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ENDRIN

FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
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Bethesda, Maryland 20014

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FOREWORD: This report presents the results of the bioassay of endrin conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected environmental chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of endrin was conducted by Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing 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. Chemical administration and observation of animals 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). Histopathology was performed by Drs. E. Bernal (4) and B. Buratto (4) at Gulf South Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (6). Statistical analyses were performed by Dr. J. R. Joiner(7) and Ms. P. L. Yong (7) using methods selected for the bioassay program by Dr. J. J. Gart (8). Chemicals used in this bioassay were analyzed under the direction of Dr. H. P. Burchfield, and the results of the analyses were reviewed by Dr. S. S. Olin (7).

This report was prepared at Tracor Jitco (7) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller and Mr. W. D. Reichardt, bioscience writers; Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley and Ms. P. J. Graboske.

The following scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Dawn G. Goodman (9), Dr. Richard A. Griesemer, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Robert A. Squire (10), Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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

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

(3) Now with the National Institute of Environmental Health Sciences, P.O. Box 12233 Research Triangle Park, North Carolina.

(4) Gulf South Research Institute, Atchafalaya Basin Laboratories, P. O. Box 1177, New Iberia, Louisiana.

(5) Now with the National Center for Toxicological Research, Jefferson, Arkansas.

(6) EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

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

(8) Mathematical Statistics and Applied Mathematics Section, Field Studies and Statistics Branch, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

(9) Now with Clement Associates, Inc., 1010 Wisconsin Avenue, N. W., Suite 660, Washington, D. C.

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

SUMMARY

A bioassay of technical-grade endrin for possible carcinogenicity was conducted by administering the test chemical in feed to Osborne-Mendel rats and B6C3F1 mice. Groups of 50 rats of each sex were administered one of two doses of endrin for 80 weeks, then observed for 31 or 34 weeks. The doses used for the male rats were 2.5 or 5 ppm. The initial doses of 5 or 10 ppm used for the females were not well tolerated and were reduced during the study. The time-weighted average doses used for the females were 3 or 6 ppm. Matched controls consisted of groups of 10 rats of each sex; pooled controls, used for statistical evaluation, consisted of the matched-control groups combined with 40 untreated male and 40 untreated female rats from similar bioassays of other test chemicals. All surviving rats were killed at 110 to 114 weeks.

Groups of 50 mice of each sex were administered endrin at one of two doses for 80 weeks, then observed for 10 or 11 weeks. Initial doses of 2.5 or 5 ppm used for the males were not well tolerated and were reduced during the study. The time-weighted average doses used for the males were 1.6 or 3.2 ppm; the doses used for the females were 2.5 or 5 ppm. Matched controls consisted of groups of 10 mice of each sex; pooled controls, used for statistical evaluation, consisted of the matched-control groups combined with 50 untreated male and 50 untreated female mice from similar bioassays of other test chemicals. All surviving mice were killed at 90 or 91 weeks.

The clinical signs observed in both rats and mice indicated that the doses of endrin used were near the maximum tolerated doses. In mice these signs included hyperexcitability, a manifestation of toxicity of the organochlorine pesticides. However, mean body weights of the rats and mice were not affected by administration of endrin.

Although the survival of the high-dose male mice at the end of the study was markedly lower than that of the controls, the survivals of the low- and high-dose female mice and male and female rats were unaffected by the endrin. The survival of the low-dose male mice could not be evaluated, due to the accidental administration of excessive quantities of endrin to this group during week 66. However, a substantial portion of all groups of rats and mice survived to an age at which tumors could be expected to occur.

In rats, the combination of adenomas and carcinomas of the adrenal occurred at the following incidences -- males: pooled controls 2/44, matched controls 2/9, low-dose 4/46, high-dose 8/44; females: pooled controls 4/46, matched controls 3/9, low-dose 16/49, high-dose 7/47. These incidences did not show consistent statistical significance. Furthermore, the incidences of the tumors in the matched controls of either sex were higher than those of the corresponding pooled controls, and the incidences in the matched controls equaled or exceeded those in any of the respective dosed groups. Thus, these tumors cannot be clearly related to administration of the test chemical.

In mice, no tumors occurred in dosed groups at incidences that were significantly higher than those in pooled or matched controls.

It is concluded that under the conditions of this bioassay, endrin was not carcinogenic for Osborne-Mendel rats or for B6C3F1 mice.

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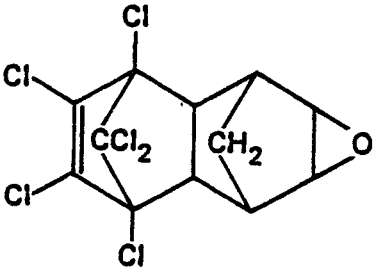
I. INTRODUCTION



Endrin

Endrin (CAS 72-20-8; NCI C00157) is an organochlorine pesticide having a structure characteristic of the cyclodiene group, which includes aldrin (CAS 309-00-2), dieldrin (CAS 60-57-1), chlordane (CAS 57-74-9), heptachlor (CAS 76-44-8), and endosulfan (CAS 115-29-7). It is the most acutely toxic compound in the cyclodiene group (Brooks, 1974 and 1975) but is less persistent in the environment than DDT or dieldrin (Hayes, 1975). As an insecticide, it is currently used for small grains, sugarcane, and cotton; as an avicide, for forest seed and perch applications; and as a rodenticide, for forest seed and orchard soil applications (EPA Compendium, 1971, 1972; Brooks, 1974).

Evidence for carcinogenicity of certain cyclodiene pesticides other than endrin, such as aldrin, dieldrin, and heptachlor (Secretary's Commission on Pesticides, 1969; Federal Register, 1974) suggested that carcinogenicity might be a property common to all pesticides of this general structure. Endrin was there-

fore selected for study in the Carcinogenesis Testing Program because its chemical structure is similar to that of these known cyclodiene carcinogens. Also, the extensive use of endrin (Agricultural Research Service, 1967, 1968, 1970; EPA, 1971) and its persistence (Brooks, 1974; Hayes, 1975) suggested there was a potential for long-term human exposure to residues of the insecticide, especially in foods.

II. MATERIALS AND METHODS

A. Chemical

Technical-grade endrin was purchased from Shell Chemical Company, Agriculture Division, San Ramon, California, for use in this study. Endrin is made by epoxidation of isodrin, the Diels-Alder adduct of cyclopentadiene and 1,2,3,4,7,7-hexachloronorbornadiene. The product was 97% pure by the manufacturer's assay. Analyses by Gulf South Research Institute confirmed the identity of the chemical and were consistent with the stated purity. Elemental analyses (C, H, Cl) were satisfactory for $C_{12}H_8Cl_6O$, the molecular formula of endrin. Gas-liquid and thin-layer chromatography showed minor impurities under a variety of chromatographic conditions. No attempt was made to identify the impurities. Infrared, nuclear magnetic resonance, and mass spectra were as expected for endrin. The chemical was stored at $4^{\circ}C$ in the original container.

B. Dietary Preparation

All diets containing endrin were formulated using Wayne® Lab

Blox animal meal (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of endrin for each dietary concentration. The 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 room temperature until used, but no longer than 1 week.

As a quality control test on the accuracy of preparation of the diets, the concentration of endrin was determined in different batches of formulated diets during the chronic study. The results are summarized in Appendix G. At each dietary concentration, the mean of the analytical concentrations for the checked samples was within 3.2% of the theoretical concentration, and the coefficient of variation was never more than 3.6%.

C. Animals

Rats and mice of each sex, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these bioassays. 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. On arrival at the laboratory, all animals were quarantined (rats for 8 days, mice for 14 days) and then assigned to control or dosed groups.

D. Animal Maintenance

All animals were housed in rooms in which the temperature ranged from 22 to 24°C, and the relative humidity from 40 to 70%. The air entering each room was filtered (Air Maze Incom International, Cleveland, Ohio), and room air was changed 10 to 12 times per hour. Fluorescent lighting provided illumination 10 hours per day. Food and water were provided ad libitum. Fresh feed was provided daily, and excess remaining feed was discarded.

The rats were housed individually in hanging galvanized steel

mesh cages (Hoeltge, Inc., Cincinnati, Ohio), and the mice were housed in polypropylene cages (Lab Products, Inc., Garfield, N.J.), five females per cage or two or three males per cage. Mouse cages were covered with polyester filter bonnets (Lab Products, Inc.). The rat racks and cages were sanitized every 2 weeks. The mouse cages were sanitized each week. These cages and racks were washed in an industrial washer at 82°C with Acclaim® detergent (Economics Laboratory, Inc., St. Paul, Minn.) and then rinsed. Absorbent Kimpak cage liners (Kimberly Clark Corp., Neenah, Wis.) were placed under the rat cages and were changed three times per week. Absorb-dri® hardwood chip bedding (Lab Products, Inc.), used in the mouse cages, was provided two times per week for males and three times per week for females. Filter bonnets were sanitized each week. Feed jars and water bottles were changed and sanitized three times per week. Sipper tubes and stoppers were sanitized two times per week.

The filter bonnets, feed jars, water bottles, sipper tubes, and stoppers were washed in a Vulcan Autosan washer (Louisville, Ky.).

Cage racks for each species were rotated to a new position in the room once per week; at the same time, each cage was moved to a different row within the same column of a rack. Rats receiving

endrin, along with their matched controls, were housed in a room by themselves. Mice were maintained in a room housing mice from the following studies:

Feed Studies

(CAS 133-90-4) chloramben
(CAS 1897-45-6) chlorothalonil
(CAS 1918-02-1) picloram

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses of endrin, on the basis of which two concentrations (hereinafter referred to as "low" and "high" doses) were determined for administration in the chronic studies. In the subchronic studies, endrin was added to the animal feed in twofold increasing concentrations, ranging from 2.5 to 80 ppm for rats and from 2.5 to 20 ppm for mice. The chemical was provided in feed to dosed groups of five male and five female animals of each species for 6 weeks, followed by observation for 2 weeks. Untreated-control groups consisted of five animals of each species and sex.

In rats, at 10 ppm there were no deaths, and mean weight gains of both males and females were comparable to those of corresponding

controls. At 20 ppm one animal of each sex died, but weights of the survivors were not significantly affected. The low and high doses for the chronic studies using rats were set at 7.5 and 15 ppm.

In mice, three males and four females in the groups at 10 ppm died during the study. At 5 ppm no animals died, and mean weight gains were comparable to those of controls. The low and high doses for the chronic studies using mice were set at 2.5 and 5 ppm.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 1 and 2. Due to high mortality in the rats at the doses set by the subchronic study, the studies with rats were terminated and restarted using lower doses of 2.5 or 5 ppm for males and 5 or 10 ppm for females. Because of subsequent toxic effects, the doses for the female rats and the male mice were reduced during the course of the studies.

Since the numbers of animals in the matched-control groups were

Table 1. Endrin Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals(a)	Endrin in Diet(b) (ppm)	Time on Study Dosed (weeks)	Time on Study Observed(c) (weeks)	Time-Weighted Average Dose(d) (ppm)
Male					
Matched-Control	10	0		110	
Low-Dose	50	2.5	80		2.5
		0		31	
High-Dose	50	5	80		5
		0		34	
Female					
Matched-Control	10	0		110	
Low-Dose	50	5	9		3
		2.5	71		
		0		31	
High-Dose	50	10	9		6
		5	71		
		0		34	

(a) All animals were 5 weeks old when placed on study.

(b) Initially, concentrations of 15 and 7.5 ppm of endrin were fed to rats of each sex; these doses were too toxic, however, and the rat study was terminated and restarted as shown in the table.

(c) When diets containing endrin were discontinued, dosed rats were fed control diets (2% corn oil added) until termination; matched-control rats received control diets throughout the study.

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

Table 2. Endrin Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals(a)	Endrin in Diet(b) (ppm)	Time on Study		Time-Weighted Average Dose(c) (ppm)
			Dosed (weeks)	Observed (weeks)	
Male					
Matched-Control	10	0		90	
Low-Dose	50	2.5	25		1.6
		1.2	55		
		0		10	
High-Dose	50	5	15		
		5(d)	10		3.2
		2.5	55		
		0		11	
Female					
Matched-Control	10	0		90	
Low-Dose	50	2.5	80		2.5
		0		10	
High-Dose	50	5	80		5
		0		11	

(a) All animals were 5 weeks old when placed on study.

(b) When diets containing endrin were discontinued, dosed mice were fed control diets (2% corn oil added) until termination; matched-control mice received control diets throughout the study.

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

(d) The diets shown and control diets were fed on alternate weeks.

small, pooled-control groups also were used for statistical evaluation. In rats, matched controls from the current bioassay on endrin were combined with matched controls from studies performed on captan (CAS 133-06-2), malathion (CAS 121-75-5), phosphamidon (CAS 13171-21-6), photodieldrin (CAS 13366-73-9), and tetrachlorvinphos (CAS 961-11-5). In mice, matched controls from endrin were combined with those from captan, chloramben, chlorothalonil, photodieldrin, and picloram. The pooled controls for statistical tests consisted of 50 rats and 60 mice of each sex. In both species, these controls were started no more than 3 months apart from the endrin controls. The studies on chemicals other than endrin were also conducted at Gulf South Research Institute and were diagnosed by the same pathologists. The matched-control groups for the different test chemicals were of the same strain and from the same supplier.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, weighed every 2 weeks for the first 12 weeks, and monthly thereafter, and palpated for masses at each weighing. Sick, tumor-bearing, and moribund animals were observed daily.

Moribund animals and animals that survived to the end of the bioassay were killed using ether and necropsied. Necropsies were also performed on all animals found dead, unless precluded by autolysis or severe cannibalization.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. 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. 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.

A few tissues from some animals were not examined, particularly from those animals that may have died early, been missing, or been in advanced states of cannibalization or autolysis. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily

represent the number of animals that were placed on study 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 appropriate 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 dosed animals at each dose level. When results for a number of dosed 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 an animal died naturally or was 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 less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with 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 dosed 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 dosed 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 dosed 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 dosed 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 (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 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.

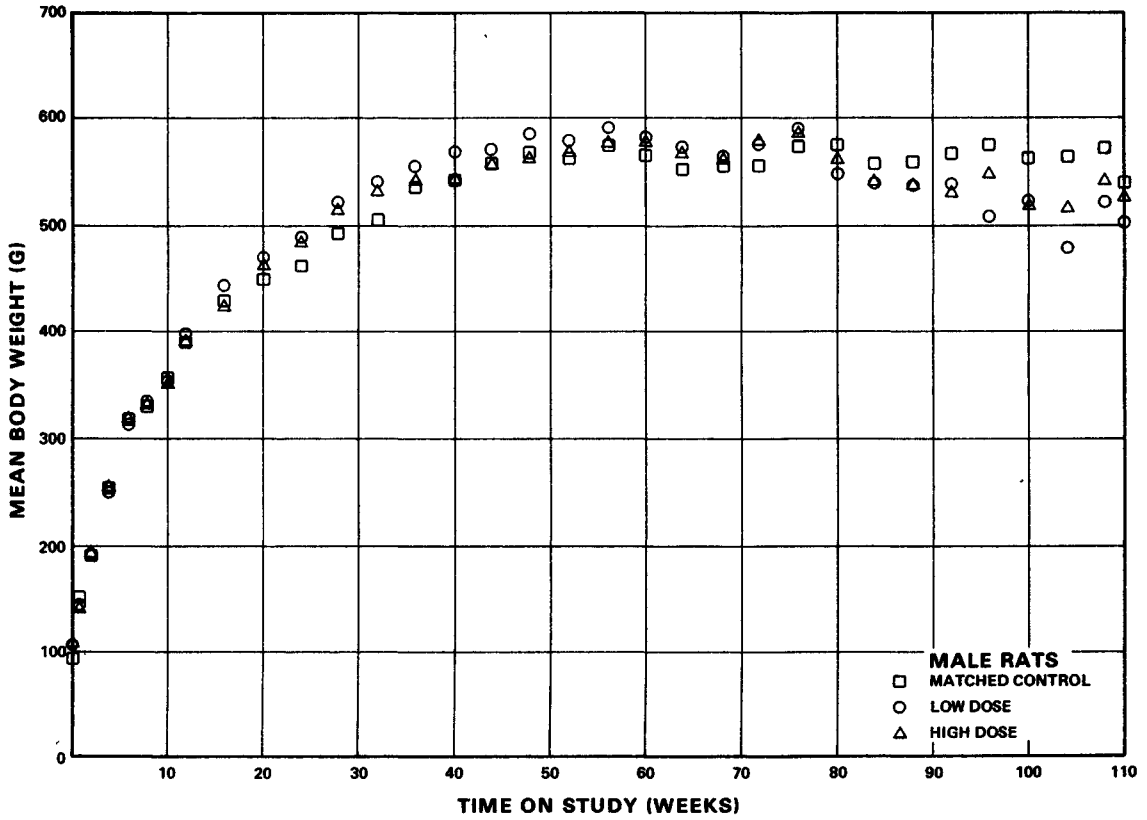
III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

The mean body weights of the dosed male and female rats were similar to those of corresponding controls (figure 1). Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation. The high-dose female rats lost weight at week 9, and the doses for the low- and high-dose females were lowered at that time, after which the weight was recovered.

During the first 16 weeks of the bioassay, clinical signs including alopecia (primarily in facial areas), diarrhea, and epistaxis were observed in a few animals in both the high- and low-dose groups. At week 8, several animals in both the dosed and control groups developed ocular infections that were diagnosed as viral conjunctivitis. For the remainder of the first year of the bioassay, the dosed animals were generally comparable to the controls in appearance and behavior.

Clinical signs were noted with increasing frequency in both the high- and low-dose groups early in the second year of the study.



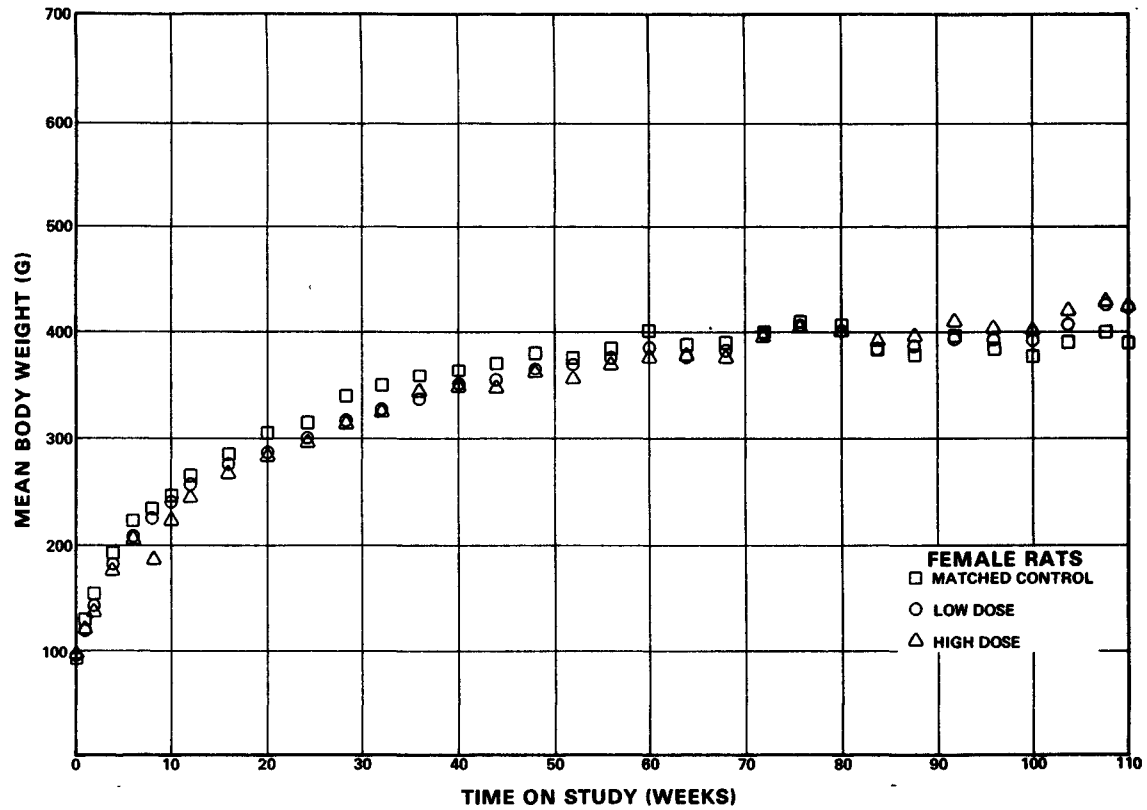


Figure 1. Growth Curves for Rats Fed Endrin in the Diet

In addition to the signs previously described, rough hair coats, dermatitis, tachypnea, pale mucous membranes, hematuria, and discolored urine also were observed. During the latter half of the second year, the dosed and control groups began to exhibit similar signs, and by the end of week 110, clinical observations were essentially the same in both groups.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats receiving endrin at the doses used in this bioassay, together with those of the controls, are shown in figure 2. The results of the Tarone test for dose-related trend in mortality are not statistically significant for either sex.

At week 110, 33/50 (66%) of the high-dose males, 30/50 (60%) of the low-dose males, and 8/10 (80%) of the control males were still alive. In females, 42/50 (84%) of the high-dose group, 38/50 (76%) of the low-dose group, and 7/10 (70%) of the control group were alive at week 110. Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

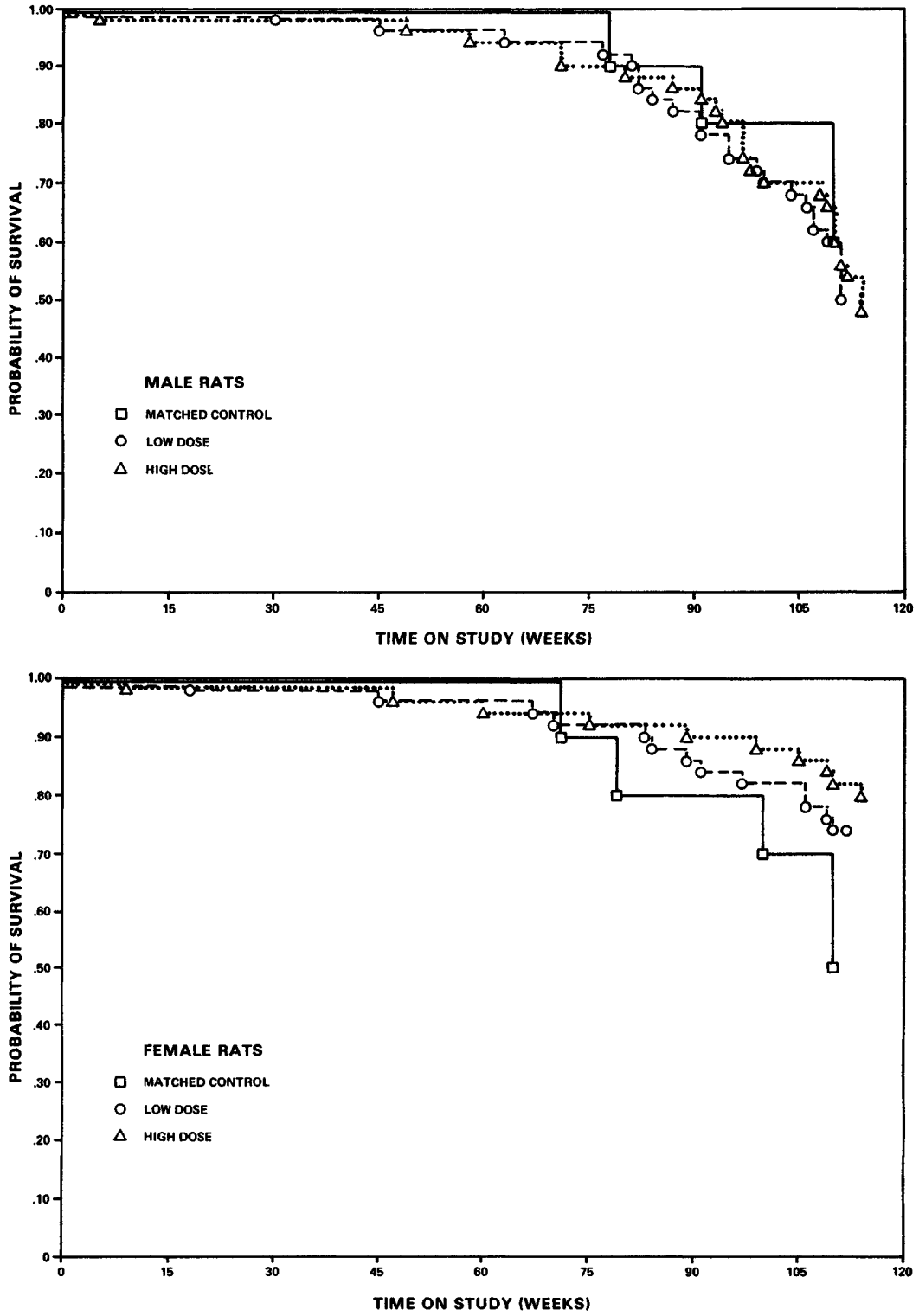


Figure 2. Survival Curves for Rats Fed Endrin in the Diet

C. Pathology (Rats)

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

A variety of tumors occurred with a low frequency in control and dosed rats. These tumors are not uncommon in this strain of rat, and have been observed in the bioassay program independent of any administration of test chemicals.

In addition to the neoplastic lesions, degenerative, proliferative, and inflammatory pathologic changes were observed in dosed and control rats, mostly with approximately equal frequency. In a few instances, some lesions affected rats of the dosed groups, but not those of the controls. These included follicular-cell hyperplasia of the thyroid, and cysts and angiectasis of the pituitary gland. The lesions observed in this study are not uncommon in aged Osborne-Mendel rats, and they have been known to occur spontaneously in this and other laboratories.

Based on the histopathologic examination, there was no evidence for the carcinogenicity of endrin in Osborne-Mendel rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In each sex, there are no significant statistical test results when the incidences in the dosed groups are compared with those in the matched controls.

In female rats, the result of the Cochran-Armitage test for the incidence of adenomas of the pituitary is significant (P = 0.015) using the pooled controls, and the results of the Fisher exact test show that the incidence in the high-dose group is significantly higher (P = 0.016) than that in the pooled controls. When the incidence of female rats with either adenomas, carcinomas, adenocarcinomas, or chromophobe adenomas of the pituitary is analyzed, there is no significant result. It should be noted that there are only three carcinomas reported; all other pituitary tumors were adenomas.

In male rats, the result of the Cochran-Armitage test for the combined incidence of adenomas and carcinomas of the adrenal,

using the pooled controls, is significant (P = 0.028). The result of the Fisher exact comparison between the incidence in the high-dose group and that in the pooled controls indicates a P value of 0.045, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. In females, although the result of the Cochran-Armitage test is not significant, an indicated departure from linear trend (P = 0.003) is observed when the pooled-control group is used, because the incidence in the low-dose group is greater than that in the high-dose group. The results of the Fisher exact test show that the incidence in the low-dose group is significantly higher (P = 0.004) than that in the pooled controls; however, a significant result is not observed in the incidence in the high-dose group. In both males and females, the incidences observed in the matched controls are higher than those reported in the pooled controls, and these incidences in the matched-control groups equal or exceed those observed in any of the respective dosed groups.

In male rats, the incidence of hemangiomas of all sites is significantly higher in the low-dose group (P = 0.024) than in the pooled controls, but a significant result is not indicated by the incidence in the high-dose group. The result of the Cochran-Armitage test for the incidences of this tumor is not significant.

In male rats, islet-cell carcinomas of the pancreas are observed exclusively in the high-dose group (3/47, or 6%), and the result of the Cochran-Armitage test shows a probability level of 0.039 using the pooled controls; however, the results of the Fisher exact test are not significant.

Significant results in the negative direction are observed in the incidence of chromophobe adenomas of the pituitary in male rats, using the pooled controls. A significant trend in the negative direction is also observed in the combined incidence of adrenal tumors in female rats when the matched-control group is used.

In summary, the statistical evidence does not indicate an association between the incidence of any tumors with the administration of the test chemical in either male or female Osborne-Mendel rats.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

The mean body weights of the dosed male and female mice were similar to those of corresponding controls (figure 3). Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation.

During the first 4 months of the study, the dosed animals were generally comparable to the controls in appearance and behavior. At week 24, all of the high-dose male group appeared hyperexcitable, and doses for the males were lowered at that time. This condition persisted in the majority of this group until termination of the study. In the latter half of the first year, clinical signs including alopecia (generalized and localized), abdominal distention, and rough hair coats became apparent.

During the second year of the study, the above clinical signs were noted with increasing frequency in all dosed groups. At week 66, administration of excessive quantities of endrin to the low-dose male group occurred, and the majority of these animals

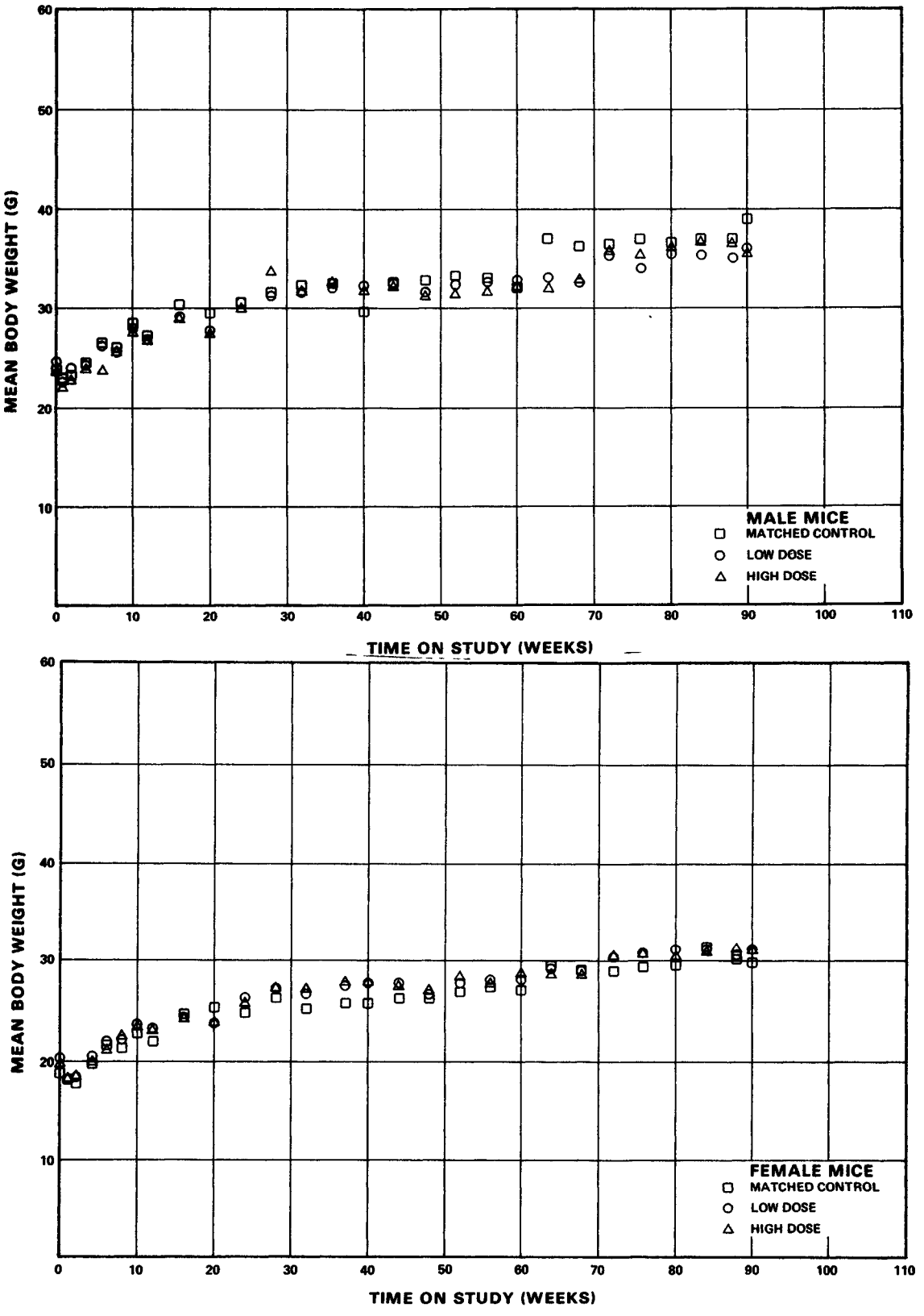


Figure 3. Growth Curves for Mice Fed Endrin in the Diet

appeared hyperexcitable. This condition persisted until termination of the study. There was also fighting among the majority of the males, which resulted in fight wounds and rough hair coats.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice receiving endrin at the doses used in this bioassay, together with those of the controls, are shown in figure 4. In male mice, the result of the Tarone test for dose-related trend in mortality is not significant. In females, the result of the Tarone test is significant ($P = 0.045$). An indicated departure ($P = 0.003$) from linear trend is observed in male mice, because of the earlier mortality of the low-dose group as compared with that of the high-dose group.

An error in preparation of the diet resulted in excess dosing of all the low-dose male mice, and 17 of this group died during week 66 and three more in week 67. However, in males, 32/50 (64%) of the high-dose group, 23/50 (46%) of the low-dose group, and all 10 of the controls survived to the end of the study. In females, 39/50 (78%) of the high-dose group, 45/50 (90%) of the low-dose

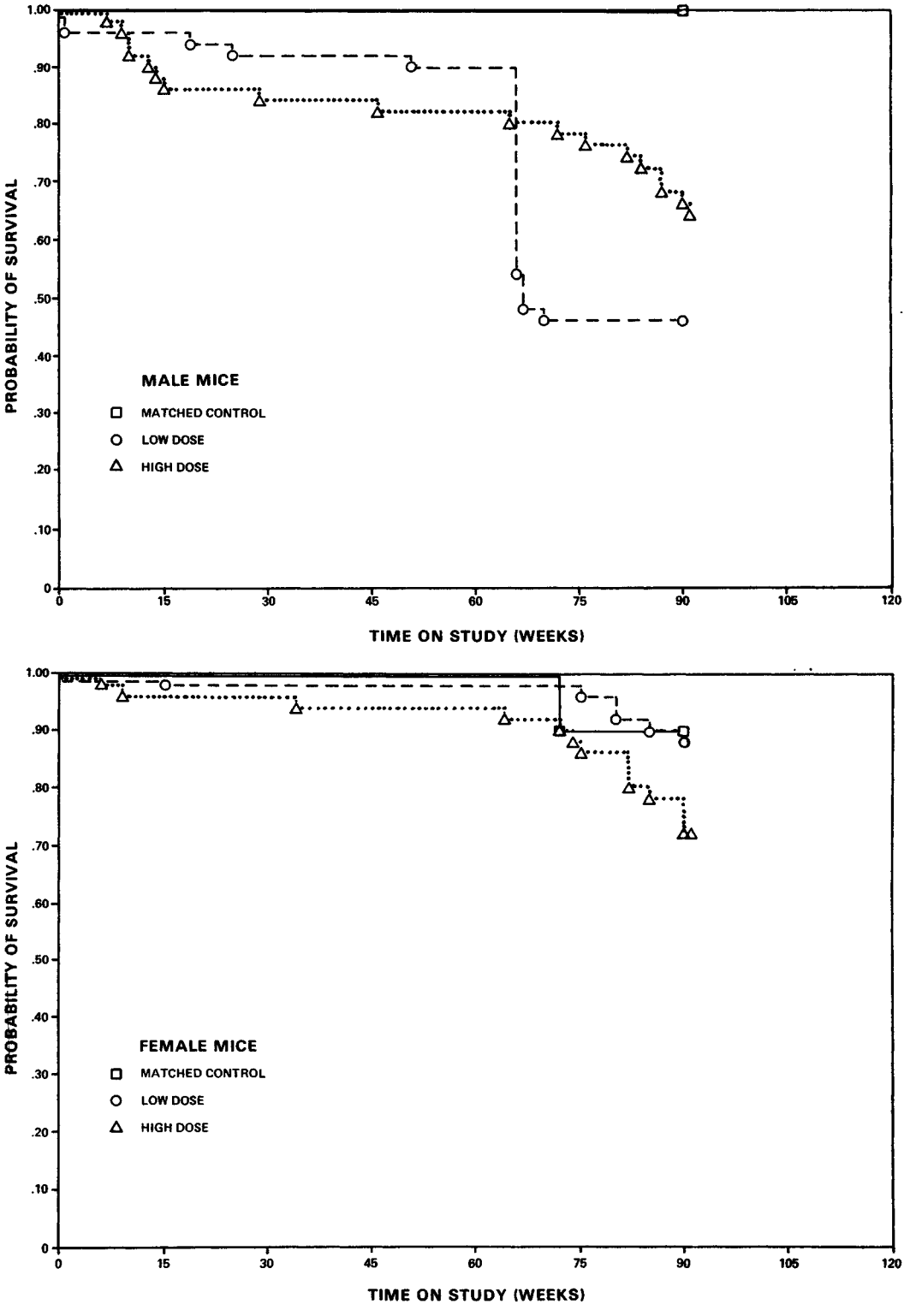


Figure 4. Survival Curves for Mice Fed Endrin in the Diet

group, and 9/10 (90%) of the controls were still alive at week 90. Sufficient numbers of mice of each sex were at risk for the development of tumors.

C. Pathology (Mice)

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

There was great variation in the types of neoplastic and nonneoplastic lesions in the mice. The lesions observed are not uncommon in aged B6C3F1 mice.

The most frequent neoplastic lesions occurred in the liver and comprised hepatocellular carcinomas and neoplastic nodules. They were observed in 1/10 (10%) control males, 3/38 (8%) low-dose males, 10/45 (22%) high-dose males; 2/10 (20%) control females, 3/50 (6%) low-dose females, and 1/47 (2%) high-dose females. The incidences were similar to those observed in other control B6C3F1 mice in this laboratory and were not considered to be related to administration of the test chemical.

Based on the histopathologic examination, there was no evidence for the carcinogenicity of endrin in B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Apendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In each sex, the results of the Cochran-Armitage test for positive dose-related trend and those of the Fisher exact test in the positive direction are not significant.

Significant results in the negative direction are observed in the incidences of hepatocellular carcinomas in each sex. In male mice, the Fisher exact test shows that the incidence of hepatocellular carcinomas in the pooled-control group is significantly ($P = 0.009$) higher than that in the low-dose group, which may be accounted for by the poorer survival of the low-dose group. This significance in the negative direction is not observed when the incidence of the tumors in the low-dose males

is compared with that in the matched-control group, nor is it observed when the incidence of neoplastic nodules or hepatocellular carcinomas in the low-dose male mice is compared with the incidences of these combined tumors in the pooled or matched controls.

In female mice, a significant trend in the negative direction is observed in the incidence of hepatocellular carcinomas (P = 0.011) and in the combined incidence of hepatocellular carcinomas and neoplastic nodules (P = 0.047) using the matched-control group. This significance in the negative direction may be due to the poorer survival of the high-dose group. The Fisher exact comparison of the incidences of hepatocellular carcinomas in the matched-control and high-dose groups indicates a P value of 0.028 in the negative direction. This P value is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The result of the Fisher exact test on the incidence of hepatocellular carcinomas or neoplastic nodules also is not significant. No significant result is observed when the pooled-control group is used for analysis of incidences of hepatocellular carcinomas or of combined hepatocellular carcinomas and neoplastic nodules in the female mice.

In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one or less than one is included, indicating the absence of significant positive results. It should also be noted that each of the intervals (except that for the incidence of hepatocellular carcinomas in high-dose female mice, using the matched controls, and in the low-dose male mice, using the pooled controls) has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by endrin, which could not be detected under the conditions of this test.

Time-adjusted analyses, eliminating animals that died before week 52 on study, were performed on the incidences of tumors shown in tables F1 and F2. No significant positive results were observed.

V. DISCUSSION

Endrin is a member of an organochlorine group of pesticides which can be classed as neurotoxins. Hyperexcitability, a manifestation of toxicity that is characteristic of these chemicals, was observed in male mice given the low or high dose of endrin. A variety of clinical signs, usually associated with aging, were observed in the dosed animals prior to their appearance in corresponding controls. In rats, these signs included alopecia, diarrhea, epistaxis, tachypnea, pale mucous membranes, hematuria, rough hair coats, and dermatitis; in mice, they included alopecia, abdominal distention, and rough hair coats. The mean body weights of the rats and mice were not affected by endrin.

The chronic study in rats was restarted at lower doses when the rats receiving doses of 7.5 or 15 ppm endrin in feed showed unacceptable rates of survival; at the new doses of 2.5 to 10 ppm the survival rates of the rats were improved and were not significantly affected by administration of the test chemical. In mice, the original doses selected, i.e., 2.5 and 5 ppm endrin, were used for females throughout the bioassay, but were lowered for males after week 25 on study. The survival rates were unaffected in the low- and high-dose female mice but decreased in

the high-dose male mice. The survival rate of the low-dose male mice could not be evaluated, since a large proportion of this group died following an accidental overdose. However, 64% of the high-dose male mice survived to the end of the study, so that adequate numbers of animals were at risk for the development of late-appearing tumors. With the exception of the low-dose male mice, a substantial proportion of all groups of rats and mice survived to an age at which tumors could be expected to appear.

In rats, the combination of adenomas and carcinomas of the adrenal occurred at the following incidences -- males: pooled controls 2/44, matched controls 2/9, low-dose 4/46, high-dose 8/44; females: pooled controls 4/46, matched controls 3/9, lw-dose 16/49, high-dose 7/47. These incidences did not show consistent statistical significance. Furthermore, the incidences of the tumors in the matched controls of either sex were higher than those of the corresponding pooled controls, and the incidences in the matched controls equaled or exceeded those in any of the respective dosed groups. Thus, these tumors cannot be clearly related to administration of the test chemical.

In male rats, hemangiomas and islet-cell carcinomas occurred in small numbers of animals and had inconsistent statistical

significance; thus, they cannot be clearly related to administration of the test chemical.

In mice, no tumors occurred in dosed groups at incidences that were significantly higher than those in pooled or matched controls.

There was no convincing evidence to show that the ingestion of endrin under the conditions of this bioassay induced any of the different types of tumors which were observed in the dosed male or female rats or mice. Tumors of the liver, which can be induced in mice by other organochlorine pesticides such as dieldrin, DDT, and benzene hexachloride (Hayes, 1975), appeared in the mice administered endrin, but not in proportions significantly higher than those in the controls.

When compared with dieldrin and other organochlorine insecticides, endrin is relatively nonpersistent in mammalian tissues (IARC Monograph, 1974; Brooks, 1975). The chemical is oxidatively metabolized in the liver, secreted in the bile, and excreted primarily in the feces and only slightly in the urine (Baldwin et al., 1970; Hutson et al., 1975). It is eliminated largely as the metabolite anti-12-hydroxyendrin, and its toxic form appears to be 12-ketoendrin. As the principal metabolite

found in the brain of dosed animals (Bedford et al., 1975), 12-ketoendrin may be responsible for the hyperexcitability observed in the dosed male mice of the present study.

In two previous studies, incidences of tumors in animals administered endrin in the diet were reported to be no different than those in controls; these tests involved Osborne-Mendel rats given 2 to 12 ppm for their lifetimes (Deichmann et al., 1970) and Carworth rats given 1 to 100 ppm for 2 years (Treon et al., 1955). In the latter study, the average ratios of the weights of livers to body weights in male rats receiving 5 or 25 ppm were significantly greater than those of the controls; furthermore, survivals of male or female rats that received 50 or 100 ppm were low, and hepatic degenerative changes were noted only in animals that survived these high doses. In a third study, carcinomas and sarcomas were reported to occur in Osborne-Mendel rats administered endrin in the diet at 0.1 to 25 ppm for 2 years (Reuber, 1978). The incidence was higher in animals administered 0.1 or 1.0 ppm than in control animals or in animals administered the higher doses. The commonest lesions observed were carcinomas of the mammary gland in the females and hyperplasia of the liver in both the males and the females. Statistical evidence for occurrence of tumors in the rats at 0.1 or 1.0 ppm compared with

controls was based on cumulative totals of tumors of all types and at all sites.

It is concluded that under the conditions of this bioassay, endrin was not carcinogenic for Osborne-Mendel rats or for B6C3F1 mice.

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APPENDIX A

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

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	46	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	46	47
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(10)	(46)	(47)
FIBROMA		1 (2%)	1 (2%)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	1 (2%)
LIPOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(10)	(45)	(47)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(46)	(47)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(10)	(46)	(45)
HEMANGIOMA		4 (9%)	2 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#PAROTID GLAND	(10)	(44)	(47)
HEMANGIOMA			1 (2%)
#STOMACH	(10)	(44)	(46)
PAPILLOMA, NOS	1 (10%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#COLON	(4)	(16)	(21)
ADENOMATOUS POLYP, NOS	1 (25%)		
URINARY SYSTEM			
#KIDNEY	(10)	(46)	(47)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
MIXED TUMOR, MALIGNANT			1 (2%)
HAMARTOMA		1 (2%)	2 (4%)
#URINARY BLADDER	(8)	(42)	(41)
PAPILLOMATOSIS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(10)	(43)	(41)
ADENOMA, NOS	4 (40%)	8 (19%)	12 (29%)
CHROMOPHOBE ADENOMA		6 (14%)	1 (2%)
#ADRENAL	(9)	(46)	(44)
CARCINOMA, NOS		2 (4%)	
ADENOMA, NOS	2 (22%)	2 (4%)	8 (18%)
#THYROID	(9)	(42)	(43)
FOLLICULAR-CELL ADENOMA		3 (7%)	
FOLLICULAR-CELL CARCINOMA	1 (11%)		1 (2%)
C-CELL ADENOMA		1 (2%)	2 (5%)
#PANCREATIC ISLETS	(10)	(45)	(47)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)
ISLET-CELL CARCINOMA			3 (6%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
#BRAIN	(10)	(44)	(47)
MENINGIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

† This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of lipocytes, tubular structures, and fibroblasts in varying proportions.

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(10)	(46)	(47)
HEMANGIOMA		1 (2%)	
*MUSCLE OF NECK	(10)	(46)	(47)
FIBROSARCOMA		1 (2%)	
*MUSCLE HIP/THIGH	(10)	(46)	(47)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
BODY CAVITIES			
*BODY CAVITIES	(10)	(46)	(47)
MESOTHELIOMA, MALIGNANT			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(46)	(47)
FIBROUS HISTIOCYTOMA, MALIGNANT			2 (4%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	2	9	10
MORIBUND SACRIFICE	2	15	16
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	6	26	24
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	25	27
TOTAL PRIMARY TUMORS	9	36	42
TOTAL ANIMALS WITH BENIGN TUMORS	5	21	23
TOTAL BENIGN TUMORS	8	29	31
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	6	9
TOTAL MALIGNANT TUMORS	1	7	11
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(10)	(49)	(50)
FIBROSARCOMA		1 (2%)	
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(10)	(49)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (10%)		
FIBROUS HISTIOCYTOMA, METASTATIC	1 (10%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(9)	(48)	(50)
FIBROMA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(9)	(49)	(49)
SARCOMA, NOS			1 (2%)
#LIVER	(10)	(49)	(50)
NEOPLASTIC NODULE		1 (2%)	1 (2%)
FIBROUS HISTIOCYTOMA, METASTATIC	1 (10%)		
*BILE DUCT	(10)	(49)	(50)
BILE DUCT ADENOMA		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(10)	(49)	(49)
HAMARTOMA	1 (10%)	3 (6%)	2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(7)	(47)	(45)
CARCINOMA,NOS		2 (4%)	
ADENOMA, NOS	2 (29%)	11 (23%)	13 (29%)
ADENOCARCINOMA, NOS		1 (2%)	
CHROMOPHOBE ADENOMA		9 (19%)	7 (16%)
#ADRENAL	(9)	(49)	(47)
CARCINOMA,NOS	1 (11%)	7 (14%)	3 (6%)
ADENOMA, NOS	2 (22%)	9 (18%)	4 (9%)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(8)	(46)	(49)
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)
C-CELL ADENOMA		4 (9%)	3 (6%)
#PANCREATIC ISLETS	(10)	(47)	(50)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(49)	(50)
ADENOMA, NOS		1 (2%)	2 (4%)
ADENOCARCINOMA, NOS		1 (2%)	
FIBROMA		3 (6%)	
FIBROADENOMA	1 (10%)	3 (6%)	2 (4%)
#UTERUS	(8)	(48)	(45)
ADENOCARCINOMA, NOS		1 (2%)	
PAPILLARY ADENOMA		1 (2%)	
LEIOMYOSARCOMA	1 (13%)		
ENDOMETRIAL STROMAL POLYP	1 (13%)	5 (10%)	2 (4%)
#OVARY	(10)	(47)	(47)
FIBROMA			1 (2%)
NERVOUS SYSTEM			
NONE			

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

† This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of lipocytes, tubular structures, and fibroblasts in varying proportions.

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(10)	(49)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (10%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(49)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (10%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	2	1	4
MORIBUND SACRIFICE	3	12	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	5	37	40
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	37	33
TOTAL PRIMARY TUMORS	12	66	45
TOTAL ANIMALS WITH BENIGN TUMORS	6	34	31
TOTAL BENIGN TUMORS	7	51	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	13	4
TOTAL MALIGNANT TUMORS	5	14	4
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

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

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	42	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	42	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(10)	(40)	(44)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (3%)	5 (11%)
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(38)	(45)
NEOPLASTIC NODULE		2 (5%)	3 (7%)
HEPATOCELLULAR CARCINOMA	1 (10%)	1 (3%)	7 (16%)
HEMANGIOMA			1 (2%)
#STOMACH	(10)	(30)	(44)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		22	10
MORIBUND SACRIFICE		5	8
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	10	23	32
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	1	3	14
TOTAL PRIMARY TUMORS	1	4	17
TOTAL ANIMALS WITH BENIGN TUMORS		1	6
TOTAL BENIGN TUMORS		1	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	1	7
TOTAL MALIGNANT TUMORS	1	1	7
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	3
TOTAL UNCERTAIN TUMORS		2	3
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 ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(10)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(50)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(50)	(47)
NEOPLASTIC NODULE		2 (4%)	1 (2%)
HEPATOCELLULAR CARCINOMA	2 (20%)	1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#UTERUS	(10)	(48)	(43)
SARCOMA, NOS			1 (2%)
#OVARY	(9)	(45)	(46)
CYSTADENOMA, NOS			1 (2%)
NERVOUS SYSTEM			
*CHOROID PLEXUS	(10)	(50)	(48)
EPENDYMOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(10)	(50)	(48)
SARCOMA, NOS			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		2	3
MORIBUND SACRIFICE	1	4	11
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	44	36
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	5	8
TOTAL PRIMARY TUMORS	2	6	8
TOTAL ANIMALS WITH BENIGN TUMORS		1	2
TOTAL BENIGN TUMORS		1	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	3	5
TOTAL MALIGNANT TUMORS	2	3	5
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	1
TOTAL UNCERTAIN TUMORS		2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

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

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	46	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	46	47
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(10)	(46)	(47)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(10)	(45)	(47)
HEMORRHAGE		1 (2%)	
#LUNG/ALVEOLI	(10)	(45)	(47)
EMPHYSEMA, NOS		2 (4%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(10)	(46)	(45)
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(10)	(45)	(47)
FIBROSIS		1 (2%)	
NECROSIS, NOS		1 (2%)	
CALCIFICATION, DYSTROPHIC		1 (2%)	
#MYOCARDIUM	(10)	(45)	(47)
INFLAMMATION, INTERSTITIAL		1 (2%)	
*ARTERY	(10)	(46)	(47)
MEDIAL CALCIFICATION		1 (2%)	
*AORTA	(10)	(46)	(47)
MEDIAL CALCIFICATION		3 (7%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(10)	(46)	(47)
INFLAMMATION, NOS		1 (2%)	
CIRRHOSIS, NOS	1 (10%)		
PARASITISM		1 (2%)	
DEGENERATION, BALLOONING		1 (2%)	
METAMORPHOSIS FATTY	1 (10%)	7 (15%)	
FOCAL CELLULAR CHANGE			1 (2%)
*BILE DUCT	(10)	(46)	(47)
DISTENTION		1 (2%)	
INFLAMMATION, CHRONIC			2 (4%)
HYPERPLASIA, NOS		3 (7%)	
#PANCREAS	(10)	(45)	(47)
PERIARTERITIS	1 (10%)	2 (4%)	
#PANCREATIC ACINUS	(10)	(45)	(47)
ATROPHY, NOS		1 (2%)	
#STOMACH	(10)	(44)	(46)
ULCER, NOS			1 (2%)
CALCIFICATION, DYSTROPHIC		1 (2%)	
#GASTRIC MUCOSA	(10)	(44)	(46)
EROSION			3 (7%)
CALCIFICATION, DYSTROPHIC		1 (2%)	
#CECUM	(4)	(16)	(21)
INFLAMMATION, ACUTE		1 (6%)	
URINARY SYSTEM			
#KIDNEY	(10)	(46)	(47)
PYELONEPHRITIS SUPPURATIVE			1 (2%)
PYELONGPHRITIS, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	4 (40%)	23 (50%)	22 (47%)
#URINARY BLADDER	(8)	(42)	(41)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#U. BLADDER/MUCOSA	(8)	(42)	(41)
HYPERPLASIA, PAPILLARY		1 (2%)	
METAPLASIA, SQUAMOUS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(10)	(43)	(41)
CYST, NOS			5 (12%)
DEGENERATION, CYSTIC		2 (5%)	
NECROSIS, HEMORRHAGIC		1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL		2 (5%)	
#ADRENAL	(9)	(46)	(44)
DEGENERATION, CYSTIC			1 (2%)
FOCAL CELLULAR CHANGE			1 (2%)
#ADRENAL CORTEX	(9)	(46)	(44)
METAMORPHOSIS FATTY			3 (7%)
#THYROID	(9)	(42)	(43)
CYSTIC FOLLICLES	1 (11%)		
FOLLICULAR CYST, NOS		1 (2%)	
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	5 (12%)
#PARATHYROID	(8)	(23)	(26)
HYPERPLASIA, NOS		2 (9%)	
REPRODUCTIVE SYSTEM			
#PROSTATE	(10)	(40)	(44)
INFLAMMATION, NOS		1 (3%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC		1 (3%)	
*SEMINAL VESICLE	(10)	(46)	(47)
ABSCESS, NOS			1 (2%)
#TESTIS	(10)	(42)	(45)
PERIARTERITIS		2 (5%)	
ATROPHY, NOS		8 (19%)	14 (31%)
NERVOUS SYSTEM			
NONE			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(10)	(46)	(47)
PERIARTERITIS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	4	3
AUTOLYSIS/NO NECROPSY		4	3

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(49)	(50)
ULCER, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(10)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#LUNG	(10)	(49)	(50)
ATELECTASIS		1 (2%)	
INFLAMMATION, FOCAL		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(9)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC	1 (11%)		
#SPLEEN	(9)	(48)	(50)
HEMORRHAGE			2 (4%)
HEMATOPOIESIS	1 (11%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(9)	(49)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
#ENDOCARDIUM	(9)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(10)	(49)	(50)
METAMORPHOSIS FATTY	1 (10%)	2 (4%)	2 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BASOPHILIC CYTO CHANGE			1 (2%)
CLEAR-CELL CHANGE		2 (4%)	3 (6%)
*BILE DUCT	(10)	(49)	(50)
HYPERPLASIA, NOS	2 (20%)	1 (2%)	5 (10%)
#STOMACH	(9)	(49)	(50)
ULCER, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(10)	(49)	(49)
INFLAMMATION, CHRONIC		3 (6%)	5 (10%)
NEPHROSIS, TOXIC		1 (2%)	
#U. BLADDER/MUCOSA	(8)	(47)	(43)
ULCER, NOS			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(9)	(49)	(47)
NECROSIS, HEMORRHAGIC		1 (2%)	
METAMORPHOSIS FATTY		3 (6%)	
ANGIECTASIS		3 (6%)	4 (9%)
#ADRENAL CORTEX	(9)	(49)	(47)
METAMORPHOSIS FATTY	1 (11%)		2 (4%)
ATROPHY, NOS			1 (2%)
ANGIECTASIS			1 (2%)
#THYROID	(8)	(46)	(49)
CYSTIC FOLLICLES		1 (2%)	
FOLLICULAR CYST, NOS		1 (2%)	1 (2%)
HYPERPLASIA, C-CELL		7 (15%)	9 (18%)
REPRODUCTIVE SYSTEM			
#CERVIX UTERI	(8)	(48)	(45)
HYPERPLASIA, STROMAL			1 (2%)
#UTERUS/ENDOMETRIUM	(8)	(48)	(45)
HYPERPLASIA, CYSTIC			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(10)	(47)	(47)
FOLLICULAR CYST, NOS		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	4	8
AUTO/NECROPSY/HISTO PERF			1
AUTOLYSIS/NO NECROPSY		1	

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

APPENDIX D

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

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	42	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	42	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(38)	(45)
INFLAMMATION, FOCAL	1 (10%)		
NECROSIS, FOCAL		1 (3%)	1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(10)	(42)	(49)
EPIDERMAL INCLUSION CYST			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	8	34	32
AUTO/NECROPSY/HISTO PERF		4	1
AUTOLYSIS/NO NECROPSY		8	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNOEPLASTIC LESIONS IN FEMALE MICE FED ENDRIN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(10)	(49)	(47)
CONGESTION, NOS	1 (10%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (10%)	1 (2%)	
#LYMPH NODE	(9)	(48)	(42)
HYPERPLASIA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*LIVER	(10)	(50)	(47)
INFLAMMATION, ACUTE	1 (10%)		
ABSCESS, NOS			1 (2%)
*BILE DUCT	(10)	(50)	(48)
INFLAMMATION, NOS		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(10)	(46)	(45)
DILATATION/DUCTS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(10)	(50)	(48)
HYDRONEPHROSIS			1 (2%)
DEGENERATION, CYSTIC			1 (2%)
#KIDNEY/CORTEX	(10)	(50)	(48)
ATROPHY, NOS			1 (2%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS/ENDOMETRIUM	(10)	(48)	(43)
HYPERPLASIA, CYSTIC	3 (30%)		6 (14%)
#OVARY	(9)	(45)	(46)
CYST, NOS			2 (4%)
FOLLICULAR CYST, NOS		1 (2%)	2 (4%)
INFLAMMATION, NOS	1 (11%)	2 (4%)	4 (9%)
INFLAMMATION, SUPPURATIVE		4 (9%)	
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 D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(50)	(48)
BACTERIAL SEPTICEMIA		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	35	25
AUTO/NECROPSY/HISTO PERF		1	
AUTOLYSIS/NO NECROPSY			2

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

APPENDIX E

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

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats
Fed Endrin in the Diet (a)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
All Sites: Hemangioma (b)	0/49 (0)	0/10 (0)	5/46 (11)	3/47 (6)
P Values (c,d)	N.S.	N.S.	P = 0.024**	N.S.
Relative Risk (Pooled Control) (f)			Infinite	Infinite
Lower Limit			1.345	0.628
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.306	0.142
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	91	114
Pituitary: Adenoma, NOS (b)	6/42 (14)	4/10 (40)	8/43 (19)	12/41 (29)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.302	2.049
Lower Limit			0.435	0.792
Upper Limit			4.171	6.005
Relative Risk (Matched Control) (f)			0.465	0.732
Lower Limit			0.176	0.315
Upper Limit			1.826	2.660
Weeks to First Observed Tumor	--	91	87	58

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	10/42 (24)	0/10 (0)	6/43 (14)	1/41 (2)
P Values (c,d)	P = 0.004 (N)	N.S.	N.S.	P = 0.004** (N)
Departure from Linear Trend (e)		P = 0.037		
Relative Risk (Pooled Control) (f)			0.586	0.102
Lower Limit			0.192	0.002
Upper Limit			1.612	0.669
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.416	0.014
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	111	93
Pituitary: Chromophobe Adenoma or Adenoma, NOS (b)	15/42 (36)	4/10 (40)	14/43 (33)	13/41 (32)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.912	0.888
Lower Limit			0.470	0.448
Upper Limit			1.761	1.736
Relative Risk (Matched Control) (f)			0.814	0.793
Lower Limit			0.362	0.347
Upper Limit			2.899	2.844
Weeks to First Observed Tumor	--	91	87	58

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Adenoma, NOS (b)	2/44 (5)	2/9 (22)	2/46 (4)	8/44 (18)
P Values (c,d)	P = 0.020	N.S.	N.S.	P = 0.045**
Departure from Linear Trend (e)		P = 0.038		
Relative Risk (Pooled Control) (f)			0.957	4.000
Lower Limit			0.072	0.858
Upper Limit			12.702	36.904
Relative Risk (Matched Control) (f)			0.196	0.818
Lower Limit			0.018	0.219
Upper Limit			2.519	7.302
Weeks to First Observed Tumor	--	110	95	108
Adrenal: Adenoma or Carcinoma, NOS (b)	2/44 (5)	2/9 (22)	4/46 (9)	8/44 (18)
P Values (c,d)	P = 0.028	N.S.	N.S.	P = 0.045**
Relative Risk (Pooled Control) (f)			1.913	4.000
Lower Limit			0.290	0.858
Upper Limit			20.310	36.904
Relative Risk (Matched Control) (f)			0.391	0.818
Lower Limit			0.073	0.219
Upper Limit			4.022	7.302
Weeks to First Observed Tumor	--	110	95	108

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	2/46 (4)	1/9 (11)	3/42 (7)	1/43 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.643	0.535
Lower Limit			0.198	0.009
Upper Limit			18.855	9.888
Relative Risk (Matched Control) (f)			0.643	0.209
Lower Limit			0.064	0.003
Upper Limit			32.958	16.081
Weeks to First Observed Tumor	--	110	95	100
Thyroid: C-cell Adenoma (b)	1/46 (2)	0/9 (0)	1/42 (2)	2/43 (5)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.095	2.140
Lower Limit			0.014	0.116
Upper Limit			83.964	123.245
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.013	0.069
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	111	112

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Carcinoma (b)	0/46 (0)	0/10 (0)	0/45 (0)	3/47 (6)
P Values (c,d)	P = 0.039	N.S.	--	N.S.
Relative Risk (Pooled Control) (f)			--	Infinite
Lower Limit			--	0.590
Upper Limit			--	Infinite
Relative Risk (Matched Control) (f)			--	Infinite
Lower Limit			--	0.142
Upper Limit			--	Infinite
Weeks to First Observed Tumor	--	--	--	100
Pancreatic Islets: Islet-cell Adenoma or Carcinoma (b)	1/46 (2)	0/10 (0)	1/45 (2)	4/47 (9)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.022	3.915
Lower Limit			0.013	0.407
Upper Limit			78.492	188.455
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.013	0.220
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	111	100

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Endrin in the Diet (a)

(continued)

(a) Dosed groups received time-weighted average doses of 2.5 or 5 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

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

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Endrin in the Diet (a)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Kidney: Hamartoma (b)	1/47 (2)	1/10 (10)	3/49 (6)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			2.878	1.918
Lower Limit			0.241	0.103
Upper Limit			147.907	110.851
Relative Risk (Matched Control) (f)			0.612	0.408
Lower Limit			0.059	0.025
Upper Limit			31.507	23.619
Weeks to First Observed Tumor	--	110	111	114
Pituitary: Adenoma, NOS (b)	4/44 (9)	2/7 (29)	11/47 (23)	13/45 (29)
P Values (c,d)	P = 0.015	N.S.	N.S.	P = 0.016**
Relative Risk (Pooled Control) (f)			2.574	3.178
Lower Limit			0.833	1.078
Upper Limit			10.320	12.369
Relative Risk (Matched Control) (f)			0.819	1.011
Lower Limit			0.264	0.338
Upper Limit			6.928	8.364
Weeks to First Observed Tumor	--	110	83	89

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Adenoma or Carcinoma, NOS (b)	7/44 (16)	2/7 (29)	12/47 (26)	13/45 (29)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.605	1.816
Lower Limit			0.645	0.749
Upper Limit			4.376	4.858
Relative Risk (Matched Control) (f)			0.894	1.011
Lower Limit			0.294	0.338
Upper Limit			7.479	8.364
Weeks to First Observed Tumor	--	110	83	89
Pituitary: Chromophobe Adenoma (B)	6/44 (14)	0/7 (0)	9/47 (19)	7/45 (16)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.404	1.141
Lower Limit			0.489	0.357
Upper Limit			4.414	3.789
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.464	0.358
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	89	99

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma, Adenoma, NOS, Carcinoma, NOS, or Adenocarcinoma, NOS (b)	13/44 (30)	2/7 (29)	21/47 (45)	20/45 (44)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.512	1.504
Lower Limit			0.833	0.821
Upper Limit			2.843	2.838
Relative Risk (Matched Control) (f)			1.564	1.556
Lower Limit			0.565	0.559
Upper Limit			12.338	12.286
Weeks to First Observed Tumor	--	110	83	89
Adrenal: Carcinoma, NOS (b)	2/46 (4)	1/9 (11)	7/49 (14)	3/47 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			3.286	1.468
Lower Limit			0.668	0.176
Upper Limit			31.129	16.917
Relative Risk (Matched Control) (f)			1.286	0.574
Lower Limit			0.211	0.057
Upper Limit			56.687	29.541
Weeks to First Observed Tumor	--	110	106	114

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Adenoma or Carcinoma, NOS (b)	4/46 (9)	3/9 (33)	16/49 (33)	7/47 (15)
P Values (c,d)	N.S.	P = 0.041 (N)	P = 0.004**	N.S.
Departure from Linear Trend (e)	P = 0.003			
Relative Risk (Pooled Control) (f)			3.755	1.713
Lower Limit			1.330	0.469
Upper Limit			14.298	7.483
Relative Risk (Matched Control) (f)			0.980	0.447
Lower Limit			0.396	0.143
Upper Limit			4.617	2.384
Weeks to First Observed Tumor	--	110	67	114
Thyroid: C-cell Adenoma (b)	1/45 (2)	0/8 (0)	4/46 (9)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			3.913	2.755
Lower Limit			0.408	0.231
Upper Limit			188.275	141.569
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.186	0.113
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	111	114

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroma (b)	1/48 (2)	0/10 (0)	3/49 (6)	0/50 (0)
P Values (c, d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			2.939	0.000
Lower Limit			0.246	0.000
Upper Limit			151.057	17.913
Relative Risk (Matched Control) (f)			Infinite	--
Lower Limit			0.136	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	70	--
Mammary Gland: Fibroadenoma (b)	6/48 (13)	1/10 (10)	3/49 (6)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.490	0.320
Lower Limit			0.083	0.033
Upper Limit			2.152	1.687
Relative Risk (Mached Control) (f)			0.612	0.400
Lower Limit			0.059	0.025
Upper Limit			31.507	23.156
Weeks to First Observed Tumor	--	100	106	109

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	5/42 (12)	1/8 (13)	5/48 (10)	2/45 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.875	0.373
Lower Limit			0.217	0.037
Upper Limit			3.551	2.142
Relative Risk (Matched Control) (f)			0.833	0.356
Lower Limit			0.122	0.023
Upper Limit			38.589	20.543
Weeks to First Observed Tumor	--	110	67	47

(a) Dosed groups received time-weighted average doses of 3 or 6 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

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

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Endrin in the Diet (a)

(continued)

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

APPENDIX F

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

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Endrin in the Diet (a)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	4/58 (7)	0/10 (0)	1/40 (3)	5/44 (11)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.362	1.648
Lower Limit			0.007	0.357
Upper Limit			3.472	7.817
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.015	0.320
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	90	87
Liver: Neoplastic Nodule (b)	1/58 (2)	0/10 (0)	2/38 (5)	3/45 (7)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			3.053	3.867
Lower Limit			0.164	0.323
Upper Limit			175.234	198.299
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.086	0.149
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	90	91

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Endrin in the Diet (a)

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	12/58 (21)	1/10 (10)	1/38 (3)	7/45 (16)
P Values (c,d)	N.S.	N.S.	P = 0.009(N)**	N.S.
Departure from Linear Trend (e)	P = 0.020			
Relative Risk (Pooled Control) (f)			0.127	0.752
Lower Limit			0.003	0.272
Upper Limit			0.800	1.887
Relative Risk (Matched Control) (f)			0.263	1.556
Lower Limit			0.004	0.249
Upper Limit			20.149	68.402
Weeks to First Observed Tumor	--	90	90	82
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	13/58 (22)	1/10 (10)	3/38 (8)	10/45 (22)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.352	0.991
Lower Limit			0.068	0.427
Upper Limit			1.173	2.204
Relative Risk (Matched Control) (f)			0.789	2.222
Lower Limit			0.077	0.397
Upper Limit			40.346	93.874
Weeks to First Observed Tumor	--	90	90	82

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Endrin in the Diet (a)

(continued)

(a) Dosed groups received time-weighted average doses of 1.6 or 3.2 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

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

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Endrin in the Diet (a)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	2/59 (3)	2/10 (20)	1/50 (2)	0/47 (0)
P Values (c,d)	N.S.	P = 0.011(N)	N.S.	P = 0.028*(N)
Departure from Linear Trend (e)		P = 0.029		
Relative Risk (Pooled Control) (f)			0.590	0.000
Lower Limit			0.010	0.000
Upper Limit			10.973	4.239
Relative Risk (Matched Control) (f)			0.100	0.000
Lower Limit			0.002	0.000
Upper Limit			1.810	0.708
Weeks to First Observed Tumor	--	90	90	--
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	3/59 (5)	2/10 (20)	3/50 (6)	1/47 (2)
P Values (c,d)	N.S.	P = 0.047 (N)	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.180	0.418
Lower Limit			0.165	0.008
Upper Limit			8.432	4.998
Relative Risk (Matched Control) (f)			0.300	0.106
Lower Limit			0.043	0.002
Upper Limit			3.368	1.922
Weeks to First Observed Tumor	--	90	90	91

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Endrin in the Diet (a)

(continued)

(a) Dosed groups received time-weighted average doses of 2.5 or 5 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

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

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF ENDRIN

APPENDIX G

Analysis of Formulated Diets for Concentrations of Endrin

A 100-g sample of the formulated diet was shaken with 125 ml hexane for 16 hours at room temperature. The extract was filtered through Celite with hexane washes and reduced in volume to 10 ml. After appropriate dilutions, the solution was analyzed quantitatively for endrin by gas-liquid chromatography (electron capture detector, 10% DC-200 on Gas Chrom Q). Recoveries were determined from spiked samples, and external standards were used for calibrations.

Theoretical Concentrations in Diet (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
1.25	13	1.29	3.6%	1.18-1.33
2.50	22	2.53	2.9%	2.40-2.65
5.00	21	5.04	3.6%	4.75-5.40
10.00	3	10.0	0.6%	9.90-10.0

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

August 31, 1978

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

The primary reviewer said that Endrin was not carcinogenic in rats or mice, under the conditions of test. He added that the negative findings could be a reflection of the high toxicity of Endrin, which permitted the administration of relatively low chronic dosages. The primary reviewer pointed out that an accidental overdose among low dose male mice resulted in the early death of a number of animals in this treatment group. He also indicated that the study was marred by the small number of matched control animals. However, this deficiency was compensated for by the use of pooled controls in the statistical analysis of the study. The primary reviewer said that the study provided little or no information on the potential risk to man of Endrin, particularly since there is no information on how chloro-cyclic alkanes act in humans.

The secondary reviewer said that the shortcomings of the study did not invalidate the conclusion that, under the conditions of test, Endrin was not carcinogenic.

A motion was as approved unanimously that the report on the bioassay of Endrin be accepted as written.

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

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