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# BIOASSAY OF METHYL PARATHION FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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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 methyl parathion 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 a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of methyl parathion 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. Histopathologic evaluations for rats and mice were performed by Dr. D. A. Willigan (3). The diagnoses included in this report represent his interpretations.

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

methods selected for the bioassay program by Dr. J. J. Gart (6). The chemicals used in this bioassay were analyzed at FCRC by Dr. W. Zielinsky (1). The chemical analyses and narrative were reviewed and approved by Dr W. 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. Waitz, Ms. M. S. King, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI 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 methyl parathion 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 methyl parathion at one of two doses, either 20 or 40 ppm, for 105 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at the end of administration of the test chemical.

Groups of 50 mice of each sex were administered methyl parathion at one of two doses, initially either 62.5 or 125 ppm. These doses were maintained for 102 weeks for the females; however, due to decreased mean body weight gain in the dosed males, the low and high doses for the males were reduced after 37 weeks to 20 and 50 ppm, respectively, and administration at the lowered doses was continued for 65 weeks. The time-weighted average doses for the male mice were 35 and 77 ppm, respectively, for the low- and high-dose groups. 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 the dosed male and female rats and mice were lower than those of the corresponding controls throughout the bioassay and were dose related. Survival was unaffected in both species except for an increase in mortality in the high-dose female rats, in which 46% of the animals were alive at the end of the study.

No tumors occurred in any of the groups of rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups.

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

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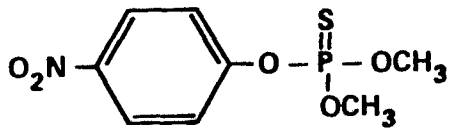
# I. INTRODUCTION

Methyl parathion, 0,0-dimethyl O(4-nitrophenyl)-phosphorothioate, (CAS 298-00-0; NCI C02971) was first marketed by Bayer AG in 1949, and today is manufactured by at least four companies in the United States (Ayers and Johnson, 1976). It was the leading organophosphate insecticide used in the United States in 1974, when usage reached 53 million pounds (Ayers and Johnson, 1976; EPA, 1975). Factors contributing to its widespread use include its relatively low mammalian toxicity compared with parathion (Gaines, 1969), its similar insecticidal activity to that of parathion (Eto, 1974), its low phytotoxicity (Martin and Worthing, 1977) and its suitability as a replacement for DDT (EPA, 1975).



Methyl parathion

Methyl parathion is used in the agricultural industry (EPA, 1975) as a contact and stomach poison with broad-spectrum insecticidal activity and some efficacy against mites (EPA, 1975, Martin and Worthing, 1977). It is sold as a wettable powder or emulsifiable

concentrate for foliage application. Several formulations contain combinations of methyl parathion and ethyl parathion as well as other registered pesticides. There are 62 crops on which methyl parathion is registered for use (EPA, 1972 and 1974), but over 90% of the total volume used in 1974 was on cotton (Ayers and Johnson, 1976). It is used to some extent in California for mosquito control (EPA, 1975).

The duration of methyl parathion's insecticidal activity ranges from 2 to 4 weeks (Eto, 1974). Its persistence in soil, which varies depending on soil type, temperature, moisture, and other variables, has been studied in the laboratory and in the field. The half-life of methyl parathion in the laboratory has been reported to be as short as 3 to 11 days (King and McCarty, 1968) and as long as 50 days (Baker and Applegate, 1970). In the field, greater than 95% loss of the chemical occurred 30 days from the time of application (Lichtenstein and Schulz, 1964). More recent research has determined that much of what was previously said to be "lost" actually is not recovered because it has been bound to soil. When this is taken into account, the half-life of methyl parathion is estimated to be 30 days (Lichtenstein et al., 1977). Monitoring studies conducted in areas devoted to cotton farming show that while residues are

apparent at the end of each growing season, they are not detectable by the following planting season (Elliott, 1975).

The toxicity of methyl parathion for mammals, like that of other organophosphorus insecticides, is due to inhibition of cholinesterase, and the symptoms include restlessness, muscular twitchings, miosis, defecation, urination, lacrimation, incoordination, prostration, generalized muscular fibrillation, convulsions, and death (EPA, 1975). Toxic symptoms may occur in humans exposed to methyl parathion in manufacturing and agricultural operations, and protective standards have been established (EPA, 1975). The average acute oral $LD_{50}$ reported from several laboratories for methyl parathion is 11 mg/kg body weight for male rats, 16 mg/kg for female rats, and 18.5 mg/kg for grouped male and female mice (EPA, 1975). In a three-generation (two-litter-per-generation) study in rats, methyl parathion at 30 ppm in the diet reduced overall reproductive performance although there was no consistent effect on individual parameters such as number of stillbirths, physical structure of newborns, litter size, weanling weights, or percentage survival to weaning; 10 ppm methyl parathion in the diet had only sporadic effects on the reproductive performance (EPA, 1975).

Although methyl parathion does not show great persistence in the environment, residues do occur in food crops (EPA, 1975). For this reason, and because of its extremely high level of production and use, methyl parathion was selected for testing in the Carcinogenesis Bioassay Program.

## II. MATERIALS AND METHODS

### A. Chemical

Methyl parathion (0,0-dimethyl 0(4-nitrophenyl)-phosphorothioate) was obtained from Monsanto as a brown semisolid. Its purity was determined by gas-liquid chromatography to be 94.6%, with one impurity greater than 1% and seven impurities less than 1%. The melting point was 33 to 34°C, and the refractive index was 1.546 at 48.5°C; these values are consistent with the melting point of 36°C and the refractive index of 1.552 at 48.5°C given in the literature (Eto, 1974). Elemental analysis showed 36.6% carbon, 3.9% hydrogen, and 5.3% nitrogen (theoretical: 36.5% C, 3.8% H, and 5.3% N).

The test material was stored at 5°C until used.

### B. Dietary Preparation

Test diets containing methyl parathion were prepared every 1 to 1-1/2 weeks in 6- to 12-kg batches at the appropriate doses. A known weight of the chemical was first mixed with an equal weight

of autoclaved Wayne® Sterilizable Lab Meal containing 4% fat (Allied Mills, Inc., Chicago, Ill.), using a mortar and pestle. The mixing was continued with second and third additions of feed, and final mixing was performed with the remaining quantity of feed for a minimim of 15 minutes in a Patterson-Kelly® twin-shell blender. The diets were routinely stored at 5°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 on a weight basis for each cage. The male rats used in the chronic study weighed 90 to 105 g, averaging at least 100 g; the female rats, 80 to 95 g, averaging at least 90 g; the male mice, 18 to 22 g, averaging at least 19.5 g; and the female mice, 17 to 21 g, averaging at least 18.5 g. Individual animals were identified by ear punch.

D. Animal Maintenance

The animals were housed in polycarbonate cages (Lab Products, Inc., Garfield, N.J.), 19 x 10-1/2 x 8 inches for the rats and 11-1/2 x 7-1/2 x 5 inches for the mice. The cages were suspended from aluminum racks (Scientific Cages, Inc., Bryan, Tex.) and were covered by nonwoven polyester-fiber 12-mil-thick filter paper (Hoeltge, Inc., Cincinnati, Ohio). The bedding used was Absorb-dri® hardwood chips (Northeastern Products, Inc., Warrenburg, N.Y.). The feed was presterilized Wayne® Sterilizable Lab Meal containing 4% fat provided ad libitum in suspended stainless steel hoppers and replenished at least three times per week. Water, acidified to pH 2.5, was supplied ad libitum from glass bottles with sipper tubes (Lab Products, Inc.) suspended through the tops of the cages.

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

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

The 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 was 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 automatically on a 12-hour-per-day cycle.

Rats administered methyl parathion and their corresponding controls were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 128-66-5) C. I. vat yellow 4
(CAS 148-18-5) sodium diethyldithiocarbamate

Mice administered methyl parathion 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 72-56-0) | p,p'-ethyl-DDD |
| (CAS 20941-65-5) | ethyl tellurac |
| (CAS 85-44-9) | phthalic anhydride |
| (CAS 51-03-6) | piperonyl butoxide |
| (CAS 86-06-2) | 2,4,6-trichlorophenol |

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of methyl parathion, on the basis of which two concentrations (referred to in this report as "low" and "high" doses) were determined for administration in the chronic studies. Groups of five rats and five mice of each sex were fed diets containing methyl parathion at one of several doses for 7 weeks, followed by 1 week of observation, and groups of five control animals of each species and sex were administered basal diet only. Each animal was weighed twice per week. Tables 1 and 2 show the doses fed, the survival of animals in each dosed group at the end of the study and the mean body weight of each dosed group at week 7, expressed as a percentage of the mean body weight of the corresponding controls. At the end of the 8 weeks,

Table 1. Methyl Parathion Subchronic Feeding Studies In Rats

| Dose (ppm) | Male | | Female | |
|---|---|---|---|---|
| | Survival (a) | Mean Weight at Week 7 as % of Control | Survival (a) | Mean Weight at Week 7 as % of Control |
| 0 | 5/5 | 100 | 5/5 | 100 |
| 10 | 5/5 | 101 | 4/5 | 102 |
| 20 | 5/5 | 97 | 5/5 | 95 |
| 30(b) | 5/5 | 98 | 4/5 | 91 |
| 40(b) | 5/5 | 98 | 4/5 | 87 |
| 50(b) | 5/5 | 90 | 3/5 | 90 |

(a) Number surviving/number in group.

(b) Tissues of males and females examined microscopically were essentially normal.

Table 2. Methyl Parathion Subchronic Feeding Studies in Mice

| | Male | | Female | |
|---|---|---|---|---|
| Dose (ppm) | Survival (a) | Mean Weight at Week 7 as % of Control | Survival (a) | Mean Weight at Week 7 as % of Control |
| 0 | 5/5 | 100 | 5/5 | 100 |
| 20 | 4/5 | 115 | 5/5 | 106 |
| 40 | 5/5 | 129 | 5/5 | 108 |
| 60 | 5/5 | 108 | 5/5 | 103 |
| 80 | 5/5 | 113 | 5/5 | 108 |
| 100 | 5/5 | 118 | 5/5 | 100 |
| 125(b) | 5/5 | 96 | 5/5 | 96 |
| 250(b,c,d) | 0/5 | | 4/5 | 94 |
| 500(c,e) | 0/5 | | 0/5 | |

(a) Number surviving/number in group.

(b) Histopathologic examination of males at 125 ppm and females at 250 ppm showed that all tissues were essentially normal.

(c) Clinical signs in both sexes at 250 and 500 ppm were rough hair coat and arched back.

(d) At necropsy five males at 250 ppm had hemorrhage of the stomach.

(e) At necropsy three males and five females at 500 ppm had hemorrhage of the stomach.

the animals were killed using $CO_2$ and necropsied. The footnotes to the tables include clinical and histopathologic findings.

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

The low and high doses for chronic studies were set at 20 and 40 ppm for rats and 62.5 and 125 ppm for mice.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 3 and 4. Due to decreased mean body weight gain in the dosed male mice, the doses were

Table 3. Methyl Parathion Chronic Feeding Studies in Rats

| Sex and Test Group | Initial No. of Animals (a) | Methyl Parathion in Diet (b) (ppm) | Time on Study (weeks) |
|---|---|---|---|
| Male | | | |
| Matched-Control | 20 | 0 | 105 |
| Low-Dose | 50 | 20 | 105 |
| High-Dose | 50 | 40 | 105 |
| Female | | | |
| Matched-Control | 20 | 0 | 105 |
| Low-Dose | 50 | 20 | 105 |
| High-Dose | 50 | 40 | 105 |

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

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

Table 4. Methyl Parathion Chronic Feeding Studies in Mice

| Sex and Test Group | Initial No. of Animals (a) | Methyl Parathion in Diet (b) (ppm) | Time on Study (weeks) | Time-weighted Average Dose (c) (ppm) |
|---|---|---|---|---|
| Male | | | | |
| Matched-Control | 20 | 0 | 102 | |
| Low-Dose | 50 | 62.5 | 37 | |
| | | 20 | 65 | 35 |
| High-Dose | 50 | 125 | 37 | |
| | | 50 | 65 | 77 |
| Female | | | | |
| Matched-Control | 20 | 0 | 102 | |
| Low-Dose | 50 | 62.5 | 102 | |
| High-Dose | 50 | 125 | 102 | |

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

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

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

reduced after week 37 to 20 ppm for the low-dose group and 50 ppm for the high-dose group.

## G. Clinical and Pathologic Examinations

All animals were observed 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 end of the bioassay were killed using $CO_2$ and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with 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 intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis,

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

Necropsies were also 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 section.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site

was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for a number of dosed groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope

of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's

methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity (P less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as $p_t/p_c$ where $p_t$ is the true binomial probability of the incidence of a specific type of tumor in a dosed group of animals and $p_c$ is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the dosed group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in

approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

## III. RESULTS - RATS

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

Mean body weights of the dosed male and female rats were lower than those of the corresponding controls, and were generally dose related throughout the bioassay (figure 1). Corneal opacity was observed in control and dosed groups. No other compound-related clinical signs were recorded.

### B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered methyl parathion in the diet at the doses of this bioassay, together with those for the matched controls, are shown by the Kaplan and Meier curves in figure 2. In male rats, the result of the Tarone test for dose-related trend in mortality is not significant. In females, the result of the Tarone test is significant (P less than 0.001). An indicated departure from linear trend is observed (P = 0.042) because of the relatively steep increase in mortality observed in the high-dose female rats.

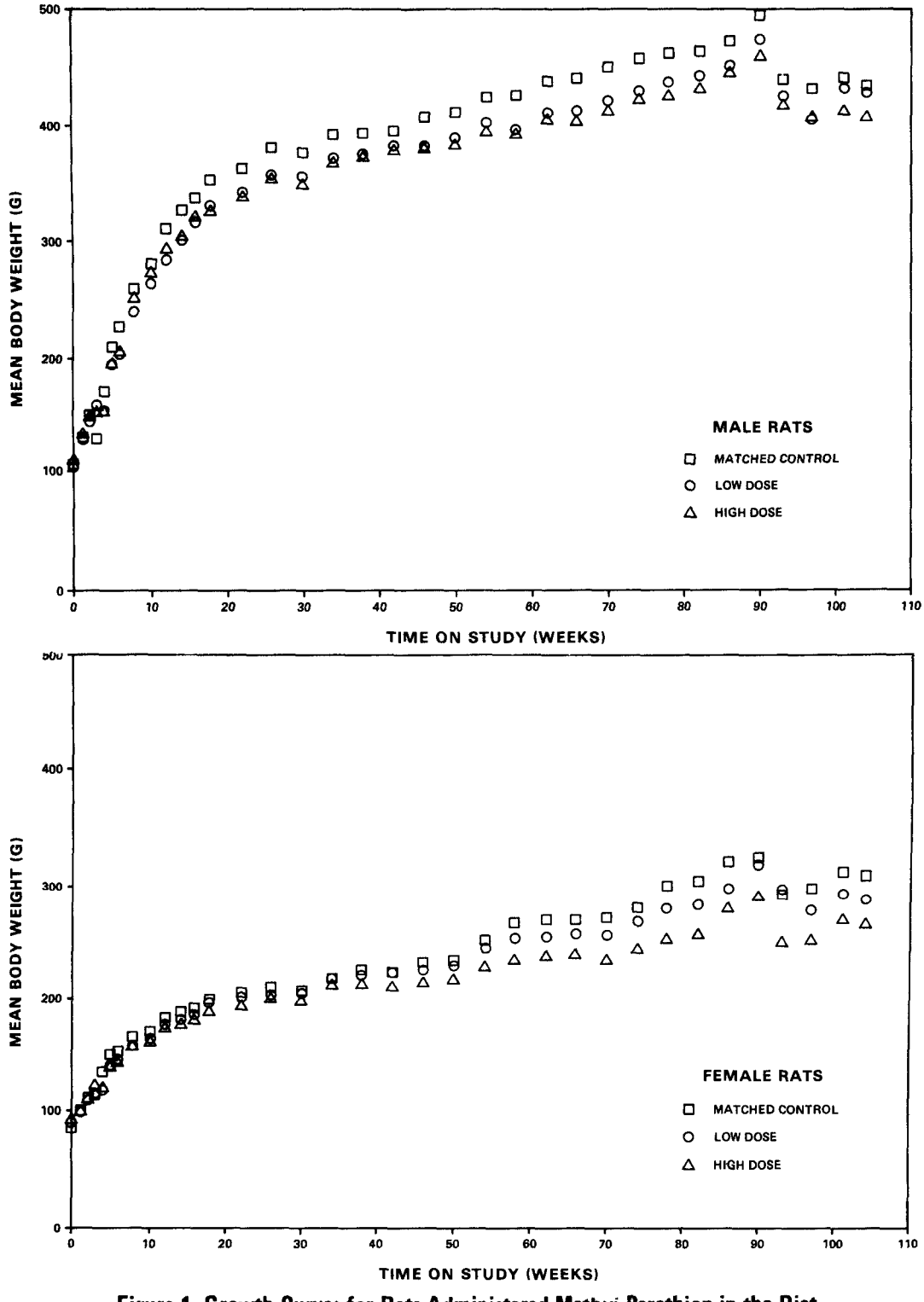



**Figure 1. Growth Curves for Rats Administered Methyl Parathion in the Diet**

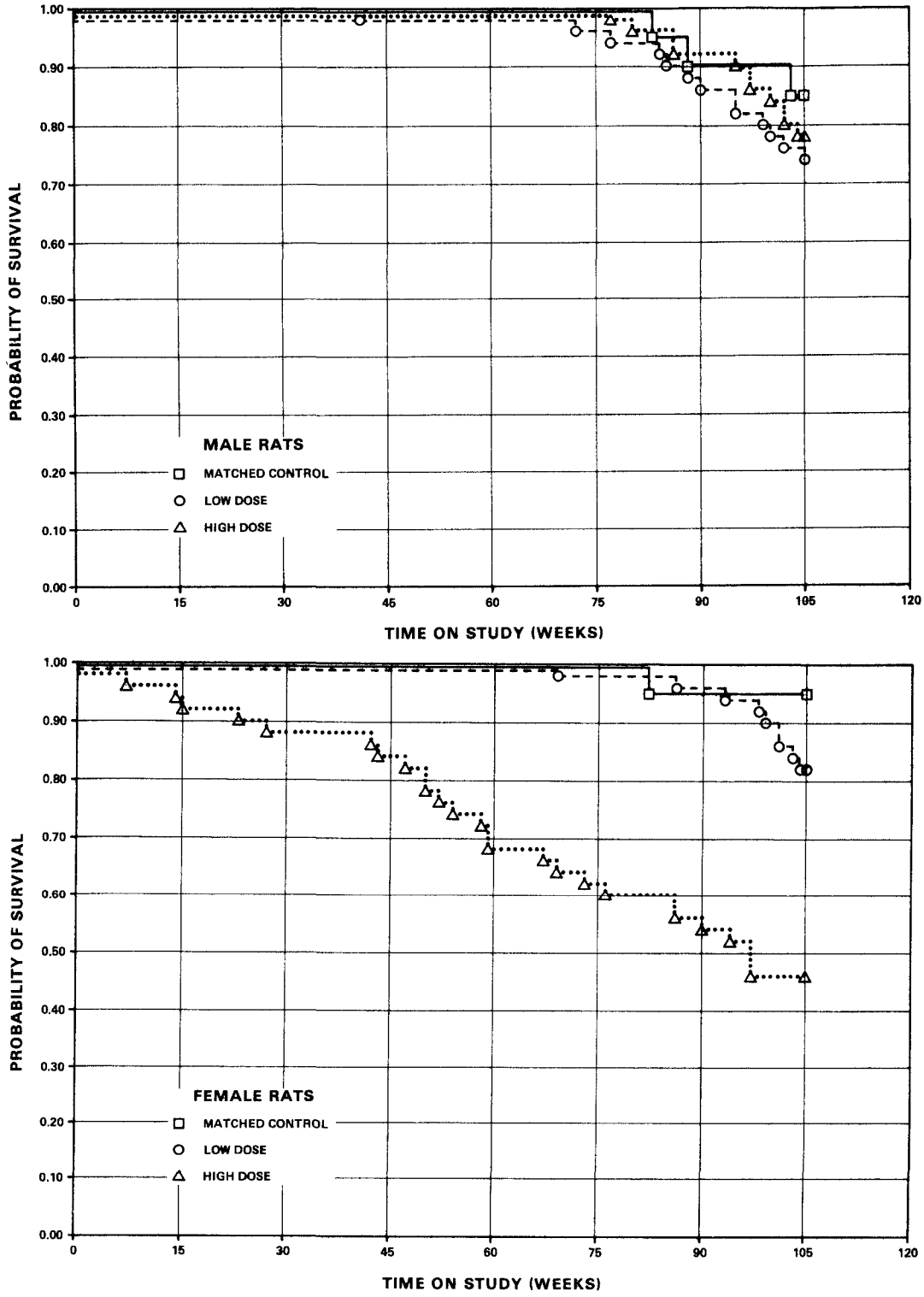



**Figure 2. Survival Curves for Rats Administered Methyl Parathion in the Diet**

In male rats, 39/50 (78%) of the high-dose group, 37/50 (74%) of the low-dose group, and 17/20 (85%) of the control group lived to the end of the bioassay. In females, 23/50 (46%) of the high-dose group, 41/50 (82%) of the low-dose group, and 19/20 (95%) 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.

A variety of neoplasms were represented among the dosed and control animals. Although a variety of benign and malignant neoplasms occurred, each type has been encountered previously in aged F344 rats. Moreover, the incidence of neoplasms by type and site, also by test group and sex of animal appears to be without relationship, and hence unattributable, to exposure to the test chemical.

Nonneoplastic responses were also represented among both control and dosed animals. Such lesions have also been encountered previously and are considered to be similar to those commonly observed in aging F344 rats.

Based on the histopathologic examination, there was no evidence that methyl parathion was carcinogenic in F344 rats under 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.

The results of the Cochran-Armitage tests for dose-related trend in the incidence of tumors and the results of the Fisher exact test comparing the incidences of tumors in the control and dosed groups are not significant in the positive direction in either sex.

Significant results in the negative direction are observed in the incidences of animals with either liver, prostate, pituitary, or mammary gland tumors. In females, this significance in the negative direction may be accounted for by the early mortality of the high-dose animals.

In each of the 95% confidence intervals for relative risk shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals, except for the incidence of mammary gland tumors in female rats, has an upper limit greater than one, indicating the theoretical possibility of tumor induction by methyl parathion, which could not be detected under the conditions of this test.

# IV. RESULTS - MICE

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

Mean body weights of the high-dose male and female mice were lower than those of the corresponding controls throughout the bioassay (figure 3); mean body weights of the low-dose males were decreased prior to lowering the dosage at week 38, while those of the low-dose females were unaffected. No other compound-related clinical signs were recorded.

## B. Survival (Mice)

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

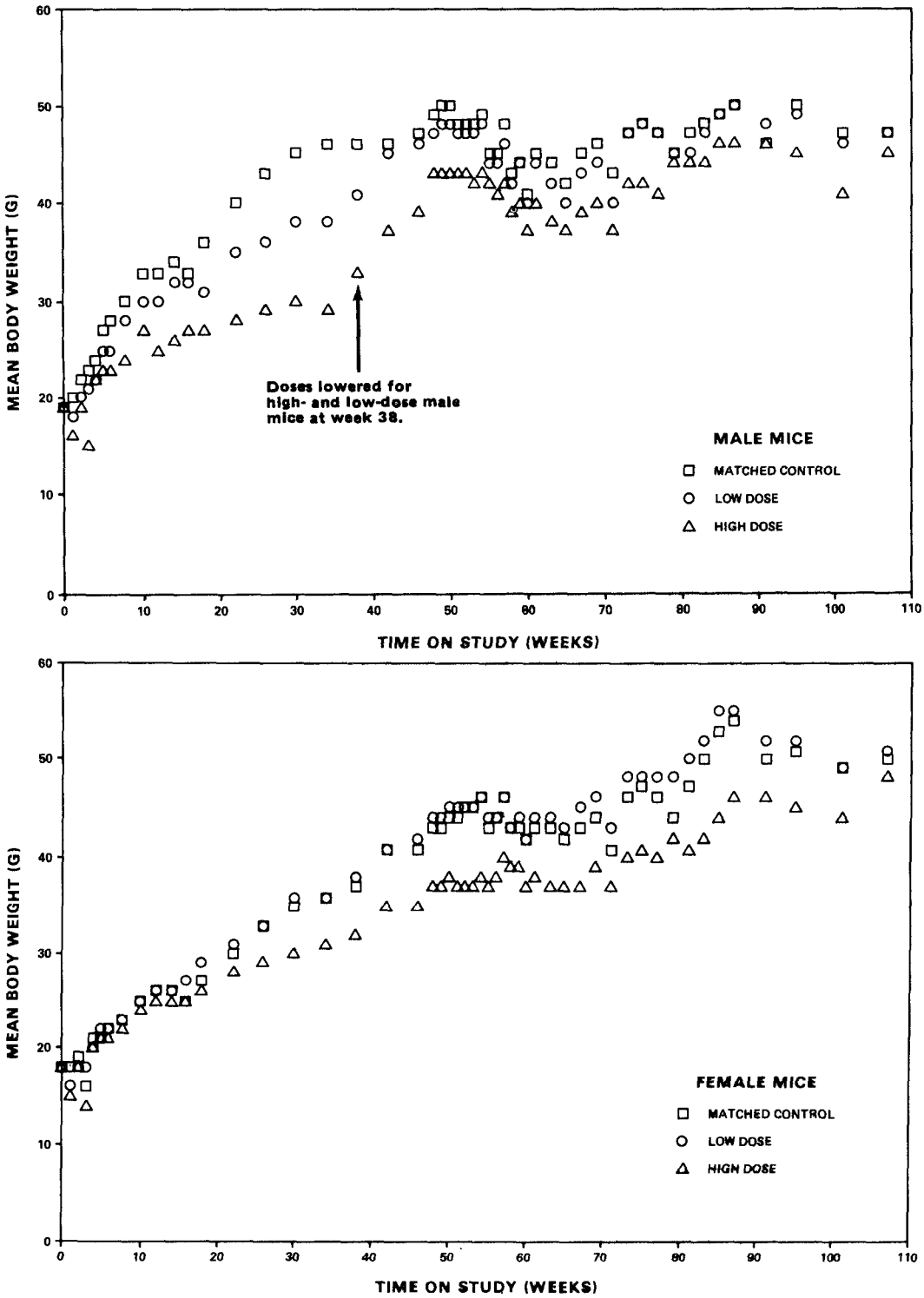



**Figure 3. Growth Curves for Mice Administered Methyl Parathion in the Diet**

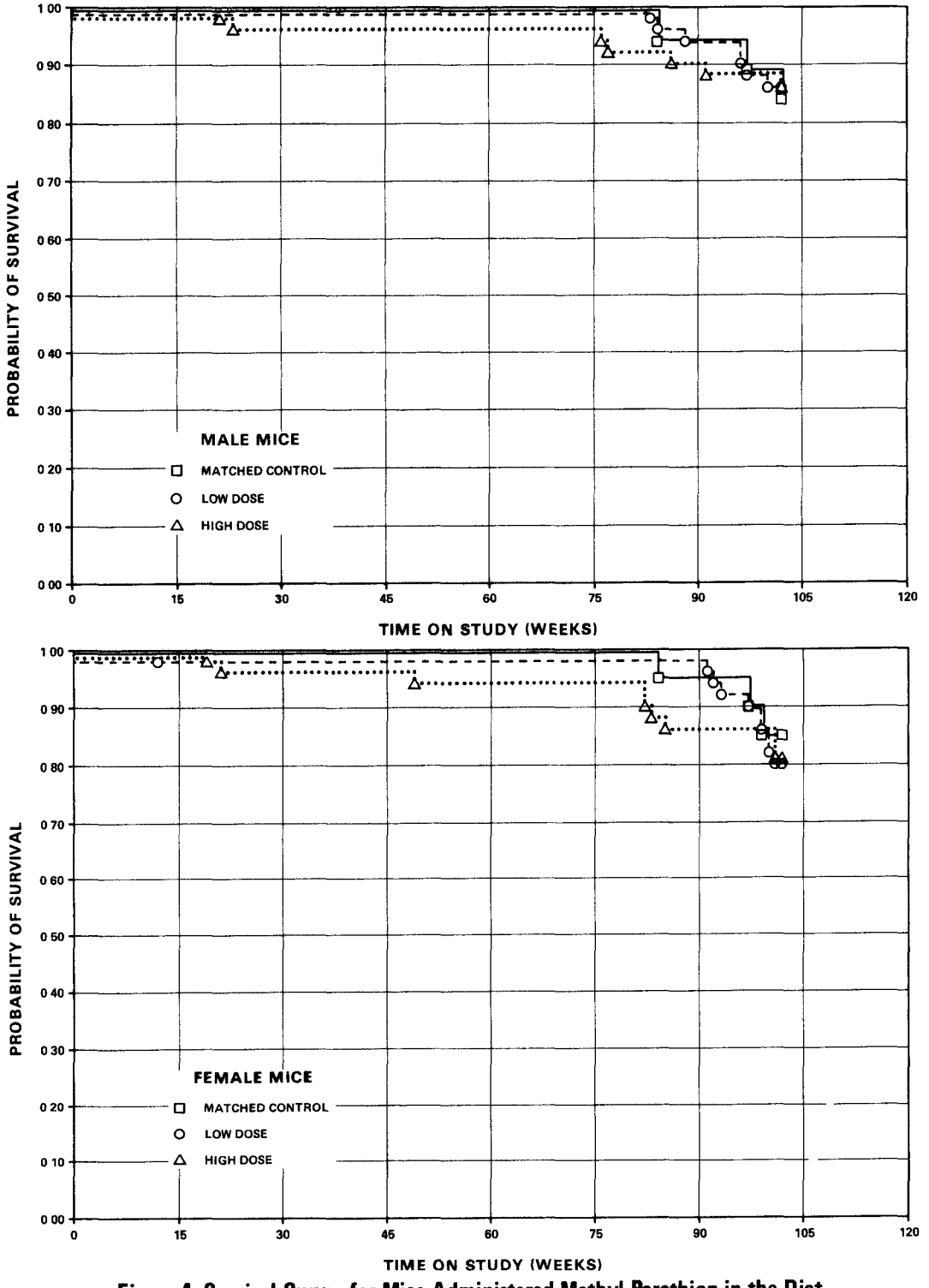



**Figure 4. Survival Curves for Mice Administered Methyl Parathion in the Diet**

In male mice, 43/50 (86%) of each dosed group and 16/20 (80%) of the control group lived to the end of the bioassay. In females, 40/50 (80%) of each dosed group and 17/20 (85%) of the control group lived to the end of the bioassay.

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

## C. Pathology (Mice)

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

A variety of neoplasms were represented among the dosed and control animals. Each type has been encountered previously in the B6C3F1 hybrid mouse. Moreover, the incidence of neoplasms by type and site, also by test group and sex of animal is without relationship, and hence unattributable, to exposure to the test chemical.

A variety of nonneoplastic responses are represented among both control and dosed animals. Such lesions have been encountered

previously and are considered to be similar to those commonly observed in aging B6C3F1 mice.

Based on the histopathologic examination, there was no evidence that methyl parathion was carcinogenic in mice under conditions of this bioassay.

## D. Statistical Analyses of Results (Mice)

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

The results of the Cochran-Armitage tests for dose-related trend in the incidence of tumors and the results of the Fisher exact test comparing the incidences of tumors in the control and dosed groups are not significant in the positive direction in either sex. However, significant results in the negative direction are observed in the combined incidence of hepatocellular carcinoma and adenoma in male mice and in the incidences of pituitary tumors and of hematopoietic tumors in female mice.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that most of the intervals have an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by methyl parathion, which could not be detected under the conditions of this test.

# V. DISCUSSION

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls and were generally dose related throughout the bioassay. Mortality was unaffected in the rats or mice except for an increase in mortality in the high-dose female rats in which 46% of the animals were alive at the end of the study. Sufficient numbers of animals were at risk for the development of late-appearing tumors.

No tumors occurred in any of the groups of rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups.

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

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# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED METHYL PARATHION IN THE DIET

## TABLE A1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED METHYL PARATHION 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) |
| PAPILLOMA, NOS | | 2 (4%) | 2 (4%) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| KERATOACANTHOMA | | | 1 (2%) |
| *SUBCUT TISSUE | (20) | (50) | (50) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| FIBROMA | 1 (5%) | 1 (2%) | 2 (4%) |
| FIBROSARCOMA | | 1 (2%) | 1 (2%) |
| LIPOSARCOMA | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (50) | (50) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 2 (10%) | 3 (6%) | 3 (6%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 1 (5%) | | |
| FOLLICULAR-CELL CARCINOMA, METAS | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (20) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 2 (10%) | 5 (10%) | 3 (6%) |
| MYELOMONOCYTIC LEUKEMIA | 1 (5%) | | |
| MONOCYTIC LEUKEMIA | | 2 (4%) | 1 (2%) |
| #SPLEEN | (20) | (50) | (49) |
| MALIGNANT LYMPHOMA, NOS | | 1 (2%) | |
| #THYMUS | (13) | (37) | (34) |
| THYMOMA | | | 1 (3%) |
| HEMANGIOMA | | 1 (3%) | |
| CIRCULATORY 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 |
|---|---|---|---|
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (20) | (50) | (50) |
| FIBROMA | 1 (5%) | | |
| MIXED TUMOR, MALIGNANT | | 1 (2%) | 1 (2%) |
| #LIVER | (20) | (49) | (50) |
| HEPATOCELLULAR ADENOMA | 1 (5%) | | |
| HEPATOCELLULAR CARCINOMA | 1 (5%) | | |
| #SMALL INTESTINE | (20) | (48) | (50) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| #COLON | (19) | (47) | (45) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (50) | (50) |
| ADENOCARCINOMA, NOS | 1 (5%) | | |
| LIPOSARCOMA | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (20) | (48) | (50) |
| ADENOMA, NOS | 1 (5%) | 3 (6%) | 5 (10%) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| CHROMOPHOBE ADENOMA | 8 (40%) | 8 (17%) | 8 (16%) |
| ACIDOPHIL ADENOMA | | | 1 (2%) |
| #ADRENAL | (20) | (50) | (50) |
| CORTICAL ADENOMA | | | 2 (4%) |
| PHEOCHROMOCYTOMA | 3 (15%) | 6 (12%) | 5 (10%) |
| #THYROID | (20) | (48) | (49) |
| OXYPHIL ADENOMA | | | 1 (2%) |
| FOLLICULAR-CELL CARCINOMA | | | 1 (2%) |
| C-CELL ADENOMA | | 2 (4%) | 2 (4%) |
| C-CELL CARCINOMA | | 1 (2%) | 1 (2%) |
| CYSTADENOMA, NOS | | | 1 (2%) |
| PAPILLARY CYSTADENOMA, NOS | | 1 (2%) | |
| #PANCREATIC ISLETS | (19) | (45) | (47) |
| ISLET-CELL ADENOMA | 2 (11%) | 4 (9%) | 2 (4%) |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (50) | (50) |
| PAPILLARY CYSTADENOCARCINOMA,NOS | 1 (5%) | | |
| FIBROADENOMA | | 1 (2%) | |
| *PROSTATE | (20) | (44) | (48) |
| PAPILLARY ADENOMA | 1 (5%) | | |
| ACINAR-CELL ADENOMA | 2 (10%) | | |
| #TESTIS | (20) | (50) | (50) |
| INTERSTITIAL-CELL TUMOR | 1 (5%) | 8 (16%) | 18 (36%) |
| INTERSTITIAL-CELL TUMOR, MALIGNA | 16 (80%) | 32 (64%) | 23 (46%) |
| *SCROTUM | (20) | (50) | (50) |
| LIPOMA | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EXTERNAL EAR | (20) | (50) | (50) |
| FIBROSARCOMA | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| *PERITONEUM | (20) | (50) | (50) |
| MESOTHELIOMA, NOS | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| NATURAL DEATH@ | 2 | 9 | 8 |
| MORIBUND SACRIFICE | 1 | 4 | 3 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 17 | 37 | 39 |
| ANIMAL MISSING | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 20 | 48 | 48 |
| TOTAL PRIMARY TUMORS | 46 | 85 | 92 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 14 | 30 | 34 |
| TOTAL BENIGN TUMORS | 23 | 41 | 54 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 18 | 38 | 31 |
| TOTAL MALIGNANT TUMORS | 23 | 44 | 38 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | 1 |
| TOTAL SECONDARY TUMORS | | | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | 1 | |
| TOTAL UNCERTAIN TUMORS | | 1 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

@ INCLUDES AUTOLYZED ANIMALS

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

## TABLE A2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED METHYL PARATHION IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS NECROPSIED | 20 | 50 | 47 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 50 | 47 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (20) | (50) | (47) |
| FIBROMA | 1 (5%) | | |
| FIBROSARCOMA | | 1 (2%) | |
| LIPOMA | 1 (5%) | | |
| FIBROADENOMA | 1 (5%) | | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (50) | (47) |
| SQUAMOUS CELL CARCINOMA, METASTA | | 1 (2%) | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | 5 (10%) | 1 (2%) |
| HEMANGIOSARCOMA, METASTATIC | 1 (5%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (20) | (50) | (47) |
| MALIGNANT LYMPHOMA, NOS | 1 (5%) | 2 (4%) | |
| MYELOMONOCYTIC LEUKEMIA | | | 1 (2%) |
| MONOCYTIC LEUKEMIA | | 1 (2%) | 3 (6%) |
| #SPLEEN | (20) | (50) | (47) |
| HEMANGIOSARCOMA, METASTATIC | 1 (5%) | | |
| #MANDIBULAR L. NODE | (20) | (49) | (47) |
| HEMANGIOSARCOMA, METASTATIC | 1 (5%) | | |
| 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 | | | |
| #LIVER | (20) | (50) | (47) |
| HEPATOCELLULAR ADENOMA | 2 (10%) | 4 (8%) | |
| HEPATOCELLULAR CARCINOMA | | 1 (2%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (50) | (47) |
| HEMANGIOSARCOMA, METASTATIC | 1 (5%) | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (20) | (50) | (47) |
| CARCINOMA,NOS | | 1 (2%) | |
| ADENOMA, NOS | | 5 (10%) | 15 (32%) |
| CHROMOPHOBE ADENOMA | 10 (50%) | 13 (26%) | |
| CHROMOPHOBE CARCINOMA | 2 (10%) | 3 (6%) | |
| #ADRENAL | (20) | (50) | (47) |
| CORTICAL ADENOMA | 1 (5%) | 2 (4%) | |
| PHEOCHROMOCYTOMA | | 1 (2%) | |
| #THYROID | (20) | (49) | (47) |
| PAPILLARY CARCINOMA | 1 (5%) | | |
| PAPILLARY ADENOCARCINOMA | | | 1 (2%) |
| C-CELL ADENOMA | 1 (5%) | | |
| C-CELL CARCINOMA | | 1 (2%) | |
| PAPILLARY CYSTADENOMA, NOS | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (50) | (47) |
| FIBROADENOMA | 5 (25%) | 2 (4%) | |
| *VAGINA | (20) | (50) | (47) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| #UTERUS | (20) | (50) | (46) |
| ENDOMETRIAL STROMAL POLYP | 4 (20%) | 6 (12%) | 4 (9%) |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| NERVOUS SYSTEM | | | |
| #BRAIN | (20) | (50) | (47) |
| CARCINOMA, NOS, METASTATIC | | 1 (2%) | |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (20) | (50) | (47) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | |
| *MANDIBLE | (20) | (50) | (47) |
| AMELOBLASTOMA | | | 1 (2%) |
| *COSTOCHONDRAL SYNCHO | (20) | (50) | (47) |
| OSTEOSARCOMA | | 1 (2%) | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| THORAX | | | |
| HEMANGIOSARCOMA | 1 | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| NATURAL DEATH@ | | 6 | 24 |
| MORIBUND SACRIFICE | 1 | 3 | 3 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 19 | 41 | 23 |
| 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* | 18 | 33 | 20 |
| TOTAL PRIMARY TUMORS | 31 | 51 | 27 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 17 | 26 | 18 |
| TOTAL BENIGN TUMORS | 26 | 39 | 21 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 4 | 10 | 5 |
| TOTAL MALIGNANT TUMORS | 5 | 12 | 6 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | 2 | |
| TOTAL SECONDARY TUMORS | 4 | 2 | |
| 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 METHYL PARATHION IN THE DIET

## TABLE B1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED METHYL PARATHION IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | 1 | | |
| ANIMALS NECROPSIED | 19 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 19 | 50 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (19) | (50) | (49) |
| KERATOACANTHOMA | | | 1 (2%) |
| FIBROSARCOMA, METASTATIC | | | 1 (2%) |
| LIPOSARCOMA, METASTATIC | | | 1 (2%) |
| *SUBCUT TISSUE | (19) | (50) | (49) |
| FIBROSARCOMA | | | 1 (2%) |
| LIPOSARCOMA | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (19) | (50) | (49) |
| HEPATOCELLULAR CARCINOMA, METAST | | 1 (2%) | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (5%) | 5 (10%) | 5 (10%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | 5 (10%) | 3 (6%) |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| LIPOSARCOMA, METASTATIC | | | 1 (2%) |
| HEMANGIOMA | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (19) | (50) | (49) |
| MALIGNANT LYMPHOMA, NOS | 1 (5%) | 4 (8%) | 2 (4%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 2 (4%) | |
| *HEMATOPOIETIC SYSTEM | (19) | (50) | (49) |
| MALIGNANT LYMPHOMA, NOS | 1 (5%) | | 1 (2%) |
| #BONE MARROW | (19) | (48) | (48) |
| SARCOMA, NOS, METASTATIC | | 1 (2%) | |
| #SPLEEN | (18) | (48) | (49) |
| SARCOMA, NOS, METASTATIC | | 1 (2%) | |

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

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HEMANGIOMA | 1 (6%) | 1 (2%) | 1 (2%) |
| HEMANGIOSARCOMA | 1 (6%) | | 1 (2%) |
| #LYMPH NODE | (17) | (47) | (48) |
| SARCOMA, NOS | | 1 (2%) | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | |
| #LIVER | (19) | (49) | (49) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | |
| **CIRCULATORY SYSTEM** | | | |
| #HEART | (19) | (50) | (49) |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (19) | (49) | (49) |
| HEPATOCELLULAR ADENOMA | 8 (42%) | 12 (24%) | 7 (14%) |
| HEPATOCELLULAR CARCINOMA | 2 (11%) | 3 (6%) | 6 (12%) |
| SARCOMA, NOS, METASTATIC | | 1 (2%) | |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| LIPOSARCOMA, METASTATIC | | | 1 (2%) |
| HEMANGIOMA | | 1 (2%) | |
| HEMANGIOSARCOMA | 1 (5%) | | |
| HEMANGIOSARCOMA, METASTATIC | | | 1 (2%) |
| ANGIOSARCOMA | | | 1 (2%) |
| #STOMACH | (19) | (48) | (49) |
| ADENOCA IN ADENOMATOUS POLYP | | | 1 (2%) |
| #ILEUM | (19) | (48) | (47) |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (19) | (48) | (49) |
| LIPOSARCOMA, METASTATIC | | | 1 (2%) |
| **ENDOCRINE SYSTEM** | | | |
| #ADRENAL | (19) | (43) | (47) |
| CORTICAL ADENOMA | 3 (16%) | 4 (9%) | 5 (11%) |

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

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #THYROID | (18) | (46) | (48) |
| FOLLICULAR-CELL CARCINOMA | 1 (6%) | 1 (2%) | |
| PAPILLARY CYSTADENOCARCINOMA,NOS | | 1 (2%) | |
| #PANCREATIC ISLETS | (17) | (45) | (49) |
| ISLET-CELL ADENOMA | 1 (6%) | 3 (7%) | |
| REPRODUCTIVE SYSTEM | | | |
| *SEMINAL VESICLE | (19) | (50) | (49) |
| PAPILLARY CYSTADENOMA, NOS | | 1 (2%) | |
| *EPIDIDYMIS | (19) | (50) | (49) |
| LIPOSARCOMA, METASTATIC | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE/LACRIMAL GLAND | (19) | (50) | (49) |
| PAPILLARY ADENOMA | 1 (5%) | 1 (2%) | 3 (6%) |
| MUSCULOSKELETAL SYSTEM | | | |
| *RIB | (19) | (50) | (49) |
| FIBROSARCOMA | | 1 (2%) | |
| BODY CAVITIES | | | |
| *MESENTERY | (19) | (50) | (49) |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |

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

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| NATURAL DEATH@ | 3 | 7 | 7 |
| MORIBUND SACRIFICE | | | |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 16 | 43 | 43 |
| ANIMAL MISSING | 1 | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 13 | 31 | 28 |
| TOTAL PRIMARY TUMORS | 22 | 49 | 39 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 8 | 21 | 18 |
| TOTAL BENIGN TUMORS | 15 | 29 | 22 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 6 | 18 | 16 |
| TOTAL MALIGNANT TUMORS | 7 | 20 | 17 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | 3 | 3 |
| TOTAL SECONDARY TUMORS | | 9 | 7 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

## TABLE B2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED METHYL PARATHION IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | | | 1 |
| ANIMALS NECROPSIED | 20 | 49 | 48 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 49 | 48 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (20) | (49) | (48) |
| FIBROSARCOMA | | 1 (2%) | 1 (2%) |
| HEMANGIOSARCOMA | | 1 (2%) | |
| NEUROFIBROSARCOMA | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (49) | (48) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | 1 (2%) | 1 (2%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | 2 (4%) | 1 (2%) |
| FIBROSARCOMA, METASTATIC | | 1 (2%) | |
| LEIOMYOSARCOMA, METASTATIC | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (20) | (49) | (48) |
| MALIGNANT LYMPHOMA, NOS | 3 (15%) | 10 (20%) | 2 (4%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | 3 (6%) |
| GRANULOCYTIC LEUKEMIA | 1 (5%) | | |
| #BONE MARROW | (20) | (49) | (48) |
| HEMANGIOMA | 1 (5%) | | |
| #SPLEEN | (20) | (49) | (47) |
| HEMANGIOSARCOMA | | 1 (2%) | |
| MALIGNANT LYMPHOMA, NOS | 2 (10%) | | |
| #MESENTERIC L. NODE | (19) | (49) | (47) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | |
| #STOMACH | (20) | (48) | (48) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | |

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

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #THYMUS | (14) | (30) | (34) |
| THYMOMA | | 1 (3%) | |
| MALIGNANT LYMPHOMA, NOS | 2 (14%) | | |
| **CIRCULATORY SYSTEM** | | | |
| NONE | | | |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (20) | (49) | (48) |
| HEPATOCELLULAR ADENOMA | 1 (5%) | 3 (6%) | 2 (4%) |
| HEPATOCELLULAR CARCINOMA | | 1 (2%) | |
| HEMANGIOSARCOMA | | | 1 (2%) |
| #STOMACH | (20) | (48) | (48) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| #DUODENUM | (20) | (49) | (46) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (20) | (49) | (48) |
| HEMANGIOMA | | 1 (2%) | |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (17) | (45) | (44) |
| ADENOMA, NOS | | 1 (2%) | 1 (2%) |
| CHROMOPHOBE ADENOMA | 4 (24%) | 4 (9%) | |
| #ADRENAL | (20) | (49) | (48) |
| CORTICAL ADENOMA | 2 (10%) | 1 (2%) | 1 (2%) |
| #THYROID | (20) | (47) | (46) |
| FOLLICULAR-CELL ADENOMA | 1 (5%) | | |
| PAPILLARY CYSTADENOMA, NOS | | 1 (2%) | |
| #PANCREATIC ISLETS | (18) | (46) | (42) |
| ISLET-CELL ADENOMA | 1 (6%) | | |

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

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (49) | (48) |
| ADENOCARCINOMA, NOS | | 3 (6%) | 1 (2%) |
| #UTERUS | (20) | (48) | (45) |
| ENDOMETRIAL STROMAL POLYP | | | 3 (7%) |
| HEMANGIOMA | | 1 (2%) | |
| HEMANGIOSARCOMA | | | 1 (2%) |
| #OVARY | (17) | (48) | (47) |
| PAPILLARY CYSTADENOMA, NOS | | 1 (2%) | |
| TERATOMA, BENIGN | | 1 (2%) | |
| HEMANGIOMA | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE/LACRIMAL GLAND | (20) | (49) | (48) |
| PAPILLARY ADENOMA | | | 1 (2%) |
| PAPILLARY CYSTADENOCARCINOMA,NOS | | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| *ABDOMINAL CAVITY | (20) | (49) | (48) |
| LEIOMYOSARCOMA | | | 1 (2%) |
| *PERITONEUM | (20) | (49) | (48) |
| MESOTHELIOMA, NOS | | | 1 (2%) |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |

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

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| NATURAL DEATH@ | 3 | 10 | 7 |
| MORIBUND SACRIFICE | | | 2 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 17 | 40 | 40 |
| ANIMAL MISSING | | | 1 |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 14 | 30 | 20 |
| TOTAL PRIMARY TUMORS | 18 | 42 | 22 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 7 | 13 | 8 |
| TOTAL BENIGN TUMORS | 10 | 17 | 9 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 8 | 22 | 11 |
| TOTAL MALIGNANT TUMORS | 8 | 25 | 12 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | 2 | 1 |
| TOTAL SECONDARY TUMORS | | 2 | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT | | | 1 |
| TOTAL UNCERTAIN TUMORS | | | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

@ INCLUDES AUTOLYZED ANIMALS

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

# APPENDIX C

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED METHYL PARATHION IN THE DIET

## TABLE C1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED METHYL PARATHION 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) |
| EPIDERMAL INCLUSION CYST | | | 2 (4%) |
| ULCER, CHRONIC | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (50) | (50) |
| EMPHYSEMA, NOS | | 1 (2%) | |
| HYPERPLASIA, ADENOMATOUS | | | 1 (2%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 1 (5%) | | |
| #LUNG/ALVEOLI | (20) | (50) | (50) |
| EDEMA, NOS | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (20) | (50) | (50) |
| HYPERPLASIA, HEMATOPOIETIC | 2 (10%) | | 3 (6%) |
| #SPLEEN | (20) | (50) | (49) |
| HEMATOPOIESIS | | 1 (2%) | 6 (12%) |
| #MANDIBULAR L. NODE | (20) | (50) | (50) |
| LYMPHANGIECTASIS | 6 (30%) | 6 (12%) | 3 (6%) |
| CONGESTION, NOS | | 2 (4%) | 3 (6%) |
| FIBROSIS | | | 1 (2%) |
| PLASMACYTOSIS | | | 1 (2%) |
| HYPERPLASIA, RETICULUM CELL | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 1 (5%) | 4 (8%) | 1 (2%) |
| #PANCREATIC L.NODE | (20) | (50) | (50) |
| LYMPHANGIECTASIS | 1 (5%) | | |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #MESENTERIC L. NODE | (20) | (50) | (50) |
| LYMPHANGIECTASIS | 1 (5%) | | 2 (4%) |
| CONGESTION, NOS | | 1 (2%) | |
| EDEMA, NOS | | 1 (2%) | |
| HEMORRHAGE | | 1 (2%) | |
| ATROPHY, NOS | 1 (5%) | 1 (2%) | |
| HYPERPLASIA, RETICULUM CELL | | 3 (6%) | 5 (10%) |
| HYPERPLASIA, LYMPHOID | | 2 (4%) | |
| #THYMUS | (13) | (37) | (34) |
| HEMORRHAGE | | | 2 (6%) |
| ATROPHY, NOS | 13 (100%) | 29 (78%) | 21 (62%) |
| CIRCULATORY SYSTEM | | | |
| #HEART | (20) | (50) | (50) |
| FIBROSIS, FOCAL | | 1 (2%) | |
| FIBROSIS, DIFFUSE | | 1 (2%) | |
| #HEART/ATRIUM | (20) | (50) | (50) |
| THROMBOSIS, NOS | | | 1 (2%) |
| #MYOCARDIUM | (20) | (50) | (50) |
| INFLAMMATION, NOS | | | 1 (2%) |
| INFLAMMATION, CHRONIC | 14 (70%) | 35 (70%) | 19 (38%) |
| FIBROSIS | 1 (5%) | | |
| *PANCREATIC ARTERY, | (20) | (50) | (50) |
| HYPERTROPHY, NOS | 1 (5%) | | |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (20) | (50) | (50) |
| FIBROSIS, DIFFUSE | | | 1 (2%) |
| #LIVER | (20) | (49) | (50) |
| FIBROSIS | 12 (60%) | 17 (35%) | 6 (12%) |
| NECROSIS, NOS | | 3 (6%) | |
| NECROSIS, COAGULATIVE | | 1 (2%) | 1 (2%) |
| LIPOIDOSIS | | 2 (4%) | 3 (6%) |
| ANGIECTASIS | | | 2 (4%) |
| #LIVER/CENTRILOBULAR | (20) | (49) | (50) |
| NECROSIS, 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 |
|---|---|---|---|
| LIPOIDOSIS | | | 1 (2%) |
| #LIVER/PERIPORTAL | (20) | (49) | (50) |
| LIPOIDOSIS | 1 (5%) | | |
| #LIVER/HEPATOCYTES | (20) | (49) | (50) |
| CYTOPLASMIC VACUOLIZATION | 12 (60%) | 25 (51%) | 11 (22%) |
| HYPERPLASIA, NOS | 15 (75%) | 16 (33%) | 3 (6%) |
| #BILE DUCT | (20) | (49) | (50) |
| HYPERPLASIA, NOS | 17 (85%) | 38 (78%) | 35 (70%) |
| #PANCREAS | (19) | (45) | (47) |
| INFLAMMATION, CHRONIC | 1 (5%) | 1 (2%) | 2 (4%) |
| PERIARTERITIS | 2 (11%) | 7 (16%) | 3 (6%) |
| #PANCREATIC ACINUS | (19) | (45) | (47) |
| ATROPHY, FOCAL | | 1 (2%) | 1 (2%) |
| #STOMACH | (20) | (48) | (50) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| #SMALL INTESTINE | (20) | (48) | (50) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #DUODENUM | (20) | (48) | (50) |
| ULCER, NOS | | 1 (2%) | |
| #DUODENAL MUCOSA | (20) | (48) | (50) |
| NECROSIS, NOS | | 1 (2%) | |
| #ILEUM | (20) | (48) | (50) |
| ULCER, CHRONIC | 1 (5%) | | |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (50) | (50) |
| INFLAMMATION, CHRONIC | 16 (80%) | 34 (68%) | 22 (44%) |
| INFLAMMATION, CHRONIC FOCAL | | | 1 (2%) |
| NEPHROPATHY | | 3 (6%) | 12 (24%) |
| #KIDNEY/CORTEX | (20) | (50) | (50) |
| CYST, NOS | | | 1 (2%) |
| FIBROSIS, DIFFUSE | | 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 |
|---|---|---|---|
| #KIDNEY/GLOMERULUS | (20) | (50) | (50) |
| NEPHROPATHY | | 3 (6%) | 1 (2%) |
| #URINARY BLADDER | (20) | (46) | (50) |
| EROSION | | 1 (2%) | |
| #U. BLADDER/MUCOSA | (20) | (46) | (50) |
| NECROSIS, NOS | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (20) | (48) | (50) |
| CYST, NOS | 2 (10%) | | 2 (4%) |
| HEMORRHAGIC CYST | 2 (10%) | 2 (4%) | |
| HYPERPLASIA, NOS | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, FOCAL | | | 2 (4%) |
| #ADRENAL | (20) | (50) | (50) |
| ANGIECTASIS | | 5 (10%) | 3 (6%) |
| #ADRENAL CORTEX | (20) | (50) | (50) |
| LIPOIDOSIS | 2 (10%) | 4 (8%) | 1 (2%) |
| HYPERPLASIA, NOS | | 2 (4%) | |
| #ADRENAL MEDULLA | (20) | (50) | (50) |
| HYPERPLASIA, NOS | 1 (5%) | | |
| #THYROID | (20) | (48) | (49) |
| FOLLICULAR CYST, NOS | 2 (10%) | | |
| HYPERPLASIA, C-CELL | 2 (10%) | 2 (4%) | 2 (4%) |
| #PARATHYROID | (2) | (8) | (14) |
| HYPERPLASIA, NOS | | 1 (13%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (50) | (50) |
| GALACTOCELE | 2 (10%) | 2 (4%) | 6 (12%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| LACTATION | 1 (5%) | | 1 (2%) |
| #PROSTATE | (20) | (44) | (48) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | 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, ACUTE | 1 (5%) | 3 (7%) | 6 (13%) |
| INFLAMMATION, CHRONIC | 1 (5%) | 1 (2%) | |
| ATROPHY, NOS | 11 (55%) | 25 (57%) | 11 (23%) |
| HYPERPLASIA, NOS | 1 (5%) | | 2 (4%) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| HYPERPLASIA, FOCAL | | | 2 (4%) |
| #TESTIS | (20) | (50) | (50) |
| ATROPHY, NOS | 1 (5%) | 2 (4%) | 2 (4%) |
| HYPERPLASIA, INTERSTITIAL CELL | | | 1 (2%) |
| #TESTIS/TUBULE | (20) | (50) | (50) |
| DEGENERATION, NOS | | 1 (2%) | |
| *EPIDIDYMIS | (20) | (50) | (50) |
| LIPOGRANULOMA | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (20) | (50) | (50) |
| CATARACT | 14 (70%) | 16 (32%) | 7 (14%) |
| *EYE ANTERIOR CHAMBER | (20) | (50) | (50) |
| HEMORRHAGE | 1 (5%) | | |
| *EYE/CORNEA | (20) | (50) | (50) |
| CALCIFICATION, FOCAL | 1 (5%) | | |
| *EYEBALL TUNICA VASCU | (20) | (50) | (50) |
| INFLAMMATION, NOS | 6 (30%) | | |
| INFLAMMATION, ACUTE | | 1 (2%) | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| *EYE/RETINA | (20) | (50) | (50) |
| ATROPHY, NOS | 13 (65%) | 16 (32%) | 6 (12%) |
| MUSCULOSKELETAL SYSTEM | | | |
| *BONE | (20) | (50) | (50) |
| FIBROUS OSTEODYSTROPHY | | 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 |
|---|---|---|---|
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NONE | | | |

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

## TABLE C2.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED METHYL PARATHION IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS NECROPSIED | 20 | 50 | 47 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 50 | 47 |
| INTEGUMENTARY SYSTEM | | | |
| NONE | | | |
| RESPIRATORY SYSTEM | | | |
| #LUNG/BRONCHUS | (20) | (50) | (47) |
| GRANULOMA, FOREIGN BODY | | | 1 (2%) |
| #LUNG/BRONCHIOLE | (20) | (50) | (47) |
| HYPERPLASIA, ADENOMATOUS | | 1 (2%) | |
| #LUNG | (20) | (50) | (47) |
| HYPEREMIA | | | 4 (9%) |
| EDEMA, NOS | | | 3 (6%) |
| HEMORRHAGE | | | 4 (9%) |
| BRONCHOPNEUMONIA, NOS | | | 1 (2%) |
| PNEUMONIA, ASPIRATION | | 1 (2%) | |
| HYPERPLASIA, ADENOMATOUS | | | 3 (6%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (20) | (50) | (47) |
| HYPOPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, HEMATOPOIETIC | 1 (5%) | | |
| #SPLEEN | (20) | (50) | (47) |
| FIBROSIS, MULTIFOCAL | | | 1 (2%) |
| SIDEROSIS | | | 1 (2%) |
| HEMATOPOIESIS | 1 (5%) | | |
| #MANDIBULAR L. NODE | (20) | (49) | (47) |
| LYMPHANGIECTASIS | | 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 |
|---|---|---|---|
| INFLAMMATION, ACUTE | 1 (5%) | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | 1 (5%) | 1 (2%) | |
| #MESENTERIC L. NODE | (20) | (49) | (47) |
| HEMORRHAGE | | | 1 (2%) |
| PIGMENTATION, NOS | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 1 (5%) | 1 (2%) | |
| #THYMUS | (20) | (46) | (39) |
| HYPEREMIA | | | 1 (3%) |
| HEMORRHAGE | | 1 (2%) | 4 (10%) |
| ATROPHY, NOS | 19 (95%) | 24 (52%) | |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #THYMIC MEDULLA | (20) | (46) | (39) |
| HEMORRHAGE | | | 1 (3%) |
| **CIRCULATORY SYSTEM** | | | |
| #HEART | (20) | (50) | (47) |
| FIBROSIS, FOCAL | | | 1 (2%) |
| #HEART/ATRIUM | (20) | (50) | (47) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #MYOCARDIUM | (20) | (50) | (47) |
| INFLAMMATION, CHRONIC | 11 (55%) | 15 (30%) | |
| FIBROSIS | | | 2 (4%) |
| DEGENERATION, NOS | | | 1 (2%) |
| NECROSIS, NOS | | | 1 (2%) |
| *AORTA | (20) | (50) | (47) |
| INFLAMMATION, FOCAL | | | 1 (2%) |
| #HEPATIC SINUSOID | (20) | (50) | (47) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| **DIGESTIVE SYSTEM** | | | |
| #SALIVARY GLAND | (20) | (49) | (46) |
| FIBROSIS, DIFFUSE | 1 (5%) | | |
| ATROPHY, NOS | | | 2 (4%) |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #LIVER | (20) | (50) | (47) |
| INFLAMMATION, GRANULOMATOUS | | 1 (2%) | |
| INFLAMMATION, NECRO GRAN | | | 1 (2%) |
| FIBROSIS | 1 (5%) | 2 (4%) | |
| NECROSIS, NOS | 1 (5%) | 1 (2%) | 1 (2%) |
| LIPOIDOSIS | | 1 (2%) | 2 (4%) |
| BASOPHILIC CYTO CHANGE | | 6 (12%) | 12 (26%) |
| FOCAL CELLULAR CHANGE | 1 (5%) | 2 (4%) | 1 (2%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| #LIVER/PERIPORTAL | (20) | (50) | (47) |
| LIPOIDOSIS | | 1 (2%) | |
| #LIVER/HEPATOCYTES | (20) | (50) | (47) |
| NECROSIS, NOS | | 1 (2%) | |
| CYTOPLASMIC VACUOLIZATION | 2 (10%) | | |
| HYPERPLASIA, NOS | 18 (90%) | 32 (64%) | |
| #BILE DUCT | (20) | (50) | (47) |
| HYPERPLASIA, NOS | 9 (45%) | 12 (24%) | |
| #PANCREAS | (20) | (50) | (44) |
| INFLAMMATION, CHRONIC | 1 (5%) | 1 (2%) | |
| #PANCREATIC ACINUS | (20) | (50) | (44) |
| ATROPHY, FOCAL | | 1 (2%) | |
| #STOMACH | (20) | (50) | (47) |
| INFLAMMATION, CHRONIC | 1 (5%) | | |
| #GASTRIC MUCOSA | (20) | (50) | (47) |
| ULCER, NOS | | 2 (4%) | 1 (2%) |
| #COLON | (20) | (48) | (47) |
| NEMATODIASIS | | 1 (2%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (50) | (47) |
| HYDRONEPHROSIS | 1 (5%) | | |
| INFLAMMATION, CHRONIC | 4 (20%) | 2 (4%) | |
| NEPHROPATHY | | 2 (4%) | 3 (6%) |
| #KIDNEY/CORTEX | (20) | (50) | (47) |
| CYST, NOS | | | 1 (2%) |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| DEGENERATION, NOS | | 1 (2%) | |
| #KIDNEY/GLOMERULUS | (20) | (50) | (47) |
| NEPHROPATHY | 1 (5%) | 1 (2%) | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (20) | (50) | (47) |
| CYST, NOS | 1 (5%) | 7 (14%) | 2 (4%) |
| HEMORRHAGIC CYST | | 2 (4%) | |
| HYPERPLASIA, CHROMOPHOBE-CELL | | 1 (2%) | |
| #ADRENAL | (20) | (50) | (47) |
| ANGIECTASIS | | 2 (4%) | |
| #ADRENAL/CAPSULE | (20) | (50) | (47) |
| FIBROSIS | | | 1 (2%) |
| #ADRENAL CORTEX | (20) | (50) | (47) |
| CYST, NOS | 1 (5%) | | |
| LIPOIDOSIS | 1 (5%) | 2 (4%) | |
| HYPERPLASIA, NOS | 7 (35%) | 4 (8%) | |
| #ADRENAL MEDULLA | (20) | (50) | (47) |
| LYMPHOCYTOSIS | | | 1 (2%) |
| #THYROID | (20) | (49) | (47) |
| FOLLICULAR CYST, NOS | | 1 (2%) | |
| HYPERPLASIA, C-CELL | 1 (5%) | 7 (14%) | 1 (2%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (50) | (47) |
| GALACTOCELE | 11 (55%) | 4 (8%) | 3 (6%) |
| HYPERPLASIA, CYSTIC | | | 1 (2%) |
| LACTATION | | 1 (2%) | 1 (2%) |
| #UTERUS | (20) | (50) | (46) |
| HYDROMETRA | | 2 (4%) | |
| LIPOGRANULOMA | 1 (5%) | | |
| #UTERUS/ENDOMETRIUM | (20) | (50) | (46) |
| CYST, NOS | 3 (15%) | 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 |
|---|---|---|---|
| INFLAMMATION, VESICULAR | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| #UTERUS/MYOMETRIUM | (20) | (50) | (46) |
| HEMORRHAGE | 1 (5%) | | |
| #OVARY | (20) | (50) | (46) |
| CORPUS LUTEUM CYST | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| #CEREBRAL VENTRICLE | (20) | (50) | (47) |
| DILATATION, NOS | | 1 (2%) | 1 (2%) |
| #BRAIN | (20) | (50) | (47) |
| ATROPHY, PRESSURE | 1 (5%) | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (20) | (50) | (47) |
| CATARACT | | 3 (6%) | 2 (4%) |
| *EYE/RETINA | (20) | (50) | (47) |
| ATROPHY, NOS | | 4 (8%) | |
| DYSPLASIA, NOS | | | 1 (2%) |
| *EYE/CRYSTALLINE LENS | (20) | (50) | (47) |
| DEGENERATION, NOS | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| ADIPOSE TISSUE | | | |
| LIPOGRANULOMA | | 1 | |

# 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 MORPHOLOGY SUMMARY | | | |
| NO LESION REPORTED | | 1 | 5 |
| AUTC/NECROPSY/HISTO PERF | | 1 | 2 |
| AUTOLYSIS/NO NECROPSY | | | 3 |

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

# APPENDIX D

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED METHYL PARATHION IN THE DIET

## TABLE D1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED METHYL PARATHION IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | 1 | | |
| ANIMALS NECROPSIED | 19 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 19 | 50 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (19) | (50) | (49) |
| CYST, NOS | | | 1 (2%) |
| EPIDERMAL INCLUSION CYST | 1 (5%) | | |
| SEBACEOUS CYST | 1 (5%) | 1 (2%) | |
| ABSCESS, CHRONIC | | | 1 (2%) |
| *SUBCUT TISSUE | (19) | (50) | (49) |
| ABSCESS, CHRONIC | 1 (5%) | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (19) | (50) | (49) |
| INFLAMMATION, FOCAL | | 1 (2%) | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 1 (5%) | 1 (2%) | |
| #LUNG/ALVEOLI | (19) | (50) | (49) |
| EDEMA, NOS | 1 (5%) | | |
| HISTIOCYTOSIS | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (19) | (48) | (48) |
| HYPERPLASIA, HEMATOPOIETIC | | | 1 (2%) |
| #SPLEEN | (18) | (48) | (49) |
| HYPERPLASIA, LYMPHOID | 7 (39%) | 17 (35%) | 14 (29%) |
| HEMATOPOIESIS | | 1 (2%) | 2 (4%) |
| #LYMPH NODE | (17) | (47) | (48) |
| GRANULOMA, NOS | | | 1 (2%) |
| #MANDIBULAR L. NODE | (17) | (47) | (48) |
| HYPERPLASIA, LYMPHOID | | 7 (15%) | 2 (4%) |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HEMATOPOIESIS | | 1 (2%) | |
| #MESENTERIC L. NODE | (17) | (47) | (48) |
| CONGESTION, NOS | 2 (12%) | | 2 (4%) |
| HEMORRHAGE | 1 (6%) | 3 (6%) | 7 (15%) |
| INFLAMMATION, NOS | | | 3 (6%) |
| INFLAMMATION, ACUTE | | 2 (4%) | |
| INFLAMMATION, ACUTE HEMORRHAGIC | | 1 (2%) | |
| LYMPHOID DEPLETION | | | 3 (6%) |
| HYPERPLASIA, RETICULUM CELL | 3 (18%) | 1 (2%) | 3 (6%) |
| HYPERPLASIA, LYMPHOID | 2 (12%) | 15 (32%) | 13 (27%) |
| HEMATOPOIESIS | 8 (47%) | 12 (26%) | |
| #THYMUS | (12) | (35) | (35) |
| ATROPHY, NOS | 8 (67%) | 32 (91%) | 30 (86%) |
| HYPERPLASIA, LYMPHOID | 1 (8%) | 1 (3%) | |
| CIRCULATORY SYSTEM | | | |
| #RIGHT VENTRICLE | (19) | (50) | (49) |
| THROMBOSIS, NOS | | 1 (2%) | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (19) | (49) | (49) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| INFARCT, NOS | 1 (5%) | | |
| LIPOIDOSIS | | 2 (4%) | 3 (6%) |
| HYPERTROPHY, FOCAL | | | 1 (2%) |
| #LIVER/HEPATOCYTES | (19) | (49) | (49) |
| LIPOIDOSIS | 1 (5%) | | 1 (2%) |
| CYTOPLASMIC VACUOLIZATION | | 1 (2%) | 2 (4%) |
| HYPERPLASIA, NOS | 1 (5%) | 1 (2%) | |
| *GALLBLADDER | (19) | (50) | (49) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| POLYP | | | 1 (2%) |
| *MUCOSA OF GALLBLADDE | (19) | (50) | (49) |
| CYST, NOS | 1 (5%) | | |
| #STOMACH | (19) | (48) | (49) |
| HYPERPLASIA, EPITHELIAL | 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 |
|---|---|---|---|
| #GASTRIC FUNDUS | (19) | (48) | (49) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| #PEYERS PATCH | (19) | (48) | (47) |
| INFLAMMATION, ACUTE | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (19) | (48) | (49) |
| HYDRONEPHROSIS | | 1 (2%) | 1 (2%) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 1 (5%) | | 4 (8%) |
| INFARCT, HEALED | | 1 (2%) | |
| #KIDNEY/CORTEX | (19) | (48) | (49) |
| CYST, NOS | | | 2 (4%) |
| #KIDNEY/PELVIS | (19) | (48) | (49) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| INFLAMMATION, ACUTE | 1 (5%) | | |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| #URINARY BLADDER | (18) | (44) | (44) |
| INFLAMMATION, NOS | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (15) | (42) | (45) |
| CYST, NOS | 2 (13%) | 1 (2%) | |
| #ADRENAL CORTEX | (19) | (43) | (47) |
| HYPERPLASIA, NOS | 1 (5%) | | |
| #ADRENAL MEDULLA | (19) | (43) | (47) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| #THYROID | (18) | (46) | (48) |
| FOLLICULAR CYST, NOS | | | 1 (2%) |
| HYPERPLASIA, FOLLICULAR-CELL | | 2 (4%) | |
| #PANCREATIC ISLETS | (17) | (45) | (49) |
| HYPERPLASIA, NOS | | 4 (9%) | 4 (8%) |

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

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

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (19) | (50) | (49) |
| GALACTOCELE | | 1 (2%) | |
| *PREPUTIAL GLAND | (19) | (50) | (49) |
| DILATATION, NOS | | 1 (2%) | |
| #PROSTATE | (17) | (46) | (46) |
| INFLAMMATION, CHRONIC | 1 (6%) | | |
| #PROSTATIC GLAND | (17) | (46) | (46) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| *SEMINAL VESICLE | (19) | (50) | (49) |
| DILATATION, NOS | 6 (32%) | 31 (62%) | 16 (33%) |
| CYST, NOS | | 1 (2%) | |
| LIPOGRANULOMA | | | 1 (2%) |
| *EPIDIDYMIS | (19) | (50) | (49) |
| GRANULOMA, NOS | | 1 (2%) | 1 (2%) |
| NERVOUS SYSTEM | | | |
| #BRAIN | (18) | (47) | (48) |
| CORPORA AMYLACEA | 3 (17%) | 8 (17%) | 4 (8%) |
| SPECIAL SENSE ORGANS | | | |
| *EYE/CORNEA | (19) | (50) | (49) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| *EYE/LACRIMAL GLAND | (19) | (50) | (49) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| *MESENTERY | (19) | (50) | (49) |
| LIPOGRANULOMA | 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 |
|---|---|---|---|
| ALL OTHER SYSTEMS | | | |
| ADIPOSE TISSUE | | | |
| LIPOGRANULOMA | | 1 | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| 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 METHYL PARATHION IN THE DIET

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 50 | 50 |
| ANIMALS MISSING | | | 1 |
| ANIMALS NECROPSIED | 20 | 49 | 48 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 20 | 49 | 48 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (20) | (49) | (48) |
| SEBACEOUS CYST | | 1 (2%) | |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| ALOPECIA | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (20) | (49) | (48) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | | 1 (2%) |
| HISTIOCYTOSIS | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (20) | (49) | (48) |
| HYPERPLASIA, HEMATOPOIETIC | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, ERYTHROID | | 1 (2%) | |
| #SPLEEN | (20) | (49) | (47) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| INFLAMMATION, FOCAL GRANULOMATOU | | 1 (2%) | |
| ADHESION, NOS | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 8 (40%) | 12 (24%) | 13 (28%) |
| HEMATOPOIESIS | 1 (5%) | 5 (10%) | 1 (2%) |
| #LYMPH NODE | (19) | (49) | (47) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #MANDIBULAR L. NODE | (19) | (49) | (47) |
| HEMORRHAGIC CYST | | | 1 (2%) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| LYMPHOID DEPLETION | | | 1 (2%) |

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

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYPERPLASIA, RETICULUM CELL | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | 1 (5%) | 6 (12%) | 3 (6%) |
| #MESENTERIC L. NODE | (19) | (49) | (47) |
| HEMORRHAGE | | 1 (2%) | 1 (2%) |
| LYMPHOID DEPLETION | | | 1 (2%) |
| HYPERPLASIA, RETICULUM CELL | | 2 (4%) | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 4 (21%) | 9 (18%) | 10 (21%) |
| HEMATOPOIESIS | 3 (16%) | | |
| #THYMUS | (14) | (30) | (34) |
| HEMORRHAGE | | | 1 (3%) |
| ATROPHY, NOS | 7 (50%) | 16 (53%) | 29 (85%) |
| HYPERPLASIA, LYMPHOID | | 2 (7%) | |
| CIRCULATORY SYSTEM | | | |
| #HEART | (20) | (49) | (48) |
| DEGENERATION, GRANULAR | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (20) | (47) | (47) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 1 (5%) | 3 (6%) | 2 (4%) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #LIVER | (20) | (49) | (48) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 2 (10%) | 4 (8%) | |
| INFLAMMATION, GRANULOMATOUS | 1 (5%) | | |
| GRANULOMA, NOS | 1 (5%) | | |
| INFLAMMATION, FOCAL GRANULOMATOU | | 1 (2%) | |
| NECROSIS, FOCAL | | | 1 (2%) |
| NECROSIS, COAGULATIVE | | 1 (2%) | |
| LIPOIDOSIS | 1 (5%) | | 1 (2%) |
| LYMPHOCYTOSIS | | 1 (2%) | |
| #LIVER/HEPATOCYTES | (20) | (49) | (48) |
| NECROSIS, NOS | 1 (5%) | | |
| *GALLBLADDER | (20) | (49) | (48) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| #PANCREAS | (18) | (46) | (42) |
| DILATATION/DUCTS | | | 1 (2%) |

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

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| #PANCREATIC ACINUS | (18) | (46) | (42) |
| ATROPHY, NOS | | | 1 (2%) |
| #STOMACH | (20) | (48) | (48) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| PERIARTERITIS | 1 (5%) | | |
| #GASTRIC MUCOSA | (20) | (48) | (48) |
| CYST, NOS | | 1 (2%) | |
| #GASTRIC SEROSA | (20) | (48) | (48) |
| INFLAMMATION, CHRONIC | 1 (5%) | | |
| #PEYERS PATCH | (20) | (49) | (46) |
| HYPERPLASIA, LYMPHOID | 1 (5%) | | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (20) | (49) | (48) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 6 (30%) | 4 (8%) | 1 (2%) |
| PERIARTERITIS | | 1 (2%) | |
| INFARCT, HEALED | | 1 (2%) | |
| PLASMACYTOSIS | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #KIDNEY/GLOMERULUS | (20) | (49) | (48) |
| NEPHROPATHY | 1 (5%) | | 1 (2%) |
| #KILNEY/PELVIS | (20) | (49) | (48) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | | 1 (2%) |
| #URINARY BLADDER | (19) | (45) | (43) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 3 (7%) | |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | | 2 (4%) | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (17) | (45) | (44) |
| CYST, NOS | | | 1 (2%) |
| #ADRENAL | (20) | (49) | (48) |
| CYST, NOS | | 1 (2%) | |

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

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | MATCHED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| INFLAMMATION, CHRONIC | 1 (5%) | | |
| HEMATOPOIESIS | 1 (5%) | | |
| #ADRENAL CORTEX | (20) | (49) | (48) |
| CYST, NOS | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| #THYROID | (20) | (47) | (46) |
| CYSTIC FOLLICLES | | 1 (2%) | |
| HYPERPLASIA, FOLLICULAR-CELL | | | 1 (2%) |
| #PANCREATIC ISLETS | (18) | (46) | (42) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (20) | (49) | (48) |
| GALACTOCELE | | | 1 (2%) |
| METAPLASIA, SQUAMOUS | | | 1 (2%) |
| LACTATION | | | 1 (2%) |
| #UTERUS | (20) | (48) | (45) |
| HYDROMETRA | 3 (15%) | 3 (6%) | 3 (7%) |
| HYPERPLASIA, STROMAL | | | 1 (2%) |
| #UTERUS/ENDOMETRIUM | (20) | (48) | (45) |
| CYST, NOS | | | 3 (7%) |
| HYPERPLASIA, NOS | 3 (15%) | 5 (10%) | 15 (33%) |
| HYPERPLASIA, CYSTIC | 14 (70%) | 31 (65%) | 16 (36%) |
| #OVARY/PAROVARIAN | (20) | (48) | (45) |
| INFARCT, NOS | | | 1 (2%) |
| #OVARY | (17) | (48) | (47) |
| CYST, NOS | | 3 (6%) | |
| FOLLICULAR CYST, NOS | 2 (12%) | 8 (17%) | 5 (11%) |
| HEMORRHAGIC CYST | | 3 (6%) | |
| ATROPHY, NOS | 15 (88%) | 25 (52%) | 28 (60%) |
| #OVARY/FOLLICLE | (17) | (48) | (47) |
| HEMORRHAGE | | 1 (2%) | |
| HEMORRHAGIC CYST | | 1 (2%) | 1 (2%) |
| NERVOUS SYSTEM | | | |
| #BRAIN | (18) | (49) | (48) |
| PERIVASCULAR CUFFING | | 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 |
|---|---|---|---|
| CORPORA AMYLACEA | 2 (11%) | 5 (10%) | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *BONE | (20) | (49) | (48) |
| RESORPTION | | 1 (2%) | |
| *JOINT | (20) | (49) | (48) |
| OSTEOARTHRITIS | | | 1 (2%) |
| BODY CAVITIES | | | |
| *ABDOMINAL CAVITY | (20) | (49) | (48) |
| LIPOGRANULOMA | | | 1 (2%) |
| *PERITONEUM | (20) | (49) | (48) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| *MESENTERY | (20) | (49) | (48) |
| HEMORRHAGIC CYST | | | 1 (2%) |
| ALL OTHER SYSTEMS | | | |
| ADIPOSE TISSUE | | | |
| LIPOGRANULOMA | 1 | 1 | 1 |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| ANIMAL MISSING/NO NECROPSY | | | 1 |
| AUTOLYSIS/NO NECROPSY | | 1 | 1 |

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

# APPENDIX E

## ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED METHYL PARATHION IN THE DIET

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

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b) | 2/20 (10) | 3/50 (6) | 3/50 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.600 | 0.600 |
| Lower Limit | | 0.076 | 0.076 |
| Upper Limit | | 6.860 | 6.860 |
| Weeks to First Observed Tumor | 105 | 105 | 105 |
| Hematopoietic System: Lymphoma or Leukemia (b) | 3/20 (15) | 8/50 (16) | 4/50 (8) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.067 | 0.533 |
| Lower Limit | | 0.295 | 0.102 |
| Upper Limit | | 5.813 | 3.410 |
| Weeks to First Observed Tumor | 88 | 90 | 102 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 2/20 (10) | 0/49 (0) | 0/50 (0) |
| P Values (c,d) | P = 0.025 (N) | N.S. | N.S. |
| Departure from Linear Trend (e) | P = 0.044 | | |
| Relative Risk (f) | | 0.000 | 0.000 |
| Lower Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.372 | 1.345 |
| Weeks to First Observed Tumor | 105 | -- | -- |
| Pituitary: Adenoma, or Adenocarcinoma (b) | 9/20 (45) | 11/48 (23) | 15/50 (30) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.509 | 0.667 |
| Lower Limit | | 0.242 | 0.346 |
| Upper Limit | | 1.197 | 1.478 |
| Weeks to First Observed Tumor | 83 | 41 | 104 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Adrenal: Pheochromocytoma (b) | 3/20 (15) | 6/50 (12) | 5/50 (10) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.800 | 0.667 |
| Lower Limit | | 0.195 | 0.147 |
| Upper Limit | | 4.615 | 4.014 |
| Weeks to First Observed Tumor | 105 | 100 | 105 |
| Thyroid: C-cell Carcinoma or Adenoma (b) | 0/20 (0) | 3/48 (6) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | Infinite | Infinite |
| Lower Limit | | 0.261 | 0.255 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 105 | 97 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Pancreatic Islets: Islet-cell Adenoma (b) | 2/19 (11) | 4/45 (9) | 2/47 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.844 | 0.404 |
| Lower Limit | | 0.136 | 0.032 |
| Upper Limit | | 8.864 | 5.318 |
| Weeks to First Observed Tumor | 105 | 95 | 104 |
| Prostate: Acinar-cell Adenoma (b) | 2/20 (10) | 0/44 (0) | 0/48 (0) |
| P Values (c,d) | P = 0.027 (N) | N.S. | N.S. |
| Relative Risk (f) | | 0.000 | 0.000 |
| Lower Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.524 | 1.400 |
| Weeks to First Observed Tumor | 105 | -- | -- |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Testis: Interstitial-cell Tumor (b) | 17/20 (85) | 40/50 (80) | 41/50 (82) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.941 | 0.965 |
| Lower Limit | | 0.781 | 0.802 |
| Upper Limit | | 1.291 | 1.310 |
| Weeks to First Observed Tumor | 88 | 41 | 80 |

(a) Dosed groups received 20 or 40 ppm.

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

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

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

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

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

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

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Adenoma (b) | 0/20 (0) | 5/50 (10) | 1/47 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Departure from Linear Trend (e) | P = 0.037 | | |
| Relative Risk (f) | | Infinite | Infinite |
| Lower Limit | | 0.525 | 0.023 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 93 | 105 |
| Hematopoietic System: Leukemia or Lymphoma (b) | 1/20 (5) | 3/50 (6) | 4/47 (9) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.200 | 1.702 |
| Lower Limit | | 0.106 | 0.186 |
| Upper Limit | | 61.724 | 81.978 |
| Weeks to First Observed Tumor | 105 | 101 | 86 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 2/20 (10) | 5/50 (10) | 0/47 (0) |
| P Values (c,d) | P = 0.046 (N) | N.S. | N.S. |
| Relative Risk (f) | | 1.000 | 0.000 |
| Lower Limit | | 0.184 | 0.000 |
| Upper Limit | | 10.007 | 1.429 |
| Weeks to First Observed Tumor | 105 | 105 | -- |
| Pituitary: Adenoma or Carcinoma (b) | 12/20 (60) | 22/50 (44) | 15/47 (32) |
| P Values (c,d) | P = 0.021 (N) | N.S. | P = 0.031 (N) |
| Relative Risk (f) | | 0.733 | 0.532 |
| Lower Limit | | 0.465 | 0.312 |
| Upper Limit | | 1.331 | 1.031 |
| Weeks to First Observed Tumor | 105 | 93 | 97 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Mammary Gland: Fibroadenoma (b) | 5/20 (25) | 2/50 (4) | 0/47 (0) |
| P Values (c,d) | P = 0.001 (N) | P = 0.018 (N) | P = 0.002 (N) |
| Relative Risk (f) | | 0.160 | 0.000 |
| Lower Limit | | 0.017 | 0.000 |
| Upper Limit | | 0.900 | 0.332 |
| Weeks to First Observed Tumor | 105 | 105 | -- |
| Uterus: Endometrial Stromal Polyp (b) | 4/20 (20) | 6/50 (12) | 4/46 (9) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Matched Control) (f) | | 0.600 | 0.435 |
| Lower Limit | | 0.164 | 0.092 |
| Upper Limit | | 2.659 | 2.148 |
| Weeks to First Observed Tumor | 105 | 105 | 86 |

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

(continued)

(a) Dosed groups received 20 or 40 ppm.

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

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

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

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

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

# APPENDIX F

## ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED METHYL PARATHION IN THE DIET

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

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma (b) | 0/19 (0) | 5/50 (10) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | Infinite | Infinite |
| Lower Limit | | 0.501 | 0.243 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 84 | 102 |
| Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b) | 1/19 (5) | 10/50 (20) | 8/49 (16) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 3.800 | 3.102 |
| Lower Limit | | 0.613 | 0.470 |
| Upper Limit | | 160.949 | 134.436 |
| Weeks to First Observed Tumor | 102 | 84 | 102 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Hematopoietic System: | | | |
| Lymphoma (b) | 2/19 (11) | 8/50 (16) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.520 | 0.582 |
| Lower Limit | | 0.348 | 0.074 |
| Upper Limit | | 13.949 | 6.640 |
| Weeks to First Observed Tumor | 97 | 96 | 23 |
| Liver: Hepatocellular Carcinoma (b) | 2/19 (11) | 3/49 (6) | 6/49 (12) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.582 | 1.163 |
| Lower Limit | | 0.074 | 0.237 |
| Upper Limit | | 6.640 | 11.202 |
| Weeks to First Observed Tumor | 84 | 102 | 102 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 10/19 (53) | 14/49 (29) | 12/49 (24) |
| P Values (c,d) | P = 0.034 (N) | N.S. | P = 0.028 (N) |
| Relative Risk (f) | | 0.543 | 0.465 |
| Lower Limit | | 0.294 | 0.241 |
| Upper Limit | | 1.152 | 1.018 |
| Weeks to First Observed Tumor | 84 | 102 | 102 |
| All Sites: Hemangiosarcoma (b) | 2/19 (11) | 0/50 (0) | 1/49 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Departure from Linear Trend (e) | P = 0.033 | | |
| Relative Risk (f) | | 0.000 | 0.194 |
| Lower Limit | | 0.000 | 0.003 |
| Upper Limit | | 1.278 | 3.563 |
| Weeks to First Observed Tumor | 102 | — | 102 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| All Sites: Hemangioma | 1/19 (5) | 3/50 (6) | 1/49 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.140 | 0.388 |
| Lower Limit | | 0.101 | 0.005 |
| Upper Limit | | 58.635 | 29.845 |
| Weeks to First Observed Tumor | 102 | 102 | 102 |
| All Sites: Hemangiosarcoma or Hemangioma (b) | 3/19 (16) | 3/50 (6) | 2/49 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.380 | 0.259 |
| Lower Limit | | 0.057 | 0.024 |
| Upper Limit | | 2.658 | 2.118 |
| Weeks to First Observed Tumor | 102 | 102 | 102 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Adrenal: Cortical Adenoma (b) | 3/19 (16) | 4/43 (9) | 5/47 (11) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.589 | 0.674 |
| Lower Limit | | 0.113 | 0.150 |
| Upper Limit | | 3.737 | 4.039 |
| Weeks to First Observed Tumor | 102 | 102 | 102 |
| Pancreatic Islets: Islet-cell Adenoma (b) | 1/17 (6) | 3/45 (7) | 0/49 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.133 | 0.000 |
| Lower Limit | | 0.101 | 0.000 |
| Upper Limit | | 58.167 | 6.484 |
| Weeks to First Observed Tumor | 102 | 102 | -- |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Eye/Lacrimal Gland: Papillary Adenoma (b) | 1/19 (5) | 1/50 (2) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.380 | 1.163 |
| Lower Limit | | 0.005 | 0.103 |
| Upper Limit | | 29.260 | 59.809 |
| Weeks to First Observed Tumor | 102 | 102 | 102 |



(a) Dosed groups received time-weighted average doses of 35 or 77 ppm.

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

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

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

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

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

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

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b) | 0/20 (0) | 3/49 (6) | 2/48 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | Infinite | Infinite |
| Lower Limit | | 0.255 | 0.128 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 102 | 102 |
| Hematopoietic System: Lymphoma or Leukemia (b) | 8/20 (40) | 12/49 (24) | 5/48 (10) |
| P Values (c,d) | P = 0.004(N) | N.S. | P = 0.008(N) |
| Relative Risk (f) | | 0.612 | 0.260 |
| Lower Limit | | 0.286 | 0.081 |
| Upper Limit | | 1.499 | 0.799 |
| Weeks to First Observed Tumor | 97 | 91 | 82 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| All Sites: Hemangiomas (b) | 1/20 (5) | 3/49 (6) | 0/48 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.224 | 0.000 |
| Lower Limit | | 0.108 | 0.000 |
| Upper Limit | | 62.958 | 7.780 |
| Weeks to First Observed Tumor | 102 | 102 | -- |
| All Sites: Hemangiosarcoma or Hemangioma (b) | 1/20 (5) | 5/49 (10) | 2/48 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 2.041 | 0.833 |
| Lower Limit | | 0.254 | 0.047 |
| Upper Limit | | 94.440 | 48.155 |
| Weeks to First Observed Tumor | 102 | 102 | 101 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 1/20 (5) | 4/49 (8) | 2/48 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 1.633 | 0.833 |
| Lower Limit | | 0.179 | 0.047 |
| Upper Limit | | 78.704 | 48.155 |
| Weeks to First Observed Tumor | 102 | 93 | 102 |
| Pituitary: Adenoma (b) | 4/17 (24) | 5/45 (11) | 1/44 (2) |
| P Values (c,d) | P = 0.010 (N) | N.S. | P = 0.019 (N) |
| Relative Risk (f) | | 0.472 | 0.097 |
| Lower Limit | | 0.120 | 0.002 |
| Upper Limit | | 2.166 | 0.902 |
| Weeks to First Observed Tumor | 102 | 100 | 82 |

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

(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Adrenal: Cortical Adenoma (b) | 2/20 (10) | 1/49 (2) | 1/48 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (f) | | 0.204 | 0.208 |
| Lower Limit | | 0.004 | 0.004 |
| Upper Limit | | 3.754 | 3.830 |
| Weeks to First Observed Tumor | 102 | 102 | 102 |
| Mammary Gland: | | | |
| Adenocarcinoma (b) | 0/20 (0) | 3/49 (6) | 1/48 (2) |
| P Values (c,d) | N.S | N.S. | N.S. |
| Relative Risk (f) | | Infinite | Infinite |
| Lower Limit | | 0.255 | 0.023 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 102 | 83 |

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Methyl Parathion in the Diet (a)
(continued)

| Topography: Morphology | Matched Control | Low Dose | High Dose |
|---|---|---|---|
| Uterus: Endometrial Stromal Polyp (b) | 0/20 (0) | 0/48 (0) | 3/45 (7) |
| P Values (c,d) | N.S. | -- | N.S. |
| Relative Risk (f) | | -- | Infinite |
| Lower Limit | | -- | 0.278 |
| Upper Limit | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | 102 |

(a) Dosed groups received 62.5 or 125 ppm.

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

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

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

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

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

Review of the Bioassay of Methyl Parathion* 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 Methyl Parathion.

The reviewer for the report on the bioassay of Methyl Parathion agreed with the conclusion that the compound was not carcinogenic under the conditions of test. After a brief description of the experimental design, he said that no data were given on the stability and content of the compound in the diet mix and that the size of the matched control groups was too small. He added, however, that the shortcomings were not significant. Based on the results of the study, the reviewer said that Methyl Parathion would not appear to pose a risk of cancer for human beings. He moved that the report on the bioassay of the compound 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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