manifestation of toxicity which is characteristic of these chemicals, was observed in all treated groups of both rats and mice, with increasing frequency and severity during the second year of the bioassays. In both the aldrin- and dieldrin-treated groups, convulsions occurred in the high-dose male and high-dose female rats.

Various nonspecific clinical signs appeared with increasing frequency in the treated rats and mice during the second year of the bioassays. These included alopecia, pale mucous membranes, dyspnea, abdominal distention, rough hair coats, and vaginal bleeding in rats, and alopecia, tachypnea, rough hair coats, and abdominal distention in mice. Mean body weights of the rats fed either aldrin or dieldrin were lower than those of the matched controls, particularly during the second year of the studies. Mean body weights of the mice fed either aldrin or dieldrin were not appreciably different from those of the matched controls.

Prior to 90 weeks on study, survival decreased in male rats treated with aldrin or dieldrin; however, deaths as calculated by

life-table analyses over the entire period of the study were not dose related in either sex. Adequate numbers of rats treated with either aldrin or dieldrin survived to provide meaningful statistical analyses of the incidences of tumors. For mice, survival was significantly affected only among high-dose females fed aldrin.

In rats, follicular-cell adenoma and carcinoma of the thyroid, taken together, occurred at significantly higher incidences in treated groups than in pooled controls in tests performed on low-dose males fed aldrin (controls 4/48, low-dose 14/38, P = 0.001) and in low-dose females fed aldrin (controls 3/52, low-dose 10/39, P = 0.009). The incidences in the treated groups were not significant, however, when matched controls were used instead of pooled controls for the comparisons. In the high-dose groups the incidences of these tumors, (males 8/38, females 7/46) were elevated but not statistically significant.

Also in rats, cortical adenoma of the adrenal occurred at a significantly higher incidence in low-dose females fed aldrin than in pooled controls (control 0/55, low dose 8/45, P = 0.001), and cortical adenoma and carcinoma of the adrenal, taken together, occurred at a significantly higher incidence in low-dose females fed dieldrin than in pooled controls (controls 0/55, low-dose 6/45, P = 0.007). The incidences in the treated

groups were not significant, however, when matched controls were used instead of pooled controls for the comparisons. In the high-dose groups there was one animal with cortical adenoma in the aldrin study and two animals with cortical adenoma in the dieldrin study.

It is interesting to note that the incidences of follicular cell tumors of the thyroid in both males and females in the aldrin study and cortical adenomas of the adrenal in females in both the aldrin and dieldrin studies were higher in the low dose than in the high-dose groups.

In mice, hepatocellular carcinoma occurred at incidences that were significantly dose related when pooled controls were used in tests performed on males fed aldrin (controls 17/92, low-dose 16/49, high-dose 25/45, $P < 0.001$) or dieldrin (controls 17/92, low-dose 12/50, high-dose 16/45, $P = 0.020$). Further, incidences in the individual treated groups were significantly higher than in the pooled controls in the tests performed on high-dose males fed either aldrin ($P < 0.001$) or dieldrin ($P = 0.025$). When matched controls were used for the comparisons, hepatocellular carcinoma occurred at a significantly high rate only in tests of dose-related trend performed on male mice fed aldrin ($P = 0.001$) and in direct comparison of high-dose aldrin-fed males with the matched controls ($P = 0.002$). However, as shown below, the

incidences of these tumors in male mice fed dieldrin and in female mice fed either aldrin or dieldrin also were consistently higher than those in the corresponding matched controls, even though they were not all statistically significant.

	Matched Controls	Low Dose	High Dose
Males: Aldrin	3/20 (15.0%)	16/49 (32.7%)	25/45 (55.6%)
Dieldrin	3/18 (16.6%)	12/50 (24.0%)	16/45 (35.6%)
Females: Aldrin	0/10 (0%)	5/48 (10.4%)	2/43 (4.7%)
Dieldrin	0/20 (0%)	6/50 (12.0%)	2/49 (4.1%)

These data demonstrate, in addition, that aldrin and dieldrin, which are structurally related compounds that are metabolized in a similar manner, produce a similar lesion in the liver of mice.

Aldrin is known to be rapidly converted to the epoxide, dieldrin, in vivo, and further metabolic degradation of both chemicals is similar (IARC, 1974). Therefore, it is not unexpected that similar tumors were encountered in these bioassays for both aldrin and dieldrin. Chronic toxicity studies have been conducted using Osborne-Mendel rats (Deichmann et al., 1970; Fitzhugh et al., 1964), Carworth Farm "E" strain rats (Walker et al., 1969; Stevenson et al., 1976), rats of unindicated strain (Cleveland, 1966), C_3Heb/Fe/J mice (Davis and Fitzhugh, 1962), or CF1 mice (Walker et al., 1972; Thorpe et al., 1973). In a review of these studies (IARC, 1974), there was no convincing evidence

that either aldrin or dieldrin was carcinogenic. However, several of the studies in mice showed an increase in liver lesions, usually termed "hepatoma," in this species. Evaluation was not always possible because detailed data were lacking.

The data for the rats in the present bioassays confirm previous chronic toxicology studies, in that aldrin and dieldrin were not shown to be carcinogenic for the livers of rats. In the present bioassays for rats, there were questionable incidences of tumors in the thyroid and adrenal glands. These organs have not previously been cited as target organs for these chemicals.

It is concluded that under the conditions of these bioassays, none of the tumors occurring in Osborne-Mendel rats treated with aldrin or dieldrin could clearly be associated with treatment.

Aldrin was carcinogenic for the liver of male B6C3F1 mice producing hepatocellular carcinomas. With dieldrin, there was a significant increase in the incidence of hepatocellular carcinomas in the high-dose males which may be associated with treatment.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED ALDRIN IN THE DIET

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RAT
FED ALDRIN IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(48)	(50)
HEMANGIOSARCOMA		1 (2%)	
*SUBCUT TISSUE	(10)	(48)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
SARCOMA, NOS	1 (10%)		
HEMANGIOSARCOMA			2 (4%)
RESPIRATORY SYSTEM			
#TRACHEA	(9)	(38)	(42)
SARCOMA, NOS	1 (11%)		
#LUNG	(10)	(47)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
C-CELL CARCINOMA, METASTATIC	1 (10%)		
MIXED TUMOR, METASTATIC		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(10)	(45)	(45)
HEMANGIOSARCOMA			1 (2%)
#MANDIBULAR L. NODE	(9)	(34)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(10)	(45)	(45)
SARCOMA, NOS	1 (10%)	1 (2%)	

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

TABLE A1 MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*AORTA	(10)	(48)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(9)	(36)	(40)
SARCOMA, NOS			1 (3%)
#LIVER	(10)	(47)	(47)
HEPATOCELLULAR CARCINOMA	1 (10%)	1 (2%)	1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
*BILE DUCT	(10)	(48)	(50)
BILE DUCT ADENOMA			1 (2%)
#ESOPHAGUS	(9)	(39)	(41)
SARCOMA, NOS	1 (11%)		
#STOMACH	(9)	(37)	(41)
C-CELL CARCINOMA, METASTATIC	1 (11%)		
SARCOMA, NOS	1 (11%)		
URINARY SYSTEM			
#KIDNEY	(10)	(46)	(46)
TUBULAR-CELL ADENOMA	1 (10%)		1 (2%)
MIXED TUMOR, MALIGNANT		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(37)	(40)
CHROMOPHOBE ADENOMA	3 (33%)	13 (35%)	11 (28%)
CHROMOPHOBE CARCINOMA			2 (5%)
#ADRENAL	(10)	(38)	(43)
CORTICAL ADENOMA	2 (20%)		2 (5%)
CORTICAL CARCINOMA		1 (3%)	
PHEOCHROMOCYTOMA		1 (3%)	
#THYROID	(7)	(38)	(38)
FOLLICULAR-CELL ADENOMA	3 (43%)	10 (26%)	6 (16%)
FOLLICULAR-CELL CARCINOMA		4 (11%)	2 (5%)

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

TABLE A1 MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
C-CELL ADENOMA	1 (14%)	4 (11%)	2 (5%)
C-CELL CARCINOMA	1 (14%)		1 (3%)
#PARATHYROID	(7)	(22)	(34)
ADENOMA, NOS	1 (14%)		1 (3%)
#PANCREATIC ISLETS	(9)	(37)	(39)
ISLET-CELL ADENOMA		5 (14%)	1 (3%)
ISLET-CELL CARCINOMA			1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(48)	(50)
FIBROSARCOMA		1 (2%)	
*EPIDIDYMIS	(10)	(48)	(50)
LIPOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(9)	(40)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
MENINGIOMA		1 (3%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKULL	(10)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
*SKELETAL MUSCLE	(10)	(48)	(50)
HEMANGIOSARCOMA			1 (2%)
*MUSCLE OF HEAD	(10)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
*MUSCLE OF NECK	(10)	(48)	(50)
SARCOMA, NOS	1 (10%)		

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

TABLE A1 MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(10)	(48)	(50)
MESOTHELIOMA, NOS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(48)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT			2 (4%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	4	12	13
MORIBUND SACRIFICE	1	12	17
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	5	26	20
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	30	30
TOTAL PRIMARY TUMORS	19	47	43
TOTAL ANIMALS WITH BENIGN TUMORS	7	25	20
TOTAL BENIGN TUMORS	11	35	26
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	10	13
TOTAL MALIGNANT TUMORS	8	12	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	3	1
TOTAL SECONDARY TUMORS	2	4	4
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 FED ALDRIN IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(10)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(9)	(43)	(46)
C-CELL CARCINOMA, METASTATIC			1 (2%)
#LUNG	(9)	(47)	(49)
C-CELL CARCINOMA, METASTATIC			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#SPLEEN	(8)	(47)	(48)
HEMANGIOMA		1 (2%)	
#MANDIBULAR L. NODE	(9)	(31)	(42)
C-CELL CARCINOMA, METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(48)	(49)
NEOPLASTIC NODULE	1 (10%)		3 (6%)

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

TABLE A2 FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(10)	(48)	(49)
HEMANGIOSARCOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(43)	(48)
CHROMOPHOBE ADENOMA	4 (44%)	15 (35%)	11 (23%)
#ADRENAL	(10)	(45)	(48)
CORTICAL ADENOMA		8 (18%)	1 (2%)
#THYROID	(9)	(39)	(46)
FOLLICULAR-CELL ADENOMA	1 (11%)	8 (21%)	3 (7%)
FOLLICULAR-CELL CARCINOMA		2 (5%)	4 (9%)
C-CELL ADENOMA	1 (11%)	6 (15%)	8 (17%)
C-CELL CARCINOMA			2 (4%)
#PANCREATIC ISLETS	(9)	(44)	(40)
ISLET-CELL ADENOMA		1 (2%)	1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(50)	(50)
PAPILLARY ADENOCARCINOMA		1 (2%)	
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	
FIBROADENOMA	3 (30%)	7 (14%)	7 (14%)
#UTERUS	(9)	(45)	(48)
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP		6 (13%)	9 (19%)
#CERVIX UTERI	(9)	(45)	(48)
HEMANGIOSARCOMA		1 (2%)	
#OVARY	(8)	(43)	(46)
GRANULOSA-CELL TUMOR		1 (2%)	4 (9%)
NERVOUS SYSTEM			
NONE			

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

TABLE A2 FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(10)	(50)	(50)
LIPOMA			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	1	4	4
MORIBUND SACRIFICE		12	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	34	40
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	35	32
TOTAL PRIMARY TUMORS	10	62	56
TOTAL ANIMALS WITH BENIGN TUMORS	5	33	26
TOTAL BENIGN TUMORS	9	53	41
TOTAL ANIMALS WITH MALIGNANT TUMORS		6	7
TOTAL MALIGNANT TUMORS		8	8
TOTAL ANIMALS WITH SECONDARY TUMORS#			2
TOTAL SECONDARY TUMORS			4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	7
TOTAL UNCERTAIN TUMORS	1	1	7
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 FED ALDRIN IN THE DIET

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED ALDRIN IN THE DIET

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	50	50
ANIMALS NECROPSIED	10	10	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	50	46
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(10)	(10)	(49)	(45)
HEPATOCELLULAR CARCINOMA, METAST	1 (10%)		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA			3 (6%)	4 (9%)
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(10)	(10)	(50)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (10%)		
#SPLEEN	(9)	(10)	(49)	(44)
SARCOMA, NOS			1 (2%)	
#LYMPH NODE	(9)	(9)	(43)	(45)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
#THYMUS	(1)	(5)	(3)	(3)
SARCOMA, NOS			1 (33%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(10)	(10)	(49)	(46)
HEPATOCELLULAR CARCINOMA	1 (10%)	2 (20%)	16 (33%)	25 (54%)

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

TABLE B1 MALE MICE: NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
SARCOMA, NOS			1 (2%)	1 (2%)
#PANCREAS	(9)	(10)	(49)	(45)
SARCOMA, NOS			1 (2%)	
#STOMACH	(10)	(10)	(49)	(45)
PAPILLOMA, NOS				1 (2%)
#SMALL INTESTINE	(10)		(49)	(45)
ADENOMA, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(10)	(10)	(49)	(45)
SARCOMA, NOS				1 (2%)
ENDOCRINE SYSTEM				
#THYROID	(9)	(8)	(46)	(41)
FOLLICULAR-CELL ADENOMA		1 (13%)	1 (2%)	
REPRODUCTIVE SYSTEM				
#TESTIS	(10)	(9)	(2)	(45)
INTERSTITIAL-CELL TUMOR	1 (10%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(10)	(10)	(50)	(48)
CYSTADENOMA, NOS	1 (10%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MESENTERY	(10)	(10)	(50)	(48)
SARCOMA, NOS				1 (2%)

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

TABLE B1 MALE MICE: NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	50	50
NATURAL DEATH@	2		1	9
MORIBUND SACRIFICE	2	1	3	4
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	6	9	46	37
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	4	18	28
TOTAL PRIMARY TUMORS	3	4	25	36
TOTAL ANIMALS WITH BENIGN TUMORS	2	1	4	5
TOTAL BENIGN TUMORS	2	1	4	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	3	17	25
TOTAL MALIGNANT TUMORS	1	3	21	30
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1	1
TOTAL SECONDARY TUMORS	1		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS				
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN				

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED ALDRIN IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	48	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	48	45
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(48)	(46)
BASAL-CELL CARCINOMA		1 (2%)	
LEIOMYOSARCOMA	1 (10%)		
RESPIRATORY SYSTEM			
#LUNG	(10)	(48)	(44)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
LEIOMYOSARCOMA	1 (10%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(48)	(46)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
GRANULOCYTIC LEUKEMIA	1 (10%)		
CIRCULATORY SYSTEM			
#HEART	(10)	(48)	(39)
LEIOMYCSARCOMA	1 (10%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(10)	(1)	(38)
LEIOMYOSARCOMA	1 (10%)		
#LIVER	(10)	(48)	(43)
HEPATOCELLULAR CARCINOMA		5 (10%)	2 (5%)

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

TABLE B2 FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(10)	(48)	(43)
LEIOMYOSARCOMA	1 (10%)		
ENDOCRINE SYSTEM			
#PITUITARY		(45)	(32)
CHROMOPHOBE ADENOMA		1 (2%)	
#ADRENAL	(10)	(47)	(36)
LEIOMYOSARCOMA	1 (10%)		
#THYROID	(10)	(46)	(32)
ADENOMA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(48)	(46)
LEIOMYOSARCOMA	1 (10%)		
#UTERUS	(10)	(47)	(43)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#OVARY	(10)	(47)	(39)
LEIOMYOSARCOMA	1 (10%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE B2 FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		4	12
MORIBUND SACRIFICE	2	2	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	8	44	33
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	1	11	5
TOTAL PRIMARY TUMORS	9	13	5
TOTAL ANIMALS WITH BENIGN TUMORS		3	1
TOTAL BENIGN TUMORS		4	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	8	4
TOTAL MALIGNANT TUMORS	9	9	4
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 NEOPLASMS IN RATS FED DIELDRIN IN THE DIET

TABLE C1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
FED DIELDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	46	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	46	50
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(46)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
SARCOMA, NOS			1 (2%)
NEURILEMOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(10)	(45)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(46)	(50)
MALIGNANT LYMPHOMA, NOS		2 (4%)	1 (2%)
#SPLEEN	(10)	(41)	(43)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA		2 (5%)	1 (2%)
#LYMPH NODE	(10)	(38)	(34)
SARCOMA, NOS	1 (10%)		
HEMANGIOMA		1 (3%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(10)	(41)	(43)
HEMANGIOSARCOMA			1 (2%)

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

TABLE C1 MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(10)	(44)	(47)
NEOPLASTIC NODULE	1 (10%)		1 (2%)
SARCOMA, NOS	1 (10%)		
#PANCREAS	(10)	(40)	(39)
SARCOMA, NOS	1 (10%)		
#STOMACH	(10)	(42)	(43)
SARCOMA, NOS	1 (10%)		
LEIOMYOSARCOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(10)	(46)	(45)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
SARCOMA, NOS	1 (10%)		
ENDOCRINE SYSTEM			
#PITUITARY	(10)	(35)	(37)
CHROMOPHOBE ADENOMA	2 (20%)	11 (31%)	12 (32%)
CHROMOPHOBE CARCINOMA	1 (10%)		
ACIDOPHIL ADENOMA		1 (3%)	
#ADRENAL	(10)	(41)	(43)
CORTICAL ADENOMA		1 (2%)	3 (7%)
PHEOCHROMOCYTOMA			1 (2%)
SARCOMA, NOS	1 (10%)		
GANGLIONEUROMA			1 (2%)
#THYROID	(10)	(40)	(36)
FOLLICULAR-CELL ADENOMA		3 (8%)	5 (14%)
FOLLICULAR-CELL CARCINOMA			1 (3%)
C-CELL ADENOMA		6 (15%)	4 (11%)
C-CELL CARCINOMA		1 (3%)	
#PARATHYROID	(6)	(32)	(28)
ADENOMA, NOS			1 (4%)
#PANCREATIC ISLETS	(10)	(40)	(39)
ISLET-CELL ADENOMA	1 (10%)	3 (8%)	2 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(46)	(50)
FIBROMA	1 (10%)	1 (2%)	

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

TABLE C1 MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#TESTIS	(10)	(41)	(46)
INTERSTITIAL-CELL TUMOR		1 (2%)	
MESOTHELIOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(10)	(46)	(50)
NEURILEMOMA			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(46)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		4 (9%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		11	9
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	10	39	41
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE C1 MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	24	22
TOTAL PRIMARY TUMORS	12	41	40
TOTAL ANIMALS WITH BENIGN TUMORS	3	22	19
TOTAL BENIGN TUMORS	4	30	32
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	10	6
TOTAL MALIGNANT TUMORS	7	10	7
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	1
TOTAL UNCERTAIN TUMORS	1	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED DIELDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(49)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(9)	(45)	(46)
FOLLICULAR-CELL CARCINOMA, METAS			1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(7)	(45)	(40)
HEMANGIOMA		1 (2%)	
#LYMPH NODE	(10)	(44)	(38)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
#MANDIBULAR L. NODE	(10)	(44)	(38)
SQUAMOUS CELL CARCINOMA, METASTA	1 (10%)		
CIRCULATORY SYSTEM			
#ENDOCARDIUM	(8)	(46)	(40)
SARCOMA, NOS	1 (13%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(9)	(46)	(40)
SQUAMOUS CELL CARCINOMA	1 (11%)		
#LIVER	(9)	(47)	(44)
NEOPLASTIC NODULE		1 (2%)	1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	

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

TABLE C2 FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*BILE DUCT	(10)	(49)	(49)
HAMARTOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(9)	(46)	(42)
MIXED TUMOR, MALIGNANT	1 (11%)		1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(6)	(41)	(33)
CHROMOPHOBE ADENOMA	3 (50%)	9 (22%)	9 (27%)
CHROMOPHOBE CARCINOMA		2 (5%)	
#ADRENAL	(9)	(45)	(40)
CORTICAL ADENOMA		5 (11%)	2 (5%)
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA			1 (3%)
#THYROID	(4)	(45)	(41)
FOLLICULAR-CELL ADENOMA		3 (7%)	6 (15%)
FOLLICULAR-CELL CARCINOMA		2 (4%)	2 (5%)
C-CELL ADENOMA	1 (25%)	10 (22%)	5 (12%)
C-CELL CARCINOMA		2 (4%)	1 (2%)
#PARATHYROID	(7)	(24)	(24)
C-CELL CARCINOMA, INVASIVE			1 (4%)
#PANCREATIC ISLETS	(9)	(46)	(37)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(49)	(49)
ADENOMA, NOS			2 (4%)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
FIBROADENOMA	1 (10%)	13 (27%)	3 (6%)
#UTERUS	(10)	(46)	(40)
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (10%)	4 (9%)	1 (3%)

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

TABLE C2 FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(10)	(45)	(41)
GRANULOSA-CELL TUMOR		2 (4%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(8)	(46)	(40)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)
SARCOMA, NOS			1 (3%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(49)	(49)
FIBROUS HISTIOCYTOMA, MALIGNANT		2 (4%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	2	6	10
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	8	44	40
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE C2 FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	39	27
TOTAL PRIMARY TUMORS	9	60	39
TOTAL ANIMALS WITH BENIGN TUMORS	4	34	22
TOTAL BENIGN TUMORS	6	46	30
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	10	7
TOTAL MALIGNANT TUMORS	3	11	7
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	3
TOTAL SECONDARY TUMORS	1	3	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		3	2
TOTAL UNCERTAIN TUMORS		3	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE FED DIELDRIN IN THE DIET

TABLE D1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIELDRIN IN THE DIET

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	50	50
ANIMALS NECROPSIED	10	10	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	8	10	50	45
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(8)	(10)	(50)	(46)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (10%)	2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(10)	(10)	(50)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (10%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(8)	(10)	(50)	(45)
HEPATOCELLULAR CARCINOMA, METAST				1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(8)	(10)	(50)	(45)
HEPATOCELLULAR CARCINOMA		3 (30%)	12 (24%)	16 (36%)
ALVEOLAR-CELL ADENOMA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(8)	(10)	(50)	(45)
HEPATOCELLULAR CARCINOMA, METAST				1 (2%)

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

TABLE D1 MALE MICE: NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PLEURA	(10)	(10)	(50)	(48)
HEPATOCELLULAR CARCINOMA, METAST				1 (2%)
ALL OTHER SYSTEMS				
DIAPHRAGM				
HEPATOCELLULAR CARCINOMA, METAST				1
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	50	50
NATURAL DEATH@	3			8
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	7	10	50	42
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE D1 MALE MICE: NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	1	3	14	18
TOTAL PRIMARY TUMORS	1	4	16	20
TOTAL ANIMALS WITH BENIGN TUMORS		1	3	2
TOTAL BENIGN TUMORS		1	3	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	3	12	17
TOTAL MALIGNANT TUMORS	1	3	13	18
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	1
TOTAL SECONDARY TUMORS			1	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED DIELDRIN IN THE DIET

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	50	50
ANIMALS NECROPSIED	10	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	50	50
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(10)	(10)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(10)	(10)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE				1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (10%)		2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (10%)		3 (6%)
GRANULOCYTIC SARCOMA			1 (2%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(10)	(10)	(50)	(49)
HEPATOCELLULAR CARCINOMA			6 (12%)	2 (4%)
HEMANGIOMA				1 (2%)
#STOMACH	(10)	(1)	(49)	(50)
PAPILLOMA, NOS		1 (100%)		
URINARY SYSTEM				
NONE				

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

TABLE D2 FEMALE MICE: NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(9)	(9)	(40)	(36)
CHROMOPHOBE ADENOMA			1 (3%)	1 (3%)
#THYROID	(10)	(9)	(50)	(49)
FOLLICULAR-CELL ADENOMA	1 (10%)			
REPRODUCTIVE SYSTEM				
#UTERUS	(10)	(10)	(48)	(50)
ENDOMETRIAL STROMAL POLYP			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKULL	(10)	(10)	(50)	(50)
OSTEOMA			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

TABLE D2 FEMALE MICE: NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	50	50
NATURAL DEATH@				1
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	10	10	50	49
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	1	13	9
TOTAL PRIMARY TUMORS	2	2	14	11
TOTAL ANIMALS WITH BENIGN TUMORS	1	1	4	3
TOTAL BENIGN TUMORS	1	1	5	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	1	9	6
TOTAL MALIGNANT TUMORS	1	1	9	7
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX E

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED ALDRIN IN THE DIET

TABLE E1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED ALDRIN IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(48)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(9)	(38)	(42)
INFLAMMATION, NOS		2 (5%)	
#LUNG	(10)	(47)	(47)
INFLAMMATION, INTERSTITIAL			1 (2%)
PNEUMONIA, ASPIRATION		2 (4%)	
INFLAMMATION, SUPPURATIVE			2 (4%)
CALCIFICATION, NOS			1 (2%)
ALVEOLAR MACROPHAGES		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(10)	(45)	(45)
THROMBOSIS, NOS		1 (2%)	
FIBROSIS		1 (2%)	1 (2%)
LYMPHOID DEPLETION		1 (2%)	2 (4%)
HYPERPLASIA, RETICULUM CELL			5 (11%)
#MANDIBULAR L. NODE	(9)	(34)	(45)
INFLAMMATION, SUPPURATIVE			1 (2%)
PERIARTERITIS			1 (2%)
HYPERPLASIA, PLASMA CELL		1 (3%)	1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (3%)	
#CERVICAL LYMPH NODE	(9)	(34)	(45)
HYPERPLASIA, NOS			1 (2%)

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

TABLE E1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(6)	(27)	(17)
CYST, NOS	3 (50%)	1 (4%)	4 (24%)
CIRCULATORY SYSTEM			
#HEART	(10)	(45)	(45)
THROMBUS, MURAL			2 (4%)
#MYOCARDIUM	(10)	(45)	(45)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS		3 (7%)	
DEGENERATION, NOS			4 (9%)
CALCIFICATION, NOS		2 (4%)	3 (7%)
*AORTA	(10)	(48)	(50)
ANEURYSM DISSECTING		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
CALCIFICATION, NOS	1 (10%)	3 (6%)	
*CORONARY ARTERY	(10)	(48)	(50)
CALCIFICATION, NOS		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(9)	(36)	(40)
FIBROSIS, FOCAL			1 (3%)
CALCIFICATION, NOS			1 (3%)
ATROPHY, FOCAL			1 (3%)
HYPERPLASIA, NOS		1 (3%)	
#LIVER	(10)	(47)	(47)
THROMBOSIS, NOS		2 (4%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
GRANULOMA, NOS			1 (2%)
FIBROSIS		1 (2%)	
PERIARTERITIS		2 (4%)	
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY			1 (2%)
HEPATOCYTOMEGALY	4 (40%)	20 (43%)	17 (36%)
HYPERPLASIA, FOCAL			2 (4%)
#LIVER/HEPATOCYTES	(10)	(47)	(47)
HYPERPLASIA, NOS	3 (30%)		

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

TABLE E1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, FOCAL			1 (2%)
*BILE DUCT	(10)	(48)	(50)
DILATATION, NOS		5 (10%)	3 (6%)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS	10 (100%)	4 (8%)	16 (32%)
HYPERPLASIA, NOS	10 (100%)	42 (88%)	44 (88%)
HYPERPLASIA, CYSTIC			1 (2%)
#PANCREAS	(9)	(37)	(39)
ECTOPIA			1 (3%)
THROMBOSIS, NOS			2 (5%)
FIBROSIS		4 (11%)	4 (10%)
PERIARTERITIS		5 (14%)	3 (8%)
ATROPHY, NOS			3 (8%)
#PANCREATIC DUCT	(9)	(37)	(39)
DILATATION, NOS	1 (11%)	2 (5%)	
FIBROSIS		2 (5%)	
HYPERPLASIA, NOS		2 (5%)	
#PANCREATIC ACINUS	(9)	(37)	(39)
HYPERTROPHY, NOS		1 (3%)	
HYPERPLASIA, NODULAR			1 (3%)
HYPERPLASIA, NOS		1 (3%)	
#STOMACH	(9)	(37)	(41)
ULCER, FOCAL			1 (2%)
ABSCESS, NOS			1 (2%)
CALCIFICATION, NOS		1 (3%)	
#GASTRIC MUCOSA	(9)	(37)	(41)
EROSION			2 (5%)
CALCIFICATION, NOS			1 (2%)
#GASTRIC SUBMUCOSA	(9)	(37)	(41)
CALCIFICATION, NOS			1 (2%)
#SMALL INTESTINE	(9)	(39)	(38)
PERIARTERITIS		3 (8%)	2 (5%)
HYPERPLASIA, EPITHELIAL			1 (3%)
#LARGE INTESTINE	(9)	(38)	(42)
PERIARTERITIS		5 (13%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(10)	(46)	(46)
PYELONEPHRITIS, NOS		1 (2%)	

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

TABLE E1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	10 (100%)	42 (91%)	46 (100%)
PERIARTERITIS		3 (7%)	
#KIDNEY/CORTEX	(10)	(46)	(46)
CYST, NOS	1 (10%)		
#KIDNEY/PELVIS	(10)	(46)	(46)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, EPITHELIAL	10 (100%)	28 (61%)	18 (39%)
#URINARY BLADDER	(9)	(40)	(38)
CALCULUS, NOS		1 (3%)	
HYPERPLASIA, EPITHELIAL	3 (33%)	9 (23%)	14 (37%)
*URETHRA	(10)	(48)	(50)
HYPERPLASIA, EPITHELIAL	1 (10%)	2 (4%)	2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(37)	(40)
CYST, NOS			1 (3%)
#ADRENAL	(10)	(38)	(43)
PERIARTERITIS			1 (2%)
CYTOMEGALY			1 (2%)
#ADRENAL CORTEX	(10)	(38)	(43)
CYTOMEGALY	5 (50%)	25 (66%)	28 (65%)
ATROPHY, FOCAL			1 (2%)
HYPERPLASIA, NOS	2 (20%)		2 (5%)
HYPERPLASIA, FOCAL		3 (8%)	11 (26%)
#THYROID	(7)	(38)	(38)
ULTIMOBRANCHIAL CYST	2 (29%)	3 (8%)	
GRANULOMA, NOS		1 (3%)	
ATROPHY, NOS			2 (5%)
HYPERPLASIA, C-CELL	6 (86%)	16 (42%)	20 (53%)
HYPERPLASIA, FOLLICULAR-CELL		1 (3%)	2 (5%)
#PARATHYROID	(7)	(22)	(34)
HYPERPLASIA, NOS		5 (23%)	7 (21%)
#PANCREATIC ISLETS	(9)	(37)	(39)
HYPERPLASIA, NOS		7 (19%)	

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

TABLE E1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(48)	(50)
GRANULOMA, NOS		1 (2%)	
#PROSTATE	(9)	(41)	(40)
INFLAMMATION, GRANULOMATOUS			2 (5%)
PERIARTERITIS		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (11%)	2 (5%)	1 (3%)
#TESTIS	(10)	(42)	(43)
PERIARTERITIS		7 (17%)	4 (9%)
ATROPHY, NOS	6 (60%)	30 (71%)	35 (81%)
ASPERMATOGENESIS		1 (2%)	
*EPIDIDYMIS	(10)	(48)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HYPERPLASIA, EPITHELIAL			2 (4%)
DYSPLASIA, EPITHELIAL			2 (4%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(9)	(40)	(42)
INFLAMMATION, NOS		1 (3%)	
FIBROSIS		3 (8%)	
CALCIFICATION, NOS		1 (3%)	
#BRAIN	(9)	(40)	(42)
INFLAMMATION, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(10)	(48)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
*EYE/CORNEA	(10)	(48)	(50)
ULCER, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
*EYE/IRIS	(10)	(48)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
*EYE/RETINA	(10)	(48)	(50)
DEGENERATION, NOS			1 (2%)

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

TABLE E1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF		1	2
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY		2	

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

TABLE E2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED ALDRIN IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(9)	(47)	(49)
EMBOLISM, NOS			1 (2%)
PNEUMONIA, ASPIRATION		2 (4%)	
INFLAMMATION, GRANULOMATOUS			2 (4%)
HEPATOCYTOMEGALY		1 (2%)	
ALVEOLAR MACROPHAGES			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		4 (9%)	2 (4%)
#LUNG/ALVEOLI	(9)	(47)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(8)	(47)	(48)
FIBROSIS		1 (2%)	1 (2%)
ATROPHY, NOS			1 (2%)
LYMPHOID DEPLETION			1 (2%)
HYPERPLASIA, RETICULUM CELL		2 (4%)	
#MANDIBULAR L. NODE	(9)	(31)	(42)
HYPERPLASIA, PLASMA CELL	1 (11%)	1 (3%)	
HYPERPLASIA, RETICULUM CELL		1 (3%)	1 (2%)
#THYMUS	(6)	(33)	(33)
CYST, NOS	3 (50%)	8 (24%)	9 (27%)
CIRCULATORY SYSTEM			
*AORTA	(10)	(50)	(50)
CALCIFICATION, NOS		1 (2%)	

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

TABLE E2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(10)	(48)	(49)
ECTOPIA		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
HEPATOCYTOMEGALY	8 (80%)	21 (44%)	35 (71%)
HYPERPLASIA, FOCAL	1 (10%)	3 (6%)	2 (4%)
ANGIECTASIS		1 (2%)	
HEMATOPOIESIS		2 (4%)	1 (2%)
*BILE DUCT	(10)	(50)	(50)
DILATATION, NOS		5 (10%)	5 (10%)
FIBROSIS	3 (30%)	12 (24%)	5 (10%)
HYPERPLASIA, NOS	9 (90%)	46 (92%)	40 (80%)
#PANCREAS	(9)	(44)	(40)
ATROPHY, FOCAL			1 (3%)
#STOMACH	(9)	(42)	(46)
ECTOPIA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(10)	(48)	(49)
PYELONEPHRITIS, NOS	1 (10%)		
INFLAMMATION, CHRONIC	8 (80%)	41 (85%)	46 (94%)
METAMORPHOSIS FATTY			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
#KIDNEY/PELVIS	(10)	(48)	(49)
INFLAMMATION, NOS	1 (10%)		
HYPERPLASIA, EPITHELIAL	5 (50%)	34 (71%)	21 (43%)
#URINARY BLADDER	(9)	(41)	(46)
HYPERPLASIA, EPITHELIAL	1 (11%)	1 (2%)	3 (7%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(10)	(45)	(48)
CYTOMEGALY	4 (40%)	21 (47%)	19 (40%)
ATROPHY, NOS			1 (2%)
HYPERPLASIA, NOS	1 (10%)	1 (2%)	2 (4%)
HYPERPLASIA, FOCAL	4 (40%)	6 (13%)	9 (19%)

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

TABLE E2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(9)	(39)	(46)
HYPERPLASIA, C-CELL	6 (67%)	23 (59%)	26 (57%)
HYPERPLASIA, FOLLICULAR-CELL		1 (3%)	2 (4%)
#PARATHYROID	(7)	(22)	(28)
HYPERPLASIA, NOS	3 (43%)	1 (5%)	2 (7%)
#PANCREATIC ISLETS	(9)	(44)	(40)
HYPERPLASIA, NOS		4 (9%)	
REPRODUCTIVE SYSTEM			
#UTERUS/ENDOMETRIUM	(9)	(45)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	3 (6%)
HYPERPLASIA, NOS			4 (8%)
HYPERPLASIA, CYSTIC		4 (9%)	
METAPLASIA, SQUAMOUS		3 (7%)	
DYSPLASIA, NOS		1 (2%)	
#OVARY	(8)	(43)	(46)
FOLLICULAR CYST, NOS	1 (13%)	1 (2%)	1 (2%)
HYPERPLASIA, GRANULOSA-CELL	1 (13%)	2 (5%)	3 (7%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(9)	(44)	(37)
FIBROSIS	1 (11%)		
#BRAIN	(9)	(44)	(37)
ECTOPIA			1 (3%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(10)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	

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

TABLE E2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
GRANULATION, TISSUE		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF		1	1
AUTO/NECROPSY/NO HISTO		1	

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

APPENDIX F

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED ALDRIN IN THE DIET

TABLE F1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED ALDRIN IN THE DIET

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	50	50
ANIMALS NECROPSIED	10	10	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	50	46
INTEGUMENTARY SYSTEM				
*SKIN	(10)	(10)	(50)	(48)
GRANULATION, TISSUE				1 (2%)
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(10)	(10)	(49)	(45)
HYPERPLASIA, LYMPHOID	5 (50%)	7 (70%)	20 (41%)	21 (47%)
#LUNG	(10)	(10)	(49)	(45)
INFLAMMATION, INTERSTITIAL				2 (4%)
HYPERPLASIA, EPITHELIAL	1 (10%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (10%)			
HYPERPLASIA, LYMPHOID	3 (30%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(9)	(10)	(49)	(44)
HEMATOPOIESIS				2 (5%)
#LYMPH NODE	(9)	(9)	(43)	(45)
HYPERPLASIA, LYMPHOID				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(10)	(10)	(49)	(43)
PERIARTERITIS				1 (2%)
#HEART/VENTRICLE	(10)	(10)	(49)	(43)
THROMBOSIS, NOS	1 (10%)			
*CORONARY ARTERY	(10)	(10)	(50)	(48)
INFLAMMATION, NOS		1 (10%)		

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

TABLE F1 MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(10)	(10)	(49)	(46)
INFLAMMATION, NOS			1 (2%)	3 (7%)
INFLAMMATION, CHRONIC		1 (10%)		
NECROSIS, NOS	1 (10%)		1 (2%)	1 (2%)
HEPATOCYTOMEGALY			5 (10%)	12 (26%)
HYPERPLASIA, NODULAR			3 (6%)	6 (13%)
*BILE DUCT	(10)	(10)	(50)	(48)
INFLAMMATION, NOS	1 (10%)	1 (10%)	1 (2%)	
#PANCREAS	(9)	(10)	(49)	(45)
PERIARTERITIS	1 (11%)			
ATROPHY, NOS		1 (10%)		
#PANCREATIC ACINUS	(9)	(10)	(49)	(45)
ATROPHY, NOS	1 (11%)		2 (4%)	3 (7%)
#LARGE INTESTINE	(10)	(9)	(48)	(45)
NEMATODIASIS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(10)	(10)	(49)	(45)
INFLAMMATION, INTERSTITIAL	8 (80%)	6 (60%)	36 (73%)	27 (60%)
INFLAMMATION, CHRONIC		4 (40%)		
PERIARTERITIS				1 (2%)
AMYLOID, NOS		1 (10%)		
#KIDNEY/TUBULE	(10)	(10)	(49)	(45)
CYTOPLASMIC VACUOLIZATION			1 (2%)	1 (2%)
#URINARY BLADDER	(10)	(10)	(49)	(44)
INFLAMMATION, ACUTE/CHRONIC		1 (10%)		
INFLAMMATION, CHRONIC		1 (10%)	1 (2%)	
PERIARTERITIS				1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
METAPLASIA, SQUAMOUS		1 (10%)		
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(9)	(10)	(47)	(42)
CYTOMEGALY			1 (2%)	

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

TABLE F1 MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	8 (89%)	9 (90%)	41 (87%)	35 (83%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(10)	(10)	(2)	(45)
INFLAMMATION, CHRONIC		1 (10%)		
#TESTIS	(10)	(9)	(2)	(45)
GRANULOMA, SPERMATIC			1 (50%)	1 (2%)
PERIARTERITIS				1 (2%)
ATROPHY, NOS			1 (50%)	1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			1	
AUTO/NECROPSY/HISTO PERF	1		1	
AUTO/NECROPSY/NO HISTO				2
AUTOLYSIS/NO NECROPSY				2

(#) NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
[*] NUMBER OF ANIMALS NECROPSIED

TABLE F2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED ALDRIN IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	48	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	48	45
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(10)	(48)	(44)
HYPERPLASIA, LYMPHOID	4 (40%)	24 (50%)	24 (55%)
HEMATOPOIESIS			1 (2%)
#LUNG	(10)	(48)	(44)
INFLAMMATION, INTERSTITIAL		2 (4%)	
INFLAMMATION, GRANULOMATOUS		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (20%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(8)	(1)	(4)
HYPERPLASIA, HEMATOPOIETIC		1 (100%)	4 (100%
#SPLEEN	(10)	(48)	(42)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HYPERPLASIA, LYMPHOID		3 (6%)	
HEMATOPOIESIS	1 (10%)	1 (2%)	3 (7%)
#LYMPH NODE	(10)	(47)	(36)
HYPERPLASIA, PLASMA CELL		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (3%)
HYPERPLASIA, LYMPHOID	1 (10%)		1 (3%)
#THYMUS	(3)	(5)	(13)
HYPERPLASIA, LYMPHOID			1 (8%)
CIRCULATORY SYSTEM			
#HEART	(10)	(48)	(39)
PERIARTERITIS			1 (3%)

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

TABLE F2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(10)	(1)	(38)
HYPERPLASIA, INTRADUCTAL		1 (100%)	
#LIVER	(10)	(48)	(43)
CYST, NOS		1 (2%)	
INFLAMMATION, NOS	2 (20%)		1 (2%)
INFLAMMATION, ACUTE			2 (5%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		11 (23%)	4 (9%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HEPATOCYTOMEGALY		1 (2%)	
HYPERPLASIA, NODULAR		2 (4%)	3 (7%)
METAPLASIA, OSSEOUS			1 (2%)
*BILE DUCT	(10)	(48)	(46)
INFLAMMATION, NOS	3 (30%)		1 (2%)
INFLAMMATION, CHRONIC		7 (15%)	4 (9%)
#PANCREAS	(10)	(48)	(43)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)	3 (7%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
PERIARTERITIS			1 (2%)
#PANCREATIC ACINUS	(10)	(48)	(43)
ATROPHY, NOS		2 (4%)	
#LARGE INTESTINE	(7)	(41)	(37)
NEMATODIASIS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(10)	(48)	(43)
INFLAMMATION, INTERSTITIAL	5 (50%)	24 (50%)	28 (65%)
INFLAMMATION, CHRONIC		1 (2%)	
AMYLOIDOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (10%)		
#URINARY BLADDER	(10)	(41)	(19)
INFLAMMATION, GRANULOMATOUS		1 (2%)	

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

TABLE F2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY		(45)	(32)
HYPERPLASIA, CHROMOPHOBE-CELL		2 (4%)	
#ADRENAL	(10)	(47)	(36)
INFLAMMATION, ACUTE	1 (10%)		
#ADRENAL CORTEX	(10)	(47)	(36)
CYTOMEGALY			1 (3%)
HYPERPLASIA, NOS	10 (100%)	46 (98%)	34 (94%)
#THYROID	(10)	(46)	(32)
HYPERPLASIA, NOS			2 (6%)
HYPERPLASIA, FOLLICULAR-CELL			1 (3%)
REPRODUCTIVE SYSTEM			
#UTERUS	(10)	(47)	(43)
INFLAMMATION, ACUTE		1 (2%)	
#UTERUS/ENDOMETRIUM	(10)	(47)	(43)
INFLAMMATION, SUPPURATIVE	1 (10%)		1 (2%)
INFLAMMATION, ACUTE		9 (19%)	5 (12%)
HYPERPLASIA, CYSTIC	8 (80%)	34 (72%)	28 (65%)
#OVARY	(10)	(47)	(39)
FOLLICULAR CYST, NOS	3 (30%)	10 (21%)	3 (8%)
INFLAMMATION, SUPPURATIVE	1 (10%)	3 (6%)	4 (10%)
INFLAMMATION, ACUTE		7 (15%)	8 (21%)
INFLAMMATION, CHRONIC		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(10)	(48)	(46)
FIBROUS DYSPLASIA	2 (20%)	6 (13%)	

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

TABLE F2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(10)	(48)	(46)
INFLAMMATION, ACUTE		4 (8%)	
INFLAMMATION, CHRONIC		1 (2%)	
*MESENTERY	(10)	(48)	(46)
INFLAMMATION, GRANULOMATOUS			1 (2%)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, NOS			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			5
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY		2	4

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

APPENDIX G

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED DIELDRIN IN THE DIET

TABLE G1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIELDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	46	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	46	50
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(46)	(50)
INFLAMMATION, GRANULOMATOUS	1 (10%)	1 (2%)	
PERIARTERITIS		2 (4%)	
RESPIRATORY SYSTEM			
#TRACHEA	(10)	(35)	(37)
INFLAMMATION, SUPPURATIVE		1 (3%)	
INFLAMMATION, CHRONIC		1 (3%)	2 (5%)
#LUNG/BRONCHIOLE	(10)	(45)	(46)
METAPLASIA, SQUAMOUS	1 (10%)		
#LUNG	(10)	(45)	(46)
INFLAMMATION, INTERSTITIAL		2 (4%)	
PNEUMONIA, ASPIRATION			1 (2%)
PERIARTERITIS		1 (2%)	
CHOLESTEROL DEPOSIT		2 (4%)	
ALVEOLAR MACROPHAGES	2 (20%)	15 (33%)	15 (33%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	8 (80%)	1 (2%)	
#LUNG/ALVEOLI	(10)	(45)	(46)
INFLAMMATION, SUPPURATIVE	1 (10%)	2 (4%)	4 (9%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(10)	(41)	(43)
HEMORRHAGE		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	1 (2%)
HEMOSIDEROSIS		5 (12%)	6 (14%)
HYPERPLASIA, RETICULUM CELL	1 (10%)		1 (2%)
HEMATOPOIESIS		5 (12%)	3 (7%)

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

TABLE G1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(10)	(38)	(34)
HEMORRHAGE		1 (3%)	
INFLAMMATION, SUPPURATIVE		1 (3%)	
NECROSIS, FOCAL			1 (3%)
HYPERPLASIA, PLASMA CELL	1 (10%)		
HYPERPLASIA, RETICULUM CELL			2 (6%)
HYPERPLASIA, LYMPHOID	1 (10%)	3 (8%)	1 (3%)
#THYMUS	(6)	(27)	(23)
CYST, NOS		6 (22%)	3 (13%)
CIRCULATORY SYSTEM			
#HEART	(10)	(43)	(45)
FIBROSIS	1 (10%)		
#MYOCARDIUM	(10)	(43)	(45)
INFLAMMATION, NOS	1 (10%)		
FIBROSIS	8 (80%)	23 (53%)	23 (51%)
CALCIFICATION, NOS		1 (2%)	
*AORTA	(10)	(46)	(50)
CALCIFICATION, NOS		1 (2%)	2 (4%)
*CORONARY ARTERY	(10)	(46)	(50)
CALCIFICATION, NOS		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(10)	(44)	(47)
INFLAMMATION, SUPPURATIVE	1 (10%)		
GRANULOMA, NOS	1 (10%)		
NECROSIS, FOCAL			1 (2%)
HEPATOCYTOMEGALY	6 (60%)	17 (39%)	20 (43%)
HYPERPLASIA, FOCAL	1 (10%)		
HEMATOPOIESIS			1 (2%)
*BILE DUCT	(10)	(46)	(50)
INFLAMMATION, NOS	6 (60%)		
FIBROSIS	2 (20%)	7 (15%)	3 (6%)
HYPERPLASIA, NOS	9 (90%)	34 (74%)	25 (50%)
#PANCREAS	(10)	(40)	(39)
INFLAMMATION, NOS	1 (10%)		
INFLAMMATION, SUPPURATIVE		2 (5%)	1 (3%)
FIBROSIS	2 (20%)		1 (3%)
PERIARTERITIS		5 (13%)	4 (10%)

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

TABLE G1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ACINUS	(10)	(40)	(39)
ATROPHY, NOS		6 (15%)	
#STOMACH	(10)	(42)	(43)
ULCER, FOCAL			2 (5%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
PERIARTERITIS		1 (2%)	
HYPERKERATOSIS		1 (2%)	
#GASTRIC MUCOSA	(10)	(42)	(43)
CALCIFICATION, NOS		2 (5%)	2 (5%)
#SMALL INTESTINE	(10)	(40)	(39)
PERIARTERITIS		2 (5%)	1 (3%)
#LARGE INTESTINE	(10)	(41)	(38)
EDEMA, NOS		1 (2%)	
PERIARTERITIS		1 (2%)	1 (3%)
URINARY SYSTEM			
#KIDNEY	(10)	(46)	(45)
INFLAMMATION, NOS	3 (30%)		
INFLAMMATION, CHRONIC	6 (60%)	45 (98%)	43 (96%)
PERIARTERITIS		1 (2%)	1 (2%)
#KIDNEY/PELVIS	(10)	(46)	(45)
INFLAMMATION, SUPPURATIVE		4 (9%)	3 (7%)
HYPERPLASIA, EPITHELIAL	6 (60%)	10 (22%)	18 (40%)
#URINARY BLADDER	(10)	(36)	(39)
INFLAMMATION, NOS			7 (18%)
HYPERPLASIA, EPITHELIAL	1 (10%)	10 (28%)	18 (46%)
ENDOCRINE SYSTEM			
#PITUITARY	(10)	(35)	(37)
CYST, NOS	1 (10%)	6 (17%)	2 (5%)
HYPERPLASIA, CHROMOPHOBE-CELL		4 (11%)	
#ADRENAL	(10)	(41)	(43)
PERIARTERITIS		1 (2%)	
CYTOMEGALY			1 (2%)

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

TABLE G1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL CORTEX	(10)	(41)	(43)
CYTOMEGALY	8 (80%)	17 (41%)	19 (44%)
HYPERPLASIA, NODULAR	1 (10%)		
HYPERPLASIA, NOS	1 (10%)		
HYPERPLASIA, FOCAL	2 (20%)	6 (15%)	6 (14%)
ANGIECTASIS	1 (10%)		
#THYROID	(10)	(40)	(36)
ULTIMOBRANCHIAL CYST		2 (5%)	
CYTOMEGALY		1 (3%)	
HYPERPLASIA, C-CELL	7 (70%)	23 (58%)	25 (69%)
HYPERPLASIA, FOLLICULAR-CELL		3 (8%)	
#PARATHYROID	(6)	(32)	(28)
HYPERPLASIA, NOS		5 (16%)	5 (18%)
#PANCREATIC ISLETS	(10)	(40)	(39)
HYPERPLASIA, NOS	2 (20%)	3 (8%)	7 (18%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(10)	(43)	(40)
INFLAMMATION, SUPPURATIVE	2 (20%)	18 (42%)	20 (50%)
PERIARTERITIS		2 (5%)	
HYPERPLASIA, NOS			1 (3%)
METAPLASIA, SQUAMOUS	1 (10%)	1 (2%)	15 (38%)
#TESTIS	(10)	(41)	(46)
PERIARTERITIS	1 (10%)	4 (10%)	3 (7%)
ATROPHY, NOS	6 (60%)	36 (88%)	32 (70%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(10)	(43)	(46)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	1 (2%)
FIBROSIS, FOCAL		1 (2%)	
#BRAIN	(10)	(43)	(46)
HEMORRHAGE		1 (2%)	
INFLAMMATION, FOCAL	1 (10%)		
NECROSIS, FOCAL	1 (10%)		
ANGIECTASIS		1 (2%)	

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

TABLE G1 MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY PERF/HISTO PERF			1
AUTOLYSIS/NO NECROPSY PERFORMED		4	

TABLE G2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED DIELDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(49)	(49)
INFLAMMATION, GRANULOMATOUS			2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(9)	(45)	(46)
INFLAMMATION, INTERSTITIAL	1 (11%)		2 (4%)
PNEUMONIA, ASPIRATION			7 (15%)
ABSCESS, NOS			1 (2%)
CHOLESTEROL DEPOSIT		1 (2%)	
ALVEOLAR MACROPHAGES	1 (11%)	16 (36%)	11 (24%)
#LUNG/ALVEOLI	(9)	(45)	(46)
INFLAMMATION, SUPPURATIVE		3 (7%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(7)	(45)	(40)
HEMOSIDEROSIS		2 (4%)	1 (3%)
HEMATOPOIESIS		3 (7%)	10 (25%)
#THYMUS	(7)	(31)	(32)
CYST, NOS	4 (57%)	8 (26%)	9 (28%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(8)	(46)	(40)
FIBROSIS	3 (38%)	18 (39%)	14 (35%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(9)	(46)	(40)
INFLAMMATION, FOCAL		1 (2%)	1 (3%)

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

TABLE G2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(9)	(47)	(44)
ECTOPIA		1 (2%)	
GRANULOMA, NOS		1 (2%)	
FIBROSIS, FOCAL			1 (2%)
NECROSIS, FOCAL		4 (9%)	1 (2%)
HEPATOCYTOMEGALY	1 (11%)	9 (19%)	2 (5%)
ANGIECTASIS		3 (6%)	2 (5%)
HEMATOPOIESIS		1 (2%)	2 (5%)
*BILE DUCT	(10)	(49)	(49)
FIBROSIS	1 (10%)	4 (8%)	4 (8%)
HYPERPLASIA, NOS	7 (70%)	38 (78%)	22 (45%)
#PANCREAS	(9)	(46)	(37)
FIBROSIS		7 (15%)	1 (3%)
PERIARTERITIS		1 (2%)	1 (3%)
#PANCREATIC ACINUS	(9)	(46)	(37)
ATROPHY, NOS	1 (11%)	7 (15%)	8 (22%)
#STOMACH	(10)	(47)	(40)
ULCER, FOCAL	1 (10%)	1 (2%)	1 (3%)
URINARY SYSTEM			
#KIDNEY	(9)	(46)	(42)
INFLAMMATION, CHRONIC	6 (67%)	39 (85%)	34 (81%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#KIDNEY/PELVIS	(9)	(46)	(42)
INFLAMMATION, SUPPURATIVE	1 (11%)		
HYPERPLASIA, EPITHELIAL	5 (56%)	9 (20%)	12 (29%)
#URINARY BLADDER	(9)	(43)	(36)
INFLAMMATION, NOS	1 (11%)	1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (11%)	7 (16%)	4 (11%)
ENDOCRINE SYSTEM			
#PITUITARY	(6)	(41)	(33)
CYST, NOS		4 (10%)	4 (12%)
CYTOMEGALY			1 (3%)
#ADRENAL CORTEX	(9)	(45)	(40)
CYTOMEGALY	4 (44%)	14 (31%)	21 (53%)
HYPERPLASIA, FOCAL	1 (11%)	1 (2%)	8 (20%)

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

TABLE G2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(4)	(45)	(41)
ULTIMOBRANCHIAL CYST		2 (4%)	3 (7%)
CYSTIC FOLLICLES	1 (25%)		
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, C-CELL	4 (100%)	32 (71%)	31 (76%)
HYPERPLASIA, FOLLICULAR-CELL	1 (25%)	4 (9%)	6 (15%)
#PARATHYROID	(7)	(24)	(24)
HYPERPLASIA, NOS		1 (4%)	
REPRODUCTIVE SYSTEM			
*VAGINA	(10)	(49)	(49)
HYPERPLASIA, PSEUDOEPITHELIOMATO		1 (2%)	
#UTERUS/ENDOMETRIUM	(10)	(46)	(40)
INFLAMMATION, SUPPURATIVE	1 (10%)	2 (4%)	1 (3%)
HYPERPLASIA, CYSTIC	1 (10%)	3 (7%)	
#OVARY	(10)	(45)	(41)
FOLLICULAR CYST, NOS		3 (7%)	
HYPERPLASIA, GRANULOSA-CELL		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(8)	(46)	(40)
FIBROSIS, FOCAL	2 (25%)	1 (2%)	3 (8%)
#BRAIN	(8)	(46)	(40)
MINERALIZATION			1 (3%)
ATROPHY, NOS			1 (3%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(10)	(49)	(49)
INFLAMMATION, SUPPURATIVE	1 (10%)		

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

TABLE G2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(10)	(49)	(49)
INFLAMMATION, GRANULOMATOUS	1 (10%)		1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY PERF/HISTO PERF	1		2
AUTOLYSIS/NECROPSY PERF/NO HISTO		2	1
AUTOLYSIS/NO NECROPSY PERFORMED		1	1

APPENDIX H

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED DIELDRIN IN THE DIET

TABLE H1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIELDRIN IN THE DIET

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	50	50
ANIMALS NECROPSIED	10	10	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	8	10	50	46
INTEGUMENTARY SYSTEM				
*SKIN	(10)	(10)	(50)	(48)
INFLAMMATION, FOCAL			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG/BRONCHIOLE	(8)	(10)	(50)	(46)
HYPERPLASIA, EPITHELIAL				1 (2%)
#LUNG	(8)	(10)	(50)	(46)
HEMORRHAGE	1 (13%)			
ALVEOLAR MACROPHAGES				1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM				1 (2%)
HEMATOPOIETIC SYSTEM				
#CERVICAL LYMPH NODE	(7)	(10)	(49)	(36)
HYPERPLASIA, LYMPHOID				1 (3%)
#TRACHEAL LYMPH NODE	(7)	(10)	(49)	(36)
HYPERPLASIA, LYMPHOID				1 (3%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(8)	(10)	(50)	(45)
FIBROSIS			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(8)	(10)	(50)	(45)
INFLAMMATION, FOCAL			1 (2%)	

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

TABLE H1 MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
LIVER CONT.				
NECROSIS, FOCAL	1 (13%)	1 (10%)	2 (4%)	
METAMORPHOSIS FATTY			1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)	
HEPATOCYTOMEGALY			2 (4%)	2 (4%)
HYPERPLASIA, NODULAR				2 (4%)
HYPERPLASIA, DIFFUSE				1 (2%)
#LIVER/CAUDATE LOBE	(8)	(10)	(50)	(45)
TORSION			1 (2%)	
*BILE DUCT	(10)	(10)	(50)	(48)
INFLAMMATION, FOCAL			1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)	
#PANCREAS	(7)	(10)	(50)	(45)
INFLAMMATION, GRANULOMATOUS	1 (14%)			
#LARGE INTESTINE	(3)	(8)	(19)	(28)
INFLAMMATION, FOCAL GRANULOMATOU				1 (4%)
NEMATODIASIS			1 (5%)	1 (4%)
URINARY SYSTEM				
#KIDNEY	(8)	(10)	(50)	(45)
MULTIPLE CYSTS	1 (13%)			
PERIARTERITIS			1 (2%)	
#KIDNEY/CORTEX	(8)	(10)	(50)	(45)
REGENERATION, NOS			1 (2%)	
#KIDNEY/TUBULE	(8)	(10)	(50)	(45)
CALCIFICATION, FOCAL	1 (13%)			
REGENERATION, NOS			1 (2%)	
#URINARY BLADDER	(7)	(10)	(49)	(36)
HYPERPLASIA, EPITHELIAL			1 (2%)	
ENDOCRINE SYSTEM				
#THYROID	(8)	(9)	(42)	(38)
HYPERPLASIA, FOLLICULAR-CELL			3 (7%)	
#PARATHYROID	(6)	(9)	(19)	(27)
HYPERPLASIA, NOS				1 (4%)

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

TABLE H1 MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
#PROSTATE	(7)	(10)	(49)	(45)
HYPERPLASIA, EPITHELIAL			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(7)	(10)	(50)	(45)
INFLAMMATION, FOCAL			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	6	28	23
AUTOLYSIS/NECROPSY PERF/NO HISTO	2			2
AUTOLYSIS/NO NECROPSY PERFORMED				2

TABLE H2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED DIELDRIN IN THE DIET

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	50	50
ANIMALS NECROPSIED	10	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	50	50
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(10)	(10)	(50)	(50)
ALVEOLAR MACROPHAGES				1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW				
FIBROSIS				
#SPLEEN	(10)	(10)	(48)	(50)
INFLAMMATION, FOCAL GRANULOMATOU	1 (10%)			
HYPERPLASIA, LYMPHOID				2 (4%)
HEMATOPOIESIS		1 (10%)	5 (10%)	4 (8%)
#LYMPH NODE	(10)	(3)	(49)	(50)
INFLAMMATION, SUPPURATIVE				1 (2%)
ANGIECTASIS				1 (2%)
HYPERPLASIA, LYMPHOID				2 (4%)
#MESENTERIC L. NODE	(10)	(3)	(49)	(50)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, GRANULOMATOUS				1 (2%)
CIRCULATORY SYSTEM				
NONE				

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

TABLE H2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(10)	(10)	(50)	(49)
INFLAMMATION, SUPPURATIVE				1 (2%)
NECROSIS, FOCAL			1 (2%)	2 (4%)
HEPATOCYTOMEGALY			1 (2%)	1 (2%)
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (10%)		
HEMATOPOIESIS			1 (2%)	
#LIVER/CENTRILOBULAR	(10)	(10)	(50)	(49)
NECROSIS, NOS			1 (2%)	
METAMORPHOSIS FATTY			1 (2%)	
*GALLBLADDER	(10)	(10)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)	
*BILE DUCT	(10)	(10)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
#PANCREAS	(10)	(10)	(50)	(50)
INFLAMMATION, NOS			2 (4%)	
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
FIBROSIS			1 (2%)	
NECROSIS, FAT			1 (2%)	
METAMORPHOSIS FATTY				1 (2%)
#PANCREATIC DUCT	(10)	(10)	(50)	(50)
DILATATION, NOS	1 (10%)		1 (2%)	
CYST, NOS			1 (2%)	
FIBROSIS			2 (4%)	
#PANCREATIC ACINUS	(10)	(10)	(50)	(50)
ATROPHY, NOS			5 (10%)	
URINARY SYSTEM				
#KIDNEY	(10)	(10)	(50)	(49)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC			1 (2%)	3 (6%)
PERIVASCULAR CUFFING	1 (10%)	2 (20%)		1 (2%)
NECROSIS, FAT			1 (2%)	
AMYLOIDOSIS			1 (2%)	

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

TABLE H2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
#KIDNEY/CORTEX	(10)	(10)	(50)	(49)
LYMPHOCYTIC INFLAM INFILTRATE				1 (2%)
#KIDNEY/TUBULE	(10)	(10)	(50)	(49)
REGENERATION, NOS				2 (4%)
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(10)	(10)	(49)	(48)
HYPERPLASIA, FOCAL			1 (2%)	
#THYROID	(10)	(9)	(50)	(49)
CYSTIC FOLLICLES			2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM				
#UTERUS/ENDOMETRIUM	(10)	(10)	(48)	(50)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, SUPPURATIVE	2 (20%)	1 (10%)	4 (8%)	10 (20%)
HYPERPLASIA, CYSTIC	7 (70%)	4 (40%)	16 (33%)	16 (32%)
#OVARY/OVIDUCT	(10)	(10)	(48)	(50)
INFLAMMATION, SUPPURATIVE				2 (4%)
#OVARY	(10)	(10)	(50)	(50)
CYST, NOS			4 (8%)	1 (2%)
INFLAMMATION, SUPPURATIVE	2 (20%)	3 (30%)	10 (20%)	23 (46%)
#OVARY/FETE OVARII	(10)	(10)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(10)	(10)	(50)	(50)
INFLAMMATION, FOCAL				1 (2%)
#CEREBELLUM	(10)	(10)	(50)	(50)
ATROPHY, NOS			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				

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

TABLE H2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	LOW DOSE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(10)	(10)	(50)	(50)
INFLAMMATION, NOS			2 (4%)	
INFLAMMATION, SUPPURATIVE			1 (2%)	1 (2%)
*PLEURA	(10)	(10)	(50)	(50)
INFLAMMATION, FOCAL			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(10)	(10)	(50)	(50)
HYPERPLASIA, LYMPHOID				1 (2%)
ADIPOSE TISSUE				
INFLAMMATION, SUPPURATIVE			1	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	2	13	11

APPENDIX I

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED ALDRIN IN THE DIET

Table I1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
All Sites: Hemangiosarcoma[b]	0/10 (0.00)	4/58 (0.07)	1/47 (0.02)	3/49 (0.06)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.137
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			0.617	0.888
Lower Limit			0.079	0.161
Upper Limit			2.971	4.985
Weeks to First Observed Tumor	111	--	48	51
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	3/7 (0.43)	4/48 (0.08)	14/38 (0.37)	8/38 (0.21)
P Values[c,d]	P = 0.075(N)	P = 0.069	P = 0.002**	N.S.
Departure from Linear Trend[e]		P = 0.006		
Relative Risk (Matched Control)[f]			0.860	0.491
Lower Limit			0.381	0.189
Upper Limit			3.959	2.470
Relative Risk (Pooled Control)[f]			4.421	2.526
Lower Limit			1.532	0.734
Upper Limit			16.808	10.634
Weeks to First Observed Tumor	111	--	83	88

Table I1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Thyroid: C-cell Adenoma or Carcinoma[b]	2/7 (0.29)	4/48 (0.08)	4/38 (0.11)	3/38 (0.08)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.368	0.276
Lower Limit			0.077	0.045
Upper Limit			3.716	3.036
Relative Risk (Pooled Control)[f]			1.263	0.947
Lower Limit			0.250	0.145
Upper Limit			6.295	5.219
Weeks to First Observed Tumor	104	--	111	94
Pancreatic Islet: Islet-cell Adenoma or Carcinoma[b]	0/9 (0.00)	1/52 (0.02)	5/37 (0.14)	2/39 (0.05)
P Values[c,d]	N.S.	N.S.	P = 0.043**	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.349	0.076
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			7.027	2.667
Lower Limit			0.831	0.143
Upper Limit			327.268	151.423
Weeks to First Observed Tumor	--	--	66	95

Table I1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	3/9 (0.33)	15/49 (0.31)	13/37 (0.35)	13/40 (0.33)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.054	0.975
Lower Limit			0.411	0.378
Upper Limit			4.972	4.660
Relative Risk (Pooled Control)[f]			1.148	1.062
Lower Limit			0.574	0.528
Upper Limit			2.232	2.086
Weeks to First Observed Tumor	104	--	92	64
Adrenal: Cortical Adenoma or Carcinoma[b]	2/10 (0.20)	3/55 (0.05)	1/38 (0.03)	2/43 (0.05)
P Values[c,d]	N.S	N.S.	P = 0.045*(N)	N.S.
Departure from Linear Trend[e]	P = 0.074			
Relative Risk (Matched Control)[f]			0.132	0.233
Lower Limit			0.003	0.020
Upper Limit			2.358	2.974
Relative Risk (Pooled Control)[f]			0.482	0.853
Lower Limit			0.009	0.074
Upper Limit			5.734	7.092
Weeks to First Observed Tumor	95	--	66	49

Table I1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aldrin in the Diet[a]

(continued)

[a]Treated groups received doses of 30 or 60 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table I2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
All Sites: Hemangiosarcoma or Hemangioma[b]	0/10 (0.00)	0/60 (0.00)	3/49 (0.06)	0/49 (0.00)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.010		
Relative Risk (Matched Control)[f]			Infinite	--
Lower Limit			0.136	--
Upper Limit			Infinite	--
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			0.733	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	79	--
Liver: Neoplastic Nodules or Hepatocellular Carcinoma[b]	1/10 (0.10)	5/59 (0.08)	1/48 (0.02)	3/49 (0.06)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.208	0.612
Lower Limit			0.006	0.062
Upper Limit			16.007	31.446
Relative Risk (Pooled Control)[f]			0.246	0.722
Lower Limit			0.011	0.117
Upper Limit			2.063	3.510
Weeks to First Observed Tumor	111	--	112	112

Table I2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	1/9 (0.11)	3/52 (0.06)	10/39 (0.20)	7/46 (0.15)
P Values[c,d]	N.S.	N.S.	P = 0.009**	N.S.
Relative Risk (Matched Control)[f]			2.308	1.370
Lower Limit			0.423	0.215
Upper Limit			96.910	59.577
Relative Risk (Pooled Control)[f]			4.444	2.638
Lower Limit			1.239	0.653
Upper Limit			23.437	14.924
Weeks to First Observed Tumors	111	--	105	112
Thyroid: C-cell Adenoma or Carcinoma[b]	1/9 (0.11)	12/52 (0.23)	6/39 (0.15)	10/46 (0.22)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.385	1.957
Lower Limit			0.205	0.343
Upper Limit			62.466	82.313
Relative Risk (Pooled Control)[f]			0.667	0.942
Lower Limit			0.235	0.408
Upper Limit			1.737	2.134
Weeks to First Observed Tumor	111	--	64	106

Table I2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	4/9 (0.44)	23/50 (0.46)	15/43 (0.35)	11/48 (0.23)
P Values[c,d]	P = 0.049(N)	P = 0.011(N)	N.S.	P = 0.014**(N)
Relative Risk (Matched Control)[f]			0.785	0.516
Lower Limit			0.371	0.227
Upper Limit			2.732	1.905
Relative Risk (Pooled Control)[f]			0.758	0.498
Lower Limit			0.428	0.252
Upper Limit			1.308	0.393
Weeks to First Observed Tumor	111	--	91	112
Adrenal: Cortical Adenoma[b]	0/10 (0.00)	0/55 (0.00)	8/45 (0.18)	1/48 (0.02)
P Values[c,d]	N.S.	N.S.	P = 0.002**	N.S.
Departure from Linear Trend[e]	P = 0.010	P < 0.001		
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.567	0.012
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			2.787	0.061
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	112	112

Table I2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pancreatic Islet: Islet-cell Adenoma or Carcinoma[b]	0/9 (0.00)	1/58 (0.02)	1/43 (0.02)	1/40 (0.03)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.013
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			1.349	1.450
Lower Limit			0.018	0.019
Upper Limit			102.887	111.302
Weeks to First Observed Tumor	--	--	112	112
Mammary Gland: Fibroma, Fibrosarcoma or Fibroadenoma[b]	3/10 (0.30)	7/60 (0.12)	9/49 (0.18)	7/49 (0.14)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.612	0.476
Lower Limit			0.203	0.143
Upper Limit			3.150	2.568
Relative Risk (Pooled Control)[f]			1.574	1.225
Lower Limit			0.572	0.406
Upper Limit			4.600	3.800
Weeks to First Observed Tumor	111	--	62	107

Table I2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp[b]	0/9 (0.00)	6/56 (0.11)	6/45 (0.13)	9/48 (0.19)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.363	0.559
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			1.244	1.750
Lower Limit			0.356	0.609
Upper Limit			4.328	5.274
Weeks to First Observed Tumor	--	--	86	101
Ovary: Granulosa-cell Tumor[b]	0/8 (0.00)	1/57 (0.02)	1/43 (0.02)	4/46 (0.09)
P Values[c,d]	N.S.	P = 0.071	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.186
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			1.326	4.957
Lower Limit			0.017	0.544
Upper Limit			102.886	235.794
Weeks to First Observed Tumor	--	--	107	107

Table I2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aldrin in the Diet[a]

(continued)

[a]Treated groups received doses of 30 or 60 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

APPENDIX J

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE FED ALDRIN IN THE DIET

Table J1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Aldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	3/20 (0.15)	17/92 (0.18)	16/49 (0.33)	25/45 (0.56)
P Values[c,d]	P = 0.001	P < 0.001	P = 0.048**	P = 0.002* P < 0.001**
Relative Risk (Matched Control)[f]			2.177	3.704
Lower Limit			0.731	1.348
Upper Limit			10.720	17.056
Relative Risk (Pooled Control)[f]			1.767	3.007
Lower Limit			0.913	1.757
Upper Limit			3.339	5.057
Weeks to First Observed Tumor	90	--	90	75
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	0/20 (0.00)	7/91 (0.08)	3/49 (0.06)	5/45 (0.11)
P Values[c,d]	P = 0.083	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.255	0.584
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			0.796	1.444
Lower Limit			0.137	0.379
Upper Limit			3.293	4.947
Weeks to First Observed Tumor	--	--	90	96

Table J1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Aldrin in the Diet[a]

(continued)

[a]Treated groups received time-weighted average doses of 4 or 8 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table J2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Aldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	0/10 (0.00)	3/78 (0.04)	5/48 (0.10)	2/43 (0.05)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.293	0.076
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			2.708	1.209
Lower Limit			0.551	0.103
Upper Limit			16.694	10.078
Weeks to First Observed Tumor	--	--	87	92
Hematopoietic System: Lymphoma or Leukemia[b]	1/10 (0.10)	8/79 (0.10)	3/48 (0.06)	2/46 (0.04)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.625	0.435
Lower Limit			0.063	0.027
Upper Limit			31.921	24.942
Relative Risk (Pooled Control)[f]			0.617	0.429
Lower Limit			0.109	0.046
Upper Limit			2.417	2.028
Weeks to First Observed Tumor	84	--	75	92

Table J2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Aldrin in the Diet[a]

(continued)

[a]Treated groups received time-weighted average doses of 3 or 6 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence intreval of the relative risk between each treated group and the specified control group.

APPENDIX K

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED DIELDRIN IN THE DIET

Table K1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dieldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Multiple Sites: Malignant Lymphoma or Histiocytoma[b]	0/10 (0.00)	3/58 (0.05)	6/46 (0.13)	1/50 (0.02)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.033	P = 0.029		
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.388	0.012
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			2.522	0.387
Lower Limit			0.571	0.008
Upper Limit			14.779	4.628
Weeks to First Observed Tumor	--	--	101	98
All Sites: Hemangioma or Hemangiosarcoma[b]	0/10 (0.00)	4/58 (0.07)	4/46 (0.09)	2/50 (0.04)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.225	0.065
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			1.261	0.580
Lower Limit			0.247	0.054
Upper Limit			6.397	3.856
Weeks to First Observed Tumor	--	--	94	17

Table K1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	3/10 (0.30)	15/48 (0.31)	11/35 (0.31)	12/37 (0.32)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.048	1.081
Lower Limit			0.377	0.398
Upper Limit			5.108	5.226
Relative Risk (Pooled Control)[f]			1.006	1.038
Lower Limit			0.475	0.505
Upper Limit			2.025	2.057
Weeks to First Observed Tumor	110	--	97	95
Adrenal: Cortical Adenoma[b]	0/10 (0.00)	3/55 (0.05)	1/41 (0.02)	3/43 (0.07)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.014	0.156
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			0.447	1.279
Lower Limit			0.009	0.179
Upper Limit			5.309	9.065
Weeks to First Observed Tumor	--	--	105	104

Table K1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	0/10 (0.00)	4/51 (0.08)	3/40 (0.08)	6/36 (0.17)
P Values[c,d]	P = 0.072	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.167	0.497
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			0.956	2.125
Lower Limit			0.147	0.542
Upper Limit			5.315	9.486
Weeks to First Observed Tumor	--	--	110	73
Thyroid: C-cell Adenoma or Carcinoma[b]	0/10 (0.00)	4/48 (0.08)	7/40 (0.18)	4/36 (0.11)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.543	0.287
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			2.100	1.333
Lower Limit			0.577	0.264
Upper Limit			9.102	6.654
Weeks to First Observed Tumor	--	--	103	78

Table K1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Pancreatic Islet: Adenoma[b]	1/10 (0.10)	1/52 (0.02)	3/40 (0.08)	2/39 (0.05)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.750	0.513
Lower Limit			0.076	0.038
Upper Limit			37.743	29.181
Relative Risk (Pooled Control)[f]			3.900	2.667
Lower Limit			0.327	0.144
Upper Limit			199.508	151.423
Weeks to First Observed Tumor	101	--	109	99

[a]Treated groups received time-weighted average doses of 29 or 59 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specific control group.

Table K2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Multiple Sites: Histiocytoma[b]	0/10 (0.00)	2/60 (0.03)	2/49 (0.04)	0/49 (0.00)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	--
Lower Limit			0.067	--
Upper Limit			Infinite	--
Relative Risk (Pooled Control)[f]			1.225	0.000
Lower Limit			0.092	0.000
Upper Limit			16.251	4.138
Weeks to First Observed Tumor	--	--	79	--
Pituitary: Chromophobe Adenoma or Carcinoma[b]	3/6 (0.50)	23/50 (0.46)	11/41 (0.27)	9/33 (0.27)
P Values[c,d]	N.S.	P = 0.038(N)	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.537	0.546
Lower Limit			0.249	0.246
Upper Limit			2.511	2.601
Relative Risk (Pooled Control)[f]			0.583	0.593
Lower Limit			0.297	0.278
Upper Limit			1.085	1.139
Weeks to First Observed Tumor	110	--	76	111

Table K2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Adrenal: Cortical Adenoma or Carcinoma[b]	0/9 (0.00)	0/55 (0.00)	6/45 (0.13)	2/40 (0.05)
P Values[c,d]	N.S.	N.S.	P = 0.007**	N.S.
Departure from Linear Trend[d,e]		P = 0.010		
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.363	0.075
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.953	0.406
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	109	111
Thyroid: Follicular-cell Adenoma[b]	0/4 (0.00)	2/52 (0.04)	3/45 (0.07)	6/41 (0.15)
P Value[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.073	0.215
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			1.733	3.805
Lower Limit			0.207	0.720
Upper Limit			19.814	37.113
Weeks to First Observed Tumor	--	--	76	82

Table K2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma[b]	0/4 (0.00)	1/52 (0.02)	2/45 (0.04)	2/41 (0.05)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.036	0.039
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			2.311	2.537
Lower Limit			0.125	0.135
Upper Limit			131.973	146.183
Weeks to First Observed Tumor	--	--	100	111
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	0/4 (0.00)	3/52 (0.06)	5/45 (0.11)	8/41 (0.20)
P Values[c,d]	N.S.	P = 0.030	N.S.	P = 0.043*
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.154	0.307
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			1.926	3.382
Lower Limit			0.397	0.876
Upper Limit			11.760	18.726
Weeks to First Observed Tumor	--	--	76	82

Table K2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Thyroid: C-cell Adenoma or Carcinoma[b]	1/4 (0.25)	12/52 (0.23)	12/45 (0.27)	6/41 (0.15)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.067	0.585
Lower Limit			0.286	0.128
Upper Limit			44.456	26.318
Relative Risk (Pooled Control)[f]			1.156	0.634
Lower Limit			0.528	0.213
Upper Limit			2.514	1.657
Weeks to First Observed Tumor	110	--	100	69
Mammary Gland: Fibroadenoma[b]	1/10 (0.10)	7/60 (0.12)	13/49 (0.27)	3/49 (0.06)
P Values[c,d]	P = 0.069(N)	N.S.	P = 0.041**	N.S.
Departure from Linear Trend[e]	P = 0.024	P = 0.004		
Relative Risk (Matched Control)[f]			2.653	0.612
Lower Limit			0.502	0.059
Upper Limit			108.727	15.192
Relative Risk (Pooled Control)[f]			2.274	0.525
Lower Limit			0.919	0.092
Upper Limit			6.186	2.159
Weeks to First Observed Tumor	96	--	99	69

Table K2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Dieldrin in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Uterus: Endrometrial Stromal Polyp[b]	1/10 (0.10)	6/56 (0.11)	4/46 (0.09)	1/40 (0.03)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.870	0.250
Lower Limit			0.104	0.004
Upper Limit			42.586	19.137
Relative Risk (Pooled Control)[f]			0.812	0.233
Lower Limit			0.178	0.005
Upper Limit			3.201	1.811
Weeks to First Observed Tumor	110	--	79	111

[a]Treated groups received time-weighted average doses of 29 or 59 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

APPENDIX L

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE FED DIELDRIN IN THE DIET

Table L1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Dieldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	3/18 (0.16)	17/92 (0.18)	12/50 (0.24)	16/45 (0.36)
P Values[c,d]	P = 0.065	P = 0.020	N.S.	P = 0.025**
Relative Risk (Matched Control)[f]			1.440	2.133
Lower Limit			0.449	0.714
Upper Limit			7.350	10.449
Relative Risk (Pooled Control)[f]			1.299	1.924
Lower Limit			0.622	1.000
Upper Limit			2.627	3.602
Weeks to First Observed Tumor	91	--	91	88
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	1/18 (0.06)	7/91 (0.08)	3/50 (0.06)	3/46 (0.07)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			1.080	1.174
Lower Limit			0.096	0.104
Upper Limit			55.520	60.443
Relative Risk (Pooled Control)[f]			0.780	0.848
Lower Limit			0.135	0.146
Upper Limit			3.193	3.461
Weeks to First Observed Tumor	91	--	91	93

Table L1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Dieldrin in the Diet[a]

(continued)

[a]Treated groups received doses of 2.5 or 5 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table L2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Dieldrin in the Diet[a]

Topography: Morphology	Matched Control	Pooled Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	0/20 (0.00)	3/78 (0.04)	6/50 (0.12)	2/49 (0.04)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.040	P = 0.047		
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.667	0.125
Upper Limit			Infinite	Infinite
Relative Risk (Pooled Control)[f]			3.120	1.061
Lower Limit			0.698	0.091
Upper Limit			18.531	8.870
Weeks to First Observed Tumor	--	--	89	93
Multiple Sites: Lymphoma[b]	2/20 (0.10)	8/79 (0.10)	2/50 (0.04)	5/50 (0.10)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.400	1.000
Lower Limit			0.032	0.187
Upper Limit			5.282	10.036
Relative Risk (Pooled Control)[f]			0.395	0.988
Lower Limit			0.042	0.267
Upper Limit			1.899	3.205
Weeks to First Observed Tumor	91	--	91	80

Table L2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Dieldrin in the Diet[a]

(continued)

[a]Treated groups received doses of 2.5 or 5 ppm.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.10$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

APPENDIX M

ANALYSES OF FORMULATED DIETS FOR CONCENTRATIONS OF ALDRIN OR DIELDRIN

APPENDIX M

Analyses of Formulated Diets for

Concentrations of Aldrin or Dieldrin

A 10-g sample of the diet mixture containing aldrin or dieldrin was shaken with 125 ml hexane at room temperature for 16 hours, then filtered through Celite with hexane washes, and reduced to 10 ml in volume. After appropriate dilutions, the solution was quantitatively analyzed for aldrin or dieldrin by gas-liquid chromatography (electron capture detector; 10% QF-1 on Chromosorb W column for aldrin, 10% DC-100 on Gas-Chrom Q column for dieldrin). Recoveries were checked with spiked samples, and external standards were used for calibration.

ALDRIN

Theoretical Dietary Level (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
2.0	13	1.9(9)	3.0	1.9-2.1
4.0	18	3.9(3)	5.4	3.5-4.3
7.5	2	7.3(5)	2.9	7.2,7.5
8.0	17	7.9(4)	3.7	7.4-8.3
15.0	2	14.8	1.0	14.7,14.9
30.0	15	29.9	2.9	28.0-31.3
60.0	16	59.3	3.8	54.5-63.5
120.0	2	119.1	0.4	118.7,119.4

DIELDRIN

Theoretical Dietary Level (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
2.5	21	2.5(1)	5.0	2.2(8)-2.7(4)
5.0	27	5.0(3)	4.8	4.3(2)-5.5(8)
10.0	2	10.1	5.0	9.7(9),10.5
20.0	12	20.6	4.0	19.2-21.3
40.0	21	40.5	4.3	36.1-43.7
80.0	12	81.1	5.3	72.7-91.0

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