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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
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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

CONTRIBUTORS: This bioassay of phthalic anhydride 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 the management of the facilities. Mr. A. Butler performed the computer services. The histopathology of early deaths was performed by Drs. B. Ulland, R. Schueler, R. Ball, and R. Cardy. The lesions of the rats and mice were reviewed by Dr. D. G. Fairchild (1), and the diagnoses included in this report represent his interpretations.

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 analyses were reviewed and approved by Dr. W. Lijinski (1).

This report was prepared by Tracor Jitco (4) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting 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.

The following scientists at NCI (2) 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. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of phthalic anhydride 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 phthalic anhydride at one of two doses, either 7,500 or 15,000 ppm, for 105 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at the end of the period of administration of the test chemical.

Groups of 50 mice of each sex were administered the test chemical at one of two doses, initially either 25,000 or 50,000 ppm, for 32 weeks. Because of excessive depressions in the amount of body weight gained in the dosed groups, the doses for the males were then reduced to 12,500 and 25,000 ppm, respectively, and the doses for the females were reduced to 6,250 and 12,500 ppm. Administration of the test chemical at the lowered doses was continued for 72 weeks. The time-weighted average doses for the males were either 16,346 or 32,692 ppm, and those for the females were either 12,019 or 24,038 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at the end of the period of administration of the test chemical.

Mean body weights of the high-dose male rats and of the low- and high-dose mice of each sex were lower than those of the corresponding controls; mean body weights of the low-dose male rats and of both the low- and high-dose female rats were essentially unaffected by administration of the test chemical. Depressions in the amount of body weight gained in the male and female mice were dose related throughout the bioassay. Survivals of the rats and mice were not affected by administration of the test chemical.

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

It is concluded that under the conditions of this bioassay, phthalic anhydride was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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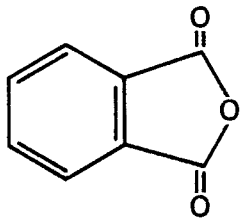
I. INTRODUCTION



Phthalic anhydride

Phthalic anhydride (CAS 85-44-9; NCI C03601) is an important chemical intermediate in the plastics industry. From it are derived numerous phthalate esters that function as plasticizers in synthetic resins (Knuth, 1973; Noller, 1966). Phthalic anhydride itself is used as a monomer for synthetic resins such as glyptal, the alkyd resins, and the polyester resins (Noller, 1966). Phthalic anhydride is a precursor of anthraquinone, phthalein, rhodamine, phthalocyanine, fluorescein, and xanthene dyes (Towle et al., 1968; Noller, 1966). Reaction of phthalic anhydride with ammonia yields phthalimide, a useful reagent in the synthesis of primary amines, the agricultural fungicide phaltan, and thalidomide (Noller, 1966). Other reactions yield phenolphthalein, benzoic acid, phthalylsulfathiazole (an intestinal antimicrobial agent), and terephthalic acid (Towle et al., 1968; Noller, 1966).

The oral LD_{50} of phthalic anhydride for rats (strains not specified) has been reported as 800-1,600 mg/kg body weight (Fassett, 1964) and as 4,020 mg/kg body weight (NIOSH, 1976); the

LD_{50} of the test chemical for white mice (route of administration and strain of mouse not specified) has been reported as 2,210 mg/kg body weight (Zhilova and Kasparov, 1968). Vapors of phthalic anhydride administered to rats over a period of 12 days caused irritation of mucous membranes of the nasal cavity and the bronchi (Policard et al., 1949). Persons in factories manufacturing phthalic acid and phthalic anhydride can develop conjunctivitis and also irritation of the skin and of mucous membranes of the respiratory tract (Baader, 1955; Merlevede and Elskens, 1957).

Phthalic anhydride was studied in the Carcinogenesis Testing Program because of its high volume of production. Domestic production of phthalic anhydride rose from 458 million pounds annually in 1963 (Noller, 1966) to 902 million pounds in 1976 (United States International Trade Commission, 1977a), with imports accounting for an additional 31 million pounds in the latter year (United States International Trade Commission, 1977b). There is evidence that human exposure to phthalic anhydride may occur not only in the manufacture of phthalate-derived products but also in the use of plastics from which phthalate plasticizers are leached, specifically certain medical plastics such as blood bags, plastic syringes, and

plastic tubing (Guess et al., 1967). Furthermore, some phthalate esters have been identified as environmental pollutants (Giam et al., 1978).

II. MATERIALS AND METHODS

A. Chemical

Phthalic anhydride was obtained from Koppers Co. as a white, granular solid. The material had a melting point of 131°C (literature: 130.8°C). Elemental analysis showed 64.8% carbon, 2.7% hydrogen, and 0.0% nitrogen (theoretical: 64.9%, 2.7%, and 0.0%). Its infrared spectrum was consistent with its chemical structure, and identical with that of an authentic standard. The purity of the material was estimated by high-pressure liquid chromatography to be 98.8%, with one impurity.

B. Dietary Preparation

Test diets containing phthalic anhydride were prepared fresh every 1 to 1-1/2 weeks in 6- to 12-kg batches at appropriate doses. A known weight of the chemical was first mixed with an equal weight of autoclaved Wayne® Sterilizable Lab Meal with 4% fat (Allied Mills, Inc., Chicago, Ill.) using a mortar and pestle. The mixing was continued with second and third additions of feed, and final mixing was performed with the remaining quantity of feed for a

minimum of 15 minutes in a Patterson-Kelly twin-shell blender. The diets were routinely stored at 5°C until used. Analyses by the Frederick Cancer Research Center indicated that when phthalic anhydride was mixed with Lab Meal at a concentration of 15,000 ppm and stored at room temperature for 2 weeks, the loss was 2.59% (372 ppm) per day.

C. Animals

Male and female F344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, from the NCI Frederick Cancer Research Center animal farm, Frederick, Maryland as 4-week-old weanlings, all within 3 days of the same age. 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 a given species and sex. For use in the chronic study, the male rats were required to weigh 90 to 105 g, averaging at least 100 g; the female rats, 80 to 95 g, averaging at least 90 g; the male mice, 18 to 22 g, averaging at least 19.5 g; and the 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. The cages 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 supplied 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 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 a temperature of 22 to 24°C and a relative humidity of 45 to 55%. 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. The rate of movement allowed 15 changes of room air 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.

Both control and dosed rats were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 95-80-7) 2,4-diaminotoluene
(CAS 95-53-4) o-toluidine hydrochloride

Both control and dosed mice were housed in the same room as mice on feeding studies of the following chemicals:

(CAS 103-33-3) azobenzene
(CAS 72-56-0) p,p'-ethyl-DDD
(CAS 20941-65-5) ethyl tellurac
(CAS 298-00-0) methyl parathion
(CAS 51-03-6) piperonyl butoxide
(CAS 88-06-2) 2,4,6-trichlorophenol
(CAS 128-66-5) C. I. vat yellow 4

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of phthalic anhydride, on the basis of which two concentrations (hereinafter referred to as "low" and "high" doses) were selected for administration in the chronic studies. Groups of five rats and five mice of each sex were administered feed containing phthalic anhydride 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 7 weeks, followed by 1 week of further observation. Each animal was weighed twice per week. Table 1 shows the doses used and the mean body weights of dosed animals at week 7 expressed as percentages of the mean weights of the controls; no animals died during the subchronic tests.

Table 1. Phthalic Anhydride Subchronic Feeding Studies in Rats and Mice

Dose (ppm)	Mean Weight at Week 7 as Percent of Control	
	Male	Female
RATS		
6,200	90	95
12,500	95	93
25,000	92	91
50,000	74	76
MICE		
6,200	114	100
12,500	113	99
25,000	111	101
50,000	104	99

At the end of the subchronic studies, all animals were killed using CO_2 inhalation and necropsied. The lowest dose at which histopathologic findings were observed in male and female rats was 25,000 ppm. At this dose, trace amounts of centrilobular cytoplasmic vacuolation were seen in the livers of four males; however, tissues were essentially normal in both males and females at 50,000 ppm. Tissues were essentially normal also in male and female mice at 50,000 ppm.

Ten percent depression in body weight was taken as the major criterion for the 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 the 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 these data, the low and high doses for the chronic studies using male and female rats were set at 7,500 and 15,000 ppm. For mice, the low dose was set at 25,000 and the high dose at 50,000 ppm, the maximum amount allowed for use in the Carcinogenesis Testing Program.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 2 and 3. Because of excessive depression of the amount of body weight gained in the dosed mice, doses for the low- and high-dose groups were reduced after week 32 as indicated.

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 necropsied. Necropsies were also performed on all animals found dead, unless precluded by autolysis or severe cannibalization.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with

Table 2. Phthalic Anhydride Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals(a)	Phthalic Anhydride in Diet(b) (ppm)	Time on Study (weeks)
Male			
Matched-Control	20	0	105
Low-Dose	50	7,500	105
High-Dose	50	15,000	105
Female			
Matched-Control	20	0	105
Low-Dose	50	7,500	105
High-Dose	50	15,000	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 3. Phthalic Anhydride Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals(a)	Phthalic Anhydride in Diet(b) (ppm)	Time on Study (weeks)	Time-Weighted Average Dose(c) (ppm)
Male				
Matched-Control	20	0	104	
Low-Dose	50	25,000	32	
		12,500	72	16,346
High-Dose	50	50,000	32	
		25,000	72	32,692
Female				
Matched-Control	20	0	104	
Low-Dose	50	25,000	32	12,019
		6,250	72	
High-Dose	50	50,000	32	
		12,500	72	24,038

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

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, pancreatic islets, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum and cerebellum), and all tissue masses. Peripheral blood smears also were made for all animals, whenever possible.

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

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay

Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the appropriate statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox 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)

The mean body weights of the high-dose male rats were lower than those of the corresponding controls from week 13 to the end of the bioassay; mean body weights of the low-dose males and both the low- and high-dose females were essentially unaffected by administration of the test chemical (figure 1). Arched back, rough hair coat, ulceration, and corneal opacity occurred only in dosed groups, but at low incidences. Wasting and tissue masses were common to the dosed and control groups. Fluctuation 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 (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered phthalic anhydride 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

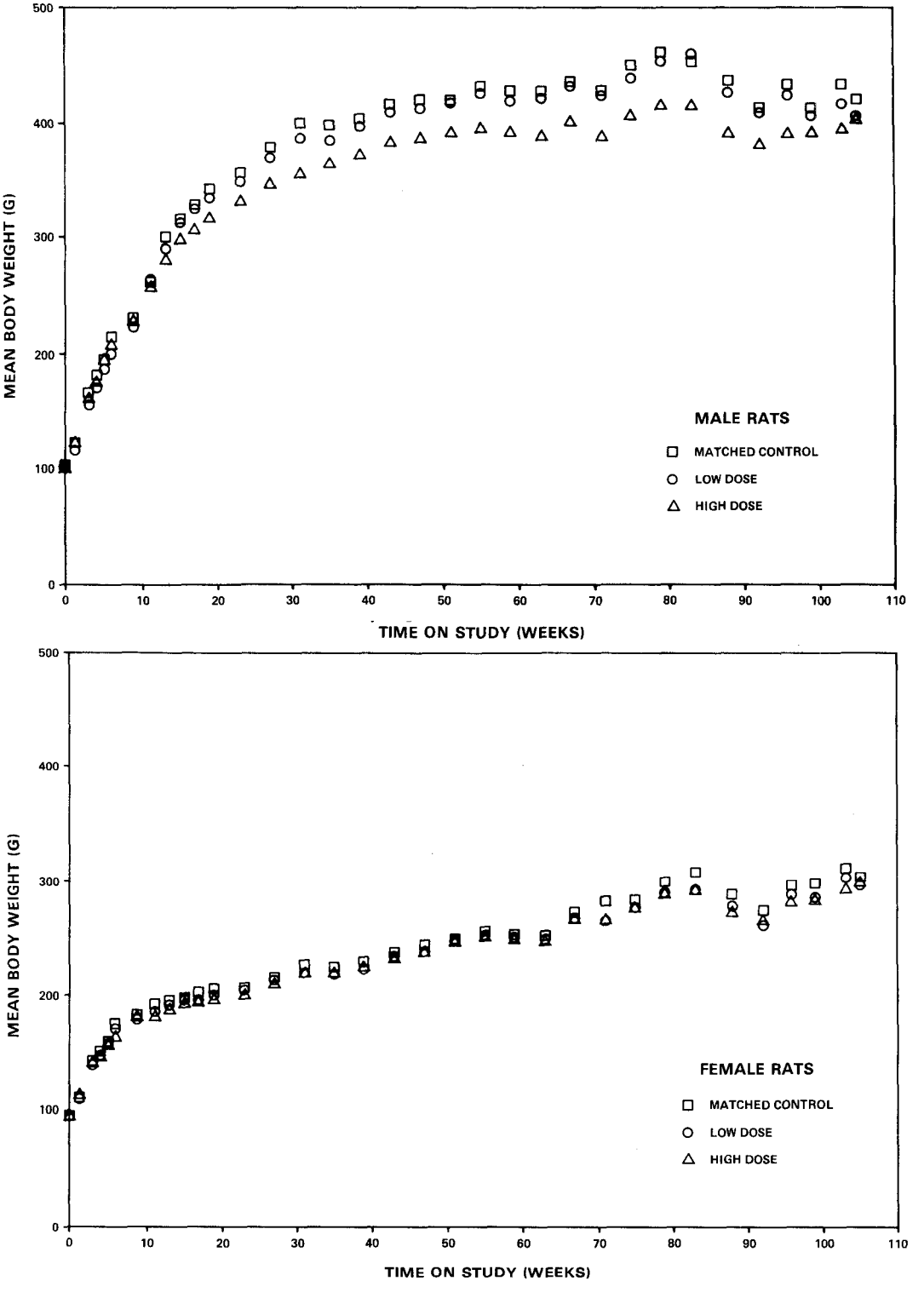


Figure 1. Growth Curves for Rats Administered Phthalic Anhydride in the Diet

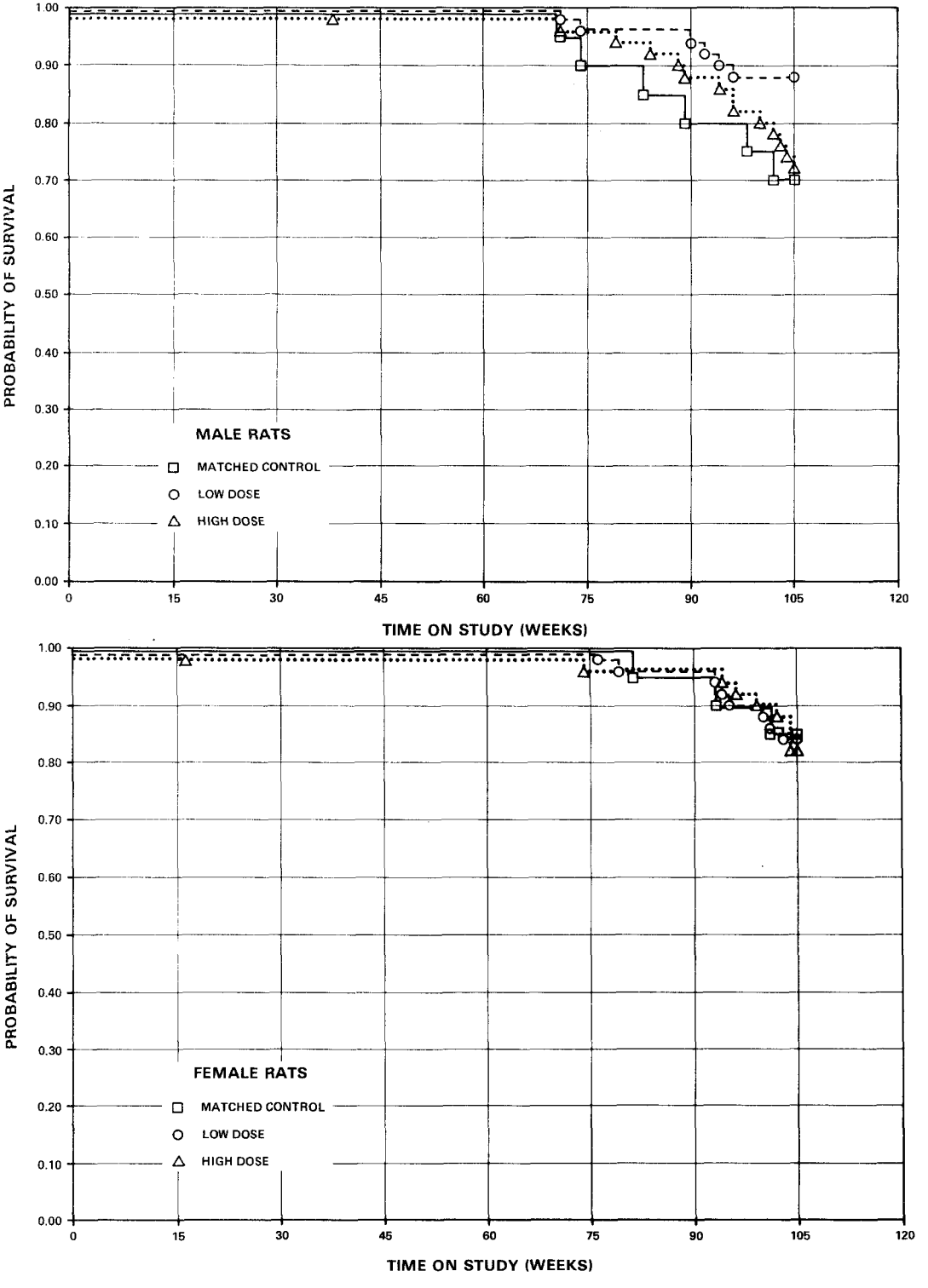


Figure 2. Survival Curves for Rats Administered Phthalic Anhydride in the Diet

in either sex. In male rats, an indicated departure from linear trend (P = 0.037) is observed, due to the earlier mortality of the control group when compared with that of either the high- or low-dose group. The results of the Cox test applied to any two of the three groups show no statistically significant difference between groups of any pair.

In male rats, 36/50 (72%) of the high-dose group, 44/50 (88%) of the low-dose group, and 14/20 (70%) of the control group lived to the end of the bioassay. In females, 41/50 (82%) of the high-dose group, 42/50 (84%) of the low-dose group, and 17/20 (85%) of the 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.

By inspection, there appeared to be no difference between the dosed and control groups in frequency or distribution of neoplasms, except for malignant lymphoma in the female rats. The incidence of malignant lymphoma in the control females was 1/20; in low-dose females, 11/50; in high-dose females, 4/50. Due to the high and fluctuating incidence of this type of malignant lymphoma in control F344 rats, the apparent differences in incidences of the tumor in the dosed and control groups were not considered to be compound related.

Severe chronic inflammatory, degenerative, or proliferative lesions frequently seen in aged rats occurred with approximately equal frequency and severity in the dosed and control groups of animals.

Based on the histopathologic examination, there was no conclusive evidence for the carcinogenicity of phthalic anhydride 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 female rats, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of alveolar/bronchiolar adenomas is significant (P = 0.020), but the results of the Fisher exact test are not significant. The results of the statistical tests on the incidences of alveolar/bronchiolar carcinomas and of alveolar/bronchiolar adenomas or carcinomas are not significant. In male rats, the results of the statistical tests on the incidences of lung tumors are not significant.

A departure from linear trend (P = 0.019) is found in the incidence of lymphoma in female rats, due to the relatively large proportion of 11/50 (22%) in the low-dose group compared with 4/50 (8%) in the high-dose group and 1/20 (5%) in the control group. The results of the Fisher exact test are not significant. Current historical records at this laboratory indicate an incidence of lymphoma in female rats of 14/285 (4.9%), and, although the majority of the control groups had incidences of less than 5%, one control group was observed to have an incidence as high as 4/20 (20%). Since the results of the Fisher exact test were not significant and since the historical data concerning lymphoma indicates the possibility of

an occasional high spontaneous rate of lymphoma, the evidence of association of the lymphomas in the dosed group of female rats with the chemical is questionable.

A significant dose-related trend (P = 0.037) in the negative direction is observed in the incidence of pheochromocytomas of the adrenal in male rats.

In each of the 95% confidence intervals for relative risk, shown in the tables, one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by phthalic anhydride, 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 throughout the bioassay, and depressions in the amount of body weight gained were dose related (figure 3). Tissue masses were observed at low incidences and were common to the dosed and control groups. Fluctuation 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 phthalic anhydride 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.

In male mice, 47/50 (94%) of the high-dose group, 37/50 (74%) of

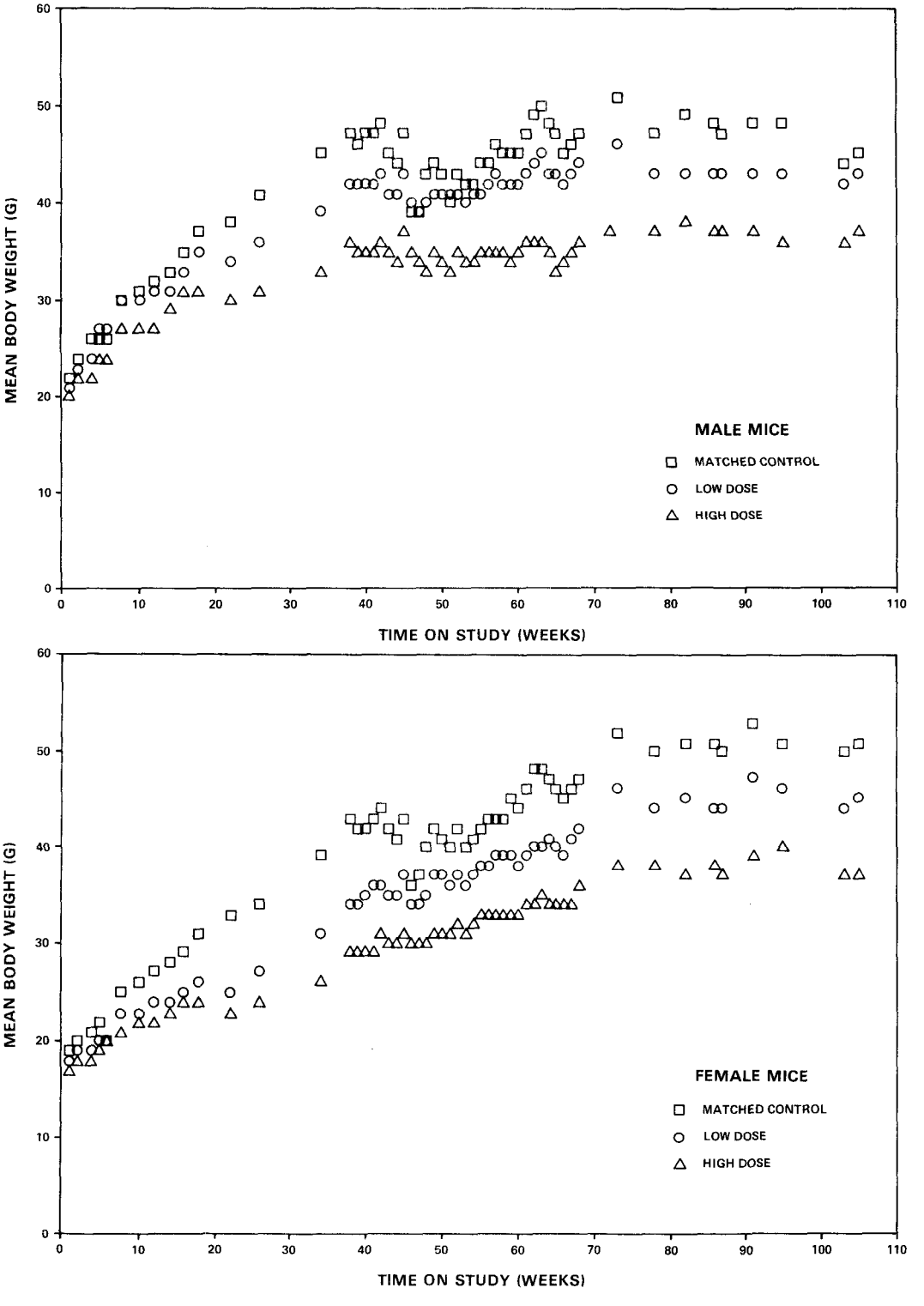


Figure 3. Growth Curves for Mice Administered Phthalic Anhydride in the Diet

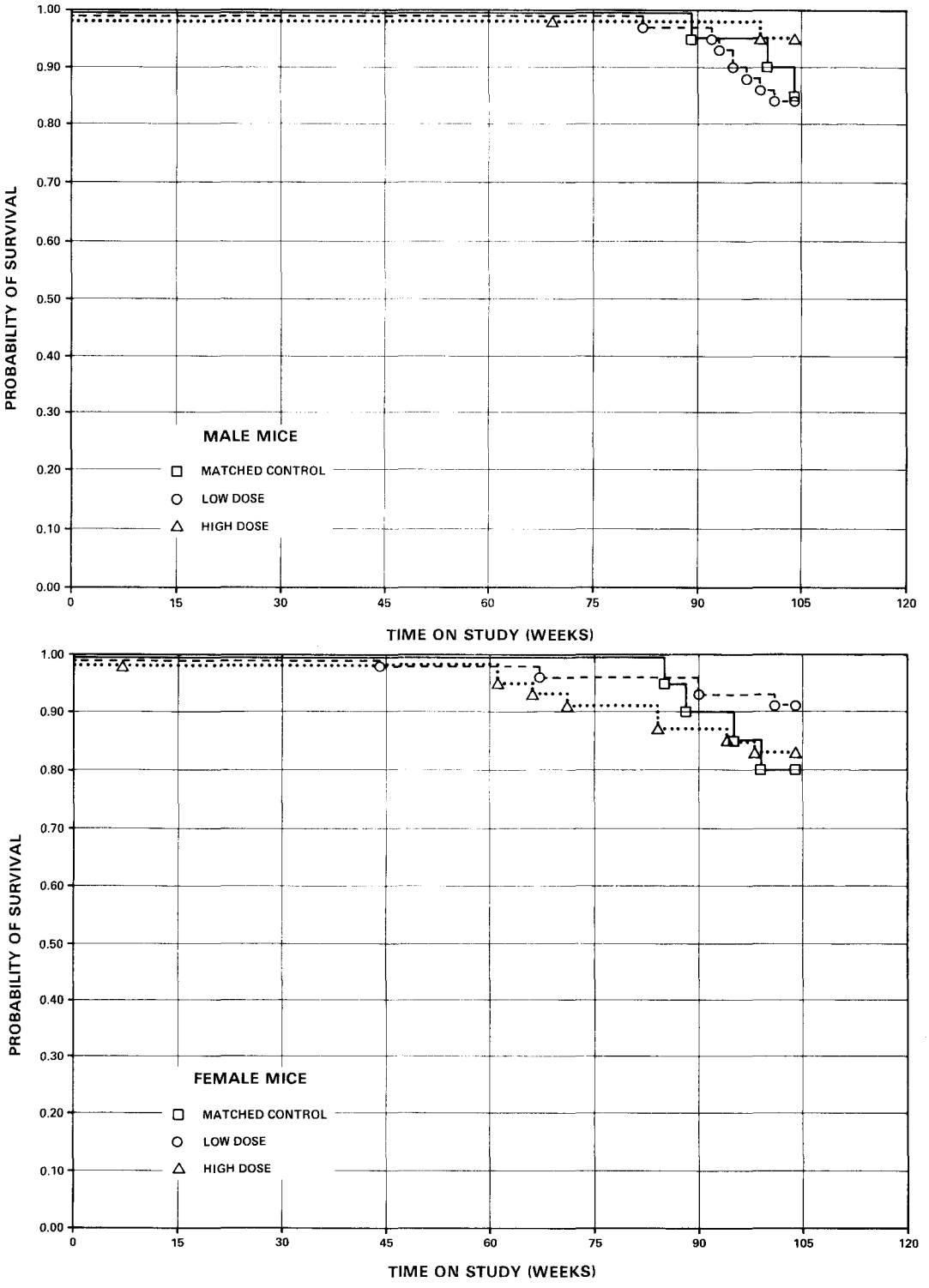


Figure 4. Survival Curves for Mice Administered Phthalic Anhydride in the Diet

the low-dose group, and 17/20 (85%) of the control group survived to the end of the bioassay. In females, 40/50 (80%) of the high-dose group, 45/50 (90%) of the low-dose group, and 16/20 (80%) of the control group survived 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.

Several chronic inflammatory, degenerative, or proliferative lesions frequently seen in aged laboratory mice occurred with approximately equal frequency and severity in the dosed and control groups of animals.

Based on the histopathologic examinations, the nature, incidence, or severity of the lesions observed provided no clear evidence of carcinogenic effect of the phthalic anhydride on 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.

The results of the Cochran-Armitage test for positive dose-related trend in incidences of tumors and those 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 either sex.

In male mice negative results are observed in the incidence of alveolar/bronchiolar carcinomas. A significant dose-related trend in the negative direction ($P = 0.025$) is also observed in the incidence of adenomas of the thyroid in the female mice.

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 for that of the incidence of alveolar/bronchiolar carcinomas of the lung in low-dose male mice) has an upper limit greater than one,

indicating the theoretical possibility of the induction of tumors by phthalic anhydride, which could not be detected under the conditions of this test.

V. DISCUSSION

Mean body weights of the high-dose male rats and of the low- and high-dose mice of each sex were lower than those of the corresponding controls; mean body weights of the low-dose male rats and of both the low- and high-dose female rats were essentially unaffected by administration of the test chemical. Depressions in the amount of body weight gained in the male and female mice were dose related throughout the bioassay. Other clinical signs were common to dosed and control groups of the rats and mice or occurred only at low incidences. Survivals of the rats and mice were not affected by administration of the test chemical. Assays of the dosed feed mixtures indicated that they may have been unstable under the conditions of use.

In the female rats, alveolar/bronchiolar adenomas occurred at incidences that were dose related in the positive direction ($P = 0.020$), but, in direct comparisons, were not significantly higher in either of the dosed groups than in the control group (controls 0/20, low-dose 0/50, high-dose 5/50). Neither these adenomas in the high-dose female rats nor any tumors in the dosed groups of male rats or male or female mice can be clearly related to administration of the test chemical.

It is concluded that under the conditions of this bioassay, phthalic anhydride was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED PHTHALIC ANHYDRIDE 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			
*SUBCUT TISSUE	(20)	(50)	(50)
BASAL-CELL CARCINOMA		1 (2%)	
TRICHOEPITHELIOMA		2 (4%)	
FIBROSARCOMA	1 (5%)		1 (2%)
LIPOMA		2 (4%)	
HEMANGIOMA			1 (2%)
NEURILEMOMA, MALIGNANT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
CARCINOMA, NOS, METASTATIC			1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	4 (8%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	4 (20%)	10 (20%)	12 (24%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MYELOMONOCYTIC LEUKEMIA	1 (5%)		
MONOCYTIC LEUKEMIA			1 (2%)
*BLOOD	(20)	(50)	(50)
LEUKEMIA,NOS		1 (2%)	1 (2%)
MONOCYTIC LEUKEMIA			1 (2%)
#BONE MARROW	(20)	(49)	(49)
RHABDOMYOSARCOMA, METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
RHABDOMYOSARCOMA			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
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
NECPLASTIC NODULE	1 (5%)		
HEPATCCELLULAR CARCINOMA		2 (4%)	
#DUCDENUM	(20)	(50)	(48)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(49)
CARCINOMA,NOS			2 (4%)
ADENOMA, NOS	5 (25%)	13 (27%)	12 (24%)
#ADRENAL	(20)	(48)	(49)
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA	6 (30%)	8 (17%)	5 (10%)
#THYROID	(20)	(50)	(48)
ADENOCARCINOMA, NOS		1 (2%)	
C-CELL ADENOMA	3 (15%)	3 (6%)	3 (6%)
#PARATHYROID	(17)	(43)	(43)
ADENOMA, NOS		1 (2%)	
#PANCREATIC ISLETS	(20)	(50)	(49)
ISLET-CELL ADENOMA			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROMA		4 (8%)	1 (2%)
LIPOSARCOMA			1 (2%)
FIBROADENOMA			1 (2%)
*PREPUTIAL GLAND	(20)	(50)	(50)
CARCINOMA,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
ADENOCARCINOMA, NOS		1 (2%)	
#TESTIS	(20)	(50)	(48)
INTERSTITIAL-CELL TUMOR	13 (65%)	40 (80%)	35 (73%)
*EPIDIDYMIS	(20)	(50)	(50)
LIPOMA			2 (4%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(49)
CARCINOMA, NOS, INVASIVE			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (5%)		
MUSCULOSKELETAL SYSTEM			
*SKULL	(20)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(50)
SARCOMA, NOS		1 (2%)	
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS	1 (5%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
FIBROSARCOMA			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
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	4	9
MORIBUND SACRIFICE	3	2	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	44	36
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	47	46
TOTAL PRIMARY TUMORS	37	101	84
TOTAL ANIMALS WITH BENIGN TUMORS	18	45	43
TOTAL BENIGN TUMORS	28	77	63
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	20	21
TOTAL MALIGNANT TUMORS	7	24	21
TOTAL ANIMALS WITH SECONDARY TUMORS#			3
TOTAL SECONDARY TUMORS			3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		
TOTAL UNCERTAIN TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* 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 PHTHALIC ANHYDRIDE 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)
TRICHOEPITHELIOMA	1 (5%)		
*SUBCUT TISSUE	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
RHABDOMYOSARCOMA		1 (2%)	
OSTEOSARCOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	3 (6%)	1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)	10 (20%)	4 (8%)
#MEDIASTINAL L.NODE	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HEPATOCELLULAR CARCINOMA		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
URINARY SYSTEM			
#URINARY BLADDER	(20)	(50)	(47)
PAPILLOMA, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(50)	(49)
CARCINOMA,NOS		1 (2%)	2 (4%)
ADENOMA, NOS	11 (55%)	18 (36%)	19 (39%)
#ADRENAL	(20)	(49)	(49)
CORTICAL ADENOMA			1 (2%)
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA			3 (6%)
#THYROID	(20)	(49)	(50)
C-CELL ADENOMA		2 (4%)	3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS			1 (2%)
CYSTADENOMA, NOS		1 (2%)	
FIBROADENOMA	2 (10%)	12 (24%)	6 (12%)
*PREPUTIAL GLAND	(20)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
*CLITORAL GLAND	(20)	(50)	(50)
ADENOMA, NOS		1 (2%)	
#UTERUS	(19)	(47)	(50)
ENDOMETRIAL STROMAL POLYP	1 (5%)	3 (6%)	6 (12%)
CARCINOSARCOMA			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(50)
CARCINOMA, NOS, INVASIVE			1 (2%)
MEDULLOBLASTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	6	2
MORIBUND SACRIFICE	1	2	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	42	41
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*	13	37	36
TOTAL PRIMARY TUMORS	18	58	53
TOTAL ANIMALS WITH BENIGN TUMORS	12	27	32
TOTAL BENIGN TUMORS	15	38	44
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	16	8
TOTAL MALIGNANT TUMORS	3	20	9
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADIMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (5%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)	4 (8%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (30%)	2 (4%)	6 (12%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(49)
MALIGNANT LYMPHOMA, NOS		3 (6%)	1 (2%)
#SPLEEN	(19)	(49)	(49)
HEMANGIOMA			2 (4%)
HEMANGIOSARCOMA	1 (5%)	1 (2%)	
#MESENTERIC L. NODE	(20)	(47)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
HEPATOCELLULAR CARCINOMA	3 (15%)	12 (24%)	7 (14%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMANGIOSARCOMA		2 (4%)	
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(49)
LIPOMA		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(49)	(48)
PHEOCHROMOCYTOMA			1 (2%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(20)	(50)	(49)
ADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(49)
CARCINOMA, NOS, 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
SARCOMA, NOS	1 (5%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	7	2
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		6	
TERMINAL SACRIFICE	17	37	47
ANIMAL MISSING			1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	21	18
TOTAL PRIMARY TUMORS	13	26	21
TOTAL ANIMALS WITH BENIGN TUMORS	2	6	5
TOTAL BENIGN TUMORS	2	6	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	16	15
TOTAL MALIGNANT TUMORS	11	20	15
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	
TOTAL SECONDARY TUMORS	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	48
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(48)
NEURILEMOMA, MALIGNANT	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (6%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	3 (6%)	1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(48)
MALIGNANT LYMPHOMA, NOS	1 (5%)	3 (6%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)	2 (4%)	3 (6%)
PLASMA-CELL TUMOR			1 (2%)
*BLOOD	(20)	(49)	(48)
LEUKEMIA,NOS			2 (4%)
*HEMATOPOIETIC SYSTEM	(20)	(49)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#SPLEEN	(20)	(48)	(48)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	1 (5%)		1 (2%)
#MESENTERIC L. NODE	(19)	(49)	(47)
MALIGNANT LYMPHOMA, NOS	1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#LIVER	(20)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC 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
*MESENTERY	(20)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
#KIDNEY	(19)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#THYMUS	(18)	(42)	(37)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(48)
HEPATOCELLULAR CARCINOMA	1 (5%)		1 (2%)
#CECUM	(20)	(49)	(48)
LEIOMYOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(46)	(41)
ADENOMA, NOS			1 (2%)
#THYROID	(19)	(48)	(46)
ADENOMA, NOS	2 (11%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(48)
ADENOCARCINOMA, NOS		2 (4%)	
#UTERUS	(19)	(48)	(46)
PAPILLARY CYSTADENOCARCINOMA, 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
ENDOMETRIAL STROMAL POLYP	1 (5%)		
#OVARY	(18)	(48)	(47)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
TERATOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(20)	(49)	(48)
ADENOMA, NOS		1 (2%)	
PAPILLARY ADENOCARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(49)	(48)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(48)
OSTEOSARCOMA, INVASIVE			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(48)
SARCOMA, NOS	1 (5%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	4	8
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	16	45	40
ANIMAL MISSING		1	1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	21	17
TOTAL PRIMARY TUMORS	11	24	19
TOTAL ANIMALS WITH BENIGN TUMORS	3	4	3
TOTAL BENIGN TUMORS	3	5	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	16	14
TOTAL MALIGNANT TUMORS	8	18	15
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED PHTHALIC ANHYDRIDE 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			
*SUBCUT TISSUE	(20)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, FAT			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(49)	(49)
INFLAMMATION, CHRONIC	1 (5%)	1 (2%)	
#LUNG	(20)	(50)	(50)
EDEMA, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (5%)		3 (6%)
PNEUMONIA, ASPIRATION		1 (2%)	
BRONCHOPNEUMONIA SUPPURATIVE			1 (2%)
INFLAMMATION PROLIFERATIVE		1 (2%)	
FIBROSIS			1 (2%)
PERIVASCULITIS			1 (2%)
ARTERIOSCLEROSIS, NOS		2 (4%)	
LYMPHOCYTOSIS	16 (80%)	39 (78%)	34 (68%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(20)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#BONE MARROW	(20)	(49)	(49)
HYPERPLASIA, HEMATOPOIETIC		4 (8%)	
#SPLEEN	(20)	(50)	(49)
CONGESTION, NOS		2 (4%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS		1 (2%)	
FIBROSIS, FOCAL			1 (2%)
INFARCT, NOS		1 (2%)	
HEMOSIDEROSIS	4 (20%)	12 (24%)	6 (12%)
HYPOPLASIA, NOS		1 (2%)	
LYMPHOID DEPLETION			1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HEMATOPOIESIS	10 (50%)	38 (76%)	28 (57%)
GRANULOPOIESIS		1 (2%)	
#LYMPH NODE	(20)	(50)	(50)
PLASMACYTOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#MANDIBULAR L. NODE	(20)	(50)	(50)
CYST, NOS	1 (5%)	6 (12%)	1 (2%)
CONGESTION, NOS			1 (2%)
EDEMA, NOS	1 (5%)	1 (2%)	
HEMORRHAGE			1 (2%)
HEMOSIDEROSIS		1 (2%)	
HYPERPLASIA, NOS		3 (6%)	
PLASMACYTOSIS	1 (5%)	4 (8%)	
#MEDIASTINAL L.NODE	(20)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(20)	(50)	(50)
CYST, NOS	2 (10%)	1 (2%)	
CONGESTION, NOS		1 (2%)	
HEMOSIDEROSIS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)
#RENAL LYMPH NODE	(20)	(50)	(50)
CONGESTION, NOS	1 (5%)		
#THYMUS	(13)	(18)	(17)
CYST, NOS		1 (6%)	
CONGESTION, NOS			1 (6%)
HEMORRHAGE		1 (6%)	
ATROPHY, NOS			1 (6%)
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
FIBROSIS	15 (75%)	44 (88%)	43 (86%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS, FOCAL		1 (2%)	
#HEART/ATRIUM	(20)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#MYOCARDIUM	(20)	(50)	(50)
FIBROSIS		1 (2%)	
*PULMONARY ARTERY	(20)	(50)	(50)
HYPERTROPHY, NOS	1 (5%)	3 (6%)	5 (10%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(19)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC		3 (6%)	1 (2%)
#LIVER	(20)	(50)	(49)
CHOLANGIOFIBROSIS	14 (70%)	42 (84%)	39 (80%)
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL		2 (4%)	
METAMORPHOSIS FATTY	5 (25%)	10 (20%)	7 (14%)
LIPOIDOSIS	1 (5%)	1 (2%)	1 (2%)
BASOPHILIC CYTO CHANGE	5 (25%)	20 (40%)	21 (43%)
FOCAL CELLULAR CHANGE			1 (2%)
CLEAR-CELL CHANGE		1 (2%)	
ANGIECTASIS	1 (5%)		
HEMATOPOIESIS		1 (2%)	
#HEPATIC CAPSULE	(20)	(50)	(49)
RUPTURE			1 (2%)
FIBROSIS, FOCAL		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(50)	(49)
NECROSIS, FOCAL	1 (5%)		
#BILE DUCT	(20)	(50)	(49)
HYPERPLASIA, NOS	1 (5%)	3 (6%)	1 (2%)
#PANCREAS	(20)	(50)	(49)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, CHRONIC	1 (5%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
FIBROSIS	4 (20%)	2 (4%)	2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
PERIARTERITIS	1 (5%)	2 (4%)	
ATROPHY, NOS	4 (20%)	2 (4%)	2 (4%)
#STOMACH	(20)	(50)	(49)
CYST, NOS			1 (2%)
HEMATOMA, ORGANIZED			1 (2%)
ULCER, NOS	1 (5%)		
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
FIBROSIS		4 (8%)	2 (4%)
LYMPHOCYTOSIS		1 (2%)	1 (2%)
#GASTRIC MUCOSA	(20)	(50)	(49)
MINERALIZATION			1 (2%)
#GASTRIC SUBMUCOSA	(20)	(50)	(49)
FIBROSIS			1 (2%)
#SMALL INTESTINE	(20)	(50)	(48)
DIVERTICULUM		1 (2%)	
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
#COLON	(19)	(50)	(48)
NEMATODIASIS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(49)
CAST, NOS	15 (75%)	45 (90%)	37 (76%)
HYDRONEPHROSIS		1 (2%)	
HEMORRHAGE			1 (2%)
INFLAMMATION, CHRONIC	16 (80%)	45 (90%)	38 (78%)
NEPHROPATHY		2 (4%)	1 (2%)
HEMOSIDEROSIS		1 (2%)	
ATROPHY, NOS	1 (5%)		
#KIDNEY/GLOMERULUS	(20)	(50)	(49)
DILATATION, NOS	1 (5%)		
#KIDNEY/TUBULE	(20)	(50)	(49)
MINERALIZATION			1 (2%)
DILATATION, NOS	1 (5%)		
NEPHROSIS, NOS			1 (2%)
ATROPHY, 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
#U. BLADDER/MUCOSA	(20)	(48)	(48)
HYPERPLASIA, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(49)
CYST, NOS	1 (5%)	5 (10%)	3 (6%)
#ADRENAL	(20)	(48)	(49)
INFARCT, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (5%)	2 (4%)	2 (4%)
HYPERTROPHY, FOCAL			4 (8%)
#ADRENAL CORTEX	(20)	(48)	(49)
HYPERTROPHY, NOS		1 (2%)	1 (2%)
HYPERTROPHY, FOCAL			1 (2%)
#ADRENAL MEDULLA	(20)	(48)	(49)
HYPERTROPHY, NOS			8 (16%)
HYPERTROPHY, FOCAL			1 (2%)
HYPERPLASIA, NOS	1 (5%)	4 (8%)	
#THYROID	(20)	(50)	(48)
HYPERPLASIA, C-CELL	3 (15%)	5 (10%)	10 (21%)
#PARATHYROID	(17)	(43)	(43)
CYST, NOS			1 (2%)
#PANCREATIC ISLETS	(20)	(50)	(49)
HYPERPLASIA, NOS		2 (4%)	
HYPERPLASIA, FOCAL			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS	5 (25%)	12 (24%)	12 (24%)
*PREPUTIAL GLAND	(20)	(50)	(50)
CYST, NOS		1 (2%)	
#PROSTATE	(20)	(48)	(45)
CALCULUS, NOS			2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE		2 (4%)	1 (2%)
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (5%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (5%)		
FIBROSIS		1 (2%)	
HYPERPLASIA, FOCAL	1 (5%)		
*SEMINAL VESICLE	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (5%)		
#TESTIS	(20)	(50)	(48)
HEMORRHAGE			1 (2%)
INFARCT, NOS		1 (2%)	
ATROPHY, NOS		3 (6%)	2 (4%)
*EPIDIDYMIS	(20)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(49)
HEMORRHAGE			2 (4%)
INFLAMMATION, FOCAL		1 (2%)	
NECROSIS, NOS			2 (4%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*ABDOMINAL MUSCLE	(20)	(50)	(50)
HEMORRHAGE			1 (2%)
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(50)
HEMORRHAGE			1 (2%)
*MESENTERY	(20)	(50)	(50)
PERIARTERITIS		1 (2%)	3 (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
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
LYMPHOCYTIC INFLAMMATORY INFILTR	1		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED PHTHALIC ANHYDRIDE 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)
ULCER, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
ATROPHY, NOS		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
INFLAMMATION, INTERSTITIAL	2 (10%)	6 (12%)	5 (10%)
INFLAMMATION, GRANULOMATOUS		3 (6%)	1 (2%)
ARTERIOSCLEROSIS, NOS	1 (5%)		1 (2%)
LYMPHOCYTOSIS	17 (85%)	44 (88%)	42 (84%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(20)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#BONE MARROW	(19)	(48)	(46)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, HEMATOPOIETIC		3 (6%)	
#SPLEEN	(20)	(50)	(50)
CONGESTION, NOS		1 (2%)	
SCLEROSIS			2 (4%)
FIBROSIS, FOCAL		1 (2%)	
INFARCT, NOS	1 (5%)		
HEMOSIDEROSIS	15 (75%)	34 (68%)	32 (64%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
HEMATOPOIESIS	16 (80%)	39 (78%)	45 (90%)
#LYMPH NODE	(20)	(50)	(50)
CONGESTION, NOS			2 (4%)
PLASMACYTOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#MANDIBULAR L. NODE	(20)	(50)	(50)
CYST, NOS		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (2%)	
#MEDIASTINAL L. NODE	(20)	(50)	(50)
CONGESTION, NOS		3 (6%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#MESENTERIC L. NODE	(20)	(50)	(50)
CYST, NOS	1 (5%)		
CONGESTION, NOS		1 (2%)	
INFLAMMATION, GRANULOMATOUS	1 (5%)		
HYPERPLASIA, RETICULUM CELL	1 (5%)		
#THYMUS	(9)	(29)	(20)
ATROPHY, NOS			1 (5%)
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
FIBROSIS	13 (65%)	34 (68%)	40 (80%)
LYMPHOCYTOSIS		1 (2%)	
#HEART/ATRIUM	(20)	(50)	(50)
THROMBOSIS, NOS	1 (5%)		
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
*ARTERY	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*PULMONARY ARTERY	(20)	(50)	(50)
HYPERTROPHY, NOS	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
*MESENTERIC ARTERY	(20)	(50)	(50)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(19)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
FIBROSIS			1 (2%)
#LIVER	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
ABSCESS, NOS			1 (2%)
GRANULOMA, NOS		1 (2%)	1 (2%)
FIBROSIS, FOCAL		3 (6%)	
CHOLANGIOFIBROSIS	16 (80%)	28 (56%)	38 (76%)
CIRRHOSIS, NOS	1 (5%)		
NECROSIS, NOS		1 (2%)	1 (2%)
NECROSIS, FOCAL		3 (6%)	1 (2%)
METAMORPHOSIS FATTY	1 (5%)	3 (6%)	4 (8%)
BASOPHILIC CYTO CHANGE	17 (85%)	43 (86%)	39 (78%)
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
MEGALOCYTOSIS	1 (5%)		
LEUKOCYTOSIS, NEUTROPHILIC			1 (2%)
#LIVER/CENTRILOBULAR	(20)	(50)	(50)
NECROSIS, NOS			1 (2%)
#LIVER/PERIPORTAL	(20)	(50)	(50)
LIPOIDOSIS			1 (2%)
#PANCREAS	(19)	(49)	(49)
FIBROSIS	1 (5%)	1 (2%)	3 (6%)
FIBROSIS, FOCAL		1 (2%)	
PERIARTERITIS		1 (2%)	
NECROSIS, FAT			1 (2%)
ATROPHY, NOS	1 (5%)	2 (4%)	2 (4%)
ATROPHY, FOCAL			1 (2%)
#STOMACH	(20)	(50)	(50)
ULCER, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS		1 (2%)	2 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, EPITHELIAL			1 (2%)
LYMPHOCYTOSIS			2 (4%)
#LARGE INTESTINE	(20)	(49)	(49)
NEMATODIASIS		1 (2%)	
#COLON	(20)	(49)	(49)
NEMATODIASIS		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
CAST, NOS	10 (50%)	19 (38%)	16 (32%)
HYDRONEPHROSIS		1 (2%)	
CONGESTION, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (5%)		
INFLAMMATION, CHRONIC	14 (70%)	42 (84%)	40 (80%)
SCLEROSIS		1 (2%)	
HEMOSIDEROSIS	1 (5%)	1 (2%)	1 (2%)
#KIDNEY/PELVIS	(20)	(50)	(50)
CALCULUS, NOS		1 (2%)	
#URINARY BLADDER	(20)	(50)	(47)
HEMORRHAGE			1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(50)	(49)
CYST, NOS	5 (25%)	22 (44%)	12 (24%)
CONGESTION, NOS			2 (4%)
HEMORRHAGIC CYST	2 (10%)	2 (4%)	1 (2%)
INFLAMMATION, OSSIFYING		1 (2%)	
ANGIECTASIS		1 (2%)	
#ADRENAL	(20)	(49)	(49)
CONGESTION, NOS			1 (2%)
HEMORRHAGIC CYST	1 (5%)		1 (2%)
METAMORPHOSIS FATTY	3 (15%)	2 (4%)	1 (2%)
PIGMENTATION, NOS			1 (2%)
HYPERTROPHY, NOS	2 (10%)		
#ADRENAL CORTEX	(20)	(49)	(49)
METAMORPHOSIS FATTY			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
HYPERTROPHY, NOS		2 (4%)	2 (4%)
HYPERTROPHY, FOCAL	1 (5%)		1 (2%)
HYPERPLASIA, NOS			1 (2%)
#ADRENAL MEDULLA	(20)	(49)	(49)
HYPERPLASIA, NOS			1 (2%)
#THYROID	(20)	(49)	(50)
ULTIMOBRANCHIAL CYST		1 (2%)	
FOLLICULAR CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
HYPERPLASIA, C-CELL	1 (5%)	9 (18%)	6 (12%)
#PANCREATIC ISLETS	(19)	(49)	(49)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS	13 (65%)	33 (66%)	24 (48%)
GALACTOCELE	1 (5%)	4 (8%)	1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
FIBROSIS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	1 (5%)		
HYPERPLASIA, CYSTIC			1 (2%)
#UTERUS	(19)	(47)	(50)
HAMARTOMA			1 (2%)
DILATATION, NOS		1 (2%)	
NECROSIS, NOS	1 (5%)		
#UTERUS/ENDOMETRIUM	(19)	(47)	(50)
DILATATION, NOS		1 (2%)	1 (2%)
CYST, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#ENDOMETRIAL GLAND	(19)	(47)	(50)
DILATATION, NOS	3 (16%)		
#OVARY	(19)	(47)	(50)
CYST, NOS	1 (5%)	3 (6%)	1 (2%)
INFLAMMATION, CHRONIC	1 (5%)		
HYPOPLASIA, 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
ATROPHY, NOS			1 (2%)
NERVOUS SYSTEM			
#LATERAL VENTRICLE	(20)	(50)	(50)
DILATATION, NOS	1 (5%)		
#BRAIN	(20)	(50)	(50)
MINERALIZATION			1 (2%)
DILATATION, NOS			1 (2%)
HYDROCEPHALUS, NOS		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
FIBROSIS			1 (2%)
*EYE/CORNEA	(20)	(50)	(50)
RUPTURE			1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKULL	(20)	(50)	(50)
EXOSTOSIS			1 (2%)
BODY CAVITIES			
*PERICARDIUM	(20)	(50)	(50)
INFLAMMATION, FIBRINOUS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(49)
ATROPHY, NOS		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(49)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(20)	(48)	(45)
HEMORRHAGE		1 (2%)	
#LUNG	(20)	(50)	(49)
HEMORRHAGE		2 (4%)	1 (2%)
BRONCHOPNEUMONIA, NOS	1 (5%)		
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (5%)		
INFLAMMATION PROLIFERATIVE		1 (2%)	
ALVEOLAR MACROPHAGES		1 (2%)	
LYMPHOCYTOSIS	6 (30%)	19 (38%)	30 (61%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(20)	(50)	(49)
LEUKOCYTOSIS, NOS			1 (2%)
#BONE MARROW	(20)	(49)	(49)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(19)	(49)	(49)
CONGESTION, NOS			1 (2%)
HYPERPLASIA, LYMPHOID			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
#SPLENIC FOLLICLES	(19)	(49)	(49)
ATROPHY, NOS		1 (2%)	
#LYMPH NODE	(20)	(47)	(49)
HYPERPLASIA, NOS			1 (2%)
#MANDIBULAR L. NODE	(20)	(47)	(49)
CYST, NOS	3 (15%)		
HEMORRHAGE	1 (5%)		
#BRONCHIAL LYMPH NODE	(20)	(47)	(49)
INFLAMMATION, CHRONIC	1 (5%)		
#MESENTERIC L. NODE	(20)	(47)	(49)
LYMPHANGIECTASIS	1 (5%)		
THROMBOSIS, NOS		1 (2%)	
CONGESTION, NOS	3 (15%)	7 (15%)	7 (14%)
HYPERPLASIA, NOS	1 (5%)		
HYPERPLASIA, RETICULUM CELL		4 (9%)	5 (10%)
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMUS	(12)	(38)	(47)
CYST, NOS	1 (8%)		
CIRCULATORY SYSTEM			
#HEART	(20)	(49)	(49)
FIBROSIS	1 (5%)		
FIBROSIS, FOCAL		1 (2%)	
PERIARTERITIS			1 (2%)
#HEART/ATRIUM	(20)	(49)	(49)
THROMBOSIS, NOS		1 (2%)	
#MYOCARDIUM	(20)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
#HEPATIC SINUSOID	(20)	(50)	(49)
LEUKOCYTOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
FIBROSIS, FOCAL			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
NECROSIS, FOCAL	2 (10%)	2 (4%)	1 (2%)
INFARCT, NOS		1 (2%)	
METAMORPHOSIS FATTY	5 (25%)	3 (6%)	3 (6%)
LIPOIDOSIS		6 (12%)	
MEGALOCYTOSIS		1 (2%)	
HYPERPLASIA, NODULAR	1 (5%)		
ANGIECTASIS	1 (5%)	1 (2%)	
#BILE DUCT	(20)	(50)	(49)
INFLAMMATION, CHRONIC	1 (5%)	7 (14%)	17 (35%)
#PANCREAS	(20)	(49)	(47)
FIBROSIS			1 (2%)
#STOMACH	(19)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL		3 (6%)	
#SMALL INTESTINE	(20)	(47)	(49)
ULCER, NOS			1 (2%)
GRANULATION, TISSUE			1 (2%)
#COLON	(20)	(48)	(49)
POLYP			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(49)
CAST, NOS	1 (5%)		
INFLAMMATION, CHRONIC	9 (45%)	22 (44%)	3 (6%)
AMYLOIDOSIS		1 (2%)	
LYMPHOCYTOSIS		15 (30%)	37 (76%)
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(49)	(48)
AMYLOIDOSIS		1 (2%)	
HYPERTROPHY, FOCAL		1 (2%)	
#ADRENAL CORTEX	(19)	(49)	(48)
ATROPHY, NOS		23 (47%)	40 (83%)
HYPERTROPHY, NOS			1 (2%)
HYPERTROPHY, FOCAL			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
REPRODUCTIVE SYSTEM			
*EPIDIDYMIS	(20)	(50)	(49)
INFLAMMATION, CHRONIC	1 (5%)		
NERVOUS SYSTEM			
#BRAIN	(19)	(50)	(49)
CONGESTION, NOS			1 (2%)
HEMORRHAGE	1 (5%)		1 (2%)
#BRAIN/THALAMUS	(19)	(50)	(49)
MINERALIZATION		18 (36%)	23 (47%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(49)
MINERALIZATION	1 (5%)		
NECROSIS, FAT	2 (10%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(49)
LYMPHOCYTOSIS			2 (4%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	2	
ANIMAL MISSING/NO NECROPSY			1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(48)
INFLAMMATION, INTERSTITIAL		2 (4%)	
LYMPHOCYTOSIS	2 (10%)	32 (65%)	34 (71%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(20)	(49)	(48)
LEUKOCYTOSIS, NEUTROPHILIC	1 (5%)		1 (2%)
#SPLEEN	(20)	(48)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	1 (5%)		
#LYMPH NODE	(19)	(49)	(47)
HYPERPLASIA, NOS	1 (5%)		
HYPERPLASIA, LYMPHOID			1 (2%)
#MANDIBULAR L. NODE	(19)	(49)	(47)
HYPERPLASIA, NOS	1 (5%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(19)	(49)	(47)
LYMPHANGIECTASIS		3 (6%)	
CONGESTION, NOS	2 (11%)	1 (2%)	3 (6%)
EDEMA, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	
INFLAMMATION, CHRONIC		1 (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
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL		9 (18%)	
HYPERPLASIA, LYMPHOID			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(19)	(48)	(47)
MINERALIZATION	1 (5%)		
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL	1 (5%)		
METAMORPHOSIS FATTY		1 (2%)	
LEUKOCYTOSIS, NOS			1 (2%)
GRANULOPOIESIS			1 (2%)
#LIVER/CENTRILOBULAR	(20)	(48)	(48)
LIPOIDOSIS		1 (2%)	
#BILE DUCT	(20)	(48)	(48)
DILATATION, NOS	1 (5%)		1 (2%)
INFLAMMATION, CHRONIC	10 (50%)	30 (63%)	36 (75%)
#PANCREAS	(18)	(49)	(47)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	1 (2%)
FIBROSIS, FOCAL			1 (2%)
ATROPHY, NOS			1 (2%)
ATROPHY, FOCAL			1 (2%)
#STOMACH	(20)	(49)	(48)
INFLAMMATION, ACUTE FOCAL	1 (5%)		
#DUODENUM	(20)	(49)	(46)
EDEMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(48)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (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
INFLAMMATION, CHRONIC	1 (5%)	9 (19%)	
LYMPHOCYTOSIS		22 (46%)	26 (54%)
HYPERPLASIA, LYMPHOID			1 (2%)
#KIDNEY/TUBULE	(19)	(48)	(48)
NECROSIS, NOS		1 (2%)	
#URINARY BLADDER	(18)	(47)	(47)
EDEMA, NOS			1 (2%)
#U. BLADDER/SUBMUCOSA	(18)	(47)	(47)
FIBROSIS	1 (6%)		
ENDOCRINE SYSTEM			
#ADRENAL	(18)	(46)	(48)
CYST, NOS		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
#ADRENAL CORTEX	(18)	(46)	(48)
ATROPHY, NOS	16 (89%)	37 (80%)	42 (88%)
HYPERTROPHY, FOCAL			1 (2%)
#ADRENAL MEDULLA	(18)	(46)	(48)
HYPERTROPHY, FOCAL			1 (2%)
#THYROID	(19)	(48)	(46)
FIBROSIS, FOCAL			1 (2%)
ATROPHY, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(48)	(46)
DILATATION, NOS	2 (11%)		
EDEMA, NOS		1 (2%)	
PYOMETRA			1 (2%)
#UTERUS/ENDOMETRIUM	(19)	(48)	(46)
DILATATION, NOS	5 (26%)	29 (60%)	20 (43%)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, PAPILLARY			1 (2%)
HYPERPLASIA, CYSTIC			1 (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
#OVARY	(18)	(48)	(47)
CYST, NOS	2 (11%)	26 (54%)	7 (15%)
HEMORRHAGIC CYST	1 (6%)	1 (2%)	1 (2%)
ATROPHY, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(48)
HEMORRHAGE			1 (2%)
NECROSIS, NOS		1 (2%)	
#BRAIN/THALAMUS	(20)	(49)	(48)
MINERALIZATION	8 (40%)	20 (41%)	26 (54%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(49)	(48)
HEALED FRACTURE			1 (2%)
OSTEOPOROSIS			4 (8%)
*FEMUR	(20)	(49)	(48)
OSTEOPOROSIS	1 (5%)		
BODY CAVITIES			
*PERITONEUM	(20)	(49)	(48)
NECROSIS, FAT			1 (2%)
*MESENTERY	(20)	(49)	(48)
NECROSIS, FAT		2 (4%)	
ALL OTHER SYSTEMS			
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
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY			1
NECROPSY PERF/NO HISTO PERFORMED		1	
AUTO/NECROPSY/HISTO PERF			2
AUTOLYSIS/NO NECROPSY			1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED PHTHALIC ANHYDRIDE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalic Anhydride in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	1/20 (5)	4/50 (8)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.600	0.400
Lower Limit		0.175	0.005
Upper Limit		77.169	30.802
Weeks to First Observed Tumor	105	105	105
Hematopoietic System: Leukemias (b)	1/20 (5)	1/50 (2)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.400	1.200
Lower Limit		0.005	0.106
Upper Limit		30.802	61.724
Weeks to First Observed Tumor	83	105	79

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphomas (b)	4/20 (20)	11/50 (22)	12/50 (24)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.100	1.200
Lower Limit		0.384	0.429
Upper Limit		4.321	4.650
Weeks to First Observed Tumor	102	94	96
Hematopoietic System:			
Lymphomas or Leukemias (b)	5/20 (25)	12/50 (24)	15/50 (30)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.960	1.200
Lower Limit		0.376	0.497
Upper Limit		3.124	3.770
Weeks to First Observed Tumor	83	94	79

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	5/20 (25)	13/49 (27)	12/49 (24)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.061	0.980
Lower Limit		0.425	0.384
Upper Limit		3.404	3.184
Weeks to First Observed Tumor	83	96	84
Adrenal: Pheochromocytoma (b)	6/20 (30)	8/48 (17)	5/49 (10)
P Values (c,d)	P = 0.037 (N)	N.S.	N.S.
Relative Risk (f)		0.556	0.340
Lower Limit		0.202	0.096
Upper Limit		1.734	1.205
Weeks to First Observed Tumor	89	94	96

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma (b)	3/20 (15)	3/50 (6)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.400	0.417
Lower Limit		0.060	0.062
Upper Limit		2.802	2.915
Weeks to First Observed Tumor	105	105	105
Mammary Gland: Fibroma (b)	0/20 (0)	4/50 (8)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.386	0.022
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor (b)	13/20 (65)	40/50 (80)	35/48 (73)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.231	1.122
Lower Limit		0.882	0.792
Upper Limit		1.864	1.766
Weeks to First Observed Tumor	74	90	84

(a) Dosed groups received 7,500 or 15,000 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 a 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 Phthalic Anhydride in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	0/20 (0)	0/50 (0)	5/50 (10)
P Values (c,d)	P = 0.020	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.525
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	105
Lung: Alveolar/Bronchiolar Carcinoma (b)	1/20 (5)	3/50 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.200	0.400
Lower Limit		0.106	0.005
Upper Limit		61.724	30.802
Weeks to First Observed Tumor	105	101	102

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	1/20 (5)	3/50 (6)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.200	2.400
Lower Limit		0.106	0.175
Upper Limit		61.724	108.021
Weeks to First Observed Tumor	105	101	102
Hematopoietic System:			
Lymphomas (b)	1/20 (5)	11/50 (22)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.019		
Relative Risk (f)		4.400	1.600
Lower Limit		0.722	0.175
Upper Limit		184.752	77.169
Weeks to First Observed Tumor	101	105	102

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	11/20 (55)	18/50 (36)	19/49 (39)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.655	0.705
Lower Limit		0.385	0.419
Upper Limit		1.280	1.363
Weeks to First Observed Tumor	81	101	16
Adrenal: Pheochromocytoma (b)	0/20 (0)	0/49 (0)	3/49 (6)
P Values (c,d)	N.S.	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.255
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	94

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma (b)	0/20 (0)	2/49 (4)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.125	0.250
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	94
Mammary Gland: Fibroadenoma (b)	2/20 (10)	12/50 (24)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.400	1.200
Lower Limit		0.614	0.243
Upper Limit		20.902	11.574
Weeks to First Observed Tumor	105	101	74

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Phthalic Anhydride in the Diet (a)
(continued)

Uterus: Endometrial Stromal Polyp (b)	1/19 (5)	3/47 (6)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.213	2.280
Lower Limit		0.107	0.311
Upper Limit		62.303	102.629
Weeks to First Observed Tumor	105	105	105

(a) Dosed groups received 7,500 or 15,000 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 a 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 PHTHALIC ANHYDRIDE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalic Anhydride in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	6/20 (30)	2/50 (4)	6/49 (12)
P Values (c,d)	N.S.	P = 0.005 (N)	N.S.
Departure from Linear Trend (e)	P = 0.007		
Relative Risk (f)		0.133	0.408
Lower Limit		0.015	0.129
Upper Limit		0.681	1.372
Weeks to First Observed Tumor	100	97	104
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	7/20 (35)	6/50 (12)	9/49 (18)
P Values (c,d)	N.S.	P = 0.032 (N)	N.S.
Relative Risk (f)		0.343	0.525
Lower Limit		0.114	0.211
Upper Limit		1.061	1.464
Weeks to First Observed Tumor	89	97	104

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphomas (b)	0/20 (0)	3/50 (6)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.250	0.125
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	93	99
Liver: Hepatocellular			
Carcinoma (b)	3/20 (15)	12/50 (24)	7/49 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.600	0.952
Lower Limit		0.503	0.250
Upper Limit		8.185	5.317
Weeks to First Observed Tumor	104	101	104

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Phthalic Anhydride in the Diet (a)

(continued)

(a) Dosed groups received time-weighted average doses of 16,346 or 32,692 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 a 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 Phthalic Anhydride in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	1/20 (5)	3/49 (6)	1/48 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.224	0.417
Lower Limit		0.108	0.006
Upper Limit		62.958	32.058
Weeks to First Observed Tumor	99	44	104
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	1/20 (5)	6/49 (12)	2/48 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.449	0.833
Lower Limit		0.332	0.047
Upper Limit		110.166	48.155
Weeks to First Observed Tumor	99	44	104

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphomas (b)	3/20 (5)	11/49 (22)	8/48 (17)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.497	1.111
Lower Limit		0.460	0.308
Upper Limit		7.741	6.043
Weeks to First Observed Tumor	104	90	71
Hematopoietic System:			
Lymphomas or Leukemias (b)	3/20 (15)	11/49 (22)	9/48 (19)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.497	1.250
Lower Limit		0.460	0.361
Upper Limit		7.741	6.662
Weeks to First Observed Tumor	104	90	71

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Phthalic Anhydride in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Adenoma, NOS (b)	2/19 (11)	0/48 (0)	0/46 (0)
P Values (c,d)	P = 0.025 (N)	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.043		
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.329	1.386
Weeks to First Observed Tumor	104	--	--

(a) Dosed groups received time-weighted average doses of 12,019 or 24,038 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 a 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 Phthalic Anhydride* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

December 13, 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 on the Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, 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 Phthalic Anhydride.

The reviewer for the report on the bioassay of Phthalic Anhydride agreed with the conclusion that the compound was not carcinogenic under the conditions of test. After a brief description of the experimental design, he said that both the dose levels tested and the animal survival were adequate. There was no objection to the reviewer's motion that the report on the bioassay of Phthalic Anhydride 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
Verald K. Rowe, Dow Chemical USA
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
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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