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# BIOASSAY OF 2, 4, 6-TRICHLOROPHENOL FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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# 2,4,6-TRICHLOROPHENOL

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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 2,4,6-trichlorophenol 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 tests and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals that are carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of 2,4,6-trichlorophenol 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 Drs. J. L. Stookey and J. M. Ward (2), and the diagnoses included in this report represent their 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 Cancer Research Center by Dr. W. Zielinsky. The chemical analyses and narrative were reviewed and approved by Dr. Lijinsky (1).

This report was prepared at Tracor Jitco (5) 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. Owen, 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 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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## SUMMARY

A bioassay of 2,4,6-trichlorophenol 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 2,4,6-trichlorophenol at one of two doses, either 5,000 or 10,000 ppm, for 106 or 107 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 2,4,6-trichlorophenol at one of two doses, either 5,000 or 10,000 ppm for 105 weeks. Groups of 50 female mice were administered the test chemical at one of two doses, initially either 10,000 or 20,000 ppm, for 38 weeks. Because of excessively lowered body weights in the dosed groups of the females, the doses for the females were then reduced to 2,500 and 5,000 ppm, respectively, and administration at the lowered doses was continued for 67 weeks. The time-weighted average doses for the female mice were either 5,214 or 10,428 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 to the end of the experiment were 68% or greater in all groups of rats and 80% or greater in all groups of mice.

In the male rats, lymphomas or leukemias occurred at incidences that were dose related ($P = 0.006$) and in direct comparisons were significantly higher in the low-dose ($P = 0.019$) and high-dose ($P = 0.004$) groups than in the corresponding control group (controls 4/20, low-dose 25/50, high-dose 29/50). Leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone marrow also occurred in some dosed male rats not having lymphoma or leukemia.

In the female rats, monocytic leukemia did not occur at incidences that were significant. However, as in the male rats, leukocytosis and monocytosis of the peripheral blood and

hyperplasia of the bone marrow occurred in the dosed female rats but not in the controls (blood leukocytosis and monocytosis: controls 0/20, low-dose 6/50, high-dose 3/50; bone marrow hyperplasia: controls 0/20, low-dose 16/50, high-dose 2/50).

In both the male and female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P less than 0.001), and in direct comparisons were significantly higher in the low- and high-dose male groups and the high-dose female group (P less than or equal to 0.001) than in the corresponding control groups (males: controls 4/20, low-dose 32/49, high-dose 39/47; females: controls 1/20, low-dose 12/50, high-dose 24/48).

It is concluded that under the conditions of this bioassay, 2,4,6-trichlorophenol was carcinogenic in male F344 rats, inducing lymphomas or leukemias. The test chemical was also carcinogenic in both sexes of B6C3F1 mice, inducing hepatocellular carcinomas or adenomas.

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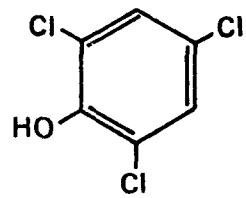
# I. INTRODUCTION

2,4,6-Trichlorophenol (CAS 88-06-2; NCI C02904) is a germicidal agent that has been used to preserve wood and glue as well as to protect textiles against mildew (Stanford Research Institute, 1976). Production of this chemical (for sale as an end product) was discontinued in 1975 by Dow Chemical Company (1978), the only manufacturer of 2,4,6-trichlorophenol in the United States, because of the high cost of removing toxic dioxin impurities. However, a small quantity (2,204 pounds) was imported for domestic use in 1976 (United States International Trade Commission, 1977).



2, 4, 6-Trichlorophenol

The chemical has been reported to be produced when water containing phenol (Eisenhauer, 1964; Smith et al., 1975) or certain aromatic acids (Larson and Rockwell, 1977) is treated with hypochlorite, suggesting the possibility of human exposure to 2,4,6-trichlorophenol in treated industrial waste water. The

chemical is also an end product of lindane metabolism in mammals (Tanaka et al., 1977).

The oral $LD_{50}$ of 2,4,6-trichlorophenol has been reported as 820 mg/kg body weight in rats of unspecified strain (NIOSH, 1976). 2,4,6-Trichlorophenol was tested by Innes et al. (1969) in a large-scale screen of industrial compounds for carcinogenic activity. The results of this preliminary bioassay in mice suggested a possible association of the incidence of tumors with administration of the test chemical; therefore, 2,4,6-trichlorophenol was selected for further testing in the Carcinogenesis Testing Program.

## II. MATERIALS AND METHODS

### A. Chemical

2,4,6-Trichlorophenol (Omal®, Dowicide® 2S) was obtained from the Dow Chemical Company as a light, pinkish-orange solid. Its melting point was 65° and its boiling point was 251 to 252°C; corresponding values given in the literature (Windholz, 1976) were 69° and 246°C, respectively. Elemental analysis showed average values of 36.2% carbon and 1.5% hydrogen (theoretical: 36.5% C and 1.5% H). Its infrared spectrum was consistent with the chemical structure, and identical to that of a standard. Mass spectral analysis showed a molecular ion as the base peak at m/e 197. Its purity was determined by gas-liquid chromatography to be 96 to 97%, with up to 17 minor contaminants. The chlorinated dibenzo-p-dioxin content of the 2,4,6-trichlorophenol was not determined.

### B. Dietary Preparation

Test diets containing 2,4,6-trichlorophenol were prepared by mixing the appropriate amount of the chemical with autoclaved

Wayne® Sterilizable Lab Meal containing 4% fat (Allied Mills, Inc., Chicago, Ill). The weighed chemical was first mixed with an equal amount of the lab meal 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 with an intensifier bar. The material was then stored in sealed 3-kg plastic bags 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 NCI Frederick Cancer Research Center (Frederick, Md.). The animals were housed within the test facility for 2 weeks and then were assigned four rats of the same sex to a cage and five mice of the same sex to a cage. For use in the chronic study, the male rats weighed 90 to 105 g, averaging at least 100 g; for female rats, 80 to 95 g, averaging at least 90 g; for male mice, 18 to 22 g, averaging at least 19.5 g; and for 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 hardwood chips (Absorb-dri®, Northeastern Products, Inc., Warrenburg, N.Y.). The feed was presterilized Wayne® Sterilizable Lab Meal containing 4% fat, provided ad libitum in suspended stainless steel hoppers and replenished as required, at least three times per week. Water, acidified to pH 2.5, was supplied ad libitum from glass bottles with sipper tubes 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 bottles 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 animal rooms were maintained at 22 to 24°C and 45 to 55% relative humidity. Incoming air was passed through a filter of 65% efficiency and a bag filter of 95% efficiency at the intake and expelled without recirculation 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.). 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 on a 12-hour-per-day automatic cycle.

Rats administered 2,4,6-trichlorophenol and their corresponding controls were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 999-81-5) (2-chloroethyl)trimethylammonium chloride (CCC)
(CAS 51-03-6) piperonyl butoxide

Mice administered 2,4,6-trichlorophenol 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 72-56-0) p,p'-ethyl-DDD
(CAS 85-44-9) phthalic anhydride
(CAS 51-03-6) piperonyl butoxide

## E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of 2,4,6-trichlorophenol, 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 rats or mice consisting of five males or five females were fed diets ad libitum which contained 10,000 to 46,000 ppm 2,4,6-trichlorophenol for rats and 6,800 to 31,500 for mice for a period of 7 weeks, followed by 1 week of additional observation. Each animal was weighed twice per week. Table 1 shows the doses fed, the survival in each dosed group at the end of the study, and the mean body weights of dosed groups

Table 1. 2,4,6-Trichlorophenol Subchronic Feeding Studies in Rats and Mice

| Dose (ppm) | Male | | Female | |
|---|---|---|---|---|
| | Survival (a) | Mean Weight at Week 7 as % of Control | Survival (a) | Mean Weight at Week 7 as % of Control |
| RATS | | | | |
| 0 | 5/5 | 100 | 5/5 | 100 |
| 10,000 | 5/5 | 96 | 5/5 | 92 |
| 14,700 | 5/5 | 89 | 5/5 | 84 |
| 21,500 | 4/5 | 73 | 5/5 | 73 |
| 31,500 | 4/5 | 47 | 4/5 | 67 |
| 46,000 | 3/5 | 39 | 2/5 | 42 |
| MICE | | | | |
| 0 | 5/5 | 100 | 4/5 | 100 |
| 6,800 | 5/5 | 99 | 5/5 | 110 |
| 10,000 | 5/5 | 99 | 5/5 | 110 |
| 14,700 | 5/5 | 83 | 5/5 | 101 |
| 21,500 | 5/5 | 79 | 5/5 | 93 |
| 31,500 | 3/5 | 57 | 3/5 | 68 |

(a) Number surviving/number in group.

of animals at week 7, expressed as percentages of mean body weights of corresponding control groups.

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 in the rats was 46,000 ppm; at this dose moderate to marked increase in splenic hematopoiesis was seen in male and female rats and midzonal vacuolation of hepatocytes was seen in two males. In male and female mice dosed at 21,500 ppm, all tissues were essentially normal.

Ten percent depression in body weight was a major criterion for the estimation of MTD's. The doses that were 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 each of the dosed groups at day 49 relative to weights of corresponding control groups were plotted against 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. No histopathologic lesions were observed at the doses selected.

The low and high doses for chronic studies were set at 5,000 and 10,000 ppm for male and female rats; 5,000 and 10,000 ppm for male mice; and 10,000 and 20,000 ppm for female mice.

## 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 in body weight gain in the dosed groups of female mice, doses administered to the females were reduced after week 38 as indicated.

## G. Clinical and Pathologic Examinations

All animals were checked twice daily. 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 termination of the bioassay were killed using $CO_2$ and necropsied.

The pathologic evaluation consisted of gross and microscopic

Table 2. 2,4,6-Trichlorophenol Chronic Feeding Studies in Rats

| Sex and Test Group | Initial No. of Animals (a) | 2,4,6-Trichlorophenol in Diet (b) (ppm) | Time on Study (weeks) |
|---|---|---|---|
| Male | | | |
| Matched-Control | 20 | 0 | 107 |
| Low-Dose | 50 | 5,000 | 106 |
| High-Dose | 50 | 10,000 | 106 |
| Female | | | |
| Matched-Control | 20 | 0 | 107 |
| Low-Dose | 50 | 5,000 | 106-107 |
| High-Dose | 50 | 10,000 | 106 |

(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. 2,4,6-Trichlorophenol Chronic Feeding Studies in Mice

| Sex and Test Group | Initial No. of Animals (a) | 2,4,6-Trichlorophenol in Diet (b) (ppm) | Time on Study (weeks) | Time-Weighted Average Dose (c) (ppm) |
|---|---|---|---|---|
| Male | | | | |
| Matched-Control | 20 | 0 | 105 | |
| Low-Dose | 50 | 5,000 | 105 | |
| High-Dose | 50 | 10,000 | 105 | |
| Female | | | | |
| Matched-Control | 20 | 0 | 105 | |
| Low-Dose | 50 | 10,000 | 38 | |
| | | 2,500 | 67 | 5,214 |
| High-Dose | 50 | 20,000 | 38 | |
| | | 5,000 | 67 | 10,428 |

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

examination of major tissues, major organs, and all gross lesions. The tissues were preserved in neutral buffered 10% 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, 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.

Necropsies were performed on all animals found dead unless precluded in whole or in part by autolysis 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 both dosed male and dosed female rats were lower than those of corresponding controls and were dose related throughout the bioassay (figure 1). Other clinical signs were common to both the dosed and the control groups. Fluctuation in the growth curves may be due to mortality; as the size of a group diminishes, the mean body weights may be subject to variation.

### B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered 2,4,6-trichlorophenol in the diet at the doses of this bioassay, together with those for the matched controls, are shown by Kaplan and Meier curves in figure 2. The result of the Tarone test indicates no statistically significant dose-related trend in mortality in either sex.

In male rats, 34/50 (68%) of the high-dose group, 35/50 (70%) of

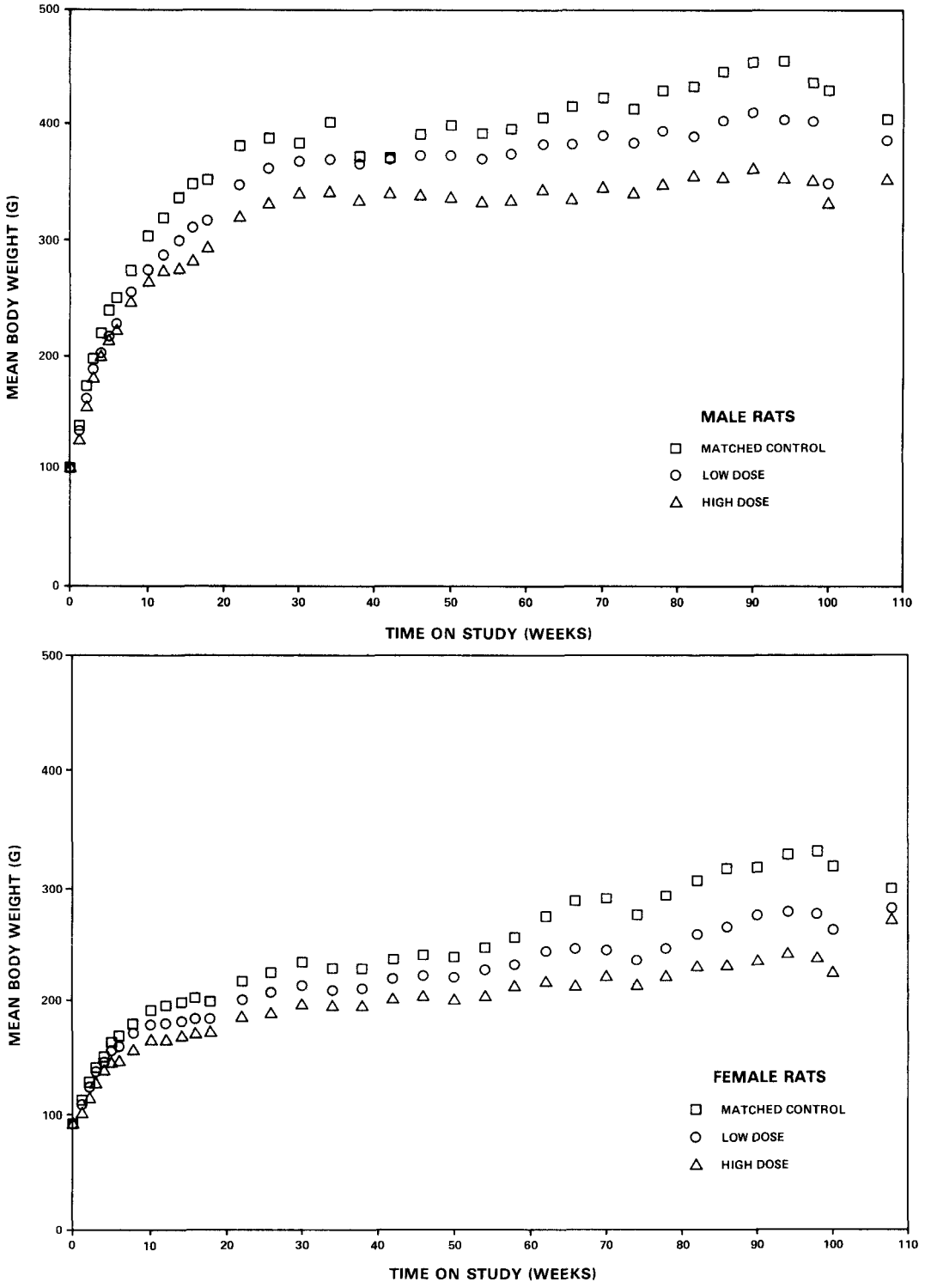



**Figure 1. Growth Curves for Rats Administered 2, 4, 6-Trichlorophenol in the Diet**

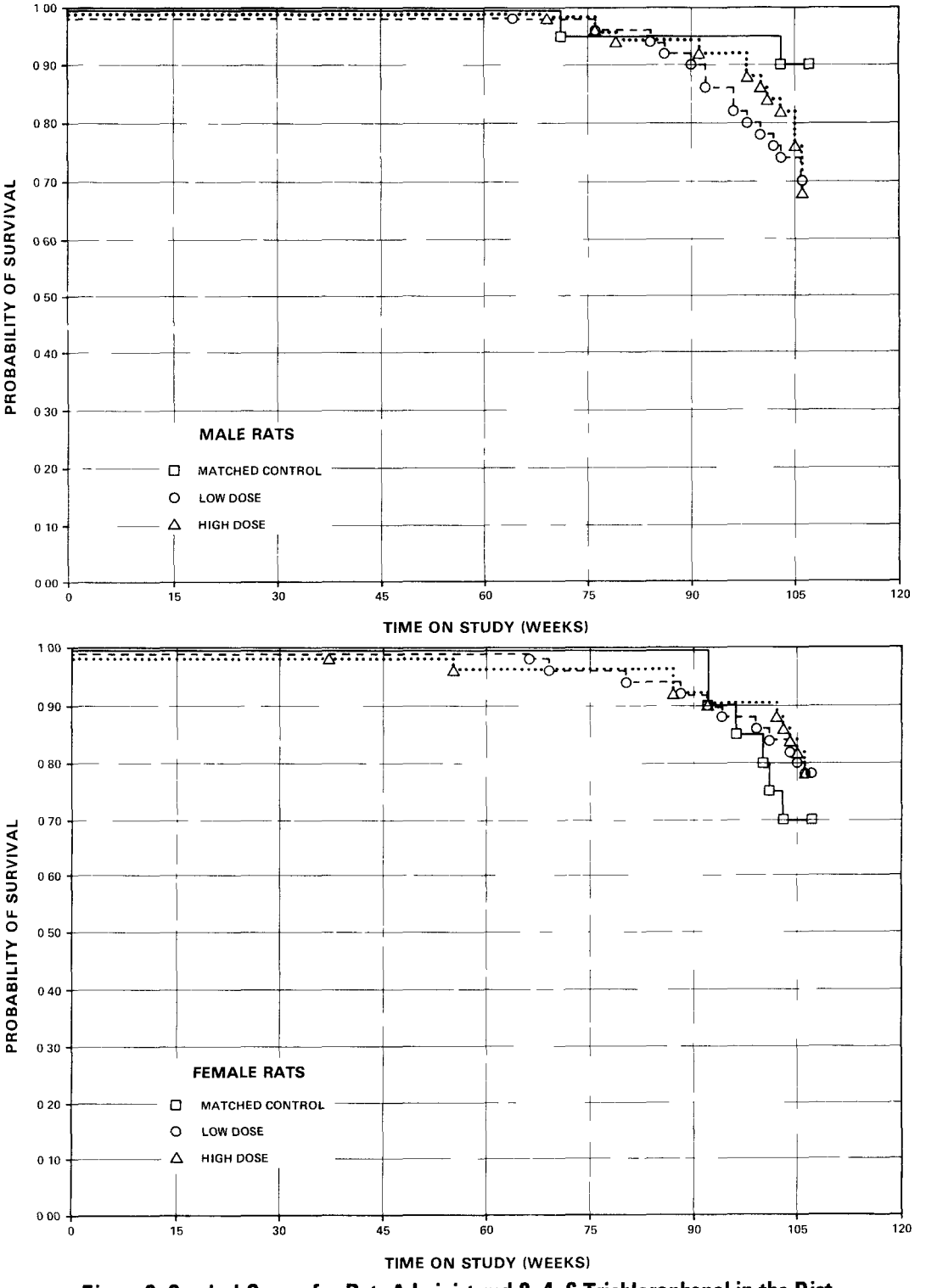



**Figure 2. Survival Curves for Rats Administered 2, 4, 6-Trichlorophenol in the Diet**

the low-dose group, and 18/20 (90%) of the control group lived to the end of the bioassay. In females, 39/50 (78%) of the high-dose group, 39/50 (78%) of the low-dose group, and 14/20 (70%) 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.

Three types of neoplasms occurred in appreciable numbers in the dosed rats, and only one of these, neoplasms of the hematopoietic system, appears to be compound related. The other two neoplasms which occurred at a high incidence were interstitial-cell tumors of the testes in male rats and pituitary chromophobe adenomas in both sexes of rats. Both of the latter neoplasms occurred with equal frequency in dosed and control groups of animals, and the type, distribution, and incidence of these neoplasms is similar to that found in aged F344 rats.

Leukemias and hematopoietic disorders have been reported in the F344 strain of rats (Davey and Moloney, 1970); however, their incidence in the dosed groups, the occurrence of hyperplasia in the bone marrow and leukocytosis in blood smears of both males and females, together with the virtual absence of any of these lesions in control males or females, indicates that the effects were compound related. The incidences of these neoplasms are summarized as follows:

| | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| | Control | Low Dose | High Dose | Control | Low Dose | High Dose |
| Number of Animals Necropsied | 20 | 50 | 50 | 20 | 50 | 50 |
| Malignant Lymphoma | 1(5%) | 2(4%) | 0(0%) | 0(0%) | 0(0%) | 2(4%) |
| Leukemia | 3(15%) | 23(46%) | 29(58%) | 3(15%) | 11(22%) | 11(22%) |
| Bone Marrow Hyperplasia | 0(0%) | 26(52%) | 15(30%) | 0(0%) | 16(32%) | 2(4%) |
| Leukocytosis | 0(0%) | 13(26%) | 11(22%) | 0(0%) | 6(12%) | 3(6%) |

The leukemias were characterized by the presence of large numbers of circulating monocytes in the blood. The cell types varied from mature, well-differentiated monocytes to a variety of immature developing and blast forms. In addition to their presence in circulating blood, similar monocytic cells were usually observed in the liver, spleen, lymph tissues, and bone

marrow and occasionally in lung, adrenals, and other organs. An aleukemic form was also observed where neoplastic cells were not found in circulating blood but were seen in the spleen and liver and occasionally in bone marrow and other organs. In addition to those rats diagnosed as having monocytic leukemia, a large number of additional dosed rats manifested hyperplastic bone marrows and/or a leukocytosis, seen on peripheral blood smears.

A variety of nonneoplastic lesions and disorders were encountered with regularity in both control and dosed animals. Such lesions were considered to be common in aged F344 rats, and the incidences of these lesions were considered to be within normal limits for this age and strain of rat.

Based on the histopathologic examination, 2,4,6-trichlorophenol was carcinogenic for male F344 rats, inducing tumors of the hematopoietic system 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 male rats, the result of the Cochran-Armitage test for positive dose-related trend is significant (P = 0.003) in the incidence of monocytic leukemia. The results of the Fisher exact test comparing the incidence of the tumors in each dosed group with that in the control group are significant (P = 0.013 in the low-dose group and P = 0.002 in the high-dose group). The statistical conclusion is that the incidence of this tumor in male rats is associated with the administration of 2,4,6-trichlorophenol. When the incidence of either lymphoma or leukemia in male rats is analyzed, the results of the statistical tests are significant, and the main contributor to this significance is the incidence of monocytic leukemia. The historical incidence to date of monocytic leukemia in male control rats at this laboratory is 11/255 (4%), compared with the following incidences in this study: controls 3/20 (15%); low-dose group, 23/50 (46%); and high-dose group, 28/50 (56%).

The results of the statistical tests on the incidence of hematopoietic tumors in female rats are not significant. The current historical records at this laboratory show that the incidence of some form of lymphoma or leukemia in female control

rats is 42/420 (10%), compared with the following incidences in this study: controls 3/20 (15%); low-dose group 11/50 (22%); high-dose group 13/50 (26%).

Significant results in the negative direction are observed in the incidences of pituitary and mammary tumors in male and female rats and of tumors of the integumentary system and the thyroid in female rats.

## IV. RESULTS - MICE

### A. Body Weights and Clinical Signs (Mice)

Mean body weights of dosed mice of each sex were lower than those of corresponding controls and were dose related throughout the bioassay (figure 3). Fluctation 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. Other clinical signs were common to both the dosed and control groups.

### B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered 2,4,6-trichlorophenol in the diet at the doses of this bioassay, together with those for the matched controls, are shown by Kaplan and Meier curves in figure 4. The result of the Tarone test indicates no statistically significant dose-related trend in mortality in either sex.

In male mice, 45/50 (90%) of the high-dose group, 44/50 (88%) of the low-dose group, and 16/20 (80%) of the control group lived to

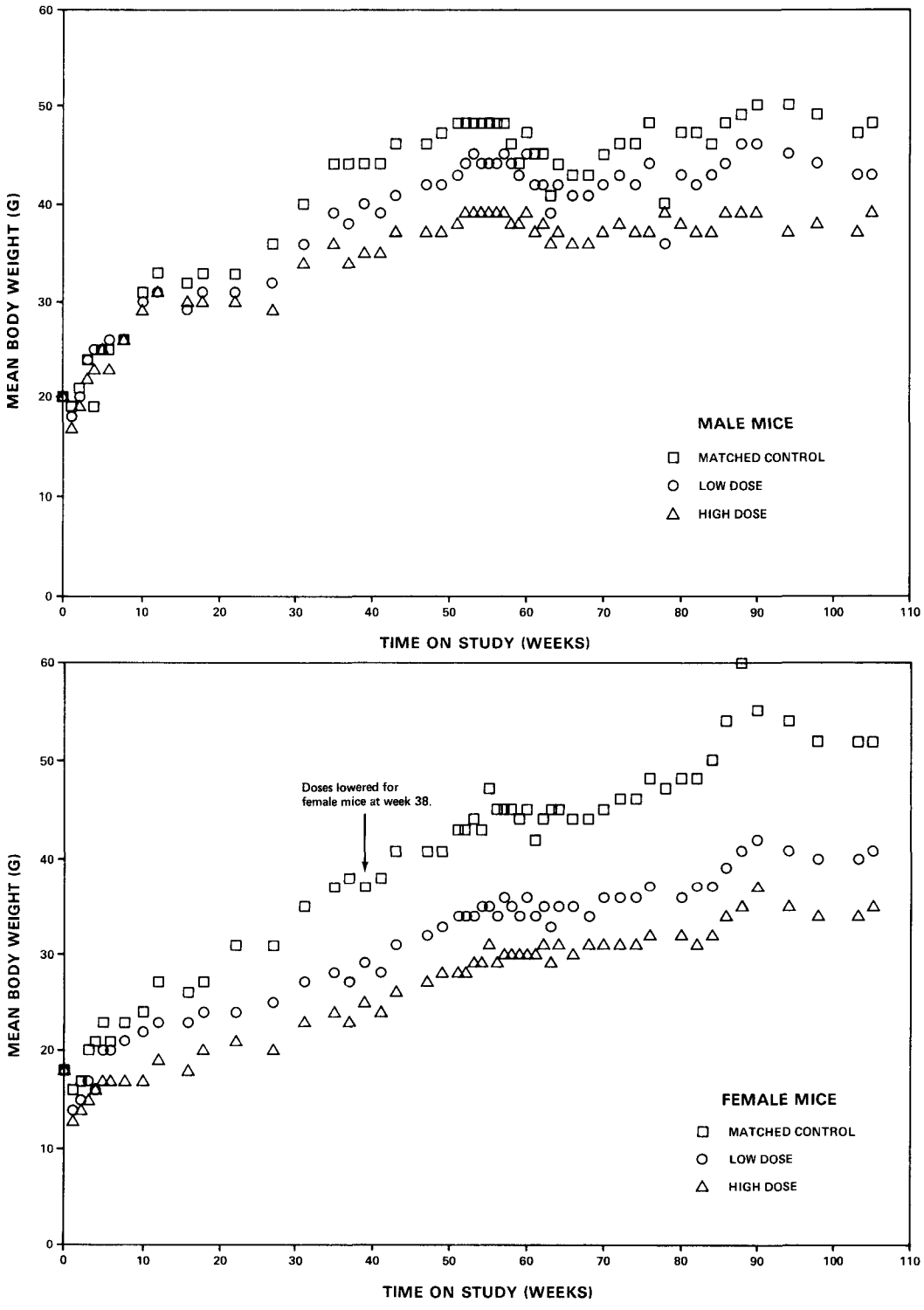



**Figure 3. Growth Curves for Mice Administered 2, 4, 6-Trichlorophenol in the Diet**

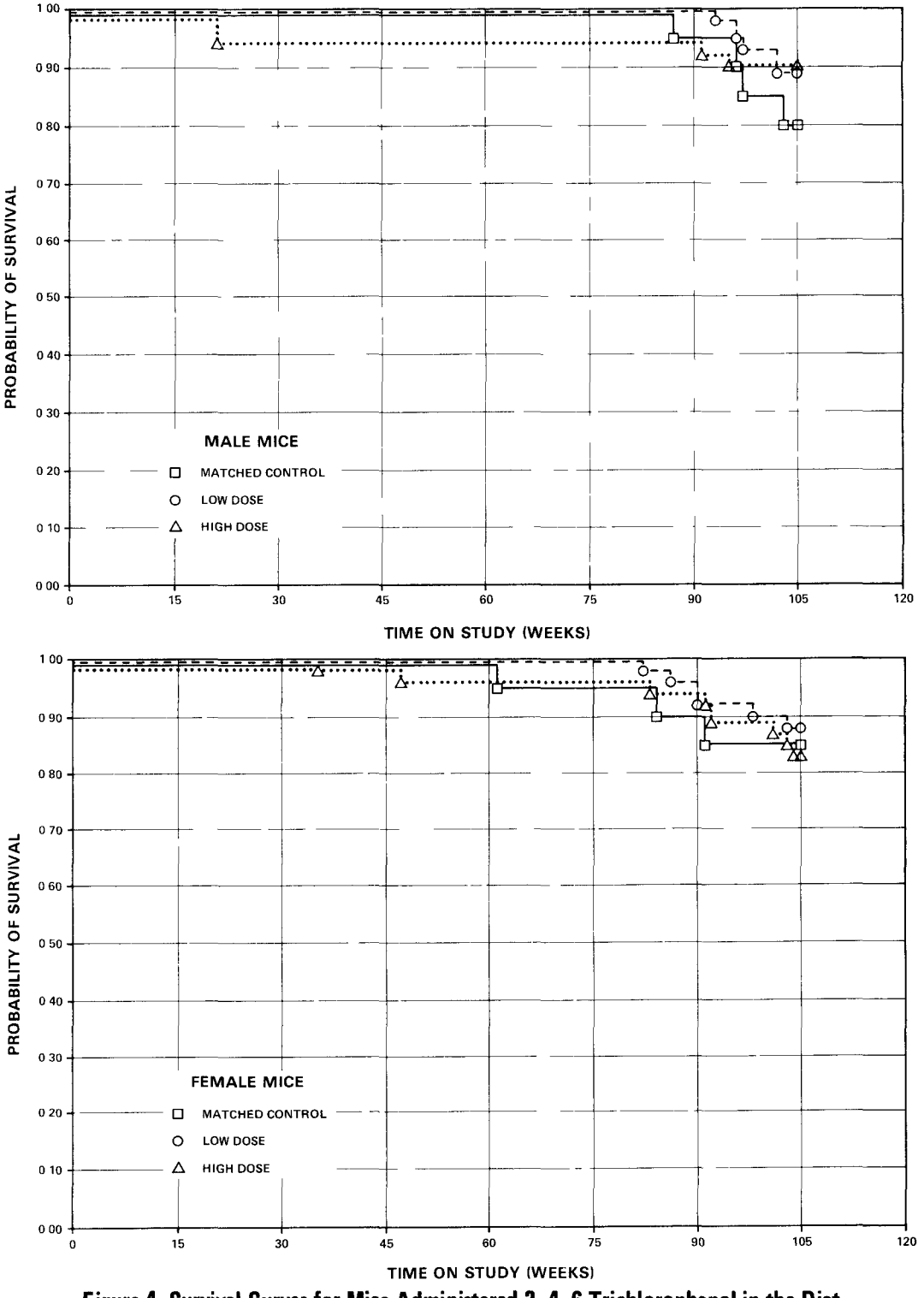



**Figure 4. Survival Curves for Mice Administered 2, 4, 6-Trichlorophenol in the Diet**

the end of the study. In females, 40/50 (80%) of the high-dose group, 44/50 (88%) of the low-dose group, and 17/20 (85%) of the control group lived to the end of the study.

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 types of neoplasms occurred frequently in dosed mice; these included hepatocellular and pulmonary neoplasms, hemangiosarcomas of various organs, and malignant lymphomas. With the exception of the hepatocellular neoplasms, however, most neoplasms occurred in equal numbers in control and dosed mice, and the type, distribution, and incidence of these neoplasms is similar to that found in aged B6C3F1 mice.

The incidence of hepatocellular neoplasms and hyperplasias was high in all dosed groups of mice, but it was especially high in

the two dosed groups of male mice, where most of the livers were affected. The incidences of these lesions are summarized in the following table:

| | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| | Control | Low Dose | High Dose | Control | Low Dose | High Dose |
| Number of Animals with Tissues Examined Microscopically | 20 | 49 | 47 | 20 | 50 | 48 |
| Hepatocellular Adenoma | 3(0%) | 22(45%) | 32(68%) | 1(5%) | 12(24%) | 17(35%) |
| Hepatocellular Carcinoma | 1(5%) | 10(20%) | 7(15%) | 0(0%) | 0(0%) | 7(14%) |
| Hyperplasia | 2(10%) | 12(24%) | 6(13%) | 1(5%) | 1(2%) | 6(13%) |

In addition to these neoplasms, hepatocellular damage, ranging from individual liver cell abnormalities, through focal areas of cellular alteration, to focal and nodular areas of hyperplasia was commonly present in the livers of dosed mice.

A variety of nonneoplastic lesions were encountered with regularity in both control and dosed animals. Such lesions are commonly seen in aged B6C3F1 mice, and occurred with no appreciable differences in frequency between control and dosed mice.

Based on the histopathologic examination, 2,4,6-trichlorophenol

was carcinogenic for B6C3F1 mice, inducing hepatocellular carcinomas and adenomas in both males and females.

## 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 result of the Cochran-Armitage test for positive dose-related trend in the incidence of male mice with hepatocellular carcinomas or adenomas is significant (P less than 0.001). The results of the Fisher exact test comparing the incidence of the tumors in the control group with that for each dosed group are significant (P less than or equal to 0.001). The historical-control male B6C3F1 mice of this laboratory have an incidence of liver tumors of 99/323 (30%), compared with 32/49 (65%) in the low-dose group and 39/47 (83%) in the high-dose group of this study. In females, the result of the Cochran-Armitage test on the incidence of hepatocellular carcinoma is significant (P = 0.005), but the results of the Fisher exact test are not significant. When the incidence of female mice with

hepatocellular carcinoma or adenoma is analyzed, the results of the Cochran-Armitage test and that of the Fisher exact test comparing the incidence in the high-dose group with that in the control group are significant (P less than 0.001). The historical-control female mice of this laboratory have an incidence of liver tumors of 14/324 (4.3%), compared with 12/50 (24%) in the low-dose group and 24/48 (50%) in the high-dose group of this study. The statistical conclusion is that the occurrence of liver tumors in male and female mice is associated with the administration of 2,4,6-trichlorophenol.

# 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. No other clinical signs could be related to administration of the test chemical. Survival of the dosed rats and mice was 68% or greater in all groups of rats and 80% or greater in all groups of mice.

In the male rats, lymphomas or leukemias occurred at incidences that were dose related ($P = 0.006$), and in direct comparisons were significantly higher in the low-dose ($P = 0.019$) and high-dose ($P = 0.004$) groups than in the corresponding control group (controls 4/20, low-dose 25/50, high-dose 29/50). Leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone marrow also occurred in some dosed male rats not having lymphoma or leukemia.

In the female rats, monocytic leukemia did not occur at incidences that were significant. Leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone marrow occurred in the dosed female rats, but not in the controls (blood leukocytosis and monocytosis: controls 0/20, low-dose 6/50,

high-dose 3/50; bone marrow hyperplasia: controls 0/20, low-dose 16/50, high-dose 2/50).

In both the male and female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P less than 0.001), and in direct comparisons were significantly higher in the low- and high-dose male groups and the high-dose female groups (P less than or equal to 0.001) than in the corresponding control groups (males: controls 4/20, low-dose 32/49, high-dose 39/47; females: controls 1/20, low-dose 12/50, high-dose 24/48).

In previous tests for tumorigenicity (National Technical Information Service, 1968; Innes et al., 1969), it was reported that when 2,4,6-trichlorophenol was administered at 100 mg/kg body weight by stomach tube for 3 weeks, then in the diet at 260 ppm for 18 months, to hybrid mice (C57BL/6 x C3H/Anf and C57BL/6 x AKR), elevated incidences of reticulum-cell sarcoma (P = 0.05) and of hepatoma (P = 0.05) were observed.

It is concluded that under the conditions of this bioassay, 2,4,6-trichlorophenol was carcinogenic in male F344 rats, inducing lymphomas or leukemias. The test chemical was also carcinogenic in both sexes of B6C3F1 mice, inducing hepatocellular carcinomas or adenomas.

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# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED 2,4,6-TRICHLOROPHENOL IN THE DIET

## TABLE A1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED 2,4,6-TRICHLOROPHENOL 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 | 1 (5%) | 1 (2%) | 1 (2%) |
| TRICHOEPITHELIOMA | 2 (10%) | 1 (2%) | 2 (4%) |
| *SUBCUT TISSUE | (20) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA, INVASIV | 1 (5%) | | |
| TRICHOEPITHELIOMA | | 3 (6%) | |
| FIBROMA | 1 (5%) | 1 (2%) | |
| FIBROSARCOMA | | 1 (2%) | |
| RHABDOMYOSARCOMA | | 1 (2%) | |
| FIBROADENOMA | | | 1 (2%) |
| **RESPIRATORY SYSTEM** | | | |
| #LUNG | (18) | (50) | (50) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | 1 (2%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 2 (11%) | 1 (2%) | 1 (2%) |
| **HEMATOPOIETIC SYSTEM** | | | |
| *MULTIPLE ORGANS | (20) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 1 (5%) | 1 (2%) | |
| LEUKEMIA,NOS | | | 1 (2%) |
| MONOCYTIC LEUKEMIA | 3 (15%) | 23 (46%) | 26 (52%) |
| *HEMATOPOIETIC SYSTEM | (20) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | | 1 (2%) | |
| MONOCYTIC LEUKEMIA | | | 2 (4%) |
| #RENAL LYMPH NODE | (20) | (50) | (50) |
| 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 |
|---|---|---|---|
| #JEJUNUM | (20) | (49) | (49) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | 1 (2%) |
| **CIRCULATORY SYSTEM** | | | |
| NONE | | | |
| **DIGESTIVE SYSTEM** | | | |
| *UPPER LIP | (20) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | |
| #SALIVARY GLAND | (20) | (50) | (50) |
| ADENOMA, NOS | 1 (5%) | | |
| FIBROADENOCARCINOMA | 1 (5%) | | |
| #LIVER | (20) | (49) | (50) |
| HEPATOCELLULAR ADENOMA | 1 (5%) | | |
| NEOPLASTIC NODULE | | 1 (2%) | |
| #STOMACH | (20) | (50) | (49) |
| SQUAMOUS CELL PAPILLOMA | | | 2 (4%) |
| #JEJUNUM | (20) | (49) | (49) |
| MUCINOUS ADENOCARCINOMA | 1 (5%) | | |
| #COLONIC SUBMUCOSA | (20) | (50) | (48) |
| LIPOMA | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| #URINARY BLADDER | (20) | (46) | (49) |
| PAPILLOMA, NOS | | | 1 (2%) |
| TRANSITIONAL-CELL PAPILLOMA | | 1 (2%) | |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (20) | (49) | (50) |
| ADENOMA, NOS | | 1 (2%) | 1 (2%) |
| CHROMOPHOBE ADENOMA | 10 (50%) | 7 (14%) | 4 (8%) |

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

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ACIDOPHIL CARCINOMA | | | 1 (2%) |
| #ADRENAL | (20) | (50) | (49) |
| CORTICAL ADENOMA | | | 1 (2%) |
| PHEOCHROMOCYTOMA | 3 (15%) | 1 (2%) | 4 (8%) |
| PHEOCHROMOCYTOMA, MALIGNANT | | 1 (2%) | 2 (4%) |
| #THYROID | (20) | (49) | (49) |
| ADENOMA, NOS | | | 1 (2%) |
| ADENOCARCINOMA, NOS | 1 (5%) | | 2 (4%) |
| C-CELL ADENOMA | 2 (10%) | 1 (2%) | 4 (8%) |
| C-CELL CARCINOMA | | 1 (2%) | 1 (2%) |
| #PARATHYROID | (17) | (39) | (43) |
| ADENOMA, NOS | | 1 (3%) | |
| ADENOCARCINOMA, NOS | | 1 (3%) | |
| #PANCREATIC ISLETS | (20) | (50) | (50) |
| ISLET-CELL ADENOMA | | | 1 (2%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (50) | (50) |
| ADENOMA, NOS | 2 (10%) | | |
| FIBROMA | | 1 (2%) | |
| LIPOMA | | 1 (2%) | |
| #TESTIS | (20) | (50) | (50) |
| INTERSTITIAL-CELL TUMOR | 18 (90%) | 40 (80%) | 37 (74%) |
| INTERSTITIAL-CELL TUMOR, MALIGNA | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| #BRAIN | (20) | (50) | (50) |
| ASTROCYTOMA | | 1 (2%) | |
| SPECIAL SENSE ORGANS | | | |
| *ZYMBAL'S GLAND | (20) | (50) | (50) |
| CARCINOMA,NOS | 1 (5%) | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |

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

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| BODY CAVITIES | | | |
| *PLEURA | (20) | (50) | (50) |
| ALVEOLAR/BRONCHIOLAR CA, METASTA | | 1 (2%) | |
| *TUNICA VAGINALIS | (20) | (50) | (50) |
| MESOTHELIOMA, NOS | 1 (5%) | 2 (4%) | 1 (2%) |
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (20) | (50) | (50) |
| MUCINOUS ADENOCARCINOMA, METASTA | 1 (5%) | | |
| MESOTHELIOMA, NOS | 1 (5%) | 1 (2%) | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| NATURAL DEATH@ | 2 | 9 | 14 |
| MORIBUND SACRIFICE | | 6 | 2 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 18 | 35 | 34 |
| ANIMAL MISSING | | | |

@ INCLUDES AUTOLYZED ANIMALS

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

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 20 | 49 | 49 |
| TOTAL PRIMARY TUMORS | 53 | 99 | 100 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 19 | 43 | 43 |
| TOTAL BENIGN TUMORS | 40 | 61 | 60 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 9 | 29 | 33 |
| TOTAL MALIGNANT TUMORS | 11 | 34 | 39 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 2 | 1 | |
| TOTAL SECONDARY TUMORS | 2 | 1 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | 2 | 4 | 1 |
| TOTAL UNCERTAIN TUMORS | 2 | 4 | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

## TABLE A2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED 2, 4, 6-TRICHLOROPHENOL 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 PAPILLOMA | | 1 (2%) | |
| TRICHOEPITHELIOMA | 1 (5%) | | |
| *SUBCUT TISSUE | (20) | (50) | (50) |
| FIBROSARCOMA | 1 (5%) | 1 (2%) | |
| LIPOMA | | 1 (2%) | |
| FIBROADENOMA | 2 (10%) | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| *NASAL MUCOSA | (20) | (50) | (50) |
| ADENOCARCINOMA, NOS | | 1 (2%) | 1 (2%) |
| #LUNG | (18) | (50) | (50) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | 1 (2%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #CEREBRUM | (20) | (50) | (49) |
| MALIGNANT RETICULOSIS | | | 1 (2%) |
| *MULTIPLE ORGANS | (20) | (50) | (50) |
| LEUKEMIA,NOS | | | 1 (2%) |
| MONOCYTIC LEUKEMIA | 3 (15%) | 11 (22%) | 10 (20%) |
| *HEMATOPOIETIC SYSTEM | (20) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | | | 2 (4%) |
| CIRCULATORY SYSTEM | | | |
| NONE | | | |

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

**TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)**

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| DIGESTIVE SYSTEM | | | |
| #SMALL INTESTINE | (20) | (48) | (48) |
| CYSTADENOCARCINOMA, NOS | | 1 (2%) | |
| MUCINOUS ADENOCARCINOMA | | 1 (2%) | |
| *RECTUM | (20) | (50) | (50) |
| ADENOCA IN ADENOMATOUS POLYP | 1 (5%) | | |
| URINARY SYSTEM | | | |
| NONE | | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (20) | (49) | (49) |
| CARCINOMA,NOS | | | 1 (2%) |
| ADENOMA, NOS | 3 (15%) | 3 (6%) | |
| CHROMOPHOBE ADENOMA | 4 (20%) | 10 (20%) | 8 (16%) |
| CHROMOPHOBE CARCINOMA | | 1 (2%) | |
| #ADRENAL | (20) | (50) | (49) |
| CORTICAL ADENOMA | 1 (5%) | | |
| PHEOCHROMOCYTOMA | 1 (5%) | | |
| #THYROID | (20) | (49) | (50) |
| ADENOCARCINOMA, NOS | | 1 (2%) | 1 (2%) |
| FOLLICULAR-CELL ADENOMA | | | 1 (2%) |
| FOLLICULAR-CELL CARCINOMA | | 1 (2%) | |
| C-CELL ADENOMA | 3 (15%) | 1 (2%) | 1 (2%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (50) | (50) |
| ADENOCARCINOMA, NOS | 1 (5%) | | |
| PAPILLARY CYSTADENOMA, NOS | | 1 (2%) | |
| FIBROADENOMA | 2 (10%) | | |
| *VAGINA | (20) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | 1 (5%) | | |
| #UTERUS | (20) | (50) | (49) |
| ENDOMETRIAL STROMAL POLYP | 1 (5%) | 3 (6%) | 2 (4%) |

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

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #OVARY | (20) | (50) | (49) |
| LIPOMA | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| #BRAIN | (20) | (50) | (49) |
| CARCINOMA, NOS, METASTATIC | | | 1 (2%) |
| ASTROCYTOMA | | | 2 (4%) |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *RIB | (20) | (50) | (50) |
| OSTEOSARCOMA | | | 1 (2%) |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| NATURAL DEATH@ | 2 | 10 | 6 |
| MORIBUND SACRIFICE | 4 | 1 | 5 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 14 | 39 | 39 |
| 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* | 16 | 32 | 27 |
| TOTAL PRIMARY TUMORS | 25 | 40 | 34 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 13 | 18 | 13 |
| TOTAL BENIGN TUMORS | 18 | 22 | 13 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 6 | 17 | 20 |
| TOTAL MALIGNANT TUMORS | 7 | 18 | 21 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | 1 |
| TOTAL SECONDARY TUMORS | | | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

# APPENDIX B

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED 2,4,6-TRICHLOROPHENOL IN THE DIET

## TABLE B1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED 2, 4, 6-TRICHLOROPHENOL IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | | 1 | |
| ANIMALS NECROPSIED | 20 | 49 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 49 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (20) | (49) | (49) |
| FIBROSARCOMA | 1 (5%) | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (48) | (47) |
| BILE DUCT CARCINOMA, METASTATIC | | | 1 (2%) |
| HEPATOCELLULAR CARCINOMA, METAST | | 1 (2%) | 1 (2%) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (5%) | 7 (15%) | 6 (13%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 2 (10%) | 6 (13%) | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (20) | (49) | (49) |
| MALIGNANT LYMPHOMA, NOS | 2 (10%) | 1 (2%) | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | 1 (2%) |
| *SUBCUT TISSUE | (20) | (49) | (49) |
| MAST-CELL TUMOR | | 1 (2%) | |
| #LYMPH NODE | (19) | (46) | (47) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (2%) | |
| #LIVER | (20) | (49) | (47) |
| KUPFFER-CELL SARCOMA | | | 1 (2%) |
| CIRCULATORY SYSTEM | | | |
| *MULTIPLE ORGANS | (20) | (49) | (49) |
| HEMANGIOMA | 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 |
|---|---|---|---|
| HEMANGIOSARCOMA | | 1 (2%) | |
| #SPLEEN | (20) | (49) | (47) |
| HEMANGIOSARCOMA | | 3 (6%) | 4 (9%) |
| #HEART | (20) | (49) | (47) |
| HEMANGIOMA | | | 1 (2%) |
| #SALIVARY GLAND | (20) | (48) | (47) |
| HEMANGIOSARCOMA | | 1 (2%) | |
| #LIVER | (20) | (49) | (47) |
| HEMANGIOSARCOMA | 1 (5%) | 1 (2%) | 2 (4%) |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (20) | (49) | (47) |
| BILE DUCT CARCINOMA | | | 1 (2%) |
| HEPATOCELLULAR ADENOMA | 3 (15%) | 22 (45%) | 32 (68%) |
| HEPATOCELLULAR CARCINOMA | 1 (5%) | 10 (20%) | 7 (15%) |
| SARCOMA, NOS | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| NONE | | | |
| **ENDOCRINE SYSTEM** | | | |
| #THYROID | (20) | (47) | (46) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| **REPRODUCTIVE SYSTEM** | | | |
| NONE | | | |
| **NERVOUS SYSTEM** | | | |
| NONE | | | |
| **SPECIAL SENSE ORGANS** | | | |
| *EYE/LACRIMAL GLAND | (20) | (49) | (49) |
| ADENOCARCINOMA, NOS | | 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 |
|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | |
| *VERTEBRAL COLUMN | (20) | (49) | (49) |
| OSTEOSARCOMA | 1 (5%) | | |
| BODY CAVITIES | | | |
| *MESENTERY | (20) | (49) | (49) |
| LIPOMA | 1 (5%) | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| NATURAL DEATH@ | 4 | 4 | 5 |
| MORIBUND SACRIFICE | | 1 | |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 16 | 44 | 45 |
| 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* | 14 | 42 | 42 |
| TOTAL PRIMARY TUMORS | 14 | 59 | 56 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 6 | 26 | 34 |
| TOTAL BENIGN TUMORS | 6 | 29 | 39 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 8 | 26 | 13 |
| TOTAL MALIGNANT TUMORS | 8 | 29 | 17 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | 1 | 2 |
| TOTAL SECONDARY TUMORS | | 1 | 2 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | 1 | |
| TOTAL UNCERTAIN TUMORS | | 1 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

## TABLE B2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED 2, 4, 6-TRICHLOROPHENOL IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | | | 2 |
| ANIMALS NECROPSIED | 20 | 50 | 48 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 50 | 48 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (20) | (50) | (48) |
| FIBROSARCOMA | 1 (5%) | | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (50) | (48) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (5%) | 4 (8%) | 1 (2%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | 2 (4%) |
| SARCOMA, NOS, METASTATIC | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (20) | (50) | (48) |
| MALIGNANT LYMPHOMA, NOS | | 5 (10%) | 4 (8%) |
| MALIG.LYMPHOMA, UNDIFFER-TYPE | | 1 (2%) | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 4 (8%) | |
| GRANULOCYTIC SARCOMA | | 1 (2%) | |
| *ABDOMINAL CAVITY | (20) | (50) | (48) |
| MALIGNANT LYMPHOMA, NOS | | 1 (2%) | |
| *HEMATOPOIETIC SYSTEM | (20) | (50) | (48) |
| MALIGNANT LYMPHOMA, NOS | 1 (5%) | | 2 (4%) |
| #SPLEEN | (20) | (50) | (48) |
| MALIGNANT LYMPHOMA, NOS | | 1 (2%) | |
| #MANDIBULAR L. NODE | (20) | (47) | (48) |
| MALIGNANT LYMPHOMA, NOS | 1 (5%) | | |
| #KIDNEY | (20) | (50) | (48) |
| MALIGNANT LYMPHOMA, 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 |
|---|---|---|---|
| CIRCULATORY SYSTEM | | | |
| *SUBCUT TISSUE | (20) | (50) | (48) |
| HEMANGIOMA | | 1 (2%) | |
| HEMANGIOSARCOMA | | | 1 (2%) |
| #BONE MARROW | (20) | (50) | (48) |
| HEMANGIOSARCOMA | | | 1 (2%) |
| #SPLEEN | (20) | (50) | (48) |
| HEMANGIOMA | | 1 (2%) | |
| HEMANGIOSARCOMA | | 2 (4%) | 1 (2%) |
| #HEART | (20) | (48) | (48) |
| HEMANGIOSARCOMA | | | 1 (2%) |
| #LIVER | (20) | (50) | (48) |
| HEMANGIOSARCOMA | 1 (5%) | | |
| #OVARY | (20) | (50) | (48) |
| HEMANGIOSARCOMA | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (20) | (50) | (48) |
| HEPATOCELLULAR ADENOMA | 1 (5%) | 12 (24%) | 17 (35%) |
| HEPATOCELLULAR CARCINOMA | | | 7 (15%) |
| SARCOMA, NOS | | | 1 (2%) |
| SARCOMA, NOS, UNC PRIM OR META | | | 1 (2%) |
| URINARY SYSTEM | | | |
| NONE | | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (20) | (49) | (46) |
| ADENOMA, NOS | | | 1 (2%) |
| CHROMOPHOBE ADENOMA | | 1 (2%) | |
| #ADRENAL | (20) | (48) | (46) |
| CORTICAL ADENOMA | 1 (5%) | 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 |
|---|---|---|---|
| PHEOCHROMOCYTOMA | | 1 (2%) | |
| **REPRODUCTIVE SYSTEM** | | | |
| #OVARY | (20) | (50) | (48) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| GRANULOSA-CELL TUMOR | | | 1 (2%) |
| TUBULAR ADENOMA | | 1 (2%) | |
| **NERVOUS SYSTEM** | | | |
| NONE | | | |
| **SPECIAL SENSE ORGANS** | | | |
| *EYE/LACRIMAL GLAND | (20) | (50) | (48) |
| CARCINOMA,NOS | | 1 (2%) | |
| ADENOMA, NOS | 1 (5%) | | |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| **MUSCULOSKELETAL SYSTEM** | | | |
| *VERTEBRAL COLUMN | (20) | (50) | (48) |
| RHABDOMYOSARCOMA, INVASIVE | 1 (5%) | | |
| *RIB | (20) | (50) | (48) |
| RHABDOMYOSARCOMA | 1 (5%) | | |
| **BODY CAVITIES** | | | |
| NONE | | | |
| **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@ | 3 | 6 | 8 |
| MORIBUND SACRIFICE | | | |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 17 | 44 | 40 |
| ANIMAL MISSING | | | 2 |
| **TUMOR SUMMARY** | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 6 | 30 | 33 |
| TOTAL PRIMARY TUMORS | 9 | 39 | 44 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 3 | 19 | 19 |
| TOTAL BENIGN TUMORS | 4 | 22 | 19 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 4 | 15 | 19 |
| TOTAL MALIGNANT TUMORS | 5 | 17 | 23 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | | 1 |
| TOTAL SECONDARY TUMORS | 1 | | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | 1 |
| TOTAL UNCERTAIN TUMORS | | | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | 1 |
| TOTAL UNCERTAIN TUMORS | | | 1 |

@ INCLUDES AUTOLYZED ANIMALS

* 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 2,4,6-TRICHLOROPHENOL IN THE DIET

## TABLE C1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED 2,4,6-TRICHLOROPHENOL 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) |
| ABSCESS, NOS | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (18) | (50) | (50) |
| EDEMA, NOS | | 1 (2%) | |
| BRONCHOPNEUMONIA SUPPURATIVE | | | 1 (2%) |
| GRANULOMA, NOS | 1 (6%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| *BLOOD | (20) | (50) | (50) |
| LEUKOCYTOSIS, NOS | | 6 (12%) | 2 (4%) |
| LEUKOCYTOSIS, NEUTROPHILIC | | 7 (14%) | 9 (18%) |
| MONOCYTOSIS | | 4 (8%) | |
| ANEMIA, NOS | | 1 (2%) | 2 (4%) |
| *HEMATOPOIETIC SYSTEM | (20) | (50) | (50) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #BONE MARROW | (20) | (49) | (50) |
| HYPERPLASIA, DIFFUSE | | 26 (53%) | 14 (28%) |
| HYPERPLASIA, HEMATOPOIETIC | | | 1 (2%) |
| #SPLEEN | (20) | (49) | (50) |
| CONGESTION, NOS | | | 1 (2%) |
| INFARCT, NOS | | | 1 (2%) |
| INFARCT, FOCAL | | | 1 (2%) |
| HEMOSIDEROSIS | 2 (10%) | | |
| #SINUSOID OF LYMPH NO | (20) | (50) | (50) |
| 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 |
|---|---|---|---|
| HEMOSIDEROSIS | | | 1 (2%) |
| #MANDIBULAR L. NODE | (20) | (50) | (50) |
| HYPERPLASIA, RETICULUM CELL | | 1 (2%) | |
| #CERVICAL LYMPH NODE | (20) | (50) | (50) |
| STEATITIS | 1 (5%) | | |
| HYPERPLASIA, LYMPHOID | 1 (5%) | | |
| #RENAL LYMPH NODE | (20) | (50) | (50) |
| EDEMA, NOS | 1 (5%) | | |
| HEMORRHAGE | 1 (5%) | | |
| HEMOSIDEROSIS | 1 (5%) | | |
| #HEPATIC SINUSOID | (20) | (49) | (50) |
| LEUKOCYTOSIS, NOS | | 2 (4%) | 2 (4%) |
| #THYMUS | (15) | (38) | (36) |
| ATROPHY, NOS | | 1 (3%) | |
| CIRCULATORY SYSTEM | | | |
| #HEART | (20) | (50) | (50) |
| FIBROSIS, DIFFUSE | | | 1 (2%) |
| #HEART/ATRIUM | (20) | (50) | (50) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #MYOCARDIUM | (20) | (50) | (50) |
| INFLAMMATION, FOCAL | 1 (5%) | | |
| INFLAMMATION, CHRONIC | 14 (70%) | 33 (66%) | 37 (74%) |
| INFLAMMATION, CHRONIC FOCAL | 2 (10%) | | 2 (4%) |
| FIBROSIS | | 2 (4%) | |
| FIBROSIS, DIFFUSE | | 1 (2%) | |
| DEGENERATION, NOS | 13 (65%) | 1 (2%) | |
| NECROSIS, FOCAL | | | 1 (2%) |
| #ENDOCARDIUM | (20) | (50) | (50) |
| THROMBOSIS, NOS | | | 1 (2%) |
| *ARTERY | (20) | (50) | (50) |
| THROMBOSIS, NOS | 1 (5%) | | |
| INFLAMMATION, NOS | 1 (5%) | | |
| *MESENTERIC ARTERY | (20) | (50) | (50) |
| MINERALIZATION | | | 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 |
|---|---|---|---|
| #LIVER | (20) | (49) | (50) |
| THROMBOSIS, NOS | | | 2 (4%) |
| PERIARTERITIS | 1 (5%) | | |
| #PANCREAS | (20) | (50) | (50) |
| PERIARTERITIS | | 1 (2%) | 3 (6%) |
| *MESENTERY | (20) | (50) | (50) |
| PERIARTERITIS | | | 1 (2%) |
| #PROSTATE | (17) | (48) | (47) |
| PERIARTERITIS | | 1 (2%) | |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| ATROPHY, NOS | 1 (5%) | | |
| #LIVER | (20) | (49) | (50) |
| CYST, NOS | | | 1 (2%) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, CHRONIC DIFFUSE | | 1 (2%) | |
| NECROSIS, NOS | 1 (5%) | 1 (2%) | |
| NECROSIS, FOCAL | | 1 (2%) | 2 (4%) |
| METAMORPHOSIS FATTY | | 3 (6%) | 4 (8%) |
| LIPOIDOSIS | 1 (5%) | 4 (8%) | 4 (8%) |
| BASOPHILIC CYTO CHANGE | | | 1 (2%) |
| HYPERPLASIA, NODULAR | | 1 (2%) | 1 (2%) |
| ANGIECTASIS | | | 1 (2%) |
| #LIVER/CENTRILOBULAR | (20) | (49) | (50) |
| DEGENERATION, NOS | | | 1 (2%) |
| NECROSIS, NOS | | | 1 (2%) |
| METAMORPHOSIS FATTY | | 1 (2%) | 3 (6%) |
| HYPERTROPHY, NOS | | | 1 (2%) |
| #LIVER/HEPATOCYTES | (20) | (49) | (50) |
| NECROSIS, NOS | 1 (5%) | | |
| #BILE DUCT | (20) | (49) | (50) |
| HYPERPLASIA, NOS | 5 (25%) | 8 (16%) | 7 (14%) |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #PANCREAS | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC | 1 (5%) | | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | 1 (5%) | | 1 (2%) |
| #PANCREATIC DUCT | (20) | (50) | (50) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #PANCREATIC ACINUS | (20) | (50) | (50) |
| ATROPHY, NOS | | | 1 (2%) |
| ATROPHY, FOCAL | 3 (15%) | 3 (6%) | 9 (18%) |
| #STOMACH | (20) | (50) | (49) |
| ULCER, NOS | | 1 (2%) | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | 1 (5%) | | 1 (2%) |
| #GASTRIC MUCOSA | (20) | (50) | (49) |
| ULCER, NOS | | | 1 (2%) |
| #GASTRIC SUBMUCOSA | (20) | (50) | (49) |
| INFLAMMATION, GRANULOMATOUS | | 1 (2%) | |
| #DUODENUM | (20) | (49) | (49) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| INFLAMMATION, CHRONIC DIFFUSE | | | 1 (2%) |
| #COLON | (20) | (50) | (48) |
| PARASITISM | | 1 (2%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (50) | (50) |
| CAST, NOS | | | 2 (4%) |
| INFLAMMATION, INTERSTITIAL | 17 (85%) | | 16 (32%) |
| INFLAMMATION, CHRONIC | 1 (5%) | 36 (72%) | 22 (44%) |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| SCLEROSIS | 10 (50%) | | 4 (8%) |
| NEPHROPATHY | 4 (20%) | 40 (80%) | 41 (82%) |
| #KIDNEY/GLOMERULUS | (20) | (50) | (50) |
| DEGENERATION, NOS | 1 (5%) | | |
| #KIDNEY/TUBULE | (20) | (50) | (50) |
| CAST, NOS | 2 (10%) | | |

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

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| DEGENERATION, NOS | | | 1 (2%) |
| PIGMENTATION, NOS | | | 1 (2%) |
| #URINARY BLADDER | (20) | (46) | (49) |
| CALCULUS, NOS | | 1 (2%) | |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (20) | (49) | (50) |
| CYST, NOS | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| ANGIECTASIS | | | 1 (2%) |
| #ADRENAL | (20) | (50) | (49) |
| NECROSIS, NOS | | 1 (2%) | |
| #ADRENAL CORTEX | (20) | (50) | (49) |
| HEMORRHAGE | 1 (5%) | | |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| #ADRENAL MEDULLA | (20) | (50) | (49) |
| HYPERPLASIA, NOS | 1 (5%) | | |
| #THYROID | (20) | (49) | (49) |
| COLLOID CYST | | 1 (2%) | 1 (2%) |
| #PARATHYROID | (17) | (39) | (43) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, DIFFUSE | | | 1 (2%) |
| **REPRODUCTIVE SYSTEM** | | | |
| *MAMMARY GLAND | (20) | (50) | (50) |
| GALACTOCELE | | | 1 (2%) |
| HYPERPLASIA, DIFFUSE | 2 (10%) | | 1 (2%) |
| LACTATION | 1 (5%) | | |
| #PROSTATE | (17) | (48) | (47) |
| INFLAMMATION, INTERSTITIAL | | 1 (2%) | |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | 1 (2%) |
| INFLAMMATION, CHRONIC | 1 (6%) | 2 (4%) | 1 (2%) |
| INFLAMMATION, CHRONIC SUPPURATIV | | 1 (2%) | |
| HYPERPLASIA, EPITHELIAL | 2 (12%) | | 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 |
|---|---|---|---|
| #PROSTATIC GLAND | (17) | (48) | (47) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, ACUTE FOCAL | | | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| #TESTIS | (20) | (50) | (50) |
| INFARCT, NOS | | | 1 (2%) |
| HYPERPLASIA, INTERSTITIAL CELL | | | 2 (4%) |
| *EPIDIDYMIS | (20) | (50) | (50) |
| GRANULOMA, SPERMATIC | | 2 (4%) | 1 (2%) |
| *SPERMATIC CORD | (20) | (50) | (50) |
| ABSCESS, NOS | 1 (5%) | | |
| GRANULOMA, NOS | 1 (5%) | | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (20) | (50) | (50) |
| CATARACT | 16 (80%) | 21 (42%) | 15 (30%) |
| *EYE/CORNEA | (20) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | 1 (5%) | | |
| *EYE/RETINA | (20) | (50) | (50) |
| DEGENERATION, NOS | 16 (80%) | 17 (34%) | 12 (24%) |
| MUSCULOSKELETAL SYSTEM | | | |
| *BONE | (20) | (50) | (50) |
| FIBROUS OSTEODYSTROPHY | | | 1 (2%) |
| *MUSCLE HIP/THIGH | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | 1 (2%) |
| BODY CAVITIES | | | |
| *PERITONEUM | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC | | 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 |
|---|---|---|---|
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| **ALL OTHER SYSTEMS** | | | |
| NONE | | | |
| **SPECIAL MORPHOLOGY SUMMARY** | | | |
| NO LESION REPORTED | | 1 | |

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

## TABLE C2.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINSTERED 2, 4, 6-TRICHLOROPHENOL 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) |
| ABSCESS, NOS | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG/BRONCHIOLE | (18) | (50) | (50) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| #LUNG | (18) | (50) | (50) |
| CONGESTION, NOS | | | 1 (2%) |
| HEMORRHAGE | | | 1 (2%) |
| INFLAMMATION, ACUTE SUPPURATIVE | 1 (6%) | | |
| GRANULOMA, NOS | | 1 (2%) | |
| INFLAMMATION, FOCAL GRANULOMATOU | | | 1 (2%) |
| HYPERPLASIA, ADENOMATOUS | 1 (6%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| *BLOOD | (20) | (50) | (50) |
| LEUKOCYTOSIS, NOS | | 3 (6%) | 3 (6%) |
| LEUKOCYTOSIS, NEUTROPHILIC | | 2 (4%) | |
| MONOCYTOSIS | | 2 (4%) | |
| #BONE MARROW | (20) | (50) | (50) |
| HYPERPLASIA, DIFFUSE | | 16 (32%) | 2 (4%) |
| #SPLEEN | (20) | (50) | (50) |
| INFARCT HEMORRHAGIC | 1 (5%) | | |
| HEMOSIDEROSIS | 12 (60%) | 14 (28%) | 13 (26%) |
| HEMATOPOIESIS | | 1 (2%) | 1 (2%) |
| GRANULOPOIESIS | | 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 |
|---|---|---|---|
| #SPLENIC FOLLICLES | (20) | (50) | (50) |
| ATROPHY, NOS | | | 1 (2%) |
| #SPLENIC RED PULP | (20) | (50) | (50) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| #LYMPH NODE | (20) | (50) | (50) |
| HEMOSIDEROSIS | 8 (40%) | | 1 (2%) |
| HYPERPLASIA, DIFFUSE | | | 1 (2%) |
| #MEDIASTINAL L.NODE | (20) | (50) | (50) |
| EDEMA, NOS | | | 1 (2%) |
| HEMORRHAGE | | | 1 (2%) |
| HEMOSIDEROSIS | | | 1 (2%) |
| #MESENTERIC L. NODE | (20) | (50) | (50) |
| HISTIOCYTOSIS | | 1 (2%) | |
| LYMPHOCYTOSIS | | 1 (2%) | |
| #HEPATIC SINUSOID | (20) | (50) | (50) |
| LEUKOCYTOSIS, NOS | | 1 (2%) | |
| CIRCULATORY SYSTEM | | | |
| #MANDIBULAR L. NODE | (20) | (50) | (50) |
| LYMPHANGIECTASIS | | | 1 (2%) |
| #HEART | (20) | (50) | (50) |
| PERIARTERITIS | | | 1 (2%) |
| #HEART/ATRIUM | (20) | (50) | (50) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #MYOCARDIUM | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC | 14 (70%) | 34 (68%) | 40 (80%) |
| FIBROSIS | | | 1 (2%) |
| DEGENERATION, NOS | | 2 (4%) | 2 (4%) |
| #CARDIAC VALVE | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| #PANCREAS | (20) | (50) | (44) |
| PERIARTERITIS | | 1 (2%) | 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 |
|---|---|---|---|
| *MESENTERY | (20) | (50) | (50) |
| PERIARTERITIS | | 1 (2%) | |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (19) | (50) | (48) |
| INFLAMMATION, CHRONIC | | 1 (2%) | 3 (6%) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| ATROPHY, NOS | | | 1 (2%) |
| #LIVER | (20) | (50) | (50) |
| INFLAMMATION, FOCAL | | 1 (2%) | |
| INFLAMMATION, CHRONIC | | 4 (8%) | |
| GRANULOMA, NOS | | | 1 (2%) |
| NECROSIS, NOS | | 3 (6%) | 1 (2%) |
| METAMORPHOSIS FATTY | 1 (5%) | 2 (4%) | 13 (26%) |
| LIPOIDOSIS | | | 3 (6%) |
| BASOPHILIC CYTO CHANGE | 2 (10%) | | |
| FOCAL CELLULAR CHANGE | 1 (5%) | 1 (2%) | 1 (2%) |
| HYPERPLASIA, NODULAR | | 3 (6%) | |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| #LIVER/CENTRILOBULAR | (20) | (50) | (50) |
| INFLAMMATION, NECROTIZING | | 1 (2%) | |
| LIPOIDOSIS | | 1 (2%) | |
| #LIVER/PERIPORTAL | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| #LIVER/HEPATOCYTES | (20) | (50) | (50) |
| METAMORPHOSIS FATTY | 1 (5%) | | |
| #BILE DUCT | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| HYPERPLASIA, NOS | 1 (5%) | | 3 (6%) |
| #PANCREAS | (20) | (50) | (44) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | | | 2 (5%) |
| #PANCREATIC ACINUS | (20) | (50) | (44) |
| FIBROSIS, FOCAL | | | 1 (2%) |
| ATROPHY, FOCAL | 2 (10%) | 6 (12%) | 7 (16%) |

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

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #ESOPHAGUS | (20) | (50) | (48) |
| INFLAMMATION, NECROTIZING | | 1 (2%) | |
| #STOMACH | (20) | (50) | (49) |
| ULCER, NOS | | | 1 (2%) |
| INFLAMMATION, NECROTIZING | | 1 (2%) | |
| #SMALL INTESTINE | (20) | (48) | (48) |
| ULCER, PERFORATED | | 2 (4%) | |
| ADHESION, NOS | | 1 (2%) | |
| #DUODENAL SEROSA | (20) | (48) | (48) |
| INFLAMMATION, CHRONIC | | | 2 (4%) |
| #COLON | (20) | (49) | (47) |
| PARASITISM | | 2 (4%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (50) | (50) |
| HYDRONEPHROSIS | | | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | 8 (40%) | | 13 (26%) |
| INFLAMMATION, CHRONIC | 1 (5%) | 27 (54%) | 26 (52%) |
| INFLAMMATION, CHRONIC FOCAL | | 2 (4%) | |
| SCLEROSIS | 1 (5%) | | |
| NEPHROPATHY | 8 (40%) | 17 (34%) | 21 (42%) |
| GLOMERULOSCLEROSIS, NOS | | | 1 (2%) |
| #KIDNEY/GLOMERULUS | (20) | (50) | (50) |
| NEPHROPATHY | 1 (5%) | | |
| #URINARY BLADDER | (19) | (48) | (48) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (20) | (49) | (49) |
| CYST, NOS | 2 (10%) | 3 (6%) | 1 (2%) |
| MULTIPLE CYSTS | | | 2 (4%) |
| #ADRENAL | (20) | (50) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 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 |
|---|---|---|---|
| #ADRENAL CORTEX | (20) | (50) | (49) |
| METAMORPHOSIS FATTY | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, NODULAR | | | 1 (2%) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #THYROID | (20) | (49) | (50) |
| COLLOID CYST | | | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (50) | (50) |
| DILATATION, NOS | | 1 (2%) | |
| DILATATION/DUCTS | 1 (5%) | 2 (4%) | 1 (2%) |
| GALACTOCELE | | 1 (2%) | 1 (2%) |
| CYST, NOS | | 1 (2%) | |
| HEMATOMA, NOS | | | 1 (2%) |
| FIBROSIS | | 1 (2%) | |
| HYPERPLASIA, EPITHELIAL | 2 (10%) | | |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| *MAMMARY DUCT | (20) | (50) | (50) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| *VAGINA | (20) | (50) | (50) |
| PROLAPSE | | | 1 (2%) |
| EPIDERMAL INCLUSION CYST | 1 (5%) | | |
| #UTERUS | (20) | (50) | (49) |
| GRANULATION, TISSUE | | | 1 (2%) |
| HEMOSIDEROSIS | | | 1 (2%) |
| #CERVIX UTERI | (20) | (50) | (49) |
| PROLAPSE | | | 1 (2%) |
| #UTERUS/ENDOMETRIUM | (20) | (50) | (49) |
| NECROSIS, FOCAL | | | 1 (2%) |
| INFARCT, NOS | | | 1 (2%) |
| #OVARY | (20) | (50) | (49) |
| FOLLICULAR CYST, NOS | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| #CEREBRAL VENTRICLE | (20) | (50) | (49) |
| DILATATION, 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 |
|---|---|---|---|
| SPECIAL SENSE ORGANS | | | |
| *EYE | (20) | (50) | (50) |
| CATARACT | 4 (20%) | 8 (16%) | 3 (6%) |
| *EYE/CORNEA | (20) | (50) | (50) |
| INFLAMMATION, NOS | 1 (5%) | | |
| *EYE/RETINA | (20) | (50) | (50) |
| DEGENERATION, NOS | 4 (20%) | 7 (14%) | 3 (6%) |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| *PERITONEUM | (20) | (50) | (50) |
| INFLAMMATION, FOCAL | | 1 (2%) | |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| *MESENTERY | (20) | (50) | (50) |
| STEATITIS | | | 2 (4%) |
| NECROSIS, FOCAL | | | 1 (2%) |
| 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 2,4,6-TRICHLOROPHENOL IN THE DIET

## TABLE D1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED 2, 4, 6-TRICHLOROPHENOL IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | | 1 | |
| ANIMALS NECROPSIED | 20 | 49 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 49 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (20) | (49) | (49) |
| CYST, NOS | 1 (5%) | | |
| *SUBCUT TISSUE | (20) | (49) | (49) |
| INFLAMMATION, NOS | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (48) | (47) |
| INFLAMMATION, CHRONIC FOCAL | 1 (5%) | | |
| GRANULOMA, NOS | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *BLOOD | (20) | (49) | (49) |
| LEUKOCYTOSIS, NEUTROPHILIC | 1 (5%) | | |
| #BONE MARROW | (20) | (47) | (47) |
| HYPOPLASIA, NOS | | 1 (2%) | |
| HYPERPLASIA, NOS | 1 (5%) | | |
| HYPERPLASIA, HEMATOPOIETIC | | 1 (2%) | |
| #SPLEEN | (20) | (49) | (47) |
| HYPERPLASIA, LYMPHOID | 3 (15%) | 2 (4%) | 2 (4%) |
| HEMATOPOIESIS | 1 (5%) | 1 (2%) | |
| #LYMPH NODE | (19) | (46) | (47) |
| CONGESTION, NOS | | | 1 (2%) |
| HEMOSIDEROSIS | | | 3 (6%) |
| HYPERPLASIA, NOS | 1 (5%) | | |
| PLASMACYTOSIS | 1 (5%) | | |

# 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, LYMPHOID | | | 1 (2%) |
| #MESENTERIC L. NODE | (19) | (46) | (47) |
| CONGESTION, NOS | 3 (16%) | 1 (2%) | 4 (9%) |
| HEMORRHAGE | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | | 4 (9%) | 3 (6%) |
| #LUNG/ALVEOLI | (20) | (48) | (47) |
| HISTIOCYTOSIS | | 1 (2%) | |
| #LIVER | (20) | (49) | (47) |
| HEMATOPOIESIS | 1 (5%) | 1 (2%) | |
| #PEYERS PATCH | (20) | (46) | (43) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | 1 (2%) |
| CIRCULATORY SYSTEM | | | |
| #HEART | (20) | (49) | (47) |
| PERIVASCULITIS | | 1 (2%) | |
| #HEART/ATRIUM | (20) | (49) | (47) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #MYOCARDIUM | (20) | (49) | (47) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | 1 (2%) |
| INFLAMMATION, PYOGRANULOMATOUS | | | 1 (2%) |
| *CORONARY ARTERY | (20) | (49) | (49) |
| INFLAMMATION, CHRONIC | | 1 (2%) | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| *MESENTERIC ARTERY | (20) | (49) | (49) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| *RENAL ARTERY | (20) | (49) | (49) |
| INFLAMMATION, CHRONIC | | 1 (2%) | 1 (2%) |
| *EPIDIDYMIS | (20) | (49) | (49) |
| PERIARTERITIS | | | 1 (2%) |
| #THYROID | (20) | (47) | (46) |
| PERIARTERITIS | | | 1 (2%) |
| PERIVASCULITIS | | 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 |
|---|---|---|---|
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (20) | (48) | (47) |
| INFLAMMATION, CHRONIC | 7 (35%) | 10 (21%) | 14 (30%) |
| INFLAMMATION, CHRONIC FOCAL | | 2 (4%) | |
| #LIVER | (20) | (49) | (47) |
| INFLAMMATION, NECROTIZING | | | 2 (4%) |
| INFLAMMATION, CHRONIC | 1 (5%) | | |
| INFLAMMATION, CHRONIC FOCAL | 1 (5%) | | |
| NECROSIS, NOS | 2 (10%) | 1 (2%) | |
| INFARCT, NOS | 1 (5%) | | |
| INFARCT, FOCAL | 1 (5%) | | 1 (2%) |
| LIPOIDOSIS | 1 (5%) | | 1 (2%) |
| HYPERPLASIA, NODULAR | 1 (5%) | | 3 (6%) |
| HYPERPLASIA, FOCAL | 1 (5%) | | |
| ANGIECTASIS | | | 1 (2%) |
| #LIVER/CENTRILOBULAR | (20) | (49) | (47) |
| NECROSIS, NOS | 1 (5%) | | |
| #LIVER/HEPATOCYTES | (20) | (49) | (47) |
| DEGENERATION, NOS | | 1 (2%) | |
| HYPERTROPHY, FOCAL | | 1 (2%) | |
| HYPERPLASIA, NODULAR | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, NOS | | 10 (20%) | 2 (4%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| #BILE DUCT | (20) | (49) | (47) |
| INFLAMMATION, NOS | | | 1 (2%) |
| INFLAMMATION, CHRONIC | | | 3 (6%) |
| INFLAMMATION, CHRONIC FOCAL | | | 2 (4%) |
| INFLAMMATION CHRONIC CYSTIC | | | 1 (2%) |
| NECROSIS, NOS | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| #PANCREAS | (20) | (48) | (47) |
| HEMORRHAGE | 1 (5%) | | |
| STEATITIS | 1 (5%) | | |
| #STOMACH | (20) | (47) | (46) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| #SMALL INTESTINE | (20) | (46) | (43) |
| DIVERTICULUM | | | 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 |
|---|---|---|---|
| #COLON | (19) | (47) | (46) |
| PARASITISM | 1 (5%) | | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (20) | (49) | (47) |
| INFLAMMATION, INTERSTITIAL | | 1 (2%) | |
| INFLAMMATION, CHRONIC | 9 (45%) | 4 (8%) | 10 (21%) |
| PYELONEPHRITIS, CHRONIC | | | 2 (4%) |
| HYPERPLASIA, TUBULAR CELL | 1 (5%) | | |
| #KIDNEY/PELVIS | (20) | (49) | (47) |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| #URINARY BLADDER | (18) | (48) | (45) |
| CALCULUS, NOS | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| **ENDOCRINE SYSTEM** | | | |
| #ADRENAL CORTEX | (20) | (49) | (45) |
| HYPERPLASIA, NODULAR | 1 (5%) | | |
| #THYROID | (20) | (47) | (46) |
| ULTIMOBRANCHIAL CYST | | | 1 (2%) |
| INFLAMMATION, FOCAL GRANULOMATOU | | | 1 (2%) |
| **REPRODUCTIVE SYSTEM** | | | |
| *PREPUTIAL GLAND | (20) | (49) | (49) |
| ABSCESS, CHRONIC | | 1 (2%) | |
| #PROSTATE | (20) | (48) | (42) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| #TESTIS | (19) | (49) | (46) |
| INFLAMMATION, FOCAL GRANULOMATOU | | 1 (2%) | |
| *EPIDIDYMIS | (20) | (49) | (49) |
| DILATATION, NOS | 1 (5%) | | |
| STEATITIS | 1 (5%) | | |

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

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| GRANULOMA, SPERMATIC | | | 1 (2%) |
| NECROSIS, FAT | 1 (5%) | | |
| **NERVOUS SYSTEM** | | | |
| NONE | | | |
| **SPECIAL SENSE ORGANS** | | | |
| NONE | | | |
| **MUSCULOSKELETAL SYSTEM** | | | |
| *ISCHIOCAVERNOSUS MUS | (20) | (49) | (49) |
| PARASITISM | 1 (5%) | | |
| **BODY CAVITIES** | | | |
| *MESENTERY | (20) | (49) | (49) |
| GRANULATION, TISSUE | | 1 (2%) | |
| **ALL OTHER SYSTEMS** | | | |
| HEAD | | | |
| HEMATOMA, ORGANIZED | | | 1 |
| **SPECIAL MORPHOLOGY SUMMARY** | | | |
| NO LESION REPORTED | 2 | | 2 |
| ANIMAL MISSING/NO NECROPSY | | 1 | |
| AUTOLYSIS/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 2, 4, 6-TRICHLOROPHENOL IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | | | 2 |
| ANIMALS NECROPSIED | 20 | 50 | 48 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 50 | 48 |
| INTEGUMENTARY SYSTEM | | | |
| NONE | | | |
| RESPIRATORY SYSTEM | | | |
| #LUNG/BRONCHIOLE | (20) | (50) | (48) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| #LUNG | (20) | (50) | (48) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (20) | (50) | (48) |
| HYPERPLASIA, HEMATOPOIETIC | | | 1 (2%) |
| #SPLEEN | (20) | (50) | (48) |
| INFLAMMATION, GRANULOMATOUS | | | 1 (2%) |
| HEMOSIDEROSIS | 3 (15%) | 2 (4%) | |
| HYPERPLASIA, RETICULUM CELL | 1 (5%) | | |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | 4 (8%) |
| HEMATOPOIESIS | | 1 (2%) | 1 (2%) |
| #SPLENIC FOLLICLES | (20) | (50) | (48) |
| NECROSIS, NOS | | 1 (2%) | |
| #LYMPH NODE | (20) | (47) | (48) |
| HYPERPLASIA, RETICULUM CELL | 1 (5%) | | |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #MANDIBULAR L. NODE | (20) | (47) | (48) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | 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 |
|---|---|---|---|
| #ABDOMINAL LYMPH NODE | (20) | (47) | (48) |
| INFLAMMATION, GRANULOMATOUS | | | 1 (2%) |
| #MESENTERIC L. NODE | (20) | (47) | (48) |
| CONGESTION, NOS | | 1 (2%) | 2 (4%) |
| EOSINOPHILIC INFILTRATE | | | 1 (2%) |
| HYPERPLASIA, RETICULUM CELL | | | 2 (4%) |
| HYPERPLASIA, LYMPHOID | | 2 (4%) | 1 (2%) |
| #LIVER | (20) | (50) | (48) |
| HEMATOPOIESIS | 1 (5%) | | |
| #PEYERS PATCH | (19) | (50) | (48) |
| HYPERPLASIA, RETICULUM CELL | | | 2 (4%) |
| HYPERPLASIA, LYMPHOID | | 2 (4%) | 1 (2%) |
| CIRCULATORY SYSTEM | | | |
| *MULTIPLE ORGANS | (20) | (50) | (48) |
| PERIARTERITIS | | 1 (2%) | |
| #LUNG | (20) | (50) | (48) |
| PERIVASCULITIS | | | 1 (2%) |
| #MYOCARDIUM | (20) | (48) | (48) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| #OVARY | (20) | (50) | (48) |
| THROMBOSIS, NOS | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (20) | (46) | (47) |
| INFLAMMATION, NOS | 1 (5%) | | |
| INFLAMMATION, CHRONIC | 10 (50%) | 15 (33%) | 18 (38%) |
| INFLAMMATION, CHRONIC FOCAL | 2 (10%) | | |
| #LIVER | (20) | (50) | (48) |
| INFLAMMATION, NECROTIZING | | | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | | 1 (2%) | |
| INFLAMMATION, CHRONIC | 6 (30%) | 6 (12%) | 16 (33%) |
| INFLAMMATION, CHRONIC NECROTIZIN | | | 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 |
|---|---|---|---|
| NECROSIS, NOS | | 1 (2%) | 1 (2%) |
| NECROSIS, FOCAL | | 1 (2%) | |
| INFARCT, FOCAL | | | 1 (2%) |
| LIPOIDOSIS | | | 2 (4%) |
| HYPERTROPHY, NOS | | | 1 (2%) |
| HYPERPLASIA, NODULAR | 1 (5%) | | |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #LIVER/HEPATOCYTES | (20) | (50) | (48) |
| HYPERPLASIA, NOS | | | 3 (6%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | 2 (4%) |
| #BILE DUCT | (20) | (50) | (48) |
| DILATATION, NOS | | | 1 (2%) |
| INFLAMMATION, CHRONIC | | | 2 (4%) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #PANCREAS | (19) | (48) | (48) |
| CYSTIC DUCTS | | | 1 (2%) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| #PANCREATIC DUCT | (19) | (48) | (48) |
| DILATATION, NOS | 1 (5%) | | |
| CYST, NOS | | 1 (2%) | |
| #STOMACH | (20) | (50) | (47) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| #COLON | (20) | (48) | (47) |
| PARASITISM | | 3 (6%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (50) | (48) |
| INFLAMMATION, CHRONIC | 6 (30%) | 4 (8%) | 6 (13%) |
| PYELONEPHRITIS, CHRONIC | 4 (20%) | 5 (10%) | 3 (6%) |
| INFARCT, NOS | | | 1 (2%) |
| #KIDNEY/CORTEX | (20) | (50) | (48) |
| INFARCT, FOCAL | | 1 (2%) | |
| #KIDNEY/PELVIS | (20) | (50) | (48) |
| INFLAMMATION, FOCAL | 1 (5%) | | |

# 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%) | | 2 (4%) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | 2 (4%) |
| #URINARY BLADDER | (20) | (47) | (46) |
| INFLAMMATION, CHRONIC | 1 (5%) | 9 (19%) | 6 (13%) |
| INFLAMMATION, CHRONIC FOCAL | 2 (10%) | 1 (2%) | |
| INFLAMMATION, CHRONIC DIFFUSE | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #ADRENAL CORTEX | (20) | (48) | (46) |
| HYPERPLASIA, NODULAR | 1 (5%) | | |
| #THYROID | (20) | (48) | (45) |
| HYPERPLASIA, FOLLICULAR-CELL | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| #UTERUS | (20) | (50) | (48) |
| HYDROMETRA | | 1 (2%) | |
| #UTERUS/ENDOMETRIUM | (20) | (50) | (48) |
| CYST, NOS | 1 (5%) | 1 (2%) | |
| MULTIPLE CYSTS | 2 (10%) | 1 (2%) | |
| HYPERPLASIA, DIFFUSE | | 3 (6%) | |
| HYPERPLASIA, PAPILLARY | | 1 (2%) | |
| HYPERPLASIA, CYSTIC | 1 (5%) | 5 (10%) | 1 (2%) |
| #UTERUS/MYOMETRIUM | (20) | (50) | (48) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| #OVARY | (20) | (50) | (48) |
| FOLLICULAR CYST, NOS | | 1 (2%) | 1 (2%) |
| NERVOUS SYSTEM | | | |
| #BRAIN/MENINGES | (20) | (50) | (48) |
| INFLAMMATION, CHRONIC | 1 (5%) | | |
| SPECIAL SENSE ORGANS | | | |
| 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 |
|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | |
| *SKELETAL MUSCLE | (20) | (50) | (48) |
| PARASITISM | | 1 (2%) | |
| BODY CAVITIES | | | |
| *PERITONEUM | (20) | (50) | (48) |
| INFLAMMATION, GRANULOMATOUS | | | 1 (2%) |
| *PLEURA | (20) | (50) | (48) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| *MESENTERY | (20) | (50) | (48) |
| CYST, NOS | 1 (5%) | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NO LESION REPORTED | | 2 | |
| ANIMAL MISSING/NO NECROPSY | | | 2 |
| AUTO/NECROPSY/HISTO PERF | | | 1 |

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

# APPENDIX E

## ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED 2,4,6-TRICHLOROPHENOL IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 2,4,6-Trichlorophenol in the Diet (a)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Integumentary System: | | | |
| Trichoepithelioma (b) | 2/20 (10) | 4/50 (8) | 2/50 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.800 | 0.400 |
| Lower Limit | | 0.128 | 0.032 |
| Upper Limit | | 8.436 | 5.277 |
| Weeks to First Observed Tumor | 107 | 106 | 106 |
| Lung: Alveolar/Bronchiolar | | | |
| Carcinoma (b) | 2/18 (11) | 1/50 (2) | 1/50 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.180 | 0.180 |
| Lower Limit | | 0.003 | 0.003 |
| Upper Limit | | 3.307 | 3.307 |
| Weeks to First Observed Tumor | 107 | 86 | 106 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b) | 2/18 (11) | 1/50 (2) | 2/50 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.180 | 0.360 |
| Lower Limit | | 0.003 | 0.029 |
| Upper Limit | | 3.307 | 4.740 |
| Weeks to First Observed Tumor | 107 | 86 | 106 |
| Hematopoietic System: Monocytic Leukemia (b) | 3/20 (15) | 23/50 (46) | 28/50 (56) |
| P Values (c,d) | P = 0.003 | P = 0.013 | P = 0.002 |
| Relative Risk (f) | | 3.067 | 3.733 |
| Lower Limit | | 1.095 | 1.373 |
| Upper Limit | | 14.502 | 17.192 |
| Weeks to First Observed Tumor | 107 | 64 | 69 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Hematopoietic System: | | | |
| Lymphoma or Leukemia (b) | 4/20 (20) | 25/50 (50) | 29/50 (58) |
| P Values (c,d) | P = 0.006 | P = 0.019 | P = 0.004 |
| Relative Risk (f) | | 2.500 | 2.900 |
| Lower Limit | | 1.036 | 1.230 |
| Upper Limit | | 8.761 | 9.922 |
| Weeks to First Observed Tumor | 107 | 64 | 69 |
| Pituitary: Chromophobe Adenoma (b) | 10/20 (50) | 7/49 (14) | 4/50 (8) |
| P Values (c,d) | P less than 0.001 (N) | P = 0.003 (N) | P less than 0.001 (N) |
| Departure from Linear Trend (e) | P = 0.044 | | |
| Relative Risk (f) | | 0.286 | 0.160 |
| Lower Limit | | 0.117 | 0.045 |
| Upper Limit | | 0.718 | 0.486 |
| Weeks to First Observed Tumor | 107 | 106 | 106 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Adrenal: Pheochromocytoma (b) | 3/20 (15) | 2/50 (4) | 6/49 (12) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.267 | 0.816 |
| Lower Limit | | 0.024 | 0.199 |
| Upper Limit | | 2.190 | 4.706 |
| Weeks to First Observed Tumor | 107 | 84 | 79 |
| Thyroid: C-cell Carcinoma or Adenoma (b) | 2/20 (10) | 2/49 (4) | 5/49 (10) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.408 | 1.020 |
| Lower Limit | | 0.032 | 0.188 |
| Upper Limit | | 5.381 | 10.204 |
| Weeks to First Observed Tumor | 107 | 96 | 98 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Thyroid: Adenoma, NOS, or Adenocarcinoma, NOS (b) | 1/20 (5) | 0/49 (0) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.000 | 1.224 |
| Lower Limit | | 0.000 | 0.108 |
| Upper Limit | | 7.624 | 62.958 |
| Weeks to First Observed Tumor | 107 | -- | 79 |
| Parathyroid: Adenoma, NOS, or Adenocarcinoma, NOS (b) | 0/17 (0) | 2/39 (5) | 0/43 (0) |
| P Values (c,d) | N.S. | N.S. | -- |
| Relative Risk (f) | | Infinite | -- |
| Lower Limit | | 0.135 | -- |
| Upper Limit | | Infinite | -- |
| Weeks to First Observed Tumor | -- | 106 | -- |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Mammary Gland: Adenoma, NOS (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 Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.345 | 1.345 |
| Weeks to First Observed Tumor | 107 | -- | -- |
| Testis: Interstitial-cell Tumor (b) | 18/20 (90) | 40/50 (80) | 38/50 (76) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.889 | 0.844 |
| Lower Limit | | 0.775 | 0.735 |
| Upper Limit | | 1.190 | 1.147 |
| Weeks to First Observed Tumor | 103 | 84 | 98 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

(a) Dosed groups received 5,000 or 10,000 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 2,4,6-Trichorophenol in the Diet (a)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Integumentary System: Fibroadenoma of the Subcutaneous Tissue (b) | 2/20 (10) | 1/50 (2) | 0/50 (0) |
| P Values (c,d) | P = 0.035 (N) | N.S. | N.S. |
| Relative Risk (f) | | 0.200 | 0.000 |
| Lower Limit | | 0.004 | 0.000 |
| Upper Limit | | 3.681 | 1.345 |
| Weeks to First Observed Tumor | 92 | 92 | -- |
| Hematopoietic System: Monocytic Leukemia (b) | 3/20 (15) | 11/50 (22) | 10/50 (20) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.467 | 1.333 |
| Lower Limit | | 0.450 | 0.398 |
| Upper Limit | | 7.595 | 7.002 |
| Weeks to First Observed Tumor | 103 | 69 | 104 |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 2,4,6-Trichorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Hematopoietic System: Lymphoma or Leukemia (b) | 3/20 (15) | 11/50 (22) | 13/50 (26) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.467 | 1.733 |
| Lower Limit | | 0.450 | 0.556 |
| Upper Limit | | 7.594 | 8.773 |
| Weeks to First Observed Tumor | 103 | 69 | 55 |
| Pituitary: Carcinoma, NOS, or Adenoma, NOS (b) | 3/20 (15) | 3/49 (6) | 1/49 (2) |
| P Values (c,d) | P = 0.042 (N) | N.S. | N.S. |
| Relative Risk (f) | | 0.408 | 0.136 |
| Lower Limit | | 0.061 | 0.003 |
| Upper Limit | | 2.857 | 1.599 |
| Weeks to First Observed Tumor | 92 | 92 | 106 |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 2,4,6-Trichorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Pituitary: Chromophobe Carcinoma or Adenoma (b) | 4/20 (20) | 11/49 (22) | 8/49 (16) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.122 | 0.816 |
| Lower Limit | | 0.392 | 0.255 |
| Upper Limit | | 4.404 | 3.392 |
| Weeks to First Observed Tumor | 107 | 107 | 106 |
| Thyroid: C-cell Adenoma (b) | 3/20 (15) | 1/49 (2) | 1/50 (2) |
| P Values (c,d) | P = 0.041 (N) | N.S. | N.S. |
| Relative Risk (f) | | 0.136 | 0.133 |
| Lower Limit | | 0.003 | 0.003 |
| Upper Limit | | 1.599 | 1.568 |
| Weeks to First Observed Tumor | 107 | 106 | 106 |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 2,4,6-Trichorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Mammary Gland: Fibroadenoma (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 Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.345 | 1.345 |
| Weeks to First Observed Tumor | 92 | -- | -- |
| Uterus: Endometrial Stromal Polyp (b) | 1/20 (5) | 3/50 (6) | 2/49 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.200 | 0.816 |
| Lower Limit | | 0.106 | 0.046 |
| Upper Limit | | 61.724 | 47.195 |
| Weeks to First Observed Tumor | 100 | 106 | 87 |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 2,4,6-Trichorophenol in the Diet (a)

(continued)

(a) Dosed groups received 5,000 or 10,000 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 2,4,6-TRICHLOROPHENOL IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 2,4,6-Trichlorophenol in the Diet (a)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma (b) | 2/20 (10) | 6/48 (13) | 1/47 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.250 | 0.213 |
| Lower Limit | | 0.253 | 0.004 |
| Upper Limit | | 12.039 | 3.909 |
| Weeks to First Observed Tumor | 105 | 93 | 105 |
| Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b) | 3/20 (15) | 13/48 (27) | 7/47 (15) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.806 | 0.993 |
| Lower Limit | | 0.579 | 0.261 |
| Upper Limit | | 9.115 | 5.532 |
| Weeks to First Observed Tumor | 105 | 93 | 95 |

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Hematopoietic System: Malignant Lymphoma (b) | 2/20 (10) | 3/49 (6) | 1/49 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.612 | 0.204 |
| Lower Limit | | 0.078 | 0.004 |
| Upper Limit | | 6.996 | 3.754 |
| Weeks to First Observed Tumor | 105 | 105 | 105 |
| All Sites: Hemangiosarcoma (b) | 1/20 (5) | 5/49 (10) | 4/49 (8) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 2.041 | 1.633 |
| Lower Limit | | 0.254 | 0.179 |
| Upper Limit | | 94.440 | 78.704 |
| Weeks to First Observed Tumor | 105 | 102 | 91 |

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| All Sites: Hemangiosarcoma or Hemangioma (b) | 2/20 (10) | 5/49 (10) | 5/49 (10) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.020 | 1.020 |
| Lower Limit | | 0.188 | 0.188 |
| Upper Limit | | 10.204 | 10.204 |
| Weeks to First Observed Tumor | 105 | 102 | 91 |
| Liver: Hepatocellular Carcinoma (b) | 1/20 (5) | 10/49 (20) | 7/47 (15) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 4.082 | 2.979 |
| Lower Limit | | 0.655 | 0.429 |
| Upper Limit | | 172.772 | 131.059 |
| Weeks to First Observed Tumor | 97 | 102 | 105 |

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 4/20 (20) | 32/49 (65) | 39/47 (83) |
| P Values (c,d) | P less than 0.001 | P = 0.001 | P less than 0.001 |
| Relative Risk (f) | | 3.265 | 4.149 |
| Lower Limit | | 1.408 | 1.878 |
| Upper Limit | | 10.877 | 12.093 |
| Weeks to First Observed Tumor | 97 | 102 | 95 |

(a) Dosed groups received 5,000 or 10,000 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 F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 2,4,6-Trichlorophenol in the Diet (a)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b) | 1/20 (5) | 4/50 (8) | 3/48 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.600 | 1.250 |
| Lower Limit | | 0.175 | 0.110 |
| Upper Limit | | 77.169 | 64.251 |
| Weeks to First Observed Tumor | 105 | 105 | 105 |
| Hematopoietic System: Malignant Lymphoma (b) | 2/20 (10) | 12/50 (24) | 7/48 (15) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 2.400 | 1.458 |
| Lower Limit | | 0.614 | 0.316 |
| Upper Limit | | 20.902 | 13.664 |
| Weeks to First Observed Tumor | 91 | 82 | 35 |

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| All Sites: Hemangiosarcoma or Hemangioma (b) | 1/20 (5) | 4/50 (8) | 5/50 (10) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.600 | 2.000 |
| Lower Limit | | 0.175 | 0.249 |
| Upper Limit | | 77.169 | 92.596 |
| Weeks to First Observed Tumor | 105 | 86 | 105 |
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 1/20 (5) | 12/50 (24) | 24/48 (50) |
| P Values (c,d) | P less than 0.001 | N.S. | P less than 0.001 |
| Relative Risk (f) | | 4.800 | 10.000 |
| Lower Limit | | 0.803 | 1.872 |
| Upper Liit | | 200.025 | 394.581 |
| Weeks to First Observed Tumor | 105 | 105 | 105 |

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 2,4,6-Trichlorophenol in the Diet (a)

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 1/20 (5) | 12/50 (24) | 24/48 (50) |
| P Values (c,d) | P less than 0.001 | N.S. | P less than 0.001 |
| Relative Risk (f) | | 4.800 | 10.000 |
| Lower Limit | | 0.803 | 1.872 |
| Upper Liit | | 200.025 | 394.581 |
| Weeks to First Observed Tumor | 105 | 105 | 105 |



(a) Dosed groups received time-weighted average doses of 5,214 or 10,428 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 2,4,6-Trichlorophenol* 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 2,4,6-Trichlorophenol.

The reviewer for the report on the bioassay of 2,4,6-Trichlorophenol agreed with the conclusion that the compound was carcinogenic in both rats and mice. After a brief description of the experimental design, he said that animal survival was adequate. He moved that the report on the bioassay of 2,4,6-Trichlorophenol be accepted as written. The motion was seconded and approved without objection.

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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