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BIOASSAY OF

p, p'-ETHYL-DDD

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 p,p'-ethyl-DDD conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that the test chemical is carcinogenic for animals under the conditions of the test and indicates 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 p,p'-ethyl-DDD was conducted by the NCI Frederick Cancer Research Center (FCRC) (1), Frederick, Maryland, operated for NCI (2) by Litton Bionetics, Inc.

The manager of the bioassay at FCRC was Dr. B. Ulland, the toxicologist was Dr. E. Gordon, and Drs. R. Cardy and D. Creasia compiled the data. Ms. S. Toms was responsible for management of data, Mr. D. Cameron for management of histopathology, Mr. L. Callahan for management of the computer branch, and Mr. R. Cypher for management of the facilities. Mr. A. Butler performed the computer services. Necropsies were performed by Drs. B. Ulland, R. Schueler, R. Ball, and R. Cardy. The lesions of the rats and mice were reviewed by Dr. W. C. Hall. The diagnoses included in this report represent his interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (3). Statistical analyses were performed by Dr. J. R. Joiner (4) and Ms. P. L. Yong (4), using methods selected for the bioassay program by Dr. J. J. Gart (5).

The chemicals used in this bioassay were analyzed at FCRC by Dr. W. Zielinsky (1). The chemical narrative and analyses were reviewed and approved by Dr. W. Lijinsky (1).

This report was prepared at Tracor Jitco (4) 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, Ms. L. A. Waitz, Ms. M. S. King, and Mr. W. D. Reichardt, bioscience writers; and 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. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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

SUMMARY

A bioassay of p,p'-ethyl-DDD for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered p,p'-ethyl-DDD at one of two doses, either 3,500 or 7,000 ppm, for 105 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at the end of administration of the test chemical.

Groups of 50 male mice were administered p,p'-ethyl-DDD at one of two doses, either 2,500 or 5,000 ppm, for 105 weeks. Groups of 50 female mice were administered the test chemical at one of two doses, initially either 5,000 or 10,000 ppm. Because of excessive lowered body weights in the dosed groups of females, the doses for the females were reduced after 48 weeks to 1,000 and 3,000 ppm, respectively, and administration at the lowered doses was continued for 57 weeks. The time-weighted average doses for the female mice were 2,828 and 6,200 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of administration of the test chemical.

Mean body weights of dosed rats and mice of each sex were lower than those of corresponding controls, and were dose related throughout the bioassay. Survivals of the rats and mice were not, however, affected by administration of the test chemical.

No tumors occurred in the male or female rats or in the male mice at incidences that could clearly be related to administration of the test chemical.

In the female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related ($P = 0.011$), but in direct comparisons the incidences in the individual dosed groups were not significantly higher than that in the corresponding control group. Although the occurrence of hepatocellular carcinomas or adenomas in the dosed female mice are not clearly related to the administration of the test chemical, the increased incidence of these tumors in the high-dose group suggests that the tumors may be related to the administration of p,p'-ethyl-DDD.

It is concluded that under the conditions of this bioassay, p,p'-ethyl-DDD was not carcinogenic for male or female F344 rats or male B6C3F1 mice. However, the occurrence of hepatocellular carcinomas and adenomas in female mice was suggestive of a carcinogenic effect.

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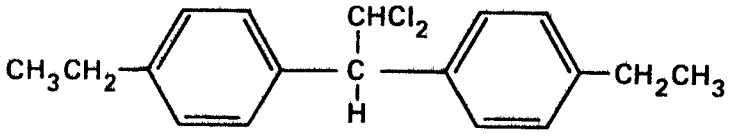
I. INTRODUCTION



p, p'-Ethyl-DDD

p,p'-Ethyl-DDD is 1,1-dichloro-2,2-bis(p-ethylphenyl)ethane (CAS 72-56-0; NCI C02868). This organochlorine insecticide, which is marketed under the trade name Perthane®, has a lower toxicity to both insects and mammals than its structural analogs, DDT and DDD (Brooks, 1975) and is of moderate persistence in the environment (Martin and Worthing, 1977). First marketed in 1950 for use against houseflies and clothes moths, it has since been used on vegetables, pears, and livestock (Finnegan et al., 1955; Brooks, 1975; Meister, 1977). In the late 1950's, this compound was one of several DDT analogs that were administered to patients with breast or prostatic cancer for adrenocortical suppression

because of the selective toxicity of these compounds for the adrenal cortex (Taliaferro and Leone, 1957).

Current production figures for p,p'-ethyl-DDD are withheld (United States International Trade Commission, 1977); however, in 1974, approximately 200,000 pounds of this pesticide were used in the United States (Ayers and Johnson, 1976). An analysis of use patterns in that year showed that all applications were in agriculture for the control of pests on fruits, nuts, and various vegetable crops (Ayers and Johnson, 1976).

The oral LD_{50} of p,p'-ethyl-DDD has been reported as 8,170 mg/kg body weight in weanling albino rats (Finnegan et al., 1955) and greater than 4,000 mg/kg body weight in adult Sherman rats (Gaines, 1969). In weanling albino mice, the oral LD_{50} has been reported as 9,340 mg/kg body weight (Finnegan et al., 1955) and in mice of unspecified strain as 6,600 mg/kg body weight (Brooks, 1975). p,p'-Ethyl-DDD causes atrophy of the adrenal cortex in dogs, a property common to DDD, the 2,2-bis(p-chlorophenyl) analog (Larson et al., 1955; Bleiberg and Larson, 1957). p,p'-Ethyl-DDD also inhibits adrenocortical function in humans (Taliaferro and Leone, 1957), but the adrenal cortex of the rat is unaffected by this or similar analogs (Bleiberg and Larson, 1957).

p,p'-Ethyl-DDD was selected for testing in the Carcinogenesis Testing Program because of its use as a pesticide and the preliminary findings of Innes et al. (1969), which suggested that further carcinogenicity testing was necessary.

II. MATERIALS AND METHODS

A. Chemical

Technical-grade Perthane® was obtained from Rohm & Haas. This material is a light-yellow, waxy semisolid at room temperature. Its purity was determined by gas-liquid chromatography to be 93%, with at least 40 contaminants ranging from 3.1% to less than 0.01%. It melting point was 38.9°C (literature value for pure crystalline solid: 60 to 61°C) and its refractive index was n_D 1.568 (literature value: n_D^{39} 1.561). Elemental analysis showed an average of 69.2% carbon and 6.4% hydrogen (theoretical: C 70.3%, and H 6.5%). Mass spectral analysis showed a molecular ion at m/e 223. The infrared spectrum of the compound was consistent with its chemical structure and identical with that of an authentic standard.

B. Dietary Preparation

Test diets containing p,p'-ethyl-DDD were prepared every week in 6- to 12-kg batches at the appropriate doses. A known weight of the chemical was first mixed with an equal weight of autoclaved

Wayne® Sterilizable Lab Meal (Allied Mills, Inc., Chicago, Ill.) using a mortar and pestle. The mixing was continued with second and third additions of feed, and the final mixing was performed with the remaining quantity of feed for a minimum of 20 minutes in a Patterson-Kelly twin-shell blender with an intensifier bar.

The diets were stored at 7°C until used.

C. Animals

Male and female F344 (Fischer) rats and B6C3F1 mice were obtained as 4-week-old weanlings, all within 3 days of the same age, from the Federick Cancer Research Center animal farm (Frederick, Md.), monitored by the Division of Cancer Treatment, NCI. The animals were housed within the test facility for 2 weeks and then were assigned four rats to a cage and five mice to a cage on a weight basis for each cage of animals of a given species and sex. For use in the chronic study, male rats were required to weigh 90 to 105 g, averaging at least 100 g; female rats, 80 to 95 g, averaging at least 90 g; male mice, 18 to 22 g, averaging at least 19.5 g; and female mice, 17 to 21 g, averaging at least 18.5 g. Individual animals were identified by ear punch.

D. Animal Maintenance

The animals were housed in polycarbonate cages (Lab Products, Inc., Garfield, N.J.), 19 x 10-1/2 x 8 inches for the rats and 11-1/2 x 7-1/2 x 5 inches for the mice, which were suspended from aluminum racks (Scientific Cages, Inc., Bryan, Tex.) and were covered by nonwoven polyester-fiber 12-mil-thick filter paper (Hoeltge, Inc., Cincinnati, Ohio). The bedding used was Absorb-dri® hardwood chips (Northeastern Products, Inc., Warrenburg, N.Y.). The feed was presterilized Wayne® Sterilizable Lab Meal, provided ad libitum in suspended stainless steel hoppers and replenished at least three times per week. Water, acidified to pH 2.5, was supplied ad libitum from glass bottles. Sipper tubes (Lab Products, Inc.) were suspended through the tops of the cages.

The contaminated bedding was disposed of through an enclosed vacuum line that led to a holding tank from which the bedding was fed periodically into an incinerator. The cages were sanitized twice per week and the feed hoppers twice per month at 82 to 88°C in a tunnel-type cagewasher (Industrial Washing Machine Corp., Mataway, N. J.), using the detergents, Clout® (Pharmacal Research Laboratories, Greenwich, Conn.) or Oxford D'Chlor (Oxford Chemicals, Atlanta, Ga.).

The glass bottles and sipper tubes were sanitized at 82 to 88°C in a tunnel-type bottle washer (Consolidated Equipment Supply Co., Mercersburg, Pa.) three times per week, using a Calgen Commercial Division detergent (St. Louis, Mo.). The racks for the cages were sanitized at or above 82°C in a rack washer (Consolidated Equipment Supply Co.) once per month, using the Calgen Commercial Division detergent, and the filter paper was changed at the same time.

The air in the animal rooms was maintained at 22 to 24°C and 45 to 55% relative humidity. Fresh air was passed through a filter of 65% efficiency and a bag filter of 95% efficiency at the intake and through a "Z"-type roughing filter of 30% efficiency and a bag system of 90 to 95% efficiency at the exhaust (American Air Filters, Louisville, Ky.; Mine Safety Appliances, Pittsburgh, Pa.) and was not recirculated. Room air was changed 15 times per hour. The air pressure was maintained negative to a clean hallway and positive to a return hallway. Fluorescent lighting was provided automatically on a 12-hour-per-day cycle.

Rats administered p,p'-ethyl-DDD and their corresponding controls were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 103-33-3) azobenzene
(CAS 51-03-6) piperonyl sulfoxide

Mice administered p,p'-ethyl-DDD and their corresponding controls were housed in the same room as mice on feeding studies of the following chemicals:

(CAS 103-33-3) azobenzene
(CAS 128-66-5) C.I. vat yellow 4
(CAS 20941-65-5) ethyl tellurac
(CAS 298-00-0) methyl parathion
(CAS 85-44-9) phthalic anhydride

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of p,p'-ethyl-DDD, on the basis of which two concentrations (referred to in this report as "low" and "high" doses) were selected for administration in the chronic studies. Groups of five rats and five mice of each sex were fed diets containing p,p'-ethyl-DDD at one of several doses, and groups of five control animals of each species and sex were administered basal diet only. The period of administration of the test chemical was 5 or 7 weeks; the 7-week groups were observed for an additional week. Tables 1 and 2 show the number of animals in each dosed group that survived to the end of the dosing period and the week on study when the last death occurred; the tables also show the mean body weights of dosed animals at

Table 1. p,p'-Ethyl-DDD Subchronic Feeding Studies In Rats

	Male			Female		
Dose (ppm)	Survival (a)	Week on Study When Last Death Occurred	Mean Weight at Week 5 as % of Control	Survival (a)	Week on Study When Last Death Occurred	Mean Weight at Week 5 as % of Control
First Study						
1,000	5/5		100	5/5		102
3,500	5/5		92	5/5		96
5,000	5/5		90	5/5		103
7,000	5/5		92	5/5		93
9,000	5/5		87	5/5		93
14,700	5/5		85	5/5		92
20,000	5/5		71	5/5		82
			Mean Weight at Week 7 as % of Control			Mean Weight at Week 7 as % of Control
Second Study						
6,800	5/5		91	5/5		93
10,000	5/5		65	5/5		90
14,700	5/5		74	5/5		76
21,500	5/5		42	5/5		62
31,500	3/5	4	28	1/5	7	33

(a) Number surviving/number in group.

Table 2. p,p'-Ethyl-DDD Subchronic Feeding Studies In Mice

	Male			Female		
Dose (ppm)	Survival (a)	Week on Study When Last Death Occurred	Mean Weight at Week 7 as % of Control	Survival (a)	Week on Study When Last Death Occurred	Mean Weight at Week 7 as % of Control
First Study						
2,000	5/5		101	5/5		93
4,000	5/5		106	5/5		95
5,000	5/5		104	5/5		90
6,000	5/5		102	5/5		105
7,000	5/5		102	5/5		94
8,000	5/5		106	5/5		92
9,000	5/5		99	5/5		82
10,000	5/5		90	5/5		84
12,000	5/5		98	5/5		85
Second Study						
10,000	5/5		89	5/5		105
14,700	4/5	2	92	4/5	3	93
21,500	5/5		77	4/5	4	93
31,500	2/5	4	83	4/5	2	84
46,500	1/5	4	73	2/5	3	73

(a) Number surviving/number in group.

week 5 or 7, expressed as percentages of mean body weights of controls.

At the end of the subchronic studies, all animals were killed using CO_2 and necropsied. The lowest dose at which histopathologic findings were observed for the male and female rats was 21,500 ppm. At this dose, there was a marked increase in splenic hematopoiesis and a generally slight decrease in bone marrow cellularity. No clinical or histopathologic findings were reported for the mice dosed at 31,500 ppm.

Ten percent depression in body weight was the major criterion for estimation of MTD's. The doses required to produce this response were determined by the following procedure: first, least squares regressions of mean body weights versus days on study were used to estimate mean body weights of each of the dosed groups at day 49. Next, probits of the percent weights of dosed groups at day 49 relative to weights of corresponding control groups were plotted against the logarithms of the doses, and least squares regressions fitted to the data were used to estimate the doses required to induce 10% depression in weight.

Based on the data thus obtained, the low and high doses for chronic studies using rats were set at 3,500 and 7,000 ppm; using

male mice, 2,500 and 5,000 ppm; and using female mice, 5,000 and 10,000 ppm.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 3 and 4. Due to excessive depression in the amount of body weight gained in the dosed female mice, doses for the low- and high-dose groups were reduced to 1,000 and 3,000 ppm, respectively, after week 48.

G. Clinical and Pathologic Examinations

All animals were checked twice daily for deaths. Observations for sick, tumor-bearing, and moribund animals were recorded daily. Clinical examination and palpation for masses were performed each month, and the animals were weighed at least once per month. Moribund animals and animals that survived to the end of the bioassay were killed using CO_2 and then necropsied.

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

Table 3. p,p'-Ethyl-DDD Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	p,p'-Ethyl-DDD in Diet (b) (ppm)	Time on Study (weeks)
Male			
Matched-Control	20	0	105
Low-Dose	50	3,500	105
High-Dose	50	7,000	105
Female			
Matched-Control	20	0	105
Low-Dose	50	3,500	105
High-Dose	50	7,000	105

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum 7 days per week.

Table 4. p,p'-Ethyl-DDD Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	p,p'-Ethyl-DDD in Diet (b) (ppm)	Time on Study (weeks)	Time-Weighted Average Dose (c) (ppm)
Male				
Matched-Control	20	0	105	
Low-Dose	50	2,500	105	
High-Dose	50	5,000	105	
Female				
Matched-Control	20	0	105	
Low-Dose	50	5,000	48	
		1,000	57	2,828
High-Dose	50	10,000	48	
		3,000	57	6,200

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum 7 days per week.

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

lesions. The tissues were preserved in 10% neutral formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (parotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestines, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, testis, prostate, uterus, ovary, brain (cerebrum and cerebellum), and all tissue masses. Peripheral blood smears also were made for all animals, whenever possible.

Necropsies were also performed on all animals found dead, unless precluded in whole or part by autolyis or cannibalization. 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 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 a 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)

Mean body weights of dosed male and female rats were lower than those of corresponding matched controls, and depressions in the amount of body weight gained were dose related throughout the bioassay (figure 1). Other clinical signs, such as corneal opacity and tissue masses, were common to both the dosed and the control groups.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered p,p'-ethyl-DDD in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2. The result of the Tarone test for dose-related trend in mortality is not significant in either sex.

In male rats, 35/50 (70%) of the high-dose group, 34/50 (68%) of the low-dose group, and 11/20 (55%) of the matched-control group

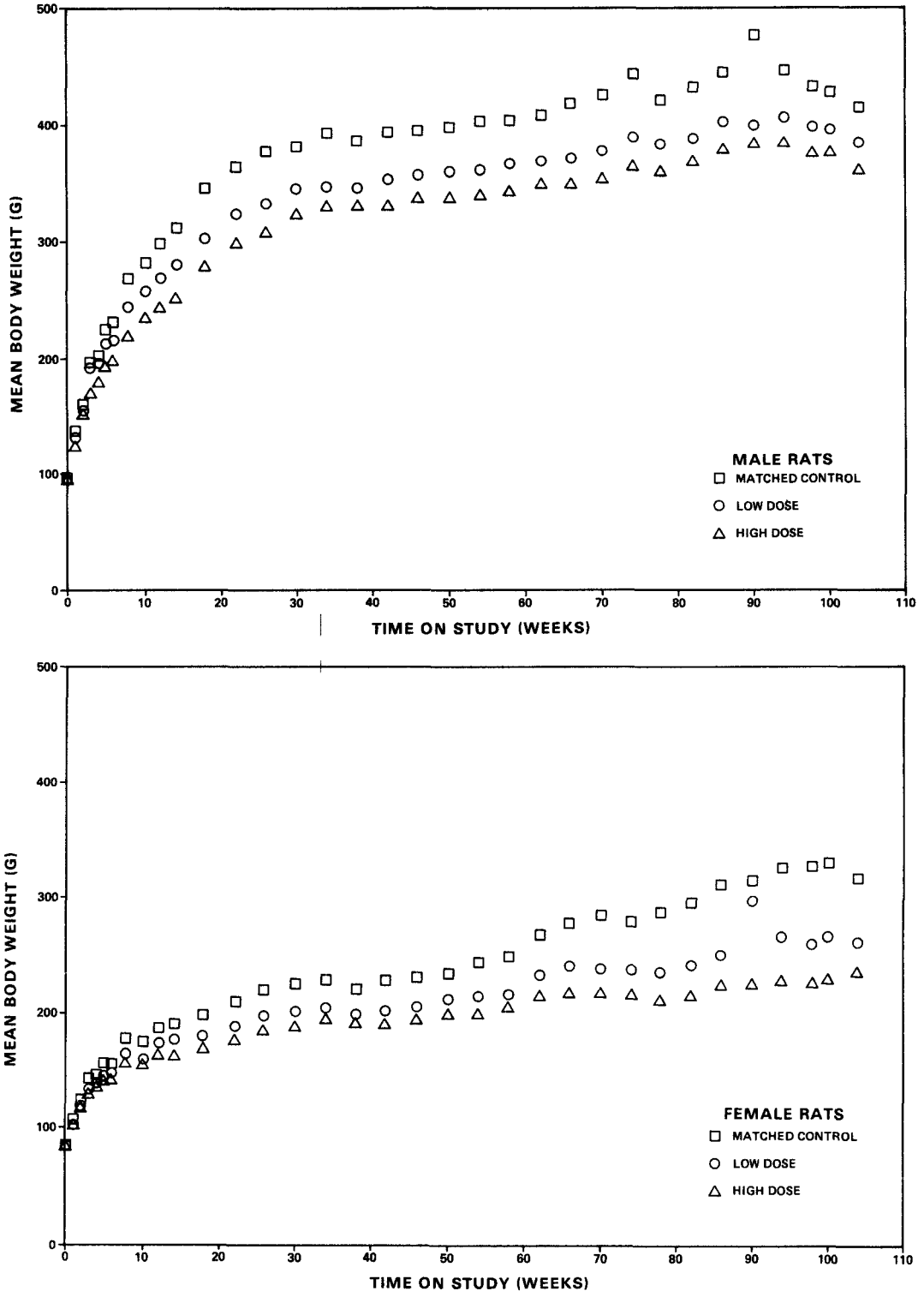


Figure 1. Growth Curves for Rats Administered p, p'-Ethyl-DDD in the Diet

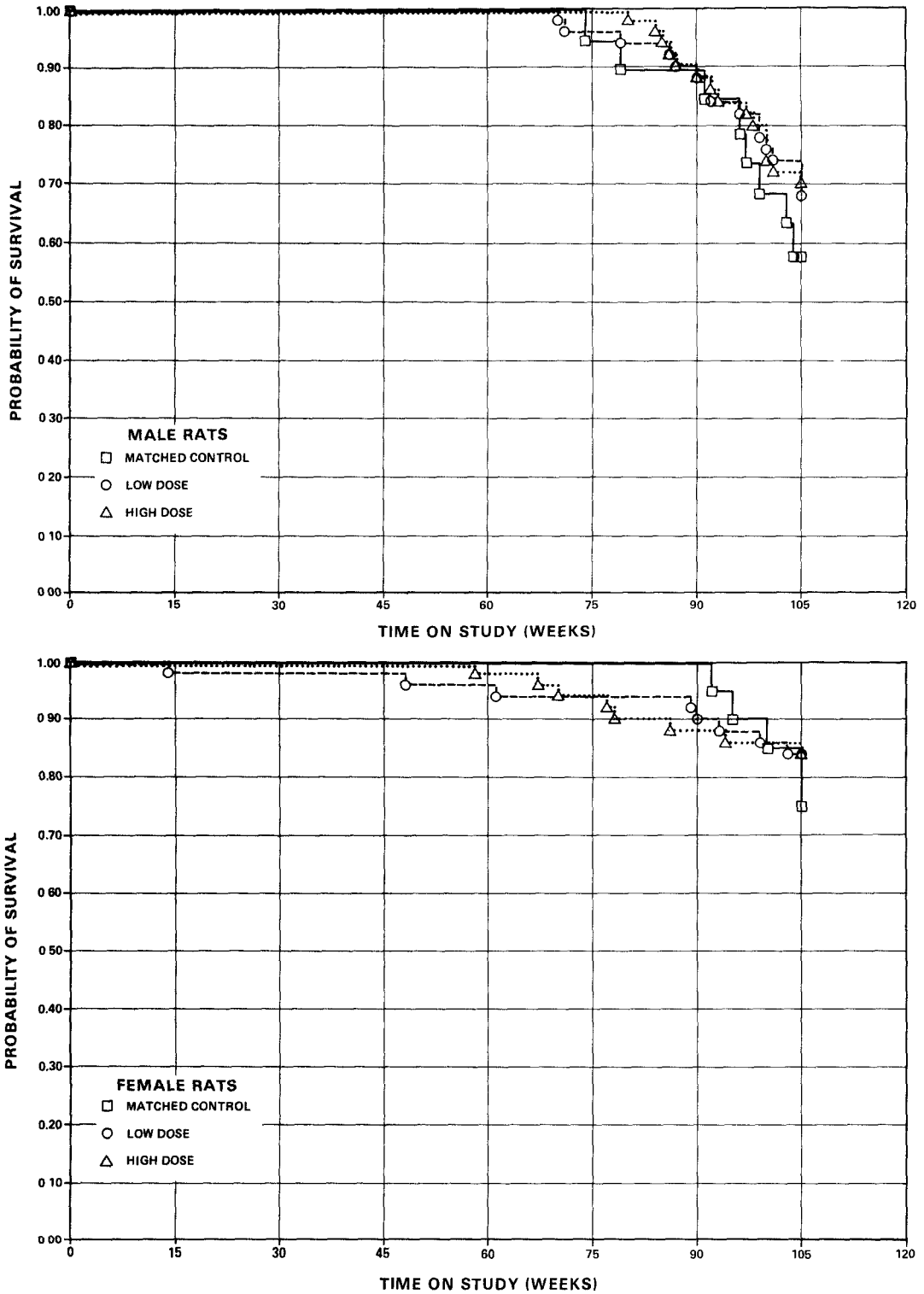


Figure 2. Survival Curves for Rats Administered p, p'-Ethyl-DDD in the Diet

lived to the end of the bioassay. In females, 42/50 (84%) of the high-dose group, 42/50 (84%) of the low-dose group, and 15/20 (75%) of the matched-control group lived to the end of the bioassay.

Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

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 neoplasms were found in dosed and control animals. The neoplasms were of a type, incidence, and distribution known to occur in aged F344 rats and are therefore not considered to be related to compound administration.

A variety of nonneoplastic lesions were encountered among both control and dosed rats. Such lesions have been encountered previously in aged laboratory rats and did not appear to be related to the chemical under study. Sialoadenitis, typical of

the disease induced by a coronavirus (Jacoby et al., 1975) was commonly encountered.

Nonneoplastic proliferative lesions, found only in dosed rats, were basophilic foci or areas of the liver (1/50 low-dose males, 6/50 high-dose males; 1/50 low-dose females, 3/50 high-dose females), stromal polyps of the uterus (5/50 low-dose and 3/50 high-dose females), and an adenomatous polyp of the uterus (1/50 high-dose females). These may be compound related, but the incidence is too low for conclusions to be formed.

Based on the histopathologic examination, there was no evidence for the carcinogenicity of p,p'-ethyl-DDD in F344 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 of rats, the results of the Cochran-Armitage test for positive dose-related trend in the incidence of tumors and the results of the Fisher exact test comparing the incidence of tumors in the control group with that in each dosed group in the positive direction are not significant. In female rats, significant results in the negative direction are observed in the incidence of squamous-cell carcinoma in the integumentary system and in the incidence of cortical adenoma of the adrenal, in which the incidences of the tumors in the control group are 2/20 (10%) and 3/20 (15%), respectively, but no such tumors are observed in the dosed groups.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals (except that for the incidence of cortical adenoma of the adrenal in female rats) has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by p,p'-ethyl-DDD, which could not be detected under the conditions of this test.

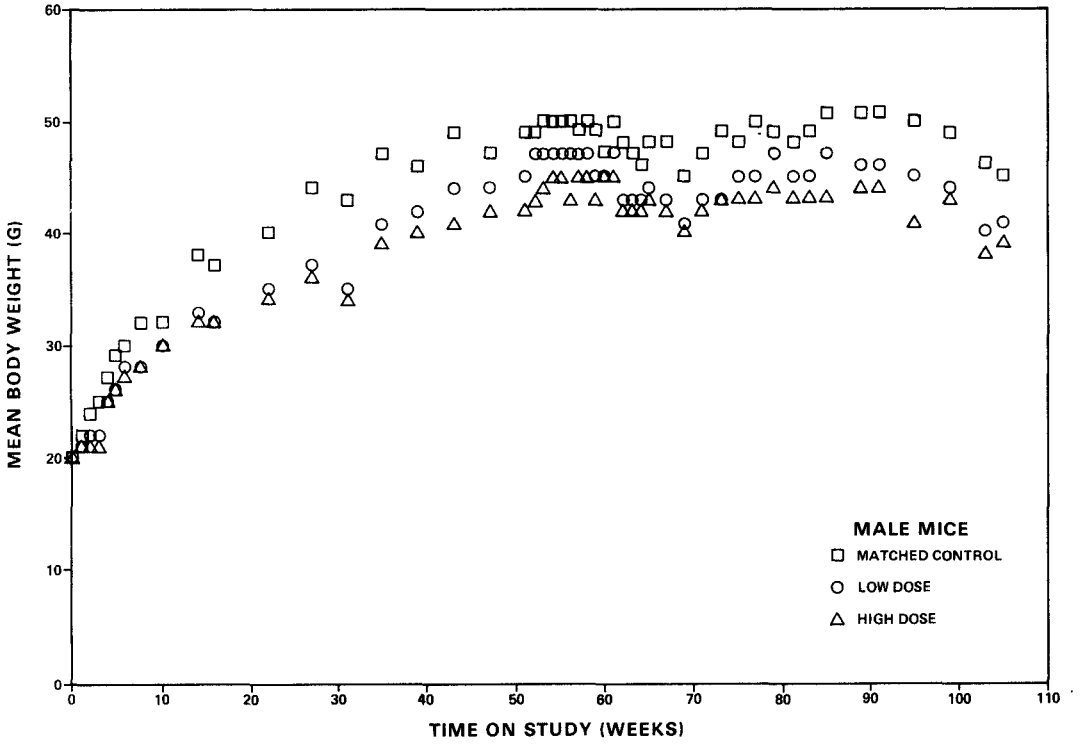
IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of dosed male and female mice were lower than those of corresponding controls, and depressions in the amount of body weight gained were dose related throughout the bioassay (figure 3). Other clinical signs, such as corneal opacity and tissue masses, were common to both dosed and control groups. Some fluctuations in the growth curves may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered p,p'-ethyl-DDD in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. The result of the Tarone test for dose-related trend in mortality is not significant in either sex.



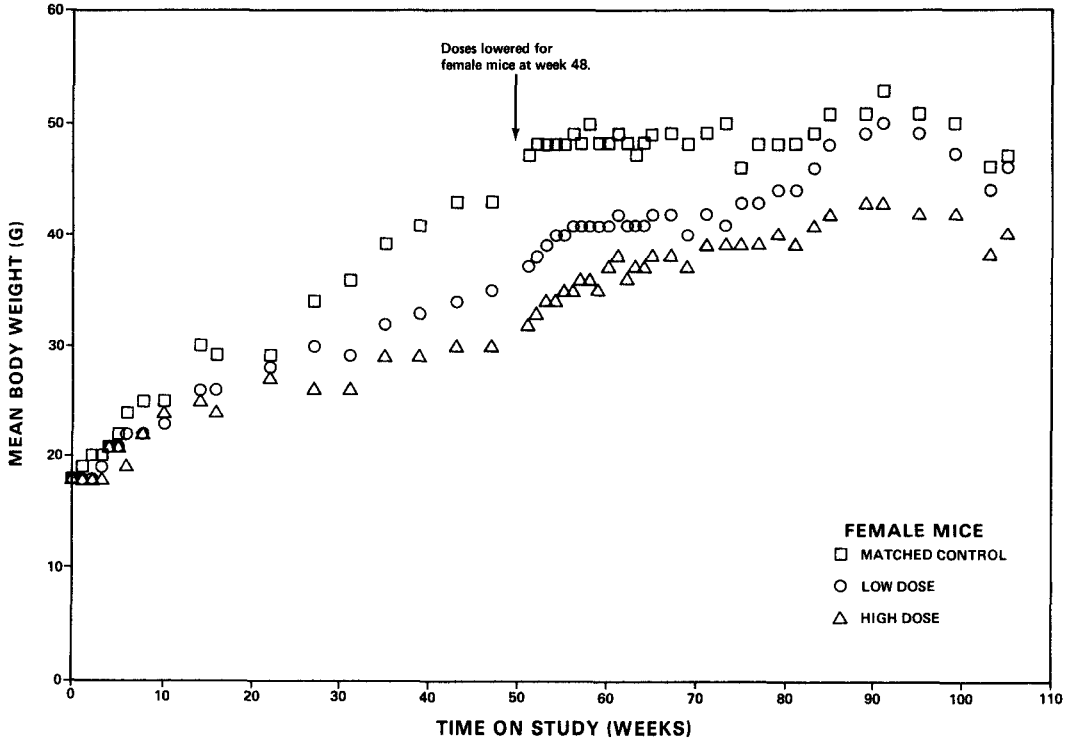
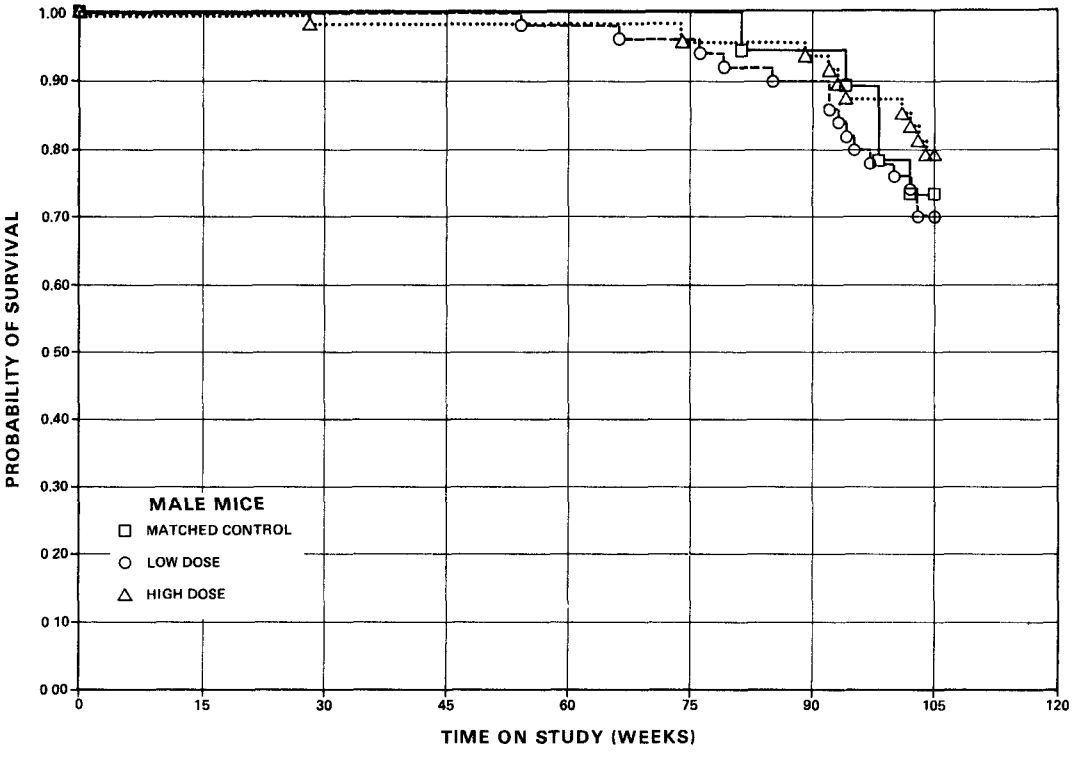


Figure 3. Growth Curves for Mice Administered p, p'-Ethyl-DDD in the Diet



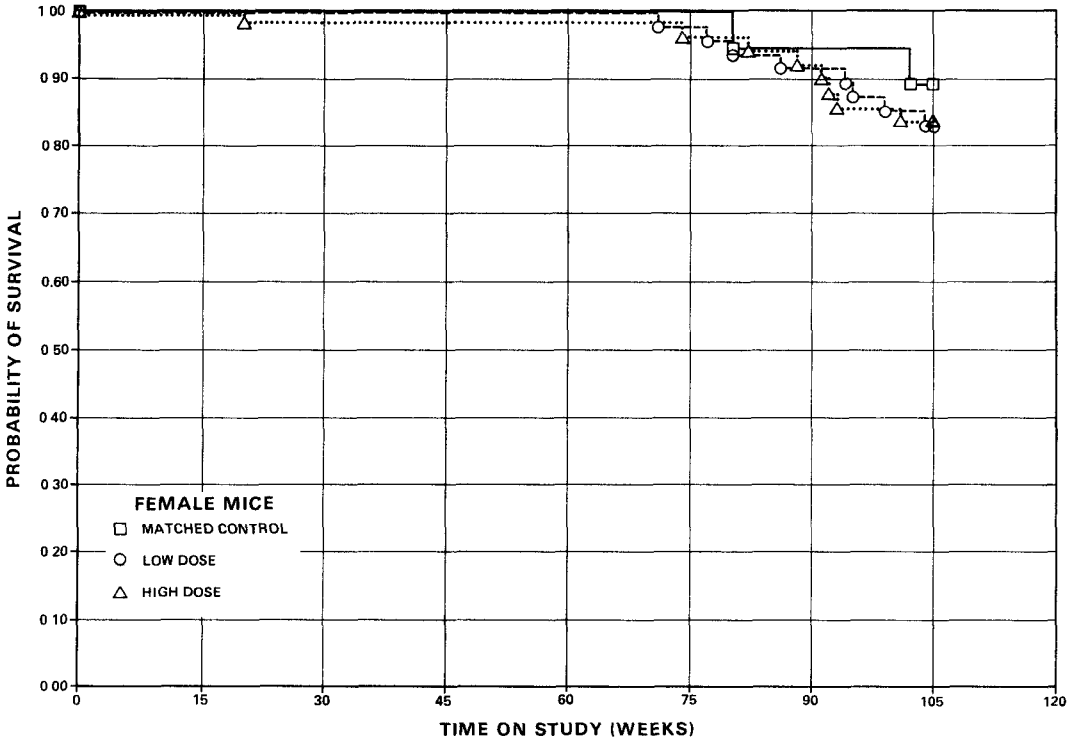


Figure 4. Survival Curves for Mice Administered p, p'-Ethyl-DDD in the Diet

In male mice, 38/50 (76%) of the high-dose group, 35/50 (70%) of the low-dose group, and 14/20 (70%) of the matched-control group lived to the end of the bioassay. In females, 41/50 (82%) of the high-dose group, 39/50 (78%) of the low-dose group, and 17/20 (85%) of the matched-control group lived to the end of the bioassay.

Sufficient numbers of mice of each sex were at risk for the development of late-appearing 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.

A variety of neoplasms were found in both dosed and control animals. With the exception of hepatic lesions, the neoplasms were of a type, incidence, and distribution known to occur in aged B6C3F1 mice and are therefore not considered to be related to compound administration.

There was an increased incidence of hepatocellular neoplasms in

the female mice. Adenomas occurred in 1/47 (2%) of the low-dose and 1/47 (2%) of the high-dose groups, but were absent in control animals. Carcinomas were found in 1/19 (5%) of the controls, 2/47 (2%) of the low-dose, and 10/47 (21%) of the high-dose female mice. The hepatocellular adenomas were characterized by compression of adjacent parenchyma, single or multiple nodules, occasional encapsulation, absence of nuclear atypia, and rare or no mitotic figures.

Hepatocellular carcinomas with pulmonary metastasis had the following characteristics: generally, they were relatively large masses with multiple anaplastic nodules throughout, which varied in appearance from nodule to nodule. The surrounding parenchyma was compressed. The tissue between the nodules was often compressed and occasionally necrotic and fibrotic. Cytoplasmic tinctorial characteristics also varied from nodule to nodule. In some areas it was basophilic while in other areas it was more eosinophilic than normal hepatocytes. Large vacuoles were seen in some cells while in other areas the cells had a foamy appearance. Councilman-like bodies were frequently found in the cytoplasm. Nuclei varied from relatively normal to large, irregularly shaped nuclei containing cytoplasmic invaginations, coarse clumped chromatin, and prominent nucleoli. Mitotic figures in the most atypical portion of the tumors ranged from

2/10 high power fields (hpf) to 36/10 hpf, with a mean of 9.5 and median of 5.5 mitoses/10 hpf. Three types of cell patterns were observed in the tumors: solid, where hepatocytes formed solid masses without apparent cord formation, nodular, where cords were formed but were oriented without regard to portal-central architecture, and trabecular, where broad hepatic cords usually two cells thick and often containing a central canal or space between them (bile canaliculus) traversed large vascular spaces in a haphazard fashion. Areas of coagulation necrosis were frequent and were occasionally observed in adjacent, uninvolved hepatic parenchyma. Bile ducts were found irregularly throughout some of the tumors but were largely absent from the more anaplastic portions of the neoplasm.

Criteria for diagnosing hepatocellular carcinoma metastasis were not demonstrated based on the above features. Those essential to a positive diagnosis were: 1) compression of adjacent parenchyma, 2) nuclear atypia, and 3) a minimum of 2 mitoses/10 hpf. Sixty-three percent of the hepatocellular carcinomas without metastatic lesions had all three patterns as described above (solid, nodular, trabecular). Multiple hepatocellular tumors were found in these mice, especially in the males. However, a difference in incidences in dosed and control groups of male mice was not observed for hepatocellular carcinoma.

A variety of nonneoplastic lesions were encountered among both control and dosed mice. Such lesions have been encountered previously in aged laboratory mice, and most did not appear to be related to the chemical. Of possible significance, however, was the finding of nonsuppurative meningitis, choroiditis, and in one mouse, encephalitis. This was observed in three high-dose and seven low-dose female mice but not in controls. The lesions were mild.

Based on the histopathologic examination, there was no conclusive evidence for the carcinogenicity of p,p'-ethyl-DDD in B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix 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 male mice, the result of the Fisher exact comparison of the incidences of alveolar/bronchiolar carcinomas in the control and high-dose groups is not significant, but the incidence in the

control group is significantly higher (P = 0.018) than that in the low-dose group. When statistical analyses are performed on the incidence of animals with alveolar/bronchiolar adenoma or carcinoma, the results are not significant.

In female mice, the results of the Cochran-Armitage test for the incidence of hepatocellular carcinoma and for the combined incidence of hepatocellular adenoma and carcinoma are significant (P = 0.013 and P = 0.011, respectively); however, the results of the Fisher exact tests are not significant. In historical-control groups of mice compiled to date at this laboratory, the incidence of hepatocellular carcinomas or adenomas ranges from 0/20 to 2/19 (11%), with an overall incidence of 14/324 (4.3%).

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals (except that for the incidence of alveoler/bronchiolar carcinoma in low-dose male mice) has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by p,p'-ethyl-DDD, which could not be detected under the conditions of this test.

V. DISCUSSION

Mean body weights of the dosed rats and mice of each sex were lower than those of corresponding controls, and were dose related throughout the bioassay. However, survivals of the dosed rats and mice were unaffected, and no other clinical signs could be related to administration of the test chemical. Since the lowered body weights in the dosed groups may have resulted from the test diets being unpalatable to the animals, there was no conclusive evidence of toxicity of p,p'-ethyl-DDD at the doses tested.

In the male and female rats and the male mice, no tumors occurred in the dosed groups at incidences that were significantly higher than those in the corresponding control groups.

In the female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related ($P = 0.011$), but in direct comparisons the incidences in the individual dosed groups were not significantly higher than that in the corresponding control group (controls 1/19 (5%), low-dose 3/47 (6%), high-dose 11/47 (23%). The incidence of hepatocellular carcinomas or adenomas in historical-control female B6C3F1 mice at this

laboratory was only 14/324 (4.3%). Thus, even though the occurrence of hepatocellular carcinomas or adenomas in the dosed female mice cannot clearly be related statistically to administration of the test chemical, the increased incidence of these tumors in the high-dose group in relation to that in the matched or historical controls suggests that the tumors may be related to the administration of p,p'-ethyl-DDD.

In previous tests for tumorigenicity (NTIS, 1968; Innes et al., 1969), it was reported that when p,p'-ethyl-DDD, called Perthane® in these reports, was administered at 215 mg/kg body weight by stomach tube for 3 weeks, then in the diet at 815 ppm for 18 months, to hybrid mice (C57BL/6 x C3H/Anf and C57BL/6 x AKR), an elevated incidence of hepatomas ($P = 0.01$) was observed. The dichlorodiphenyl-tri-chloroethane analog, p,p'-DDT, has also been reported to induce hepatomas in various strains of mice (International Agency for Research on Cancer, 1974), and the p,p'-dichlorodiphenyl-dichloro-ethylene analog, DDE, has been reported to induce hepatomas in CF-1 mice (Tomatis et al., 1974). Thus, tumors of the same cell type, i.e., hepatocytes of the liver, have been observed previously with p,p'-ethyl-DDD and related compounds.

It is concluded that under the conditions of this bioassay, p,p'-ethyl-DDD was not carcinogenic for male or female F344 rats or male B6C3F1 mice. However, the occurrence of hepatocellular carcinomas and adenomas in female mice was suggestive of a carcinogenic effect.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED p,p'-ETHYL-DDD IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(50)	(50)
CARCINOMA,NOS			1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)	3 (6%)
KERATOACANTHOMA		1 (2%)	
LEIOMYOSARCOMA			1 (2%)
*SUBCUT TISSUE	(19)	(50)	(50)
FIBROSARCOMA		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
*LUNG	(16)	(47)	(48)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (6%)	2 (4%)	
FIBROSARCOMA, METASTATIC		1 (2%)	
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BRAIN	(19)	(48)	(50)
MALIGNANT RETICULOSIS		1 (2%)	
*MULTIPLE ORGANS	(19)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)		1 (2%)
*HEMATOPOIETIC SYSTEM	(19)	(50)	(50)
NEOPLASM, NOS	4 (21%)	11 (22%)	10 (20%)
#SPLEEN	(19)	(50)	(48)
SARCOMA, NOS		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
#THYMUS	(14)	(43)	(43)
FIBROSARCOMA, METASTATIC		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(19)	(49)	(49)
FIBROSARCOMA, METASTATIC		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(19)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	
HEPATOCELLULAR CARCINOMA		1 (2%)	
#S.INTESTINE/MUCOSA	(19)	(50)	(49)
PAPILLARY ADENOCARCINOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(50)	(49)
TUBULAR-CELL ADENOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(47)	(48)
ADENOMA, NOS		1 (2%)	3 (6%)
ADENOCARCINOMA, NOS		1 (2%)	
CHROMOPHOBE ADENOMA	3 (16%)	7 (15%)	2 (4%)
ACIDOPHIL ADENOMA		1 (2%)	
#ADRENAL	(19)	(50)	(49)
NEOPLASM, NOS		1 (2%)	
CORTICAL ADENOMA	1 (5%)	1 (2%)	
PHEOCHROMOCYTOMA	2 (11%)	5 (10%)	3 (6%)
PHEOCHROMOCYTOMA, MALIGNANT			2 (4%)
#THYROID	(19)	(50)	(50)
FOLLICULAR-CELL CARCINOMA		1 (2%)	1 (2%)
C-CELL ADENOMA	2 (11%)	7 (14%)	6 (12%)
#PANCREATIC ISLETS	(16)	(47)	(47)
ISLET-CELL ADENOMA	1 (6%)		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
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
FIBROADENOMA	1 (5%)		
#TESTIS	(19)	(50)	(49)
INTERSTITIAL-CELL TUMOR	17 (89%)	35 (70%)	35 (71%)
#TUNICA ALBUGINEA	(19)	(50)	(49)
MESOTHELIOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*BODY CAVITIES	(19)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
*ABDOMINAL CAVITY	(19)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
*PERITONEUM	(19)	(50)	(50)
PAPILLARY ADENOCARCINOMA, METAST			1 (2%)
*MESENTERY	(19)	(50)	(50)
ADENOMA, NOS			1 (2%)
LIPOMA			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
*TUNICA VAGINALIS	(19)	(50)	(50)
PAPILLARY ADENOCARCINOMA, METAST			1 (2%)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
AXILLA			
SARCOMA, NOS		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	5	11	8
MORIBUND SACRIFICE	3	5	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11	34	35
ANIMAL MISSING	1		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	18	46	42
TOTAL PRIMARY TUMORS	33	86	77
TOTAL ANIMALS WITH BENIGN TUMORS	17	39	36
TOTAL BENIGN TUMORS	27	59	54
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	11	12
TOTAL MALIGNANT TUMORS	2	11	12
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	2
TOTAL SECONDARY TUMORS		4	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	4	16	11
TOTAL UNCERTAIN TUMORS	4	16	11
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 ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA	2 (10%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
MONOCYTIC LEUKEMIA			1 (2%)
*HEMATOPOIETIC SYSTEM	(20)	(50)	(50)
NEOPLASM, NOS	3 (15%)	8 (16%)	6 (12%)
#BONE MARROW	(20)	(50)	(50)
GRANULOCYTIC SARCOMA	1 (5%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*ORAL CAVITY	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
#LIVER	(20)	(49)	(50)
NEOPLASTIC NODULE			1 (2%)

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		2 (4%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(50)	(49)
ADENOMA, NOS	1 (5%)		
CHROMOPHOBE ADENOMA	4 (20%)	13 (26%)	6 (12%)
ACIDOPHIL ADENOMA	1 (5%)		
#ADRENAL	(20)	(50)	(48)
CORTICAL ADENOMA	3 (15%)		
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(19)	(49)	(49)
PAPILLARY ADENOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA	1 (5%)		
C-CELL ADENOMA	2 (11%)	4 (8%)	4 (8%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS	1 (5%)		
FIBROMA	1 (5%)		
FIBROADENOMA	1 (5%)	1 (2%)	
*VAGINA	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#UTERUS	(19)	(50)	(49)
PAPILLARY ADENOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP		5 (10%)	3 (6%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(50)
EPENDYMOMA	1 (5%)		

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			
*EAR CANAL	(20)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	6	6
MORIBUND SACRIFICE	3	2	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	15	42	42
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*	15	32	21
TOTAL PRIMARY TUMORS	23	38	24
TOTAL ANIMALS WITH BENIGN TUMORS	10	22	12
TOTAL BENIGN TUMORS	14	26	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	4	4
TOTAL MALIGNANT TUMORS	6	4	4
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	8	7
TOTAL UNCERTAIN TUMORS	3	8	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 ADMINISTERED p,p'-ETHYL-DDD IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(19)	(50)	(50)
FIBROSARCOMA	1 (5%)		
HEMANGIOSARCOMA, METASTATIC			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(49)
UNDIFFERENTIATED CARCINOMA METAS			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	2 (11%)	2 (4%)	6 (12%)
ALVEOLAR/BRONCHIOLAR ADENOMA		4 (8%)	9 (18%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	4 (21%)	1 (2%)	3 (6%)
RHABDOMYOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (11%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)	
MALIGNANT LYMPHOMA, MIXED TYPE		3 (6%)	
#BONE MARROW	(18)	(50)	(49)
MAST-CELL TUMOR		1 (2%)	
#SPLEEN	(19)	(48)	(47)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
#LYMPH NODE	(18)	(45)	(47)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
RHABDOMYOSARCOMA, METASTATIC		1 (2%)	
#LUNG	(19)	(50)	(49)
THYMOMA, METASTATIC			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(16)	(39)	(40)
THYMOMA, MALIGNANT			1 (3%)
MALIGNANT LYMPHOMA, NOS			1 (3%)
CIRCULATORY SYSTEM			
#HEART	(19)	(47)	(50)
RHABDOMYOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(50)
BILE DUCT CARCINOMA			1 (2%)
HEPATOCELLULAR ADENOMA	1 (5%)	7 (14%)	5 (10%)
NEOPLASTIC NODULE		1 (2%)	
HEPATOCELLULAR CARCINOMA	7 (37%)	19 (39%)	20 (40%)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
ANGIOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(18)	(47)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(19)	(50)	(50)
ADENOMA, NOS	1 (5%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*HARDERIAN GLAND	(19)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
*EAR	(19)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(19)	(50)	(50)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)
*PLEURA	(19)	(50)	(50)
RHABDOMYOSARCOMA, METASTATIC		1 (2%)	
ALL OTHER SYSTEMS			
DIAPHRAGM			
ALVEOLAR/BRONCHIOLAR CA, METASTA		1	
SITE UNKNOWN			
UNDIFFERENTIATED CARCINOMA			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	5	15	9
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			2
TERMINAL SACRIFICE	14	35	38
ANIMAL MISSING	1		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	38	33
TOTAL PRIMARY TUMORS	16	48	45
TOTAL ANIMALS WITH BENIGN TUMORS	2	11	11
TOTAL BENIGN TUMORS	2	13	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	27	27
TOTAL MALIGNANT TUMORS	14	33	31
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	4	8
TOTAL SECONDARY TUMORS	2	7	10
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	
TOTAL UNCERTAIN TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		3	1
ANIMALS NECROPSIED	20	47	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(47)	(49)
HEMANGIOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(47)	(49)
SARCOMA, NOS		1 (2%)	2 (4%)
FIBROSARCOMA	1 (5%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(18)	(47)	(47)
HEPATOCELLULAR CARCINOMA, METAST			2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(47)	(49)
MALIGNANT LYMPHOMA, NOS	1 (5%)	5 (11%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (10%)	2 (4%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(19)	(46)	(46)
HEMANGIOSARCOMA		1 (2%)	
#LYMPH NODE	(20)	(46)	(46)
SARCOMA, NOS, METASTATIC			1 (2%)
#ABDOMINAL LYMPH NODE	(20)	(46)	(46)
FIBROSARCOMA, METASTATIC		1 (2%)	
*MESENTERY	(20)	(47)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#CECUM	(20)	(44)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#THYMUS	(18)	(41)	(44)
THYMOMA		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(47)	(47)
HEPATOCELLULAR ADENOMA		1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	1 (5%)	2 (4%)	10 (21%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(42)	(46)
ADENOMA, NOS		1 (2%)	
CHROMOPHOBE ADENOMA	1 (6%)	4 (10%)	5 (11%)
#ADRENAL	(20)	(46)	(45)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
#THYROID	(18)	(41)	(46)
PAPILLARY ADENOMA			1 (2%)
C-CELL ADENOMA			1 (2%)
#PANCREATIC ISLETS	(19)	(45)	(46)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(47)	(49)
ADENOMA, NOS			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
FIBROSARCOMA		1 (2%)	
#UTERUS	(19)	(45)	(42)
LEIOMYOMA			1 (2%)
LEIOMYOSARCOMA		1 (2%)	1 (2%)
#OVARY/OVIDUCT	(19)	(45)	(42)
PAPILLARY ADENOMA		1 (2%)	
#OVARY	(19)	(42)	(44)
GRANULOSA-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(20)	(47)	(49)
CYSTADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(47)	(49)
HEMANGIOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	8	6
MORIBUND SACRIFICE			2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	17	39	41
ANIMAL MISSING		3	1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	24	26
TOTAL PRIMARY TUMORS	7	31	34
TOTAL ANIMALS WITH BENIGN TUMORS	1	12	10
TOTAL BENIGN TUMORS	1	14	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	15	21
TOTAL MALIGNANT TUMORS	6	17	22
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	3
TOTAL SECONDARY TUMORS		1	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED p,p'-ETHYL-DDD IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(50)	(50)
ECTOPIA		1 (2%)	
EOSINOPHILIC GRANULOMA			1 (2%)
*SUBCUT TISSUE	(19)	(50)	(50)
HEMORRHAGE		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE	1 (5%)		
INFLAMMATION, ACUTE/CHRONIC	1 (5%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (5%)	1 (2%)	
#LUNG	(16)	(47)	(48)
ECTOPIA		1 (2%)	
MINERALIZATION		1 (2%)	
INFLAMMATION, NOS			1 (2%)
PNEUMONIA, ASPIRATION			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	2 (13%)		2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (6%)		
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
HYPERPLASIA, ADENOMATOUS	2 (13%)		
HEMATOPOIETIC SYSTEM			
*BLOOD	(19)	(50)	(50)
ANEMIA, NOS			1 (2%)
#BONE MARROW	(18)	(50)	(50)
HYPERPLASIA, NOS	1 (6%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(19)	(50)	(48)
HEMORRHAGE		1 (2%)	
SCLEROSIS			1 (2%)
INFARCT, ACUTE		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	1 (5%)	1 (2%)	1 (2%)
#SPLENIC CAPSULE	(19)	(50)	(48)
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
#SPLENIC RED PULP	(19)	(50)	(48)
LEUKOCYTOSIS, NOS	1 (5%)		
#SUBMANDIBULAR L.NODE	(18)	(50)	(48)
INFLAMMATION, ACUTE			1 (2%)
#MEDIASTINAL L.NODE	(18)	(50)	(48)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#MESENTERIC L. NODE	(18)	(50)	(48)
HISTIOCYTOSIS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(19)	(49)	(49)
THROMBOSIS, NOS	1 (5%)		
THROMBUS, MURAL		1 (2%)	
ATROPHY, NOS		1 (2%)	
#HEART/ATRIUM	(19)	(49)	(49)
THROMBOSIS, NOS			1 (2%)
#MYOCARDIUM	(19)	(49)	(49)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, CHRONIC	3 (16%)		
INFLAMMATION, CHRONIC FOCAL		4 (8%)	8 (16%)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
FIBROSIS	1 (5%)	2 (4%)	5 (10%)
FIBROSIS, FOCAL	1 (5%)	2 (4%)	5 (10%)
SCAR		1 (2%)	1 (2%)
FIBROSIS, MULTIFOCAL	4 (21%)	25 (51%)	15 (31%)
FIBROSIS, DIFFUSE	4 (21%)		
DEGENERATION, NOS	6 (32%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*PULMONARY ARTERY	(19)	(50)	(50)
MINERALIZATION	1 (5%)	6 (12%)	2 (4%)
CALCIFICATION, FOCAL			1 (2%)
#HEPATIC SINUSOID	(19)	(50)	(50)
LEUKOCYTOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*TOOTH	(19)	(50)	(50)
DYSPLASIA, NOS			1 (2%)
#SALIVARY GLAND	(18)	(50)	(48)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (6%)	6 (12%)	16 (33%)
INFLAMMATION, CHRONIC FOCAL	1 (6%)		
INFLAMMATION, CHRONIC DIFFUSE	2 (11%)	9 (18%)	4 (8%)
#SALIVARY SEROUS GLAN	(18)	(50)	(48)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	2 (4%)
INFLAMMATION, CHRONIC DIFFUSE	1 (6%)	1 (2%)	3 (6%)
#LIVER	(19)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
CONGESTION, CHRONIC PASSIVE	1 (5%)		
INFLAMMATION, ACUTE FOCAL	1 (5%)		
INFLAMMATION, CHRONIC FOCAL	4 (21%)	2 (4%)	1 (2%)
CHOLANGIOFIBROSIS	1 (5%)	2 (4%)	
CIRRHOSIS, NOS	1 (5%)		
HEPATITIS, TOXIC	3 (16%)	1 (2%)	
PELIOSIS HEPATIS	1 (5%)	2 (4%)	7 (14%)
METAMORPHOSIS FATTY		1 (2%)	
BASOPHILIC CYTO CHANGE		1 (2%)	6 (12%)
FOCAL CELLULAR CHANGE			1 (2%)
CLEAR-CELL CHANGE			1 (2%)
HEMATOPOIESIS	1 (5%)		1 (2%)
#LIVER/CENTRILOBULAR	(19)	(50)	(50)
METAMORPHOSIS FATTY	1 (5%)		
#LIVER/PERIPORTAL	(19)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	3 (16%)	3 (6%)	1 (2%)
#LIVER/HEPATOCYTES	(19)	(50)	(50)
CYTOPLASMIC VACUOLIZATION			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#BILE DUCT	(19)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)	3 (6%)	1 (2%)
HYPERPLASIA, FOCAL	11 (58%)	7 (14%)	9 (18%)
#PANCREAS	(16)	(47)	(47)
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (6%)	1 (2%)	2 (4%)
#PANCREATIC ACINUS	(16)	(47)	(47)
FIBROSIS, FOCAL	1 (6%)	1 (2%)	
ATROPHY, NOS	1 (6%)		
#STOMACH	(18)	(50)	(49)
ULCER, NOS		1 (2%)	
ULCER, CHRONIC		1 (2%)	
#GASTRIC SUBMUCOSA	(18)	(50)	(49)
GRANULOMA, FOREIGN BODY	1 (6%)		
#PEYERS PATCH	(19)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(19)	(50)	(49)
INFLAMMATION, CHRONIC	11 (58%)	32 (64%)	34 (69%)
NEPHROPATHY		2 (4%)	
#KIDNEY/TUBULE	(19)	(50)	(49)
NEPHROPATHY		1 (2%)	
#URINARY BLADDER	(18)	(49)	(46)
INFLAMMATION, NOS			1 (2%)
ULCER, FOCAL			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(47)	(48)
CYST, NOS		1 (2%)	1 (2%)
#ADRENAL CORTEX	(19)	(50)	(49)
CONGESTION, NOS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE		1 (2%)	
ATROPHY, FOCAL	1 (5%)		
HYPERPLASIA, NODULAR	1 (5%)		
#THYROID	(19)	(50)	(50)
CYST, NOS			1 (2%)
COLLOID CYST			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(50)	(50)
HEMORRHAGE		1 (2%)	
METAPLASIA, SQUAMOUS			1 (2%)
*PREPUTIAL GLAND	(19)	(50)	(50)
DILATATION, NOS		1 (2%)	
CYST, NOS		1 (2%)	
ABSCESS, NOS			1 (2%)
#PROSTATE	(14)	(45)	(43)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (7%)	3 (7%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE		3 (7%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	2 (14%)	2 (4%)	1 (2%)
#TESTIS	(19)	(50)	(49)
GRANULOMA, SPERMATIC	1 (5%)	1 (2%)	
ATROPHY, NOS			1 (2%)
*VAS DEFERENS	(19)	(50)	(50)
INFLAMMATION, CHRONIC	1 (5%)		
NERVOUS SYSTEM			
*CHOROID PLEXUS	(19)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(19)	(50)	(50)
CATARACT	5 (26%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*EYE/CHOROID	(19)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE	1 (5%)		
*EYE/CILIARY BODY	(19)	(50)	(50)
INFLAMMATION, CHRONIC	1 (5%)		
*EYE/IRIS	(19)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE	1 (5%)		
INFLAMMATION, ACUTE/CHRONIC	2 (11%)		
INFLAMMATION, CHRONIC	1 (5%)		
*EYE/RETINA	(19)	(50)	(50)
DEGENERATION, NOS	2 (11%)		
ATROPHY, DIFFUSE	3 (16%)		
MUSCULOSKELETAL SYSTEM			
*FEMUR	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(19)	(50)	(50)
NECROSIS, FAT		2 (4%)	
*PERITONEUM	(19)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
*PLEURA	(19)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
*EPICARDIUM	(19)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
*MESENTERY	(19)	(50)	(50)
STEATITIS			1 (2%)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY	1		
AUTO/NECROPSY/HISTO PERF			1

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(20)	(50)	(49)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			5 (10%)
INFLAMMATION, CHRONIC FOCAL	1 (5%)		1 (2%)
#LUNG	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL		2 (4%)	5 (10%)
PNEUMONIA, ASPIRATION	1 (5%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	1 (5%)	8 (16%)	5 (10%)
INFLAMMATION, CHRONIC FOCAL			2 (4%)
BRONCHOPNEUMONIA CHRONIC SUPPURA			1 (2%)
GRANULOMA, FOREIGN BODY			2 (4%)
HISTIOCYTOSIS		2 (4%)	2 (4%)
#LUNG/ALVEOLI	(20)	(50)	(50)
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#SPLEEN	(20)	(48)	(50)
HEMOSIDEROSIS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIESIS	1 (5%)	2 (4%)	1 (2%)
#MEDIASTINAL L.NODE	(20)	(50)	(49)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
#THYMUS	(19)	(40)	(46)
HEMORRHAGE			1 (2%)
ATROPHY, NOS		1 (3%)	1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL	4 (20%)	1 (2%)	12 (24%)
FIBROSIS			5 (10%)
FIBROSIS, FOCAL	1 (5%)	3 (6%)	4 (8%)
FIBROSIS, MULTIFOCAL	8 (40%)	32 (64%)	7 (14%)
FIBROSIS, DIFFUSE		1 (2%)	
DEGENERATION, NOS			3 (6%)
*PULMONARY ARTERY	(20)	(50)	(50)
MINERALIZATION	3 (15%)	1 (2%)	1 (2%)
MEDIAL CALCIFICATION			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(49)	(49)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, ACUTE DIFFUSE	1 (5%)	2 (4%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	5 (25%)	21 (43%)	17 (35%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE		4 (8%)	5 (10%)
ATROPHY, FOCAL		1 (2%)	
#SALIVARY SEROUS GLAN	(20)	(49)	(49)
INFLAMMATION, ACUTE/CHRONIC			7 (14%)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
#LIVER	(20)	(49)	(50)
INFLAMMATION, NECROTIZING	1 (5%)		
INFLAMMATION, ACUTE NECROTIZING	1 (5%)		
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
INFLAMMATION, CHRONIC FOCAL		2 (4%)	3 (6%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CHOLANGIOFIBROSIS	1 (5%)	1 (2%)	
HEPATITIS, TOXIC		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	2 (10%)		
BASOPHILIC CYTO CHANGE		1 (2%)	3 (6%)
HYPERPLASIA, FOCAL	1 (5%)		
HEMATOPOIESIS			1 (2%)
#LIVER/PERIPORTAL	(20)	(49)	(50)
INFLAMMATION, MULTIFOCAL	1 (5%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
#BILE DUCT	(20)	(49)	(50)
HYPERPLASIA, NOS	1 (5%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	3 (15%)	12 (24%)	9 (18%)
#PANCREAS	(19)	(50)	(48)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (5%)	5 (10%)	1 (2%)
FIBROSIS			1 (2%)
FIBROSIS, FOCAL		1 (2%)	
#PANCREATIC ACINUS	(19)	(50)	(48)
ATROPHY, NOS			1 (2%)
#STOMACH	(20)	(50)	(48)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#GASTRIC MUCOSA	(20)	(50)	(48)
EOSINOPHILIC INFILTRATE			1 (2%)
HYPERPLASIA, PSEUDOEPITHELIOMATO			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(49)
CALCULUS, NOS		1 (2%)	
MULTILOCULAR CYST			1 (2%)
INFLAMMATION, DIFFUSE			1 (2%)
INFLAMMATION, ACUTE DIFFUSE	1 (5%)		
INFLAMMATION, CHRONIC	11 (55%)	33 (66%)	33 (67%)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
NEPHROPATHY			1 (2%)
CALCINOSIS, NOS			2 (4%)
#KIDNEY/CAPSULE	(20)	(50)	(49)
GRANULOMA, NOS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#KIDNEY/MEDULLA	(20)	(50)	(49)
MINERALIZATION			1 (2%)
#KIDNEY/PELVIS	(20)	(50)	(49)
CALCULUS, NOS		1 (2%)	
MINERALIZATION			2 (4%)
CALCINOSIS, NOS			1 (2%)
#URINARY BLADDER	(20)	(50)	(48)
CALCULUS, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL			2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(50)	(49)
CYST, NOS		1 (2%)	1 (2%)
#ADRENAL	(20)	(50)	(48)
DEGENERATION, CYSTIC		1 (2%)	
#ADRENAL CORTEX	(20)	(50)	(48)
DEGENERATION, NOS	1 (5%)		
ATROPHY, FOCAL	1 (5%)		
HYPERPLASIA, NODULAR	1 (5%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	1 (5%)		
#ADRENAL MEDULLA	(20)	(50)	(48)
HYPERPLASIA, FOCAL	1 (5%)		
#THYROID	(19)	(49)	(49)
COLLOID CYST		1 (2%)	1 (2%)
HYPERPLASIA, C-CELL	2 (11%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
ABSCESS, NOS		1 (2%)	
HYPERPLASIA, CYSTIC		1 (2%)	
HYPERPLASIA, STROMAL		2 (4%)	
EPITHELIALIZATION	1 (5%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*MAMMARY LOBULE	(20)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)		
*PREPUTIAL GLAND	(20)	(50)	(50)
HYPERPLASIA, DIFFUSE		1 (2%)	
*VAGINA	(20)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#UTERUS	(19)	(50)	(49)
DECIDUAL AITEPATION, NOS	1 (5%)	1 (2%)	1 (2%)
#UTERUS/ENDOMETRIUM	(19)	(50)	(49)
CYST, NOS		3 (6%)	1 (2%)
HYPERPLASIA, STROMAL			1 (2%)
*OVARY	(20)	(50)	(47)
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS			5 (11%)
CORPUS LUTEUM CYST			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(50)
INFLAMMATION, FOCAL	1 (5%)		
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
CATARACT	2 (10%)		
*EYE/CHOROID	(20)	(50)	(50)
INFLAMMATION, CHRONIC	1 (5%)		
*EYE/IRIS	(20)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (5%)		
*EYE/RETINA	(20)	(50)	(50)
DEGENERATION, NOS	3 (15%)		
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
NECROSIS, FAT		2 (4%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED p,p'-ETHYL-DDD IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
GRANULATION, TISSUE		1 (2%)	
*SUBCUT TISSUE	(19)	(50)	(50)
ABSCESS, NOS	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(49)
HEMORRHAGE	1 (5%)		
BRONCHOPNEUMONIA, FOCAL	1 (5%)		
INFLAMMATION, INTERSTITIAL	1 (5%)	1 (2%)	
PNEUMONIA, ASPIRATION		1 (2%)	
HEMOSIDEROSIS		1 (2%)	
HISTIOCYTOSIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(18)	(50)	(49)
HYPERPLASIA, HEMATOPOIETIC	1 (6%)		
HYPERPLASIA, ERYTHROID	1 (6%)		
#SPLEEN	(19)	(48)	(47)
THROMBOSIS, NOS		1 (2%)	1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS			1 (2%)
INFARCT, FOCAL			1 (2%)
HEMATOPOIESIS	1 (5%)	1 (2%)	
#SPLENIC FOLLICLES	(19)	(48)	(47)
ATROPHY, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(18)	(45)	(47)
CYST, NOS		1 (2%)	
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HISTIOCYTOSIS			1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIESIS	1 (6%)	1 (2%)	3 (6%)
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(19)	(47)	(50)
THROMBUS, MURAL		1 (2%)	
#MYOCARDIUM	(19)	(47)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
SCAR		1 (2%)	
DEGENERATION, NOS			1 (2%)
#CARDIAC VALVE	(19)	(47)	(50)
INFLAMMATION, FOCAL		1 (2%)	
*AORTA	(19)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
*HEPATIC VEIN	(19)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(50)
THROMBOSIS, NOS		1 (2%)	
INFLAMMATION, MULTIFOCAL			1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (5%)		
PELIOSIS HEPATIS	1 (5%)	1 (2%)	2 (4%)
NECROSIS, NOS		1 (2%)	
NECROSIS, COAGULATIVE			1 (2%)
CLEAR-CELL CHANGE			2 (4%)
HYPERPLASIA, NODULAR		1 (2%)	
HYPERPLASIA, NOS	1 (5%)	2 (4%)	2 (4%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, DIFFUSE		1 (2%)	
HEMATOPOIESIS	1 (5%)	1 (2%)	
#HEPATIC CAPSULE	(19)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
#PANCREAS	(17)	(46)	(48)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#STOMACH	(19)	(49)	(49)
ABSCESS, NOS			1 (2%)
ACANTHOSIS	1 (5%)		
#PEYERS PATCH	(18)	(43)	(49)
HYPERPLASIA, NOS	1 (6%)		
URINARY SYSTEM			
#KIDNEY	(19)	(49)	(50)
INFLAMMATION, INTERSTITIAL	2 (11%)	1 (2%)	3 (6%)
GLOMERULONEPHRITIS, CHRONIC			1 (2%)
NEPHROSIS, NOS		1 (2%)	
GLOMERULOSCLEROSIS, NOS			1 (2%)
#KIDNEY/TUBULE	(19)	(49)	(50)
DEGENERATION, NOS			1 (2%)
ENDOCRINE SYSTEM			
#THYROID	(18)	(47)	(50)
THYROGLOSSAL DUCT CYST		1 (2%)	
ULTIMOBRANCHIAL CYST			1 (2%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(19)	(50)	(50)
DILATATION/DUCTS			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
#PROSTATE	(16)	(43)	(39)
INFLAMMATION, INTERSTITIAL			1 (3%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*SEMINAL VESICLE	(19)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
*EPIDIDYMIS	(19)	(50)	(50)
ABSCESS, CHRONIC	1 (5%)		
NERVOUS SYSTEM			
*CEREBELLUM	(18)	(48)	(47)
HEMORRHAGE			1 (2%)
*MEDULLA OBLONGATA	(18)	(48)	(47)
HEMORRHAGE			1 (2%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(19)	(50)	(50)
CYST, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(19)	(50)	(50)
NECROSIS, FAT	1 (5%)		
*PLEURA	(19)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*MESENTERY	(19)	(50)	(50)
STEATITIS			1 (2%)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
OMENTUM			
STEATITIS	1		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPOFTED	1	4	7
ANIMAL MISSING/NO NECPOPSY	1		

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICPOSCOPICALLY
* NUMBER OF ANIMALS NECPOPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED p, p'-ETHYL-DDD IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		3	1
ANIMALS NECROPSIED	20	47	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	47	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(18)	(47)	(47)
INFLAMMATION, INTERSTITIAL	2 (11%)	1 (2%)	1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC	1 (6%)		1 (2%)
HISTIOCYTOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIETIC SYSTEM			
*BLOOD	(20)	(47)	(49)
LYMPHOPENIA		1 (2%)	
#BONE MARROW	(20)	(45)	(47)
HYPERPLASIA, NOS			1 (2%)
*SPLEEN	(19)	(46)	(46)
THROMBOSIS, NOS			1 (2%)
SCLEROSIS			1 (2%)
NECROSIS, FAT			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)		
HEMATOPOIESIS			1 (2%)
#MESENTERIC L. NODE	(20)	(46)	(46)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(18)	(43)	(46)
INFLAMMATION, CHRONIC FOCAL	1 (6%)		
#LIVER	(19)	(47)	(47)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING	1 (5%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC NECROTIZIN			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
PELIOSIS HEPATIS			2 (4%)
NECROSIS, FOCAL			1 (2%)
NECROSIS, COAGULATIVE			1 (2%)
METAMORPHOSIS FATTY		1 (2%)	
BASOPHILIC CYTO CHANGE		1 (2%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	2 (4%)
#PANCREAS	(19)	(45)	(46)
CYSTIC DUCTS			1 (2%)
HEMORRHAGE			1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (5%)		2 (4%)
NECROSIS, FAT	1 (5%)		
ATROPHY, NOS			1 (2%)
#ILEUM	(17)	(42)	(44)
ULCER, FOCAL			1 (2%)
#COLON	(20)	(44)	(48)
INFLAMMATION, FOCAL		1 (2%)	
*RECTUM	(20)	(47)	(49)
ABSCESS, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(47)	(47)
CYST, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL	2 (10%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
NEPHROSIS, NOS		1 (2%)	2 (4%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
GLOMERULOSCLEROSIS, NOS		1 (2%)	
#KIDNEY/TUBULE	(20)	(47)	(47)
DEGENERATION, NOS		1 (2%)	
#URINARY BLADDER	(18)	(42)	(45)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
ENDOCRINE SYSTEM			
#THYROID	(18)	(41)	(46)
THYROGLOSSAL DUCT CYST			1 (2%)
ULTIMOBRANCHIAL CYST	1 (6%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(47)	(49)
ABSCESS, NOS		1 (2%)	
#UTERUS	(19)	(45)	(42)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#UTERUS/ENDOMETRIUM	(19)	(45)	(42)
CYST, NOS		14 (31%)	13 (31%)
#UTERUS/MYOMETRIUM	(19)	(45)	(42)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(18)	(44)	(48)
INFLAMMATION, NOS		2 (5%)	
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, MULTIFOCAL		1 (2%)	
PERIVASCULITIS		3 (7%)	
*CHOROID PLEXUS	(20)	(47)	(49)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, MULTIFOCAL		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
#BRAIN	(18)	(44)	(48)
INFLAMMATION, FOCAL			3 (6%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(20)	(47)	(49)
CYST, NOS		1 (2%)	
INFLAMMATION, FOCAL			1 (2%)
*HARDERIAN GLAND	(20)	(47)	(49)
DILATATION, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(20)	(47)	(49)
PERIVASCULITIS		1 (2%)	
*ABDOMINAL CAVITY	(20)	(47)	(49)
CYST, NOS		1 (2%)	
NECROSIS, FAT	1 (5%)		1 (2%)
*PELVIS	(20)	(47)	(49)
NECROSIS, FAT			1 (2%)
*PLEURA	(20)	(47)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
*MESENTERY	(20)	(47)	(49)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(47)	(49)
HEMATOPOIESIS	1 (5%)	1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	6	4	2

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL MISSING/NO NECROPSY		3	1
AUTO/NECROPSY/HISTO PERF			1
AUTO/NECROPSY/NO HISTO			1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED p,p'-ETHYL-DDD IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered p,p'-Ethyl-DDD in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System:			
Squamous-cell Carcinoma of the Skin (b)	0/19 (0)	1/50 (2)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.021	0.238
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	87	87
Hematopoietic System:			
Neoplasm, NOS (b)	4/19 (21)	11/50 (22)	10/50 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.045	0.950
Lower Limit		0.367	0.324
Upper Limit		4.095	3.782
Weeks to First Observed Tumor	91	79	84

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	0/19 (0)	1/47 (2)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.022	0.248
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105
Pituitary: Chromophobe Adenoma (b)	3/19 (16)	7/47 (15)	2/48 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.943	0.264
Lower Limit		0.250	0.024
Upper Limit		5.246	2.160
Weeks to First Observed Tumor	105	105	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Adenoma, NOS (b)	3/19 (16)	8/47 (17)	5/48 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.078	0.660
Lower Limit		0.301	0.147
Upper Limit		5.847	3.959
Weeks to First Observed Tumor	105	105	100
Adrenal: Pheochromocytoma (b)	2/19 (11)	5/50 (10)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.950	0.582
Lower Limit		0.176	0.074
Upper Limit		9.498	6.640
Weeks to First Observed Tumor	105	105	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma (b)	2/19 (11)	7/50 (14)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.330	1.140
Lower Limit		0.289	0.232
Upper Limit		12.469	10.985
Weeks to First Observed Tumor	105	105	105
Testis: Interstitial-cell Tumor (b)	17/19 (89)	35/50 (70)	35/49 (71)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.782	0.789
Lower Limit		0.675	0.688
Upper Limit		1.097	1.115
Weeks to First Observed Tumor	74	87	100

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

(a) Dosed groups received 3,500 or 7,000 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is 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 when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

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

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

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

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered p,p'-Ethyl-DDD in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System:			
Squamous-cell Carcinoma of the Skin (b)	2/20 (10)	0/50 (0)	0/50 (0)
P Values (c,d)	P = 0.024 (N)	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.042		
Relative Risk (f)		0.000	0.000
Lower Risk		0.000	0.000
Upper Limit		1.345	1.345
Weeks to First Observed Tumor	100	--	--
Hematopoietic System:			
Neoplasm, NOS (b)	3/20 (15)	8/50 (16)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.067	0.800
Lower Limit		0.295	0.195
Upper Limit		5.813	4.615
Weeks to First Observed Tumor	105	93	70

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe			
Adenoma or Adenoma, NOS (b)	5/20 (25)	13/50 (26)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.040	0.490
Lower Limit		0.416	0.146
Upper Limit		3.341	1.842
Weeks to First Observed Tumor	92	105	105
Adrenal: Cortical			
Adenoma (b)	3/20 (15)	0/50 (0)	0/48 (6)
P Values (c,d)	P = 0.005 (N)	P = 0.021 (N)	P = 0.023 (N)
Departure from Linear Trend (e)	P = 0.014		
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		0.659	0.686
Weeks to First Observed Tumor	92	--	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma (b)	2/19 (11)	4/49 (8)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.776	0.776
Lower Limit		0.125	0.125
Upper Limit		8.165	8.165
Weeks to First Observed Tumor	105	105	105
Uterus: Endometrial Stromal Polyp (b)	0/19 (0)	5/50 (10)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.501	0.243
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

(a) Dosed groups received 3,500 or 7,000 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is 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 when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

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

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

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

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED p,p'-ETHYL-DDD IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered p,p'-Ethyl-DDD in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	0/19 (0)	4/50 (8)	9/49 (18)
P Values (c,d)	P = 0.017	N.S.	P = 0.042
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.368	1.066
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	100	105
Lung: Alveolar/Bronchiolar Carcinoma (b)	4/19 (21)	1/50 (2)	3/49 (6)
P Values (c,d)	N.S.	P = 0.018 (N)	N.S.
Departure from Linear Trend (e)	P = 0.018		
Relative Risk (f)		0.095	0.291
Lower Limit		0.002	0.048
Upper Limit		0.895	1.587
Weeks to First Observed Tumor	105	103	105

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	4/19 (21)	5/50 (10)	12/49 (24)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.475	1.163
Lower Limit		0.118	0.419
Upper Limit		2.201	4.490
Weeks to First Observed Tumor	98	66	104
Hematopoietic System: Lymphoma (b)	2/19 (11)	9/50 (18)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.710	0.380
Lower Limit		0.407	0.030
Upper Limit		15.426	5.009
Weeks to First Observed Tumor	98	66	104

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	7/19 (37)	19/49 (39)	20/50 (40)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.052	1.086
Lower Limit		0.530	0.552
Upper Limit		2.547	2.611
Weeks to First Observed Tumor	94	76	28
Liver: Hepatocellular Carcinoma, Adenoma, or Neoplastic Nodule (b)	8/19 (42)	27/49 (55)	25/50 (50)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.309	1.188
Lower Limit		0.740	0.662
Upper Limit		2.765	2.553
Weeks to First Observed Tumor	94	76	28

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

(a) Dosed groups received 2,500 or 5,000 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is 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 when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

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

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

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered p,p'-Ethyl-DDD in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	0/18 (0)	3/47 (6)	1/47 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.241	0.021
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105
Hematopoietic System: Malignant Lymphoma or Lymphocytic Leukemia (b)	4/20 (20)	9/47 (19)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.957	0.612
Lower Limit		0.313	0.168
Upper Limit		3.880	2.710
Weeks to First Observed Tumor	80	86	101

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	1/19 (5)	2/47 (4)	10/47 (21)
P Values (c,d)	P = 0.013	N.S.	N.S.
Relative Risk (f)		0.809	4.043
Lower Limit		0.046	0.653
Upper Limit		46.702	170.880
Weeks to First Observed Tumor	105	105	105
Liver: Hepatocellular Carcinoma or Adenoma (b)	1/19 (5)	3/47 (6)	11/47 (23)
P Values (c,d)	P = 0.011	N.S.	N.S.
Relative Risk (f)		1.213	4.447
Lower Limit		0.107	0.735
Upper Limit		62.303	186.311
Weeks to First Observed Tumor	105	105	105

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	1/18 (6)	4/42 (10)	5/46 (11)
P Values (c,d)	N S.	N.S.	N.S.
Relative Risk (f)		1.714	1.957
Lower Limit		0.190	0.246
Upper Limit		82.316	90.394
Weeks to First Observed Tumor	105	105	105
All Sites: Hemangioma or Hemangiosarcoma (b)	0/20 (0)	3/47 (6)	0/49 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.044		
Relative Risk (f)		Infinite	--
Lower Limit		0.266	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	95	--

Table F2. Analysis of the Incidence of Primary Tumors in Female Mice Administered p,p'-Ethyl-DDD in the Diet (a)

(continued)

(a) Dosed groups received time-weighted average doses of 2,828 or 6,200 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is 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 when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

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

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

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

Review of the Bioassay of *p,p'*-Ethyl DDD* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

October 25, 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, and State health officials. 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 *p,p'*-Ethyl DDD for carcinogenicity.

The reviewer for the report on the bioassay of *p,p'*-Ethyl DDD agreed with the conclusion in the report that the compound was not carcinogenic in either sex of treated rats or male mice. The increased incidence of liver neoplasms in treated female mice suggested a possible carcinogenic effect in this sex and strain. After briefly describing the experimental design, the reviewer said that there were no unusual highlights or other significant effects upon which to comment. There was no objection to a recommendation that the report on the bioassay of *p,p'*-Ethyl DDD be accepted as written.

Clearinghouse Members present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Kenneth Wilcox, Michigan State Health Department

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

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